

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 (<i>n</i>) 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> 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 <i>d</i> , Pearson's <i>r</i>), 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	Nanopore sequencing was done using a P2 solo with MinKnow 23.04.6 (ultra kits) or 23.11.4 (ligation kits), and a P24 with MinKnow 23.07.12 (scaled ligation). All raw data was duplex basecalled with standalone Dorado 0.4.1+6c4c636
Data analysis	Publicly available vsearch 2.28.1, GNU parallel 20230922, Chopper v0.6.0, Flye v2.9.3-b1797, Medaka v1.11.3, Bakta v1.10.4, GTDB-tk v2.4.0, GNU AWK script 5.3.0, tRNAscan-SE v2.0.9, networkD3 R package 0.4, antiSMASH v6.1.1, FastTree v2.1.11, HMMER v3.1b2, proovframe-v0.9.7, CheckM v1.2.3, Barrnap 0.9, BigSCAPE v1.1.5, minimap2 2.28-r1209 and Snippy 4.6.0 were used for sequence assembly and analysis. PEAQ-ITC analysis software 1.41 was used for ITC 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 563 high-quality metagenomic assemblies, the 338 large NRPS assemblies, the genomes of the 30 cultured isolates, and the extracted 16S rRNA datasets have been submitted to GenBank under Bioproject PRJNA1226572. Publicly available Genome Taxonomy Database release 09-RS220 was used for taxonomic assignment and comparison. Publicly available AMP-binding protein PFAM PF00501.23 was used for Hidden Markov Model searches. Publicly available SILVA database release 138.2 was used for taxonomic assignment of 16S rRNA sequences. All other data is available in the main text or the supplementary materials.

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	No statistical methods were used to determine sample size, biologically independent repeats were performed to ensure result accuracy and reproducibility.
Data exclusions	No data was excluded
Replication	Compound characterization results were confirmed through three biologically independent experiments, ITC experiments were multiple independent measurement experiments, synBNP MIC screening was performed in duplicate with all other MIC experiments performed in biologically independent triplicate
Randomization	Randomization was not required as each experimental replicate was grown under identical conditions.
Blinding	Blinding was not relevant as each experimental replicate was grown under identical conditions.

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

Methods

n/a	Involvement in the study
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

n/a	Involvement 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)	HEK293 (ATCC, CRL-1573), origin of HeLa is unknown
Authentication	cell lines were not authenticated
Mycoplasma contamination	MycoAlert detection kit (Lonza Bioscience)
Commonly misidentified lines (See ICLAC register)	n/a

Plants

Seed stocks	Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.
Novel plant genotypes	Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.
Authentication	Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.