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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	XFEL data were collected at the CXI instrument at LCLS using in-house DAQ software.
Data analysis	NCBI blastp server (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins; queried in 2015-2018) Prodrg server (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg/submit.html; queried in 2017-2018) CHARMM-GUI web-server (http://www.charmm-gui.org/; queried in January 2018) GPCRdb (http://gpcrdb.org/; queried in 2015-2018) MolProbity server v.4.4 (http://molprobity.biochem.duke.edu/; queried in 2018) QC Check server v.3.1 (https://smb.slac.stanford.edu/jcsg/QC/; queried in 2018) OPM database (http://opm.phar.umich.edu; queried in January 2018) ChEMBL24 (https://www.ebi.ac.uk/chembl/; queried in 2018) UniProt (https://www.uniprot.org/; queried in July 2018) TMHMM server v.2.0 (http://www.cbs.dtu.dk/services/TMHMM/; queried in 2018) Cheetah v.2017.3; CrystFEL v.0.6.2; Refmac5 v.5.0.32; Phaser v.2.1; Buster v.2.10.2; PHENIX-1.9.1692; WinCoot v.0.8.6; CCP4 v.7.0.044; Rotor-Gene Q v.2.3.1.49; GraphPad Prism v.5.0; Python v.2.7; Biopython v.1.65; rdkit (Release_2017.09.1); CAVER analyst v. 2.0; ICM-Pro v.3.8-6; PyMOL v.1.3 and 2.1.1; OpenBabel v.2.4.0; DSSP v3.0

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Coordinates and structure factors were deposited in the Protein Data Bank (PDB) under the following accession codes: 6ME2 (MT1-CC-ramelteon), 6ME3 (MT1-CC-2-pmt), 6ME4 (MT1-CC-2-iodomelatonin), and 6ME5 (MT1-CC-agomelatine). Data will be released upon publication.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to predetermine sample size. Thermostability and pharmacological characterization were conducted at least in n=3 independent experiments and are comparable to other published studies. Wild-type constructs were used as internal controls, resulting in larger number of independent repeats. Diffraction data from thousands of protein crystals were integrated and scaled to ensure 100% completeness of the dataset.
Data exclusions	No data were excluded.
Replication	All measurements were done at least in triplicate and all attempts at replication were successful and presented.
Randomization	This study did not allocate experimental groups thus no randomization was required for the reported experiments.
Blinding	The researchers were not blinded to allocation during experiments and outcome assessment. Blinding was not required for the reported experiments because all functional and structural data were analyzed using the same methods, and results are not subjective.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Cell lines were purchased from the American Type Culture Collection (ATCC). Sf9: ATCC CRL-1711. HEK293T cells: ATCC CRL-11268.
Authentication	The cell lines were authenticated by the supplier (ATCC) using morphology and growth characteristics (for Sf9 and HEK293T), and STR profiling (for HEK293T).
Mycoplasma contamination	Both Sf9 and HEK293T cells have been tested and shown to be free from mycoplasma (Hoechst DNA strain and Direct Culture methods employed).

Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.