

Reporting Summary

Nature Portfolio 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 Portfolio policies, see our [Editorial Policies](#) 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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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	Sciex OS v3.4, Agilent Open lab 2.5, BD FACSDiva v.9.7, FV31S-SW v 2.5.1.228, Living Image v4.8.3, DIFFRAC.SUITE, Gaussian 16, Xcalibur v4.6
Data analysis	BPV Flex v2.1, ImageJ v1.54f, FlowJo v3.0, Living Image v4.8.3, Sciex OS v3.4, Diamond v4.0, GraphPad Prism, Pymol v2.5.5, Origin v2018, Proteome Discoverer v2.5

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

All the data for this study are included in this Article and its Supplementary Information and are available from the corresponding author(s) upon request. Crystallographic data for the structure of 9a reported in this study have been deposited with the Cambridge Crystallographic Data Centre (CCDC), under deposition number 2493333. The Supporting Information contains additional experimental methods, synthesis of reagents, NMR and MS-based analytical data for reagents,

MS-based analysis data for bioconjugates, late-stage modifications, and serum stability. The data for enzymatic assay, insulin bioactivity assay, live cell, in vitro and in vivo detection and inhibition, additional schematic illustrations, and discussion supporting the main findings are incorporated into Supporting Information. The raw data generated in this study have been deposited in the repository (<https://doi.org/10.6084/m9.figshare.30819182>). The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD082695 and 10.6019/PXD082695.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	NA
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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	Sample sizes were not predetermined but were chosen based on prior experience and published studies, and were sufficient to yield reproducible and statistically interpretable results.
Data exclusions	NA
Replication	Biological replicates were reproducible.
Randomization	Samples were randomly assigned to experimental groups prior to treatment.
Blinding	NA

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 and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	Anti-pAkt-S473 (1:2000, CST #4060), anti-GAPDH (1:3000, CST #5174S), anti-Discs large (1:100, DSHB_S1_209)
Validation	Anti-pAkt-S473 and anti-GAPDH were validated by the manufacturer for Western blotting. Specificity was confirmed by detection of a ~60 kDa band and modulation of signal upon Akt pathway activation. Similarly, GAPDH was confirmed by detection of a ~37 kDa band. Anti-Discs large was validated by immunofluorescence staining of epithelial membrane of Drosophila gut.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	HeLa cells (#CRM-CCL-2), HEK293T cells (#CRL-3216), and Vero cells (#CCI-81) are from ATCC.
Authentication	All the cells used were authenticated via STR profiling and procured from ATCC.
Mycoplasma contamination	All cell lines tested were mycoplasma negative
Commonly misidentified lines (See ICLAC register)	NA

Animals and other research organisms

Policy information about [studies involving animals; ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	CD-1 mice, Age: 6-8 week, Sex: male and female
Wild animals	The study did not involve wild animals
Reporting on sex	The study design was gender neutral
Field-collected samples	The study did not involve samples collected from field
Ethics oversight	Institutional Animal Ethics Committee (IAEC) of IISER Bhopal (Approval Number: 2025-IISERB-7.1-IAEC)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA

Flow Cytometry

Plots

Confirm that:

- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☐ All plots are contour plots with outliers or pseudocolor plots.
- ☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cells were obtained from BEI Resources/ATCC. Following treatment, cells were washed and resuspended in phosphate-buffered saline (PBS) and subjected to flow cytometric analysis.
Instrument	FACS BD Aria III
Software	Software for acquisition: BD FACSDiva Software for analysis: FlowJo
Cell population abundance	Minimum of 10000 events acquired per sample; population frequencies expressed as % of gated cells; post-sort purity >95%.
Gating strategy	Cells were gated on FSC and SSC to exclude debris, followed by FSC-A versus FSC-H gating to remove doublets. Positive and negative populations were defined based on unstained controls, and gates were applied consistently across all samples.

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.