nature portfolio

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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 *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	Empower 3 software (Waters, Milford, MA); MassLynx V4.2 software (Waters, Milford, MA); TRIOS software V5.1.1 (Waters/TA Instruments, New Castle, DE); SoftMax Pro 6.2 software (Sunnyvale, CA).
Data analysis	Empower 3 software (Waters, Milford, MA); MassLynx V4.2 software (Waters, Milford, MA); Microsoft Excel V16.49 (Redmond, WA); GraphPad Prism V9.3.0 (San Diego, CA); Non-compartmental PK analysis for plasma drug levels was performed using Phoenix WinNonlin 8.3.3 software (Certara, Princeton, NJ)

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

Source Data are provided in the Figshare dataset under digital object identifier. All Figures and Supplementary Information: https://figshare.com/s/5be62cce2cd541f12208

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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 chosen to achieve statistical significance while considering cost and ethical animal use criteria. Although the sample size was not determined through power analysis, it proved adequate to establish statistical significance in all PK experiments. For Rat PK studies, the sample size was 4 or 8 per group.
Data exclusions	Exclusion criteria were predetermined. Extreme outliers falling outside the 99% confidence interval of the mean and exceeding three times the standard error of the mean (SEM) were excluded. Any excluded values are highlighted in blue and marked with an asterisk in the raw data files.
Replication	All attempts to reproduce the experimental findings were successful. Experiments involving chemical synthesis, characterization, and formulation production were independently repeated at least five times, yielding consistent results. In vitro cellular assays were independently repeated at least twice, with similar results. Prodrug hydrolysis studies were independently repeated twice, yielding comparable results.
Randomization	For all studies, samples/cells/animals were randomly allocated into experimental groups at the beginning of each study.
Blinding	Due to experimental constraints, investigators were not blinded during experiments or sample collection but employed an unbiased approach. Nevertheless, all animals were randomly allocated to the experimental groups, and efforts were made to ensure unbiased data through separate roles of investigators in sample and data collection/analysis for animal experiments (including drug quantification, CBC counts, and serum chemistry) and blinded pathological evaluation by the pathologist.

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

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Human peripheral blood monocytes
Authentication	Human peripheral blood monocytes were isolated by leukapheresis from HIV-1/2 and hepatitis B seronegative donors and purified by centrifugal elutriation from the University of Nebraska Medical Center (UNMC) Elutriation and Cell Separation Core according to a UNMC Institutional Review Board exempt protocol with informed consent. Monocytes were cultured for the first seven days in macrophage colony stimulating factor enriched media (MCSF, 1000 U/ml) to facilitate cell vitality and differentiation into macrophages.
Mycoplasma contamination	Cells obtained from elutriation were negative for mycoplasma
Commonly misidentified lines (See ICLAC register)	N/A

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	Rats: Sprague Dawley, male, 8 weeks
Wild animals	The study did not involve wild animals.
Reporting on sex	Sex/Gender information for each study involving animal subject has been provided.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The University of Nebraska Medical Center Institutional Animal Care and Use Committee (IACUC) approved all the PK studies involving laboratory animals by the standards incorporated in the Guide for the Care and Use of Laboratory Animals (UNMC IACUC protocol number: 23-056-09-EP). Human peripheral blood monocyte isolation and purification from HIV-1/2 and HBV seronegative participants were performed according to an exempt protocol by the UNMC Institutional Review Board (IRB) with informed consent.

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A