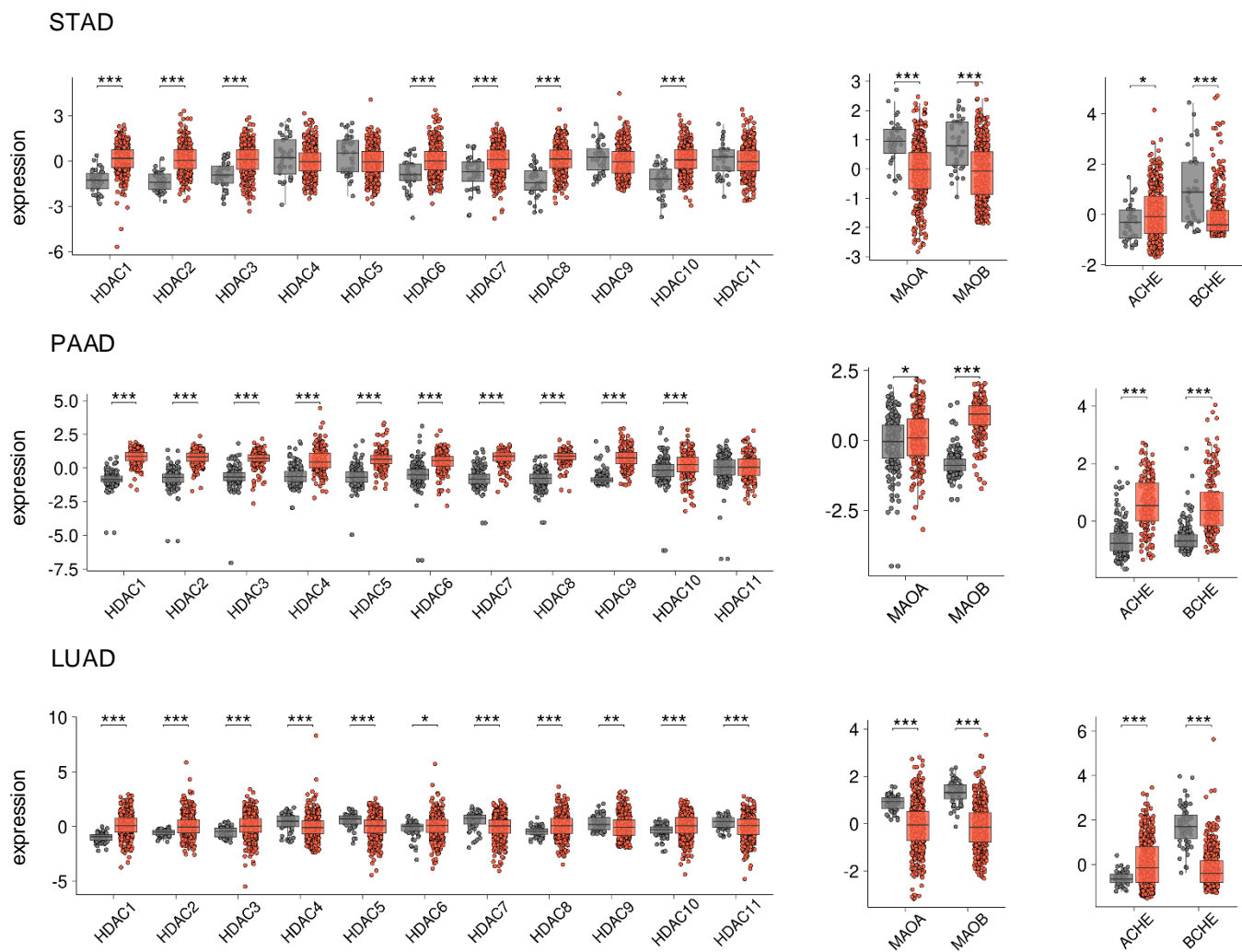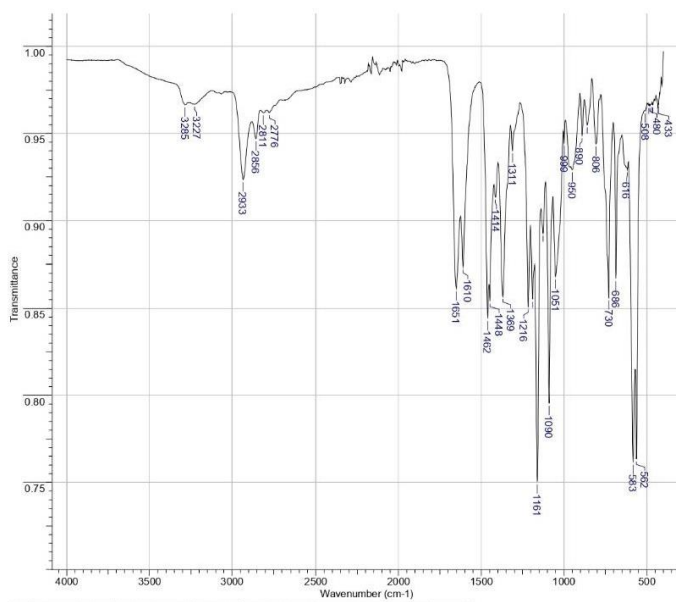**Suppl. Fig. 1. A)** Expression of target genes in normal tissue (grey) versus glioblastoma samples (red) in Gill cohort. **B)** Kaplan-Meier survival curves of patients with low vs highEx expression of target genes in Joo cohort. **C)** Expression and percentage of expressing cells of target genes in cell types from single-cell RNAseq of glioblastoma samples.
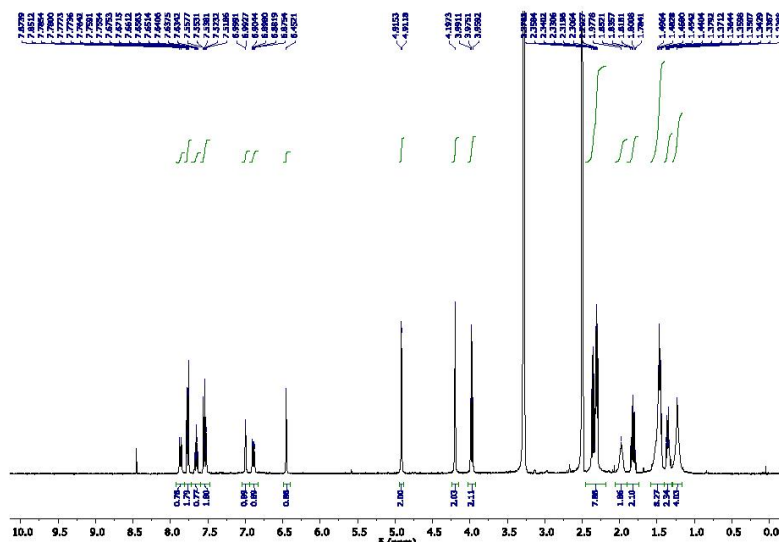
Suppl. Fig. 2. Expression of target genes in normal tissue (grey) versus cancer samples (red) in gastric (STAD), pancreatic (PAAD) and lung (LUAD) cancer in TCGA cohort.
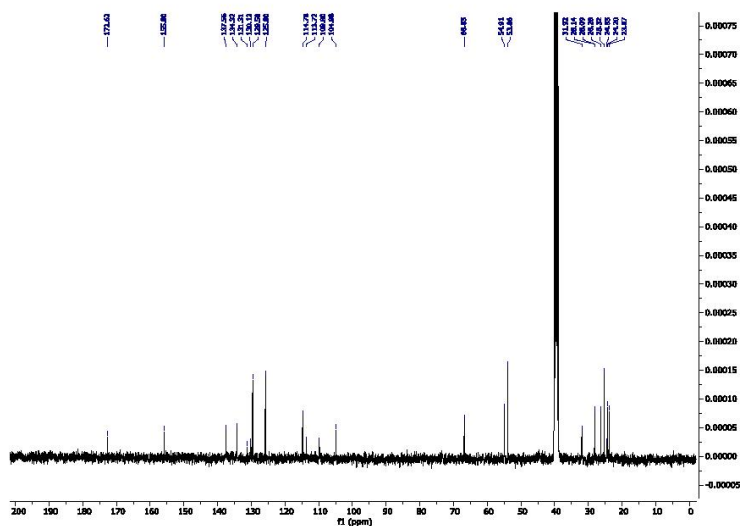
A

IR spectrum

No	cm-1	T	FWHH	Asym	Intensity		No	cm-1	T	FWHH	Asym	Intensity
1	428.00	0.967	-	-	W		19	1090.00	0.795	-1.00	0.00	S
2	433.00	0.965	-	-	W		20	1127.00	0.893	-	-	M
3	464.00	0.966	-	-	W		21	1161.00	0.750	-1.00	0.00	VS
4	471.00	0.967	-	-	W		22	1190.00	0.855	-	-	M
5	480.00	0.966	-	-	W		23	1216.00	0.851	-	-	M
6	488.00	0.966	-	-	W		24	1311.00	0.940	-	-	W
7	508.00	0.963	-	-	W		25	1369.00	0.857	-1.00	0.00	M
8	562.00	0.763	-	-	VS		26	1414.00	0.913	-	-	M
9	583.00	0.761	-	-	VS		27	1448.00	0.854	-	-	M
10	616.00	0.929	-	-	W		28	1462.00	0.844	-	-	S
11	686.00	0.867	-1.00	0.00	M		29	1610.00	0.874	-	-	M
12	730.00	0.856	-	-	M		30	1651.00	0.861	-	-	M
13	806.00	0.944	-1.00	0.00	W		31	2776.00	0.962	-	-	W
14	859.00	0.955	-	-	W		32	2811.00	0.962	-	-	W
15	890.00	0.949	-	-	W		33	2856.00	0.947	-	-	W
16	950.00	0.929	-	-	W		34	2933.00	0.924	-	-	W
17	999.00	0.944	-	-	W		35	3227.00	0.967	-	-	W
18	1051.00	0.868	-	-	M		36	3285.00	0.966	-	-	W

B

^{1}H NMR (100 ºC) spectrum

C

^{13}C NMR spectrum

D

HRMS spectrum

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	Hits (DB)
Cpd 1: C34 H44 N4 O6 S; 2.129	2.129	636.2974	1934371	C34 H44 N4 O6 S	636.2982	-1.12	1

Compound Label	m/z	RT	Algorithm	Mass
Cpd 1: C34 H44 N4 O6 S; 2.129	637.3045	2.129	Find by Formula	636.2974
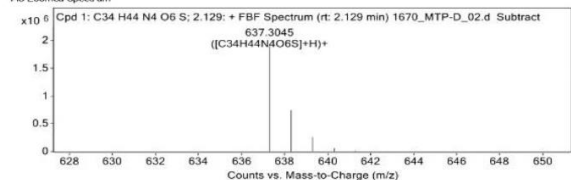
MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
637.3045	1	1934370.88	C34H44N4O6S	(M+H)+
638.3082	1	744057.25	C34H44N4O6S	(M+H)+
639.3074	1	259578.28	C34H44N4O6S	(M+H)+
640.3084	1	60391.55	C34H44N4O6S	(M+H)+
641.3108	1	11383.89	C34H44N4O6S	(M+H)+

MS Spectrum Peak List
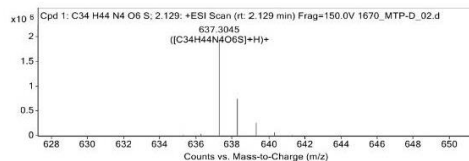
m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
637.3045	637.3054	1.4	1	1934370.88	C34H44N4O6S	(M+H)+
638.3082	638.3085	-0.53	1	744057.25	C34H44N4O6S	(M+H)+
639.3074	639.308	-0.85	1	259578.28	C34H44N4O6S	(M+H)+
640.3084	640.3088	-0.61	1	60391.55	C34H44N4O6S	(M+H)+
641.3108	641.3102	0.94	1	11383.89	C34H44N4O6S	(M+H)+

Suppl. Fig. 3. Structure of DDI199 molecule based on spectroscopic and analytical data. Analysis with **A)** Infrared spectroscopy (IR), **B)** Proton nuclear magnetic resonance (^{i}H NMR), **C)** Carbon-13 nuclear magnetic resonance (^{13}C NMR), and **D)** High resolution mass spectrometry (HRMS).

HPLC-MS
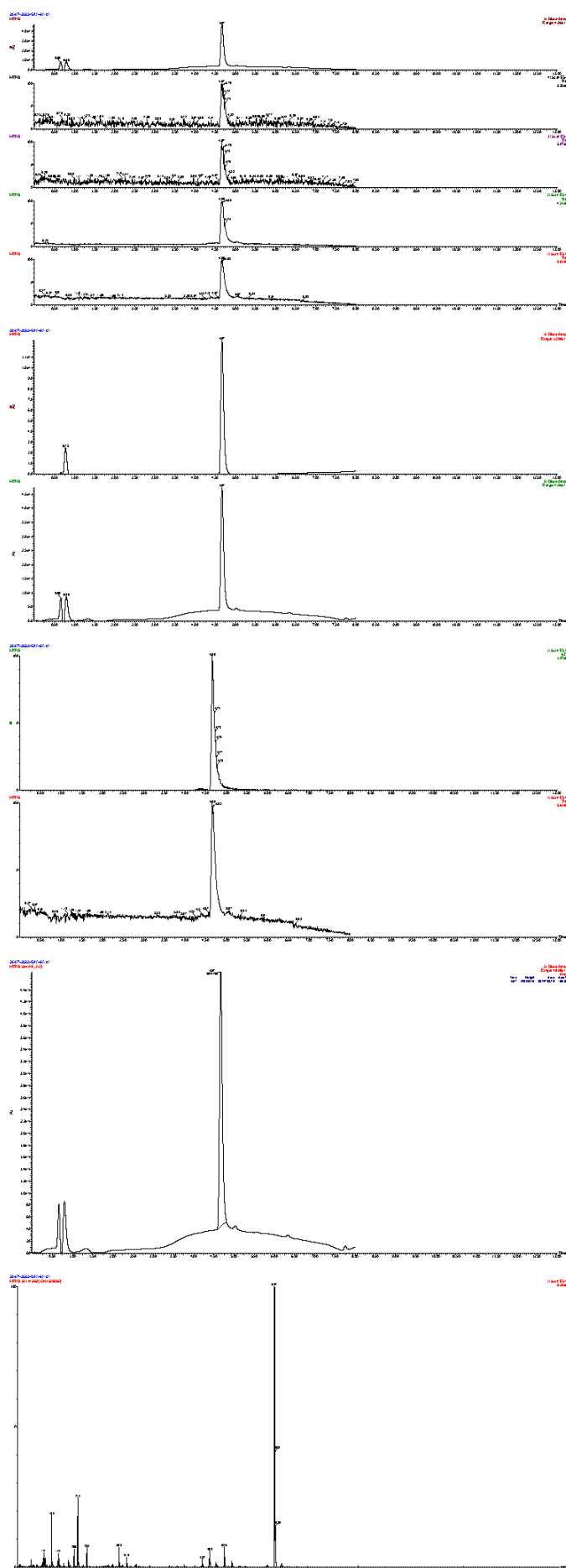
Suppl. Fig. 4. Purity of DDI199. Analysis with High-performance liquid chromatograph with mass spectrometry (HPLC-MS).
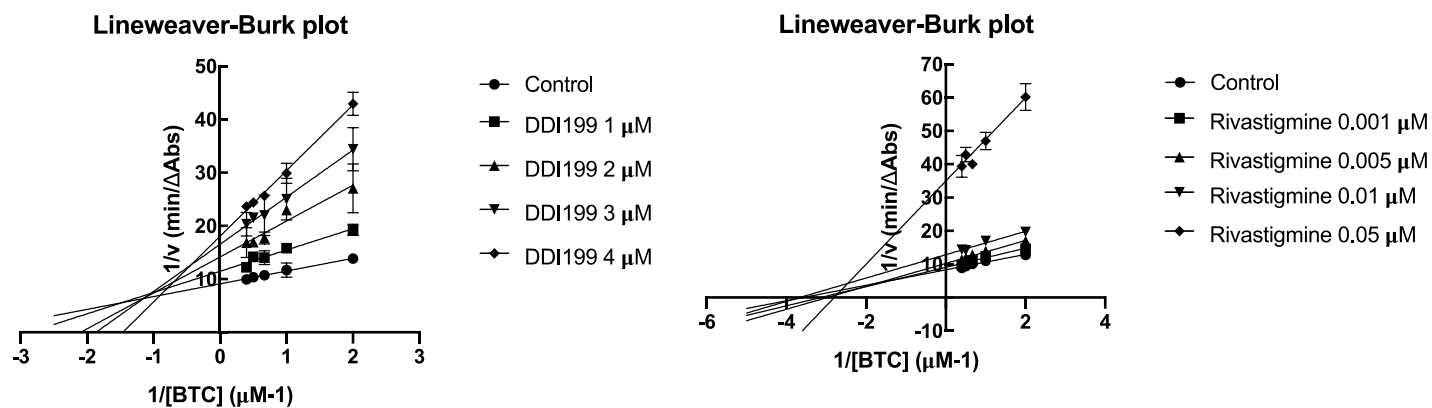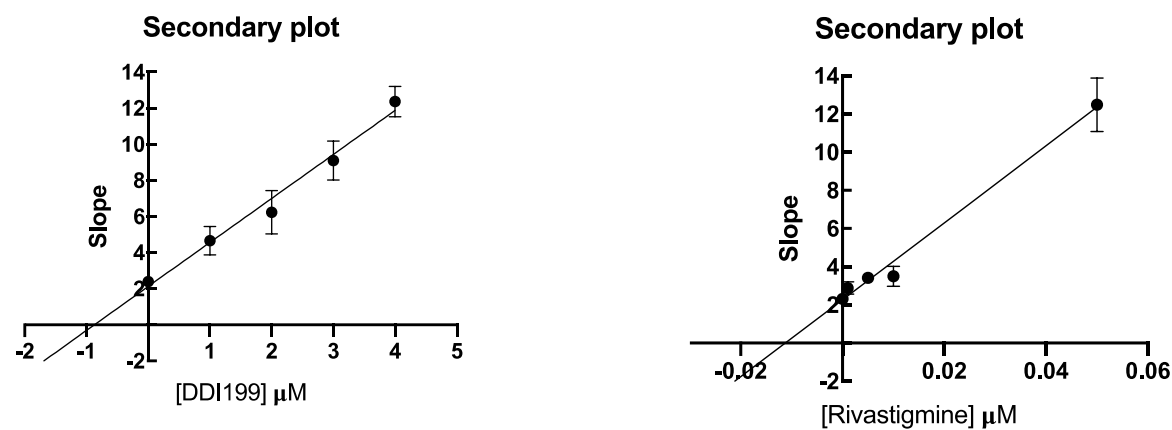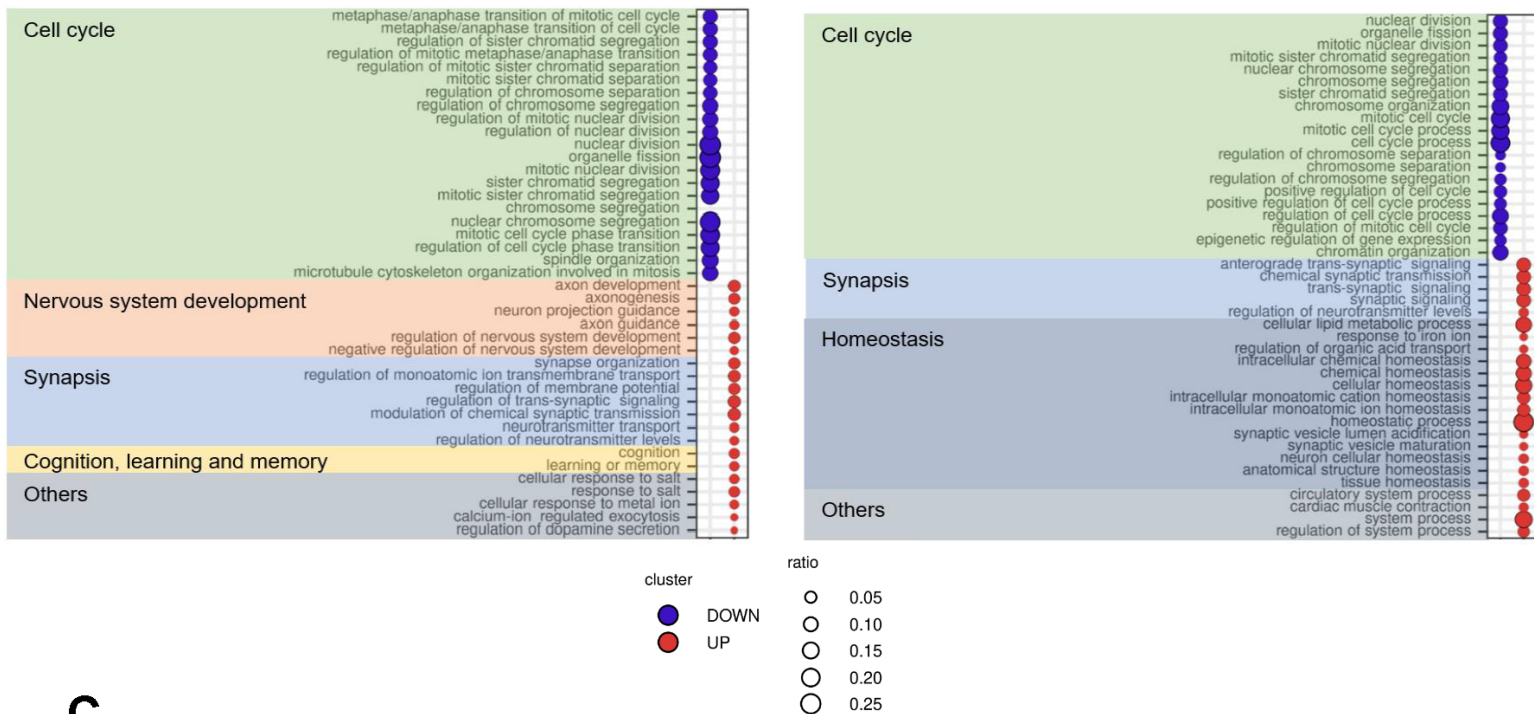
Suppl. Fig. 5 A) Lineweaver-Burk plot representing reciprocal of BChE velocity versus reciprocal of different substrate concentrations at different concentrations of DDI199 or Rivastigmine. **B)** Secondary plot of slopes obtained in Lineweaver-Burk plot versus different inhibitor concentrations for the estimation of Ki for DDI199 and Rivastigmine.
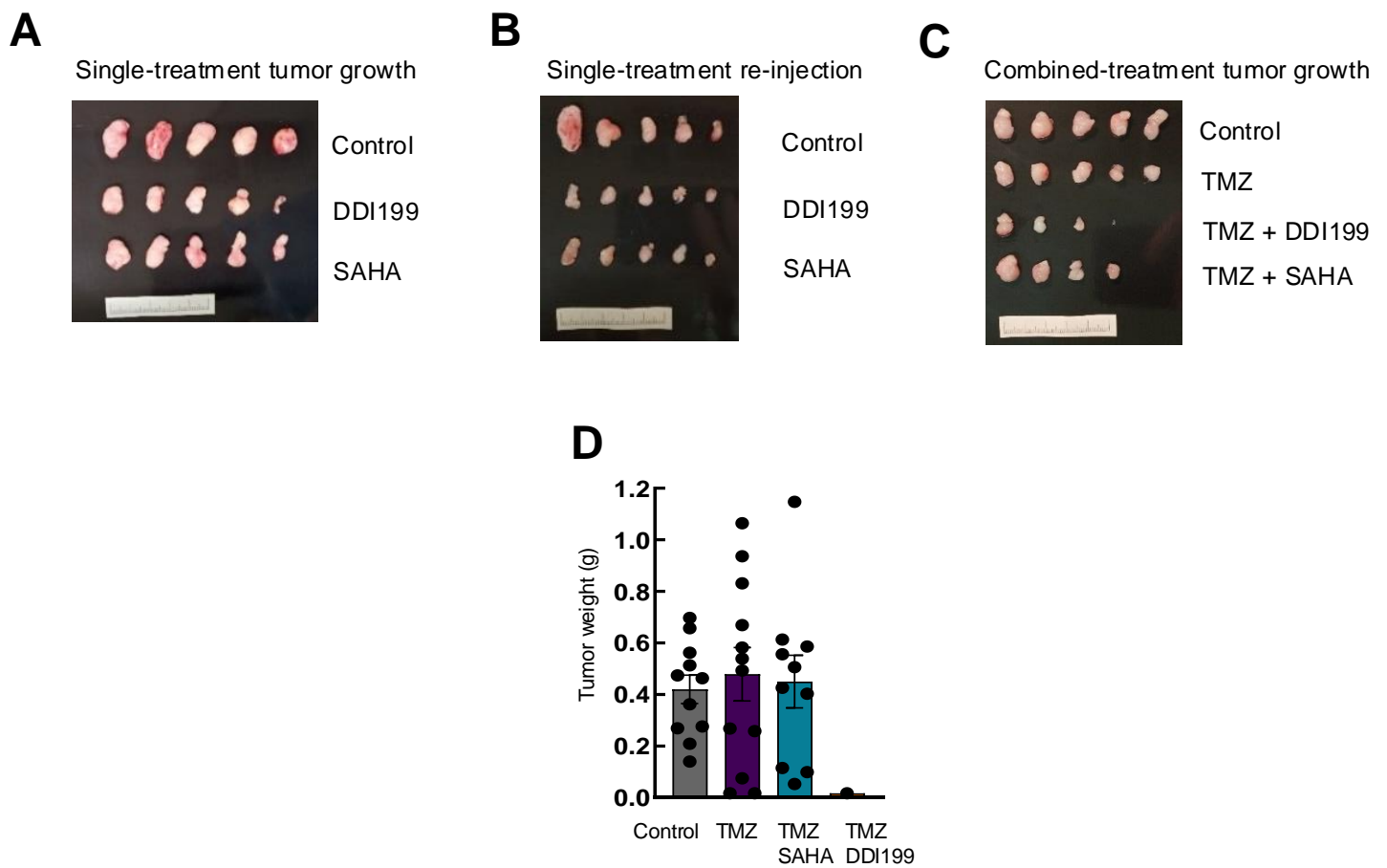
A RNAseq **B** Proteomics

Panel A categories and terms (Cell cycle, DOWN - blue):
- Cell cycle:
  - metaphase/anaphase transition of mitotic cell cycle
  - metaphase/anaphase transition of cell cycle
  - regulation of sister chromatid segregation
  - regulation of mitotic metaphase/anaphase transition
  - regulation of mitotic sister chromatid separation
  - mitotic sister chromatid separation
  - regulation of chromosome separation
  - regulation of chromosome segregation
  - regulation of mitotic nuclear division
  - nuclear division
  - organelle fission
  - mitotic nuclear division
  - sister chromatid segregation
  - mitotic sister chromatid segregation
  - chromosome segregation
  - nuclear chromosome segregation
  - mitotic cell cycle phase transition
  - regulation of cell cycle phase transition
  - spindle organization
  - microtubule cytoskeleton organization involved in mitosis
- Nervous system development:
  - axon development
  - axonogenesis
  - neuron projection guidance
  - axon guidance
  - regulation of nervous system development
  - negative regulation of nervous system development
- Synapse:
  - synapse organization
  - regulation of monoatomic ion transmembrane transport
  - regulation of membrane potential
  - regulation of trans-synaptic signaling
  - modulation of chemical synaptic transmission
  - neurotransmitter transport
  - regulation of neurotransmitter levels
- Cognition, learning and memory:
  - cognition
  - learning or memory
  - cellular response to salt
  - response to salt
- Others:
  - cellular response to metal ion
  - calcium-ion regulated exocytosis
  - regulation of dopamine secretion

Panel B categories and terms:
- Cell cycle:
  - nuclear division
  - organelle fission
  - mitotic nuclear division
  - mitotic sister chromatid segregation
  - nuclear chromosome segregation
  - chromosome segregation
  - sister chromatid segregation
  - chromosome organization
  - mitotic cell cycle
  - mitotic cell cycle process
  - cell cycle process
  - regulation of chromosome separation
  - chromosome separation
  - regulation of chromosome segregation
  - positive regulation of cell cycle
  - positive regulation of cell cycle process
  - regulation of cell cycle process
  - regulation of mitotic cell cycle
  - epigenetic regulation of gene expression
  - chromatin organization
- Synapse:
  - anterograde trans-synaptic signaling
  - chemical synaptic transmission
  - trans-synaptic signaling
  - synaptic signaling
  - regulation of neurotransmitter levels
- Homeostasis:
  - cellular lipid metabolic process
  - response to iron ion
  - regulation of organic acid transport
  - intracellular chemical homeostasis
  - chemical homeostasis
  - cellular homeostasis
  - intracellular monoatomic cation homeostasis
  - intracellular monoatomic ion homeostasis
  - homeostatic process
  - synaptic vesicle lumen acidification
  - synaptic vesicle maturation
  - neuron cellular homeostasis
  - anatomical structure homeostasis
  - tissue homeostasis
- Others:
  - circulatory system process
  - cardiac muscle contraction
  - system process
  - regulation of system process

cluster: ● DOWN (blue) ● UP (red)

ratio: ○ 0.05 ○ 0.10 ○ 0.15 ○ 0.20 ○ 0.25

C

Cell cycle
1 ATP hydrolysis activity
2 cell cycle G2/M phase transition
3 mitotic cytokinesis
4 microtubule motor activity
5 midbody
6 microtubule binding
7 chromosome localization
8 regulation of cell cycle phase transition
9 chromosome, centromeric region
10 mitotic nuclear division
11 meiotic chromosome segregation
12 non-membrane-bounded organelle assembly
13 negative regulation of chromosome organization
14 spindle organization
15 spindle assembly checkpoint signaling
16 nuclear division
17 mitotic spindle checkpoint signaling
18 spindle
19 regulation of mitotic nuclear division
20 regulation of nuclear division
21 chromosome segregation
22 nuclear chromosome segregation
23 regulation of chromosome segregation
24 regulation of chromosome separation
25 sister chromatid segregation
26 regulation of chromosome organization
27 mitotic cell cycle phase transition
28 condensed chromosome
29 regulation of mitotic cell cycle phase transition
30 kinetochore organization
31 chromosome condensation
32 nuclear chromosome
33 centromere complex assembly

DNA remodeling
1 cadherin binding
2 nucleosome organization
3 nucleosome assembly
4 protein-DNA complex assembly
5 nucleosome
6 protein-DNA complex organization
7 epigenetic regulation of gene expression
8 chromatin remodeling
9 SWI/SNF superfamily-type complex

Vesicle
1 extrinsic component of synaptic vesicle membrane
2 ATPase-coupled ion transmembrane transporter activity
3 diphosphate hydrolysis-driven proton transmembrane transporter activity
4 proton-transporting V-type ATPase, V1 domain
5 synaptic vesicle maturation
6 neuron cellular homeostasis
7 vacuolar proton-transporting V-type ATPase, V1 domain
8 proton-transporting ATPase activity, rotational mechanism
9 clathrin-coated vesicle membrane
10 synaptic vesicle lumen acidification
11 clathrin-coated vesicle
12 ATPase activity, coupled to transmembrane movement of ions, rotational mechanism
13 macroautophagy

Synapsis
1 neuron to neuron synapse
2 glutamatergic synapse
3 postsynaptic specialization
4 neurotransmitter transport
5 synaptic membrane
6 modulation of chemical synaptic transmission
7 regulation of trans-synaptic signaling
8 synapse organization
9 cognition
10 regulation of nervous system development
11 axon development

Transport
1 regulation of membrane potential
2 transporter complex
3 regulation of monoatomic ion transmembrane transport
4 monoatomic ion channel complex
5 voltage-gated monoatomic ion channel activity
6 metal ion transmembrane transporter activity
7 monoatomic ion gated channel activity
8 monoatomic ion channel activity
9 gated channel activity
10 voltage-gated channel activity

Suppl. Fig. 6 A-B) Gene ontology study of RNAseq and proteomics representing the 20 most correlated pathways with upregulated and downregulated DEGs. **C)** List of ontologies conforming each of the clusters from the combined study of RNAseq and proteomic results.

A Single-treatment tumor growth

Control

DDI199

SAHA

B Single-treatment re-injection

Control

DDI199

SAHA

C Combined-treatment tumor growth

Control

TMZ

TMZ + DDI199

TMZ + SAHA

D

Suppl. Fig. 7 A) Representative images of subcutaneous tumors from single-treatment tumor growth experiment. **B)** Representative images of subcutaneous tumors from single-treatment re-injection experiment. **C)** Representative images of subcutaneous tumors from combined-treatment tumor growth experiment. **D)** Tumor weight at end-point day 36 of combined-treatment re-injection experiment.