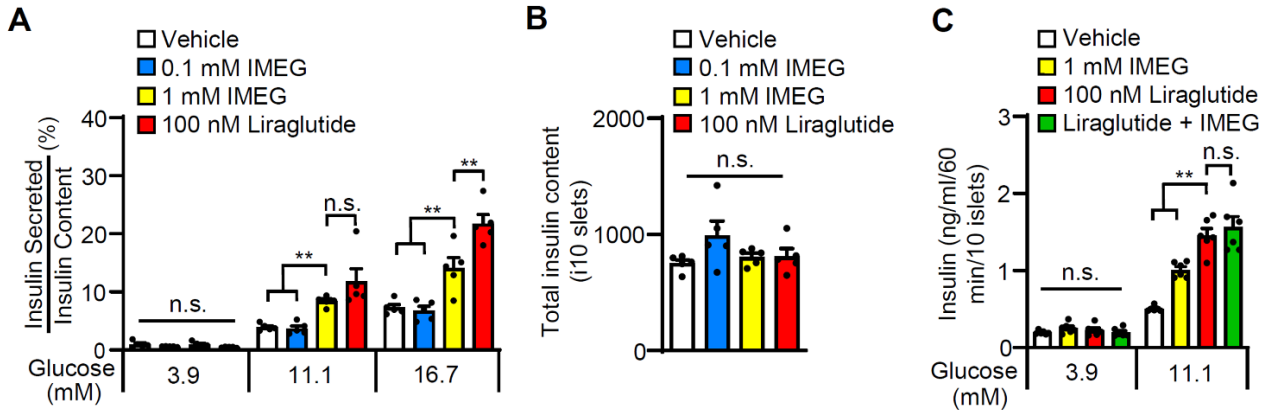
Online Supplementary materials

Supplementary Fig.1



Supplementary Fig.1 Imeglimin did not increase the insulin content in isolated islets.

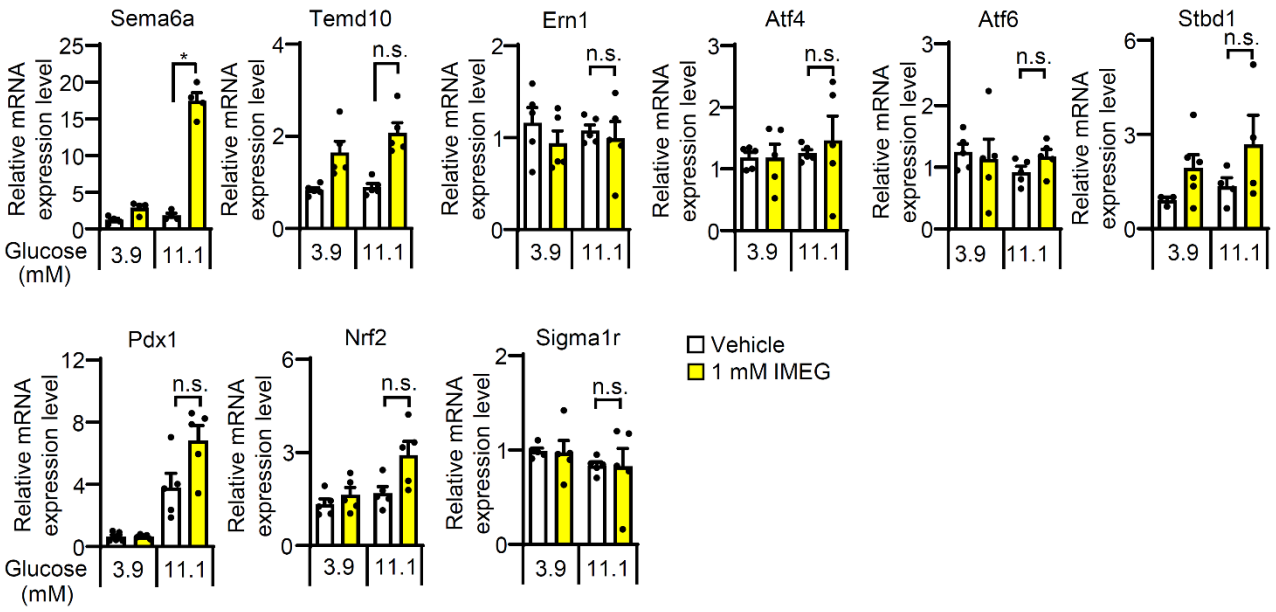
(A) Glucose-stimulated insulin secretion (GSIS) from islets of 8-week-old C57B6J mice treated with or without 0.1 mM or 1 mM imeglimin (IMEG) or 100 nM liraglutide in the presence of 3.9 mM (70 mg/dL), 11.1 mM (200 mg/dL), or 16.7 mM (300 mg/dL) glucose. The radio of insulin secretion to insulin content. *$p < 0.05$, **$p < 0.01$ (n=5).

(B) Insulin contents of the indicated islets (n=5).

(C) Glucose-stimulated insulin secretion (GSIS) from the islets of 8-week-old C57B6J mice treated with or without 1 mM imeglimin (IMEG), 100 nM liraglutide, or a combination of 1 mM IMEG and 100 nM liraglutide in the presence of 3.9 mM (70 mg/dL) or 11.1 mM (200 mg/dL) glucose (n=5).

All data are represented as means ± SEM in (A-C).

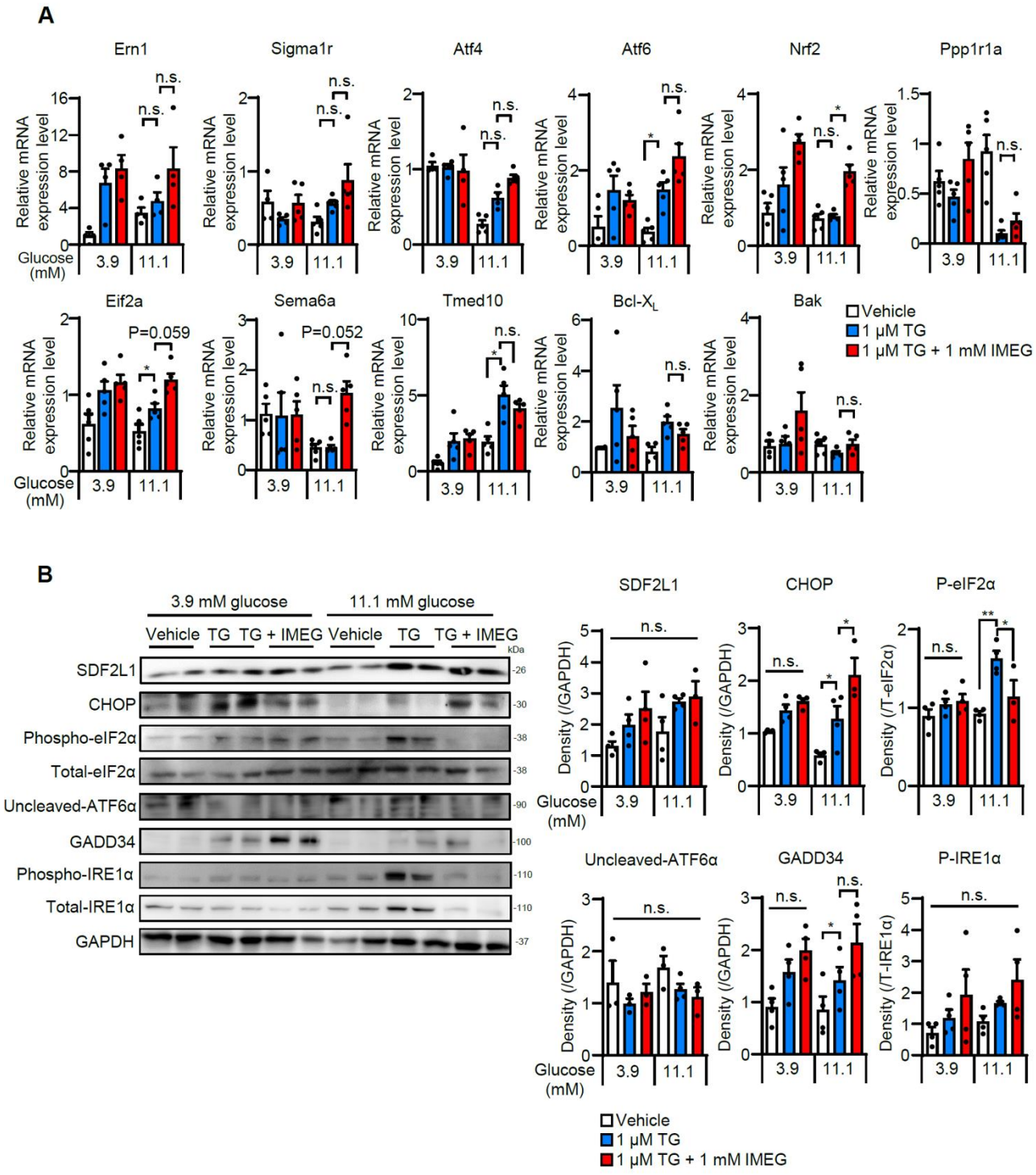
Supplementary Fig. 2



Supplementary Fig. 2 Gene expression in isolated islets from mice after treatment with imeglimin.

mRNA expressions of the indicated genes in isolated islets from 8-week-old C57B6J mice after treatment with 1 mM imeglimin (IMEG) or the vehicle alone at 3.9 mM or 11.1 mM glucose for 24 hours. *$p < 0.05$ (n=4-5). The data are represented as means ± SEM.

Supplementary Fig.3

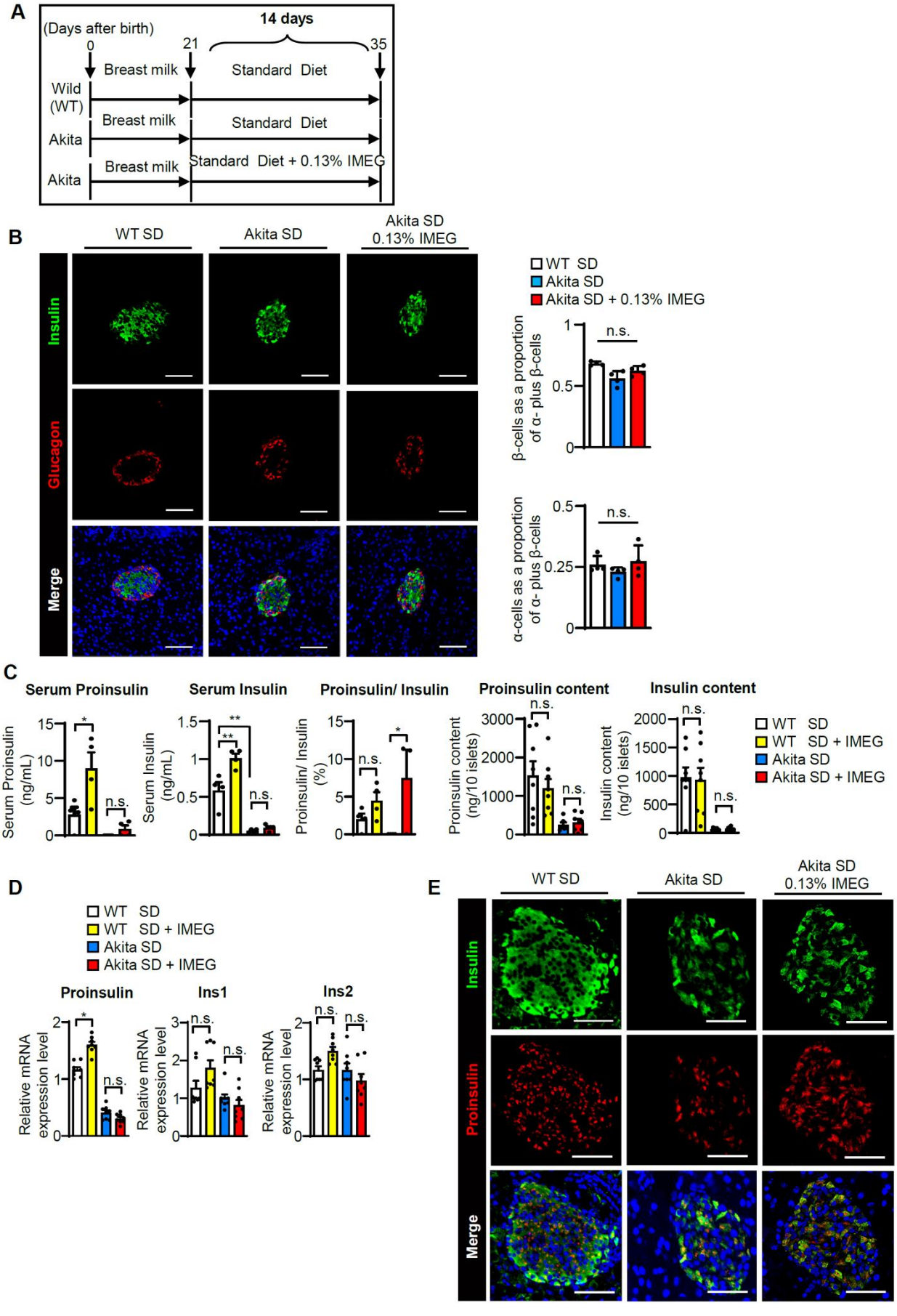


Supplementary Fig. 3 Imeglimin regulated ER stress-induced gene and protein expression levels in mouse isolated islets.

(A) mRNA expressions of the indicated genes in isolated islets from 8-week-old C57B6J mice after treatment with 1 mM imeglimin (IMEG), 1 μM thapsigargin (TG), or the vehicle alone at 3.9 mM or

11.1 mM glucose for 24 hours. *$p < 0.05$ (n=4-5).
(B) Left panel; Western blot of indicated proteins in isolated islets from 8-week-old C57B6J mice after treatment with 1 mM imeglimin (IMEG), 1 μM thapsigargin (TG), or the vehicle alone for 24 hours at 3.9 mM or 11.1 mM glucose. Right panel; Intensity of the signals quantified by densitometry normalized to GAPDH, T-eIF2α (total eIF2α) or T-IRE1α (total IRE1α). **$p < 0.01$, *$p < 0.05$ (n=3-4). All data are represented as means ± SEM in (A-B).

Supplementary Fig. 4



Supplementary Fig. 4 Effects of imeglimin on islets from Akita mice.

(A) Experimental protocol. Akita and wild-type (WT) mice were weaned 21 days after birth. Then, the wild-type mice were fed a standard diet for 14 days until day 35 after birth; the Akita mice were fed a standard diet containing or not containing 0.13% imeglimin (IMEG).

(B) Pancreatic sections were stained with antibodies to insulin (green) and glucagon (red). The scale bar represents 50 μm. Left panel; Representative images of staining in islets. Right panel; Insulin-positive β-cells as a proportion of insulin-positive β-cells plus glucagon-positive α-cells, and glucagon-positive α-cells as proportion of insulin-positive β-cells plus glucagon-positive α-cells (aged 5 weeks, n=4).

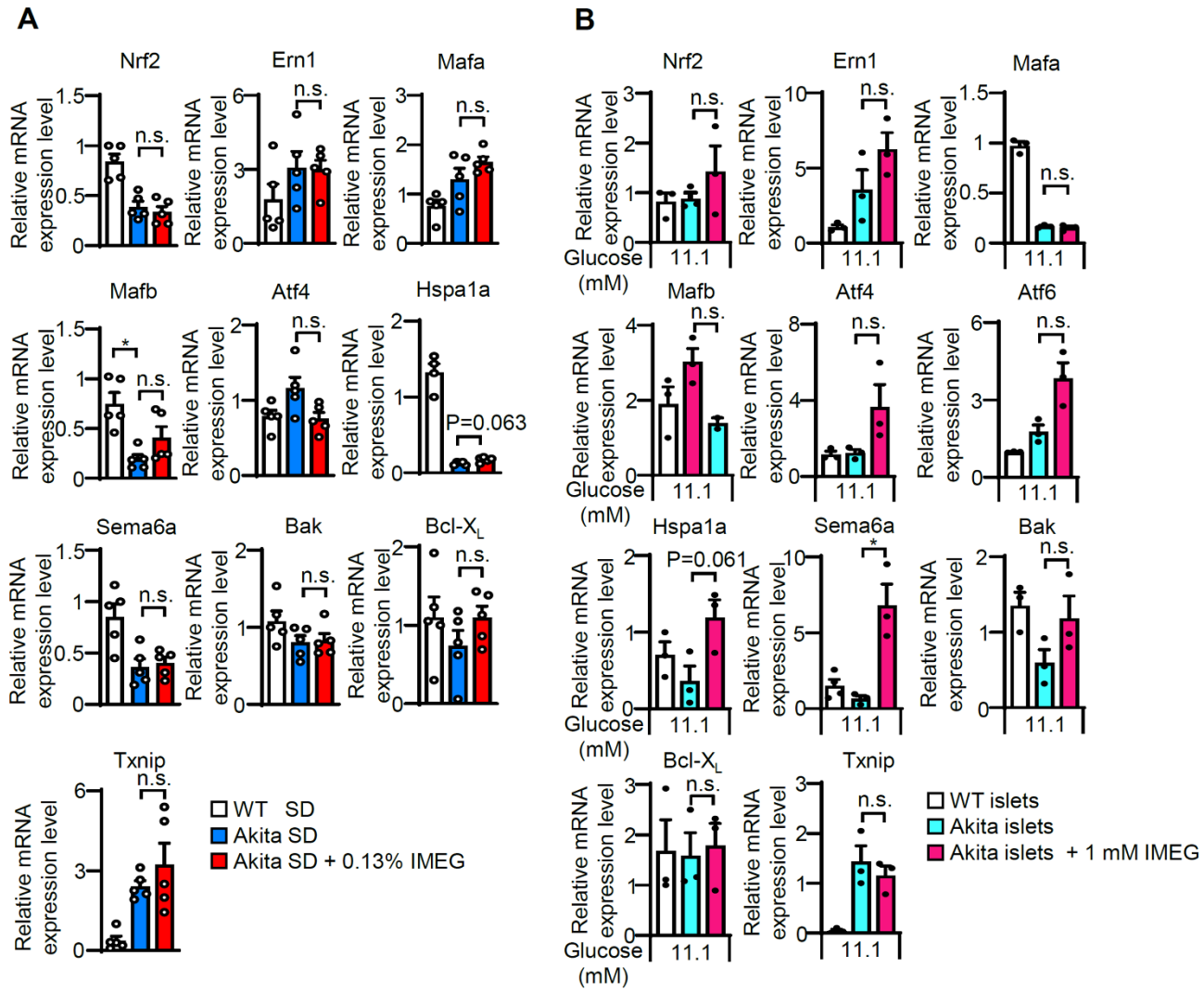
(C and D) 5-week-old Akita and wild-type (WT) mice were fed a standard diet containing or not containing imeglimin (IMEG) for 3 days.

(C) Serum proinsulin, serum insulin levels and the ratio of proinsulin and insulin. *$p < 0.05$, **$p < 0.01$ (n=4). Proinsulin content and insulin content (n=6-8).

(D) Proinsulin, Ins1 and Ins2 mRNA expression from wild-type or Akita mice fed a standard diet or a diet containing IMEG for 3 days. *$p < 0.05$, **$p < 0.01$ (aged 5 weeks, n=8).

(E) Representative images of pancreatic sections. Pancreatic sections were stained with anti-insulin (green), anti-proinsulin (red), and DAPI (blue). The scale bar represents 30 μm. All data are represented as means ± SEM in (B-D).

Supplementary Fig. 5

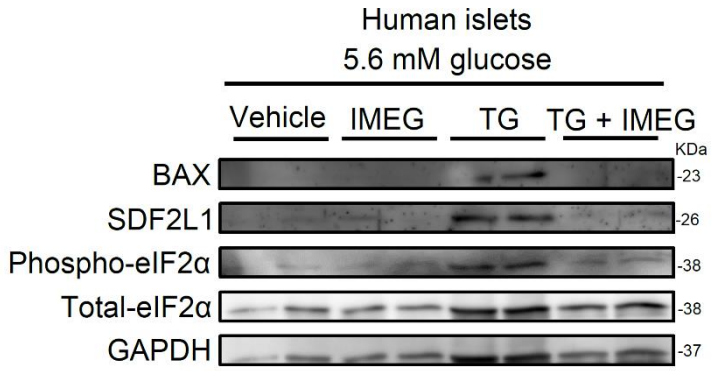


Supplementary Fig. 5 The gene expression in isolated islets from Akita mice treated with imeglimin.

(A) mRNA expressions of indicated genes in isolated islets from wild-type or Akita mice fed a standard diet containing or not containing 0.13% imeglimin (IMEG) from days 21 to 35 after birth. *p < 0.05 (aged 5 weeks, n=5).

(B) mRNA expressions of indicated genes in isolated islets from wild-type or Akita mice after treatment with 1 mM imeglimin (IMEG) or the vehicle alone at 11.1 mM glucose for 24 hours (aged 5 weeks, n=3). All data are represented as means ± SEM in (A-B).

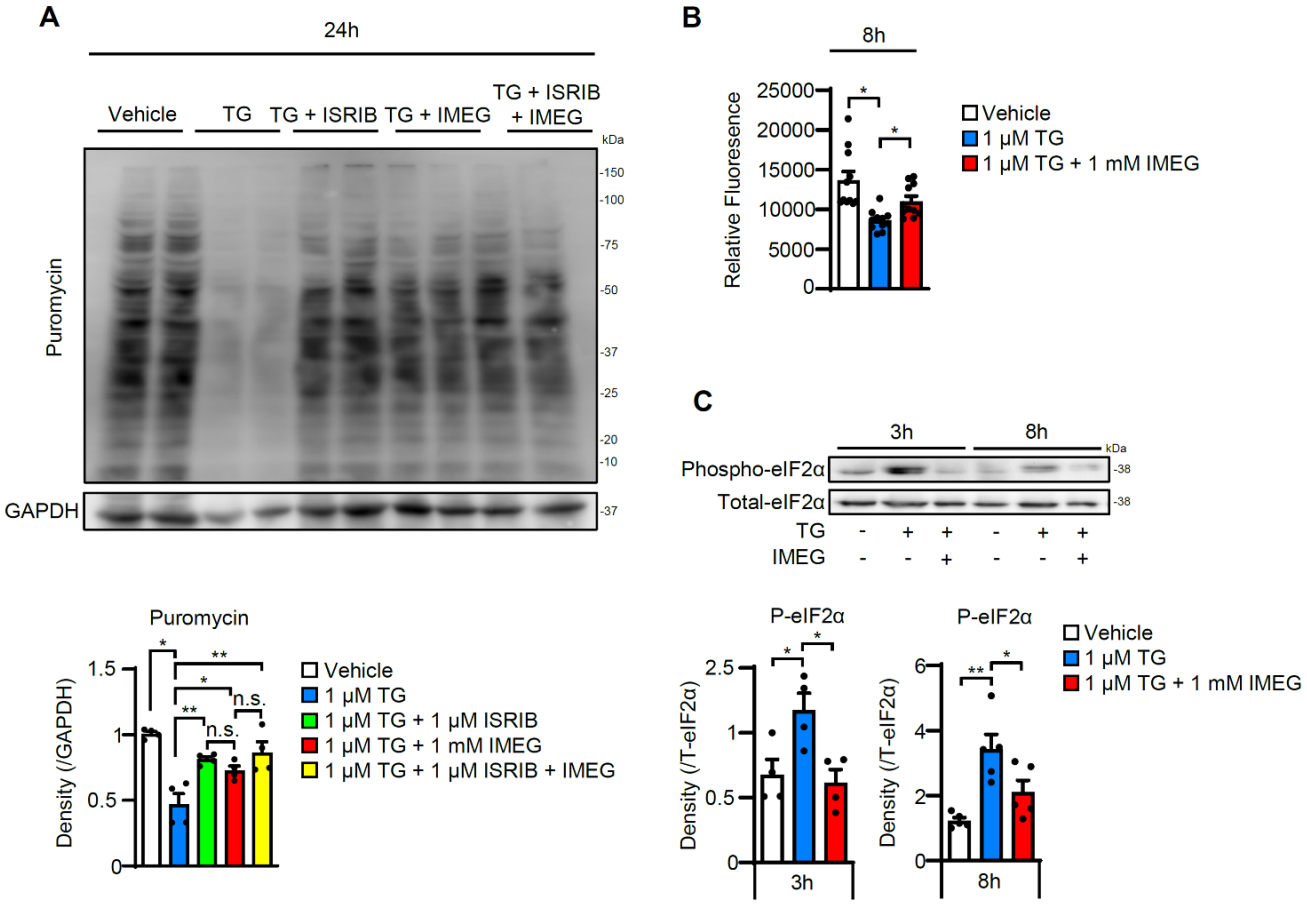
Supplementary Fig. 6



Supplementary Fig. 6 Effects of imeglimin on human islets.

Western blot of indicated proteins in human islets from non-diabetes donors after treatment with 1 mM imeglimin (IMEG), 1 μM thapsigargin (TG), or the vehicle alone for 24 hours at 5.6 mM glucose. (n=2).

Supplementary Fig. 7



Supplementary Fig. 7 The effects of imeglimin on MIN6K8 cells.

(A) Upper panel; Western blotting for indicated proteins in MIN6K8 cells after treatment with or without 1 μM puromycin (last 10 min) in the presence or absence of 1 mM imeglimin (IMEG), 1 μM thapsigargin (TG), 1 μM ISRIB, or the vehicle alone for 24 hours. Lower panel; Intensity of signals quantified by densitometry normalized to GAPDH. **p < 0.01, *p < 0.05 (n=4).

(B) MIN6K8 cells were plated at a density of 3 x 10^4 cells/well in a 96-well plate. After treatement with or without 1 mM imeglimin (IMEG) or 1 μM thapsigargin (TG) for 8 hours, cell protein synthesis was assessed by O-propargyl-puromycin (OPP) as described in Method section. *p < 0.05 (n=7-9).

(C) Upper panel; Western blot of phospho-eIF2α proteins in MIN6K8 cells after treatment with 1 mM imeglimin (IMEG), 1 μM thapsigargin (TG), or the vehicle alone for 3 hours and 8 hours. Lower panel; Intensity of signals quantified by densitometry normalized to T-eIF2α (total eIF2α). **p < 0.01, *p < 0.05 (n=4-5). All data are represented as means ± SEM in (A-C).

Supplementary Table 1. Antibodies used for western blotting and immunohistochemistry (IHC)

Antibody	Supplier
Mouse anti-CHOP (B-3)	Santa Cruz Biotechnology Cat# sc-7351; RRID: AB_627411
Rabbit anti-CHOP (F-168)	Santa Cruz Biotechnology Cat# sc-575; RRID: AB 631365
Mouse anti-Bax (B-9)	Santa Cruz Biotechnology Cat# sc-7480; RRID: AB_626729
Mouse anti-Bcl2 (C-2)	Santa Cruz Biotechnology Cat# sc-7382; RRID: AB 626736
Rabbit anti-SDF2L1	Abcam Cat# 231797;
Rabbit anti-P-eIF2α (Ser51)	Cell Signaling Technology Cat# 9721s; RRID: AB 330951
Rabbit anti-eIF2α	Cell Signaling Technology Cat# 5324s; RRID: AB 10692650
Mouse anti-Puromycin (12D10)	Millipore Cat# MABE 343; RRID: AB 2566826
Rabbit anti-P-IRE1α	Invitrogen Cat# PA1-16927; RRID: AB_2262241
Rabbit anti-T-IRE1α	Cell Signaling Technology Cat# 3294s; RRID: AB_823545
Rabbit anti-ATF6α (37-1)	Bio Academia Cat# 73-505;
Mouse anti-Total OXPHOS Rodent	Abcam Cat# MS-604-300; RRID: AB_2629281
Mouse anti-α-tubulin	Abcam Cat# 7291; RRID: AB 2241126
Rabbit anti-GAPDH	Abcam Cat# 9485; RRID: AB_307275
Rabbit anti-insulin (clone EPR17359)	Abcam Cat# 181547; RRID: AB 2716761
Mouse anti-Insulin B (C-12)	Santa Cruz Biotechnology Cat# 377071; RRID: AB_2800506
Mouse anti-PROINS	DSHB Cat# GS-9A8; RRID: AB 532383
Mouse anti-Glucagon (K79bB10)	Abcam Cat# 10988; RRID: AB_297642
DAPI	Invitrogen Cat# D1306; RRID: AB 2629482

Supplementary Table 2. qPCR primer sequences

Species	Gene (Forward/Reverse)	Sequence
Mouse	β-actin Forward	GGCTGTATTCCCCTCCATCG
Mouse	β-actin Reverse	CCAGTTGGTAACAATGCCATGT
Mouse	Atf3 Forward	GAGGATTTTGCTAACCTGACACC
Mouse	Atf3 Reverse	TTGACGGTAACTGACTCCAGC
Mouse	Atf4 Forward	CCTGAACAGCGAAGTGTTGG
Mouse	Atf4 Reverse	TGGAGAACCCATGAGGTTTCAA
Mouse	Atf6 Forward	TCGCCTTTTAGTCCGGTTCTT
Mouse	Atf6 Reverse	GGCTCCATAGGTCTGACTCC
Mouse	Bak Forward	CTTTGGCTACCGTCTGGC
Mouse	Bak Reverse	CAACCGCCTCTCTGTGCGA
Mouse	Bax Forward	GGAGCAGCTTGGGAGCG
Mouse	Bax Reverse	AAAAGGCCCCTGTCTTCATGA
Mouse	Bcl2 Forward	TTATAAGCTGTCACAGAGGGGCTAC
Mouse	Bcl2 Reverse	GAACTCAAAGAAGGCCACAATCCTC
Mouse	Bcl2-xl Forward	TGGAGTCAGTTTAGTGATGTCGAAG
Mouse	Bcl2-xl Reverse	AGTTTACTCCATCCCGAAAGAGTTC
Mouse	Txnip Forward	TCACATTATCTCAGGGACTT
Mouse	Txnip Reverse	GGTATCTGGGATGTTTAGG
Mouse	Ccna2 Forward	GCCTTCACCATTCATGTGGAT
Mouse	Ccna2 Reverse	TTGCTGCGGGTAAAGAGACAG
Mouse	Ccnd2 Forward	GAGTGGGAACTGGTAGTGTTG
Mouse	Ccnd2 Reverse	CGCACAGAGCGATGAAGGT
Mouse	Cenpa Forward	TTGGCCCTTCAGGAGGCAGCA
Mouse	Cenpa Reverse	AAGCGTGACCCGACCAGCAT
Mouse	Ddit3 (Chop) Forward	CTGGAAGCCTGGTATGAGGAT
Mouse	Ddit3 (Chop) Reverse	CAGGGTCAAGAGTAGTGAAGGT
Mouse	Eif2α Forward	CACCGCTGTTGACAGTCAGAG
Mouse	Eif2α Reverse	GCAAACAATGTCCCATCCTTACT
Mouse	Ern1 (Ire1α) Forward	ACACCGACCACCGTATCTCA
Mouse	Ern1 (Ire1α) Reverse	CTCAGGATAATGGTAGCCATGTC
Mouse	Ins1 Forward	GAGATGGGGAAGATGCTGGG
Mouse	Ins1 Reverse	GGAGGACACAGTCAGGGAGA
Mouse	Ins2 Forward	GCTTCTTCTACACACCCATGTC
Mouse	Ins2 Reverse	AGCACTGATCTACAATGCCAC
Mouse	Proinsulin Forward	TGGCTTCTACACACCCAAG
Mouse	Proinsulin Reverse	ACAATGCCACGCTTCTGCC
Mouse	Tmed10 Forward	TTGCCTTTACCACGGAAGAC
Mouse	Tmed10 Reverse	ACTCCACCTCCAGTGGTTTG
Mouse	Ppp1r15a (Gadd34) Forward	CTTTTGGCAACCAGAACCG
Mouse	Ppp1r15a (Gadd34) Reverse	CAGAGCCGCAGCTTCTATCT
Mouse	Mafa Forward	AGGAGGAGGTCATCCGACTG

Mouse	Mafa Reverse	CTTCTCGCTCTCCAGAATGTG
Mouse	Mafb Forward	GGTATAAACGCGTCCAGCAG
Mouse	Mafb Reverse	CGAGTTTCTCGCACTTGACC
Mouse	Nrf2 Forward	CGAGATATACGCAGGAGAGGTAAG
Mouse	Nrf2 Reverse	GCTCGACAATGTTCTCCAGCTT
Mouse	Hspa1a Forward	TGGTGCTGACGAAGATGAAG
Mouse	Hspa1a Reverse	AGGTCGAAGATGAGCACGTT
Mouse	Pdx1 Forward	GAACCCGAGGAAAACAAGAGG
Mouse	Pdx1 Reverse	GTTCAACATCACTGCCAGCTC
Mouse	Plk1 Forward	CCGTCATTGTAGAGAATCAGGCG
Mouse	Plk1 Reverse	CCATCTTCTGGGTCAGCAAGTG
Mouse	Ppp1r1a Forward	CGGAAGAAGATGACAAGGACC
Mouse	Ppp1r1a Reverse	TTGCCCTAGGTGATGTTCAACC
Mouse	Sdf2l1 Forward	CTGGCCTTTGACCTCTCTTC
Mouse	Sdf2l1 Reverse	ACTTGGCAATGGGAACTGTC
Mouse	Sema6a Forward	TCTACGTTGCTGCTCGAGACC
Mouse	Sema6a Reverse	AGGTATCGACCCTGTAGTTTCTGC
Mouse	Stbd1 Forward	TGAGCCCTGAACCTTCCGATC
Mouse	Stbd1 Reverse	GTGCTGTCGTCCATTCTCTGA
Mouse	Sigma1r Forward	CTGGGCACTCAAAACTTCGTC
Mouse	Sigma1r Reverse	CTCCACGATCAGCCGAGAGA
Human	GAPDH Forward	AGGGCTGCTTTTAACTCTGGT
Human	GAPDH Reverse	CCCCACTTGATTTTGGAGGGA
Human	ATF3 Forward	ATCTCCTTCACCGTGGCTAC
Human	ATF3 Reverse	AGGACCTGCCATCATACTGC
Human	ATF4 Forward	AGCACTCAGACTACGTGCACCTCT
Human	ATF4 Reverse	GAAGAGTCAATACCGCCAGAATCC
Human	DDIT3 (CHOP) Forward	GGAGCATCAGTCCCCCACTT
Human	DDIT3 (CHOP) Reverse	TGTGGGATTGAGGGTCACATC
Human	NRF2 Forward	TCAGCCAGCCCAGCACATCC
Human	NRF2 Reverse	TCTGCGCCAAAAGCTGCATGC
Human	PPP1R15A (GADD34) Forward	GAGGAGGCTGAAGACAGTGG
Human	PPP1R15A (GADD34) Reverse	AGAGCCGAGCCGACAGAG
Human	HSPA1A Forward	GGAGCATCAGTCCCCCACTT
Human	HSPA1A Reverse	CACCTTGCCGTGTTGGAA
Human	SDF2L1 Forward	CTTACGGGCAAGAACCTG
Human	SDF2L1 Reverse	GCACTGTCCATAGGTCCA

Supplementary Table 3. Up-regulated and down-regulated genes in islets after treatment with imeglimin

Fold Change	p-value	Gene Symbol	Ref Seq Accession	Gene Name
8.66	2.93E-04	*Hspa1a*	NM_010479	heat shock protein 1A
6.06	2.45E-04	*Hspa1b*	NM_010478	heat shock protein 1B
4.96	2.692E-05	*Tac1*	NM_009311	tachykinin 1 transcript variant 1
4.46	6.958E-06	*Qpct*	NM_027455	glutaminyl-peptide cyclotransferase
3.99	0.0026141	*Stc2*	NM_011491	stanniocalcin 2
3.50	2.835E-06	*Stbd1*	NM_175096	starch binding domain 1
3.26	2.245E-06	*Insl6*	NM_013754	insulin-like 6
3.24	1.628E-06	*Sema6a*	NM_018744	semaphorin 6A
3.14	2.40E-04	*Ddit3 (Chop)*	NM_007837	DNA-damage inducible transcript 3
3.12	5.59E-04	*Atf3*	NM_007498	activating transcription factor 3
2.76	1.01E-04	*Cdkn1a*	NM_007669	cyclin-dependent kinase inhibitor 1A (P21)
2.71	8.11E-04	*Me2*	TC1634609	NAD-dependent malic enzyme 2
2.58	0.0185517	*Igf1r*	ENSMUST 00000207621	insulin-like growth factor I receptor
2.38	0.0139391	*Ern1 (Ire1a)*	ENSMUST 00000106800	endoplasmic reticulum to nucleus signalling 1
2.38	2.31E-04	*Nr4a2*	NM_013613	nuclear receptor subfamily 4, group A, 2
2.25	0.0052762	*Ppp1r16b*	NM_001159662	protein phosphatase 1, regulatory subunit 16B
2.24	0.0412463	*Foxd2*	NM_008593	forkhead box D2
2.13	0.0152559	*Ero1l*	NM_015774	ERO1-like (S. cerevisiae)
2.05	4.02E-04	*Ppp1r15a (Gadd34)*	NM_008654	protein phosphatase 1, regulatory subunit 15A
0.49	8.23E-04	*Pdx1*	NM_008814	pancreatic and duodenal homeobox 1
0.44	7.67E-05	*Glp1r*	NM_021332	glucagon-like peptide 1 receptor
0.25	2.86E-07	*Gcgr*	NM_008101	glucagon receptor

Mouse islets were treated with 1 mM imeglimin (IMEG) or the vehicle alone (DMSO) for 24 hours. Replicate (n=4) microarray studies were performed for each treatment. The results were filtered according to the fold change (> 2-fold change up-regulation, < 0.5-fold down-regulation, *p* values < 0.05) and analyzed using Genespring GX software. The listed genes represent some of those significantly up-regulated (> 2-fold) or down-regulated (< 0.5-fold) by IMEG.

Supplementary Table 4. Partial pathway analysis of the up-regulation and the down-regulation of genes by imeglimin

Pathway in upregulated genes	p-value	Matched Entities	Pathway Entities of Experiment Type
Mm_MAPK_signaling_pathway WP493_78412	5.40E-05	8	159
Mm_White_fat_cell_differentiation WP2872_90848	1.35E-04	4	32
Mm_Kit_Receptor_Signaling_Pathway WP407_69079	2.34E-04	5	67
Mm_Adipogenesis_genes WP447_87026	8.20E-04	6	133
Mm_Spinal_Cord_Injury WP2432_87679	0.0014	5	102
Mm_Regulation_of_Actin_Cytoskeleton WP523_71326	0.0016	6	151
Mm_Insulin_Signaling WP65_88446	0.0021	6	160
Mm_EGFR1_Signaling_Pathway WP572_82883	0.0035	6	176
Mm_IL-2_Signaling_Pathway WP450_89849	0.0036	4	76
Mm_Mitochondrial_LC-Fatty_Acid_ Beta_Oxidation_WP401_89972	0.0075	2	16
Mm_Id_Signaling_Pathway WP512_69147	0.0086	3	52
Mm_IL-3_Signaling_Pathway WP373_69196	0.0092	4	100
Mm_Integrin-mediated_Cell_Adhesion WP6_97547	0.0095	4	101
Mm_TYROBP_Causal_Network WP3625_90841	0.0111	3	58
Mm_Hypertrophy_Model WP202_95798	0.0116	2	20
Mm_Purine_metabolism WP2185_97551	0.0146	5	176
Mm_Endochondral_Ossification WP1270_87973	0.0146	3	62
Mm_Focal_Adhesion WP85_94410	0.0174	5	185

Pathway in downregulated genes	p-value	Matched Entities	Pathway Entities of Experiment Type
Mm_Non-odorant_GPCRs WP1396_69993	2.03E-06	16	267
Mm_Metapathway_biotransformation WP1251_94721	1.47E-04	9	143
Mm_Retinol_metabolism WP1259_89974	2.05E-04	5	39
Mm_Myometrial_Relaxation_and_ Contraction_Pathways_WP385_95806	3.42E-04	9	150
Mm_Myometrial_Relaxation_and_ Contraction_Pathways_WP385_87897	4.55E-04	9	157
Mm_Biogenic_Amine_Synthesis WP522_89981	0.0012	3	15
Mm_Tryptophan_metabolism WP79_91016	0.0036	4	44
Mm_Folic_Acid_Network WP1273_85058	0.0042	3	27
Mm_One_carbon_metabolism_and_ related_pathways_WP1770_94313	0.0054	4	49
Mm_GPCRs, Class_A_Rhodopsin-like WP189_79710	0.0057	9	231
Mm_Methylation WP1247_69203	0.0069	2	9
Mm_One_carbon_metabolism_and related_pathways_WP1770_96354	0.0076	4	55
Mm_Calcium_Regulation in_the_Cardiac_Cell_WP553_80276	0.0076	7	157
Mm_One_Carbon_Metabolism WP435_89673	0.0082	3	29
Mm_Glutathione_and_one_carbon_ Metabolism_WP730_87554	0.0098	3	44
Mm_Hypothetical_Network_for_ Drug_Addiction_WP1246_69102	0.0098	3	32
Mm_Complement_and_Coagulation Cascades_WP449_71733	0.0116	4	62
Mm_Adipogenesis_genes WP447_87026	0.0123	6	133
Mm_SREBF_and_miR33_in_cholesterol and_lipid_homeostasis_WP2084_87683	0.0124	2	13
Mm_Neural_Crest_Differentiation WP2074_94468	0.0149	5	101
Mm_Chemokine_signaling_pathway WP2292_97515	0.0167	7	191

Supplementary Table 5. Targets of imeglimin as determined using SwissTargetPrediction and combinations of 2D or 3D similarity measures with known ligands

Target	Common name	Uniprot ID	ChEMBL ID	Target Class
Nitric oxide synthase, inducible (homolog)	NOS2	P35228	CHEMBL 4481	Enzyme
Alpha-2a adrenergic receptor	ADRA2A	P08913	CHEMBL 1867	Family A G protein-coupled receptor
Adrenergic receptor alpha-2	ADRA2C	P18825	CHEMBL 1916	Family A G protein-coupled receptor
Alpha-2b adrenergic receptor	ADRA2B	P18089	CHEMBL 1942	Family A G protein-coupled receptor
Alpha-1d adrenergic receptor	ADRA1D	P25100	CHEMBL 223	Family A G protein-coupled receptor
Alpha-1a adrenergic receptor	ADRA1A	P35348	CHEMBL 229	Family A G protein-coupled receptor
Alpha-1b adrenergic receptor	ADRA1B	P35368	CHEMBL 232	Family A G protein-coupled receptor
Trace amine associated receptor 1	TAAR1	Q96RJ0	CHEMBL 5857	Family A G protein-coupled receptor
Nischarin	NISCH	Q9Y2I1	CHEMBL 3923	Other cytosolic protein
Nitric-oxide synthase, brain	NOS1	P29475	CHEMBL 3568	Enzyme
Dopamine transporter (by homology)	SLC6A3	Q01959	CHEMBL 238	Electrochemical transporter
Nitric-oxide synthase, endothelial	NOS3	P29474	CHEMBL 4803	Enzyme
Tyrosine-protein kinase JAK3	JAK3	P52333	CHEMBL 2148	Kinase
Serotonin 2b (5-HT2b) receptor	HTR2B	P41595	CHEMBL 1833	Family A G protein-coupled receptor
Serotonin 1b (5-HT1b) receptor	HTR1B	P28222	CHEMBL 1898	Family A G protein-coupled receptor
Serotonin 1d (5-HT1d) receptor	HTR1D	P28221	CHEMBL 1983	Family A G protein-coupled receptor
Serotonin 1a (5-HT1a) receptor	HTR1A	P08908	CHEMBL 214	Family A G protein-coupled receptor
Serotonin 2a (5-HT2a) receptor	HTR2A	P28223	CHEMBL 224	Family A G protein-coupled receptor
Serotonin 2c (5-HT2c) receptor	HTR2C	P28335	CHEMBL 225	Family A G protein-coupled receptor
Serotonin 7 (5-HT7) receptor	HTR7	P34969	CHEMBL 3155	Family A G protein-coupled receptor
Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL 3371	Family A G protein-coupled receptor

Serotonin 5a (5-HT5a) receptor	HTR5A	P47898	CHEMBL 3426	Family A G protein-coupled receptor
Tyrosine-protein kinase JAK1	JAK1	P23458	CHEMBL 2835	Kinase
Sigma-1 receptor	SIGMA1R	Q99720	CHEMBL 287	Membrane receptor
Cyclin-dependent kinase 7/ cyclin H	CDK7 CCNH	P50613 P51946	CHEMBL 2111288	Other cytosolic protein
Potassium-transporting ATPase	ATP4B ATP4A	P51164 P20648	CHEMBL 2095173	Primary active transporter
Muscarinic acetylcholine receptor	CHRM1	P11229	CHEMBL 216	Family A G protein-coupled receptor
Glutamate receptor subunit epsilon 2	GRIN2B	Q13224	CHEMBL 1904	Ligand-gated ion channel
Solute carrier family 22 member 2	SLC22A2	O15244	CHEMBL 1743122	Electrochemical transporter
Multidrug and toxin extrusion protein 1	SLC47A1	Q96FL8	CHEMBL 1743126	Electrochemical transporter
Butyrylcholinesterase	BCHE	P06276	CHEMBL 1914	Hydrolase
Acetylcholinesterase	ACHE	P22303	CHEMBL 220	Hydrolase
Cytochrome P450 1A2	CYP1A2	P05177	CHEMBL 3356	Cytochrome P450
Toll-like receptor 8	TLR8	Q9NR97	CHEMBL 5805	Toll-like and Il-1 receptors
Amine oxidase, copper containing	AOC3	Q16853	CHEMBL 3437	Enzyme
Epidermal growth factor receptor erbB1	EGFR	P00533	CHEMBL 203	Kinase
Carbonic anhydrase II	CA2	P00918	CHEMBL 205	Lyase
Carbonic anhydrase I	CA1	P00915	CHEMBL 261	Lyase
Carbonic anhydrase IX	CA9	Q16790	CHEMBL 3594	Lyase
Urotensin II receptor	UTS2R	Q9UKP6	CHEMBL 3764	Family A G protein-coupled receptor
Dihydrofolate reductase	DHFR	P00374	CHEMBL 202	Oxidoreductase