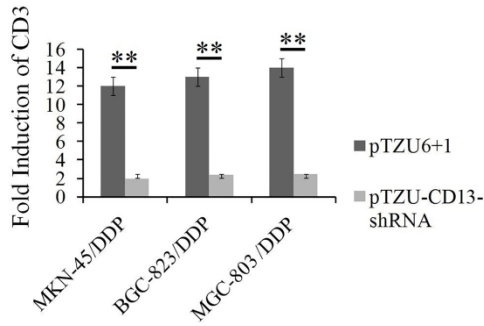
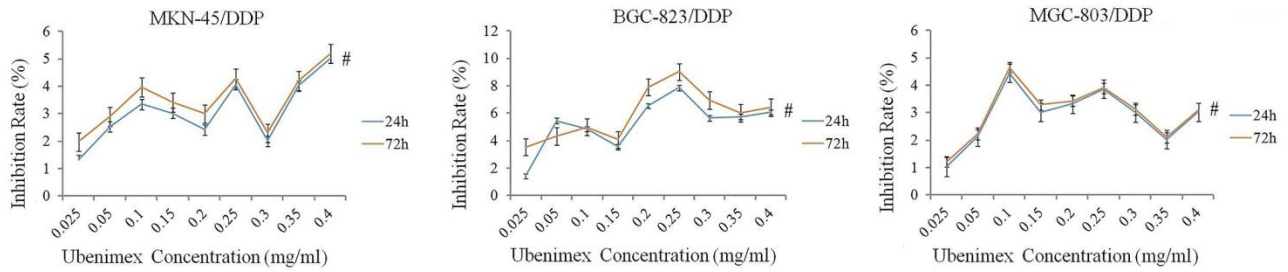


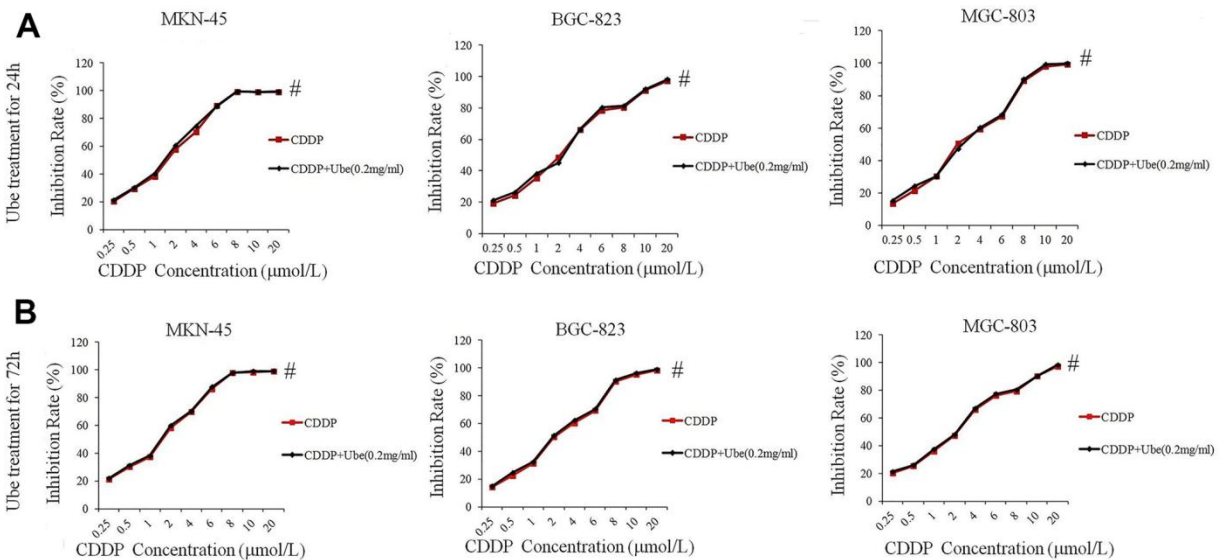
SUPPLEMENTARY FIGURES



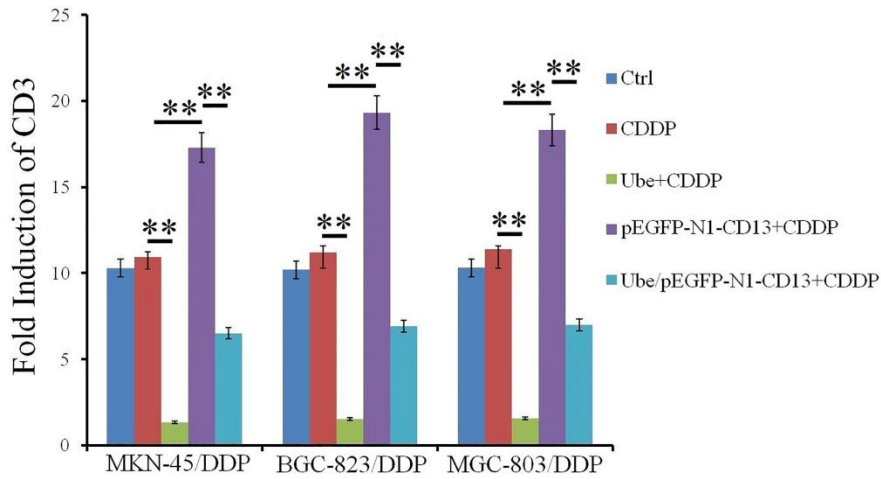
Supplementary Figure 1. Quantitative study of CD13 mRNA expression in CDDP-resistant GC cells after CD13 knockdown. CDDP-resistant GC cells were pre-stimulated with pTZU6+1 or pTZU-CD13-shRNA plasmids, Real-time PCR assay was performed to check the CD13 expression. The results are demonstrated as the representative of three independent experiments. **P<0.01.



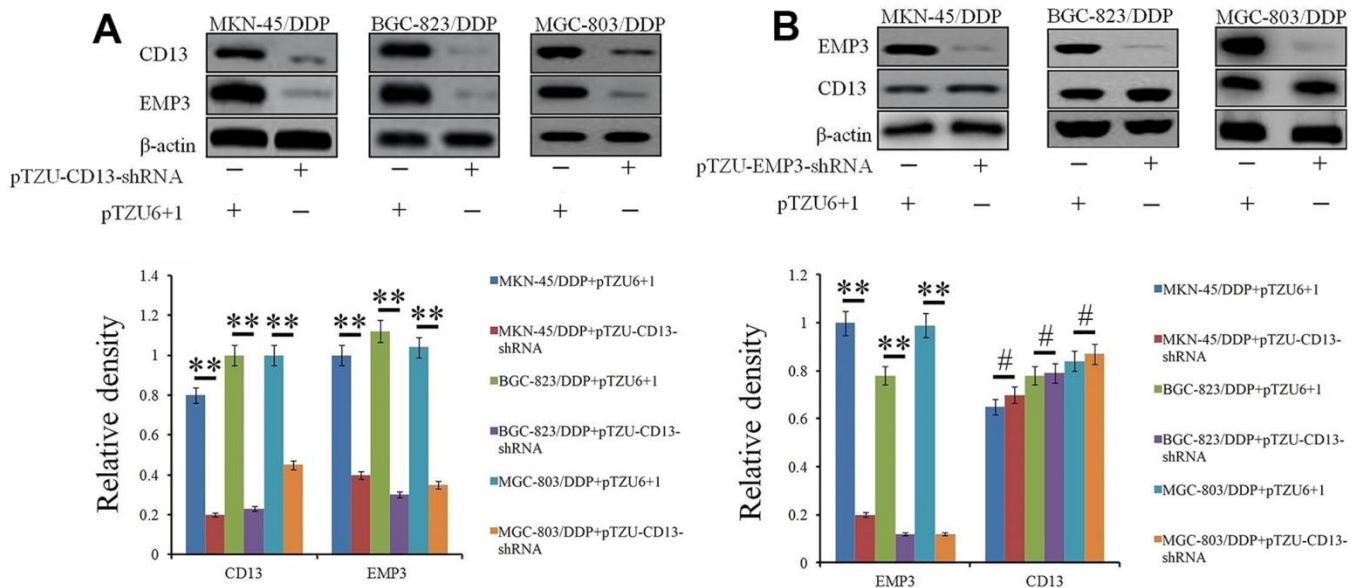
Supplementary Figure 2. Ubenimex has no direct cytotoxicity on CDDP-resistant GC cells. CDDP-resistant GC cells were treated with increasing concentrations of Ubenimex for 24h and 72h. Inhibition rate on cell growth was calculated by CCK-8 method. #P>0.05.



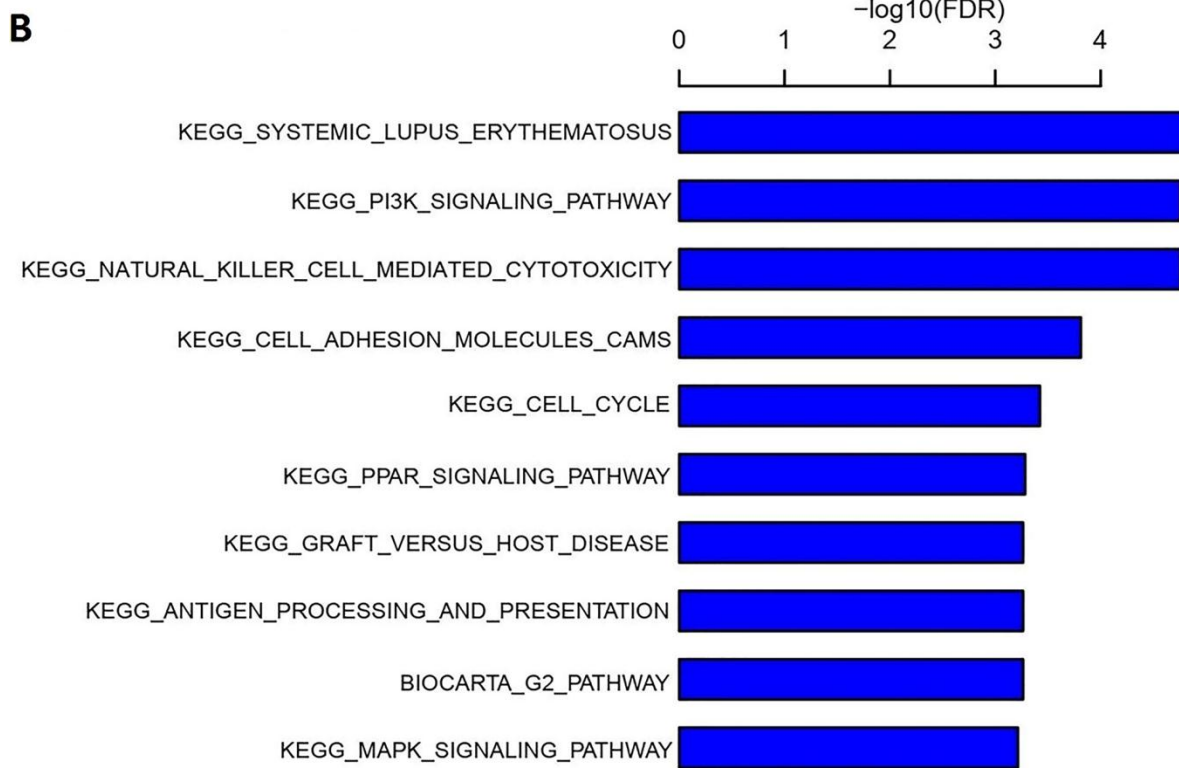
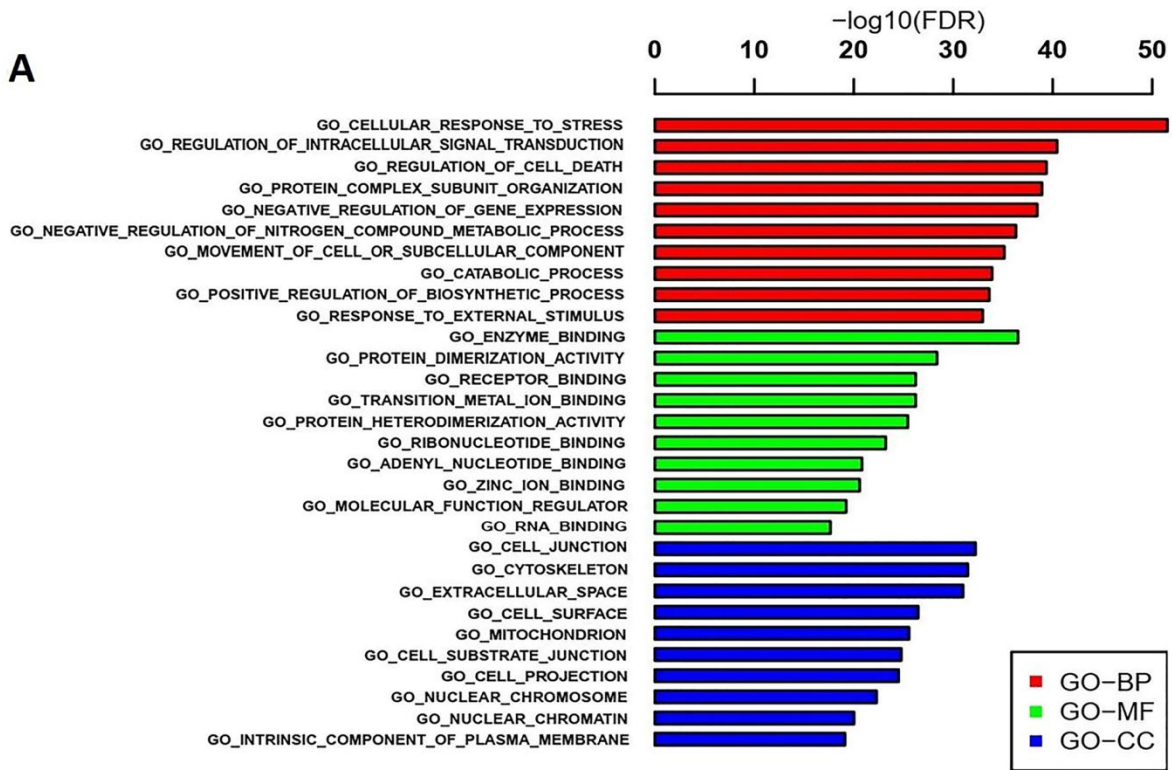
Supplementary Figure 3. Ubenimex has no effect on cytotoxicity of CDDP towards parental GC cells. GC cells were treated with or without Ubenimex (0.2mg/mL) for 24h and 72h, followed by incubation with CDDP at increasing concentrations (0.25, 0.5, 1, 2, 4, 6, 8, 10, and 20 μ mol/L) for 48h. Inhibition rate on cell growth was measured with CCK-8 method. #P>0.05.



Supplementary Figure 4. Quantitative study of CD13 mRNA expression in CDDP-resistant GC cells after Ubenimex treatment. CDDP-resistant GC cells were pre-stimulated with indicated treatment as described in the Figure 3, and was prepared for Real-time PCR assay. The results are demonstrated as the representative of three independent experiments. **P<0.01.



Supplementary Figure 5. CD13 has a one-way regulatory effect on EMP3 expression. (A) EMP3 expression was identified by Western blot assay in CDDP-resistant GC cells after CD13 was knockdown. (B) CD13 expression was determined by Western blot assay in CDDP-resistant GC cells after EMP3 was silenced. **P<0.01 and #P>0.05.



Supplementary Figure 6. Gene function and pathway enrichment of differentially expressed genes (DEGs) were determined by GO and KEGG analysis. (A) GO analysis was performed to evaluate the Biological Process (BP), Molecular Function (MF), and Cellular Component (CC) of these DEGs in Ubenimex- treated MKN-45/DDP cells, as described as the enrichment map of GO terms. **(B)** BioCarta or KEGG pathway analysis were carried out to clarify the pathway enrichment in these DEGs, as shown as the enrichment map of the top 10 over-represented canonical pathways following Ubenimex treatment.

Gene Set Name	Gene Symbol	Description	Fold Change
KEGG_PI3K_SIGNALING_PATH	NFKBIB	NFKB Inhibitor , beta	1.344551077
KEGG_PI3K_SIGNALING_PATH	NKRF	NFKB repressing factor	8.406317901
KEGG_PI3K_SIGNALING_PATH	PIK3R1	phosphoinositide-3-Kinase Regulatory Subunit 1	-12.908943940
KEGG_PI3K_SIGNALING_PATH	PIK3C2B	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 beta	-1.384418211
KEGG_PI3K_SIGNALING_PATH	PIK3R3	phosphoinositide-3-kinase, regulatory subunit 3 (gamma)	-1.181440701
KEGG_PI3K_SIGNALING_PATH	PIK3CB	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit beta	-1.116603143
KEGG_PI3K_SIGNALING_PATH	PIK3CG	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma	-1.382075605
KEGG_PI3K_SIGNALING_PATH	PIK3C2A	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	-1.176025937
KEGG_PI3K_SIGNALING_PATH	PIK3CD	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta	-1.012538491
KEGG_PI3K_SIGNALING_PATH	PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	-1.416046764
KEGG_PI3K_SIGNALING_PATH	PIK3R5	phosphoinositide-3-kinase, regulatory subunit 5	-1.259684137
KEGG_PI3K_SIGNALING_PATH	PIK3IP1	phosphoinositide-3-kinase interacting protein 1	1.475801979
KEGG_PI3K_SIGNALING_PATH	PIK3C2G	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 gamma	-1.206000268
KEGG_PI3K_SIGNALING_PATH	PIK3R6	phosphoinositide-3-kinase, regulatory subunit 6	-1.107038243
KEGG_PI3K_SIGNALING_PATH	PIK3AP1	phosphoinositide-3-kinase adaptor protein 1	-1.170605016
KEGG_PI3K_SIGNALING_PATH	PIK3R4	phosphoinositide-3-kinase, regulatory subunit 4	-1.245926519
KEGG_PI3K_SIGNALING_PATH	NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	-1.189951472
KEGG_PI3K_SIGNALING_PATH	NKAP	NFKB activating protein	-4.987823698
KEGG_PI3K_SIGNALING_PATH	NKIRAS2	NFKB inhibitor interacting Ras-like 2	1.383398614
KEGG_PI3K_SIGNALING_PATH	NKAPL	NFKB activating protein-like	-1.392148168
KEGG_PI3K_SIGNALING_PATH	NFKBIA	NFKB Inhibitor Alpha	9.558331407
KEGG_PI3K_SIGNALING_PATH	NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	-1.810258653
KEGG_PI3K_SIGNALING_PATH	RELA	nuclear factor NF-kappa-B p65 subunit, Transcription factor p65	-10.434542180
KEGG_PI3K_SIGNALING_PATH	NFKBIE	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	1.347048682
KEGG_PI3K_SIGNALING_PATH	NFKBID	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, delta	1.382075605
KEGG_PI3K_SIGNALING_PATH	MTOR	mechanistic target of rapamycin (serine/threonine kinase)	-1.797650315
KEGG_PI3K_SIGNALING_PATH	GSKIP	GSK3B interacting protein	-1.848404711
KEGG_PI3K_SIGNALING_PATH	GSK3A	glycogen synthase kinase 3 alpha	1.101603517
KEGG_PI3K_SIGNALING_PATH	GSK3B	glycogen synthase kinase 3 beta	2.267654591
KEGG_PI3K_SIGNALING_PATH	IKKBK	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	-1.609856482
KEGG_PI3K_SIGNALING_PATH	IKBKG	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma	-1.739533094
KEGG_PI3K_SIGNALING_PATH	IKBKE	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon	-1.895365326
KEGG_PI3K_SIGNALING_PATH	AKT1	RAC-alpha serine/threonine-protein kinase	-11.554549540
KEGG_PI3K_SIGNALING_PATH	AKT2	AKT serine/threonine kinase 2;PKB beta	-6.545451724
KEGG_PI3K_SIGNALING_PATH	AKT3	AKT serine/threonine kinase 3;PKB gamma	-1.232389998
KEGG_PI3K_SIGNALING_PATH	AKTIP	AKT interacting protein	-1.257153923

Supplementary Figure 7. Details for the differentially expressed genes that were enriched in PI3K signaling pathway.