

## 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

Data analysis

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](#)

The cryo-EM data generated in this study have been deposited in the PDB and in the EM data bank under accession codes 8A1R [<https://www.rcsb.org/structure/8A1R>] and EMD-15084 [<https://www.ebi.ac.uk/emdb/EMD-15084>], respectively. The cryo-EM data will be released immediately upon publication. The X-ray-derived data of small molecular fragments in complex with TGR used in this study to design the compounds here described are available in the PDB under accession codes 6FTC [<https://www.rcsb.org/structure/6FTC>], 6FMU [<https://www.rcsb.org/structure/6FMU>], 6FMZ [<https://www.rcsb.org/structure/6FMZ>] and 6FP4 [<https://www.rcsb.org/structure/6FP4>], 2X99 [<https://www.rcsb.org/structure/3X99>], 2X8G [<https://www.rcsb.org/structure/2X8G>], 2X8H [<https://www.rcsb.org/structure/2X8H>], 6ZST [<https://www.rcsb.org/structure/6ZST>], 6ZP3 [<https://www.rcsb.org/structure/6ZP3>], 6ZLP [<https://www.rcsb.org/structure/6ZLP>], 6ZLB [<https://www.rcsb.org/structure/6ZLB>], 7B02 [<https://www.rcsb.org/structure/7B02>], 7NPX [<https://www.rcsb.org/structure/7NPX>], 2V6O [<https://www.rcsb.org/structure/2V6O>], 6RTJ [<https://www.rcsb.org/structure/6RTJ>], 6RTO [<https://www.rcsb.org/structure/6RTO>], 6RTM [<https://www.rcsb.org/structure/6RTM>], 3H4K [<https://www.rcsb.org/structure/3H4K>]. The X-ray-derived data of human GR in complex with NAPD+ used in this study to formulate the inhibition mechanism of the compounds depicted in Fig. 5 is available in the PDB under accession codes 3D4K [<https://www.rcsb.org/structure/3D4K>]. Plasmodium falciparum thioredoxin reductase protein sequence: <https://www.ncbi.nlm.nih.gov/protein/CAA60574.1/> Design of inhibitors was facilitated by ChEMBL25 database [<http://doi.org/10.6019/CHEMBL.database.25>]

## Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender	<input type="text" value="not applicable"/>
Population characteristics	<input type="text" value="not applicable"/>
Recruitment	<input type="text" value="not applicable"/>
Ethics oversight	<input type="text" value="not applicable"/>

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](https://www.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	<input type="text" value="Sample size calculations for means to obtain statistical power of 80% to detect 90% decrease in worm burden between the treated and the control groups at alpha=0.05, 5 mice per group were required."/>
Data exclusions	<input type="text" value="No data excluded."/>
Replication	<input type="text" value="All biochemical assays were done in triplicate. Experiments with cultured worms and Vero cells were done in triplicate, on mixed sex worms. In vivo experiments were done one time at the indicated dosage on 5 mice in each treatment and control. Each mouse treated is an experimental replicate. Five mice were used for each treatment to obtain statistical significance due to variability in infection rates. Age- and sex-matched outbred mice were infected with pools of cercariae obtained from &gt;100 infected, outbred snails. This is standard operating procedure in the field. All attempts at replication were successful."/>
Randomization	<input type="text" value="Mice were randomly distributed in cages by animal care personnel not involved in the studies. Mice were randomly assigned for the control and experiment groups using a randomization tool embedded in GraphPad Prism."/>
Blinding	<input type="text" value="The person administering drugs was not aware of the treatments being given. Assessment of worm burdens was done by a person not administering the treatments. The investigators were blinded by which group of mice received a treatment and the vehicle, as injection was done by technicians from the Comparative Research Center of Rush University Medical Center."/>

# 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	Involvement
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

## Methods

n/a	Involvement
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Eukaryotic cell lines

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

Cell line source(s)	VERO cells were obtained from ATCC.
Authentication	Short tandem repeat profiling was used to authenticate the cell line.
Mycoplasma contamination	Cells were conformed to be mycoplasma-free using a biochemical test kit from Lonza.
Commonly misidentified lines (See <a href="#">ICLAC</a> register)	No commonly misidentified cell lines were used in the study

## 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	Mus musculus, Swiss-Webster, female, 8 to 10 weeks old Schistosoma mansoni, NMRI strain, male/female, age not applicable Biomphalaria glabrata snails, strain NMRI, male/female, one month old Schistosoma japonicum, Chinese strain, male/female, age not applicable Oncomelania hupensis hupensis snails, Chinese strain, male/female, one month old  Mice were housed in 12 h light:dark cycle at 22-25 degrees temperature with relative humidity of 50-70%.
Wild animals	The study did not involve wild animals
Reporting on sex	Only female mice used in the study. Standard practice for maintaining the schistosome lifecycle and drug studies at this stage of development.
Field-collected samples	The study did not involve samples collected from the field
Ethics oversight	This study was approved by the Institutional Animal Care and Use Committee of Rush University Medical Center (20-069; Department of Health and Human Services animal welfare assurance number A-3120-01) and the Institutional Animal Care and Use Committee (IACUC) of the University of Illinois at Chicago (Protocol 19-049).

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