

Table S1. List of compounds utilized within this study, the solvents used for reconstitution, and compound suppliers.

Compound	Solvent	Supplier
18 α -glycyrrhetic acid	Ethanol	Sigma-Aldrich, USA
3,4-Methylenedioxy- β -nitrostyrene	DMSO	Sapphire North America, USA
ABC294640	DMSO	Selleckchem, USA
Atorvastatin	DMSO	Sapphire North America, USA
Bosutinib	DMSO	Cayman Chemical, USA
Brefeldin A	DMSO	Selleckchem, USA
Carbenoxolone	Milli-Q H ₂ O	Tocris Bioscience, UK
Chloroquine	Milli-Q H ₂ O	Selleckchem, USA
Chlorpromazine	DMSO	Selleckchem, USA
Concanavalin A	PBS	Sigma-Aldrich, USA
Cyclosporin	DMSO	Selleckchem, USA
DBeQ	DMSO	Selleckchem, USA
Dyngo-4a	DMSO	Selleckchem, USA
EGA	DMSO	Sigma-Aldrich, USA
Fingolimod	DMSO	Cayman Chemical, USA
Fumonisin B1	DMSO	Sigma-Aldrich, USA
Genistein	DMSO	Selleckchem, USA
Golgicide A	DMSO	Selleckchem, USA
GW4869	DMSO	Cayman Chemical, USA
Hydroxy-chloroquine	Milli-Q H ₂ O	Selleckchem, USA
JTE-013	DMSO	Cayman Chemical, USA
L-cycloserine	DMSO	Selleckchem, USA
Lck inhibitor	DMSO	Cayman Chemical, USA
Leptomycin B	Ethanol	Tocris Bioscience, UK
MP A08	DMSO	Cayman Chemical, USA
Myriocin	DMSO	Sigma-Aldrich, USA
N-Acetyl-2,3-dehydro-2-deoxyneuraminic acid	Milli-Q H ₂ O	Sigma-Aldrich, USA
NMS-873	DMSO	Selleckchem, USA
Oseltamivir	DMSO	Selleckchem, USA
PACOCF3	DMSO	Tocris Bioscience, UK
PF-543	DMSO	Selleckchem, USA
Phenylarsine oxide	DMSO	Sigma-Aldrich, USA
Ponesimod	DMSO	Selleckchem, USA
PP1	DMSO	Selleckchem, USA
PP2	DMSO	Selleckchem, USA
SKI-11	DMSO	Selleckchem, USA
SKI 178	DMSO	Cayman Chemical, USA
SLC5111312	DMSO	Cayman Chemical, USA
STF-62247	DMSO	Cayman Chemical, USA
SU6656	DMSO	Selleckchem, USA
VPC 23019	DMSO	Cayman Chemical, USA
W123	DMSO	Cayman Chemical, USA

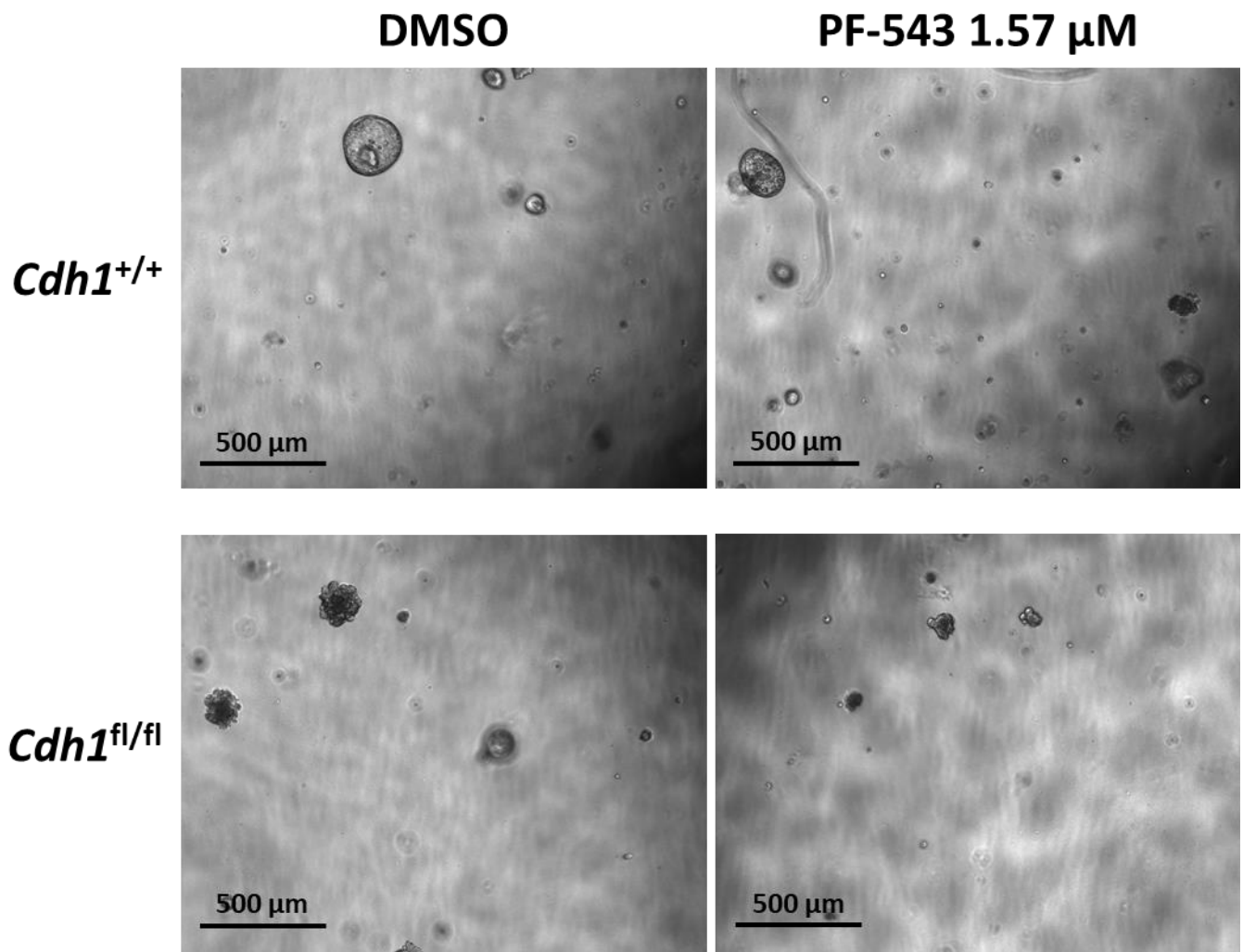


Figure S1. Representative brightfield microscopy images of organoids following treatment with either DMSO or PF-543. Multiple images were captured across the surface area of each well, and across multiple focal planes.

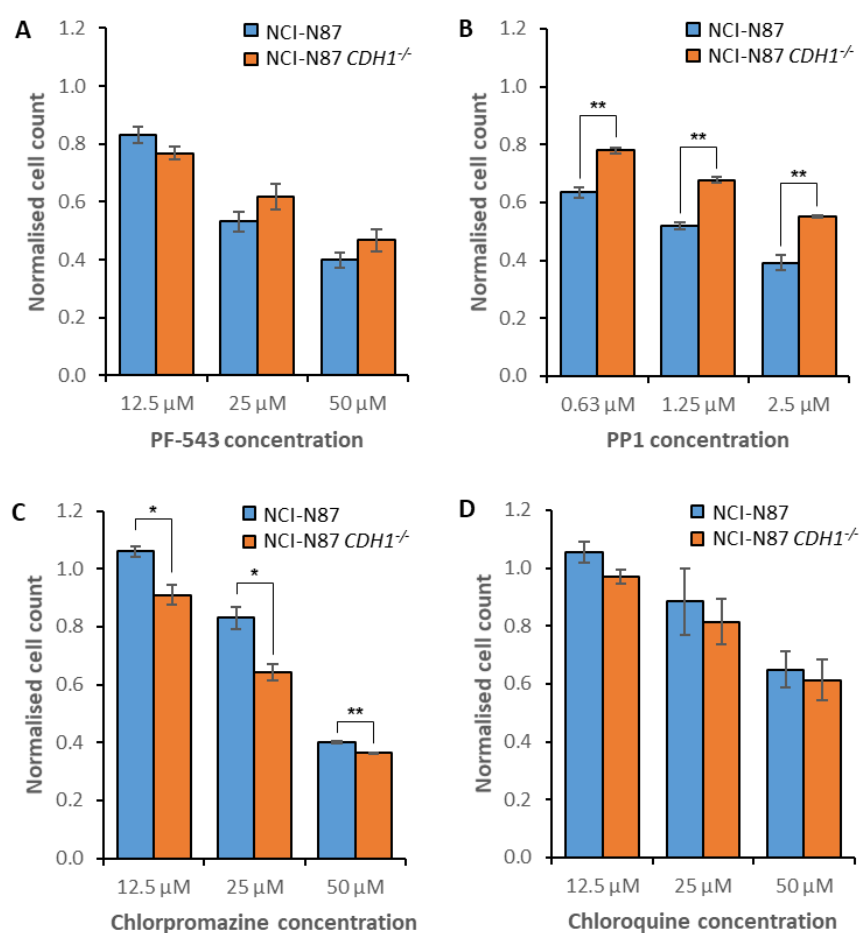


Figure S2. Efficacy of candidate synthetic lethal compounds in isogenic NCI-N87 cells. NCI-N87 and NCI-N87 *CDH1*^{-/-} cells were drugged with inhibitors of (A) sphingolipid metabolism, (B) clathrin-mediated endocytosis, (C) flotillin-mediated endocytosis or (D) autophagy. Viability was quantified through nuclei counting, and normalisation to vehicle controls. Although a nine-point serial dilution was assessed, only the three consecutive compound concentrations that exhibited the greatest difference in viability between *CDH1*^{+/+} and *CDH1*^{-/-} cells are depicted. Average values were calculated from three biological replicates, with \pm 1 standard error of the mean depicted by error bars. *P*-values were calculated using Student's *t*-test; * *P* < 0.05, ** *P* < 0.01.

Table S2. Cell viability ratios from initial drug screening.

Compound	Concentration (μ M)	Ratio of MCF10A <i>CDH1</i> ^{+/−} to MCF10A viability
PF-543	0.2	1.00
	0.39	1.00
	0.78	0.92
	1.56	0.90
	3.13	0.97
	6.25	0.92
	12.5	0.68
	25	0.58
	50	0.68
Chlorpromazine	0.2	1.00
	0.39	0.98
	0.78	0.98
	1.56	0.94
	3.13	0.96
	6.25	0.80
	12.5	0.61
	25	0.34
	50	0.40
PP1	0.64	1.00
	0.98	0.93
	1.51	0.88
	2.32	0.92
	3.57	0.84
	5.49	0.73
	8.45	0.65
	13	0.59
	20	0.53
PP2	0.64	0.91
	0.98	0.88
	1.51	0.84
	2.32	0.84
	3.57	0.81
	5.49	0.70
	8.45	0.66
	13	0.61
	20	0.59
SU6656	1	1.04
	1.33	1.02
	1.78	0.94
	2.37	0.96
	3.16	0.84
	4.22	0.74
	5.63	0.75
	7.5	0.79
	10	0.89

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Compound	Concentration (μ M)	Ratio of MCF10A <i>CDH1</i> ^{-/-} to MCF10A viability
3,4-Methylenedioxy- β -nitrostyrene	0.9	0.98
	1.2	0.97
	1.6	0.95
	2.14	0.99
	2.85	0.87
	3.8	0.71
	5.06	0.62
	6.75	0.52
	9	0.58
Chloroquine	0.2	0.98
	0.39	0.94
	0.78	0.92
	1.56	0.91
	3.13	0.94
	6.25	0.88
	12.5	0.73
	25	0.58
	50	0.62
Hydroxy-chloroquine	0.2	1.02
	0.39	1.02
	0.78	1.07
	1.56	1.06
	3.13	0.93
	6.25	0.94
	12.5	0.83
	25	0.73
	50	0.76

Table S3. IC₅₀ values from initial drug screening.

Compound	Cell line	IC ₅₀ (μM)
PF-543	MCF10A	33.92
	MCF10A <i>CDH1</i> ^{-/-}	14.46
Chlorpromazine	MCF10A	9.55
	MCF10A <i>CDH1</i> ^{-/-}	5.79
PP1	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	11.16
PP2	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	12.66
SU6656	MCF10A	4.81
	MCF10A <i>CDH1</i> ^{-/-}	4.19
3,4-Methylenedioxy-β-nitrostyrene	MCF10A	5.74
	MCF10A <i>CDH1</i> ^{-/-}	4.15
Chloroquine	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	21.08
Hydroxy-chloroquine	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	35.69

Table S4. Cell viability ratios following inhibition of sphingolipid metabolism and signaling.

Compound	Concentration (μM)	Ratio of MCF10A <i>CDH1</i> ^{+/−} to MCF10A viability
SKI 178	0.31	0.99
	0.42	1.04
	0.56	0.98
	0.74	0.95
	0.99	1.06
	1.32	1.00
	1.76	0.96
	2.34	0.87
	3.12	0.91
MP A08	0.18	0.97
	0.36	1.01
	0.72	0.99
	1.44	1.04
	2.89	0.95
	5.78	0.97
	11.55	1.02
	23.1	0.96
	46.2	1.20
SLC5111312	0.05	1.04
	0.11	1.02
	0.21	1.03
	0.42	1.07
	0.84	0.92
	1.68	0.88
	3.37	0.86
	6.73	0.79
	13.46	0.85
L-cycloserine	0.2	1.08
	0.39	0.99
	0.78	1.01
	1.56	1.02
	3.13	1.03
	6.25	1.02
	12.5	0.98
	25	0.97
	50	1.00
GW4869	1.51	0.92
	1.67	0.89
	1.86	0.86
	2.07	0.84
	2.3	0.88
	2.55	0.84
	2.84	0.84
	3.15	0.75
	3.5	0.77

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Compound	Concentration (μ M)	Ratio of MCF10A <i>CDH1</i> ^{-/-} to MCF10A viability
W123	0.2	0.98
	0.39	1.04
	0.78	1.01
	1.56	1.00
	3.13	0.94
	6.25	0.89
	12.5	0.84
	25	0.75
	50	0.73
JTE-013	3.23	1.03
	4.55	1.02
	6.41	1.01
	9.02	1.01
	12.7	1.03
	17.9	0.99
	25.2	0.96
	35.5	0.91
	50	0.94
VPC 23019	0.005	0.96
	0.01	0.96
	0.02	0.99
	0.04	0.95
	0.08	0.98
	0.17	0.96
	0.34	0.95
	0.67	0.94
	1.34	0.94
Fingolimod	0.21	0.94
	0.35	0.89
	0.58	0.90
	0.97	0.87
	1.62	0.93
	2.7	1.08
	4.5	1.03
	7.5	1.18
	12.5	1.51

Table S5. IC₅₀ values from inhibition of sphingolipid metabolism and signaling.

Compound	Cell line	IC ₅₀ (μM)
SKI 178	MCF10A	1.83
	MCF10A <i>CDH1</i> ^{-/-}	1.75
MP A08	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
SLC5111312	MCF10A	7.04
	MCF10A <i>CDH1</i> ^{-/-}	4.99
L-cycloserine	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
GW4869	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	6.13
W123	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	43.40
JTE-013	MCF10A	46.55
	MCF10A <i>CDH1</i> ^{-/-}	44.54
VPC 23019	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
Fingolimod	MCF10A	3.35
	MCF10A <i>CDH1</i> ^{-/-}	2.75

Table S6. Cell viability ratios following inhibition of endocytosis or Src family kinases.

Compound	Concentration (μ M)	Ratio of MCF10A <i>CDH1</i> ^{+/−} to MCF10A viability
PACOCF3	0.2	1.01
	0.39	0.97
	0.78	1.00
	1.56	1.01
	3.13	0.98
	6.25	1.03
	12.5	1.00
	25	0.97
	50	1.14
Dyngo-4a	0.64	1.02
	0.98	1.04
	1.51	1.01
	2.32	1.06
	3.57	0.99
	5.49	1.07
	8.45	1.07
	13	1.05
	20	1.07
EGA	0.2	1.00
	0.39	0.98
	0.78	0.97
	1.56	0.99
	3.13	0.97
	6.25	0.93
	12.5	0.86
	25	0.83
	50	0.78
Lck inhibitor	0.05	1.03
	0.11	1.01
	0.21	1.01
	0.42	0.99
	0.84	0.92
	1.69	1.00
	3.38	0.94
	6.75	0.99
	13.5	0.90
Bosutinib	0.2	0.98
	0.39	1.02
	0.78	0.87
	1.56	0.85
	3.13	0.90
	6.25	0.87
	12.5	0.91
	25	0.79
	50	0.81

Table S7. IC₅₀ values from inhibition of endocytosis or Src family kinases.

Compound	Cell line	IC ₅₀ (μM)
PACOCF3	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
Dyngo-4a	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
EGA	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
Lck inhibitor	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	≥50
Bosutinib	MCF10A	3.16
	MCF10A <i>CDH1</i> ^{-/-}	2.55

Table S8. Targets of Src family kinase inhibitors. Targets are ordered in ascending order of IC₅₀ values.

Compound	Target	IC ₅₀ (nM)
PP1	Lck	5
	Fyn	6
	Hck	20
	c-Src	170
PP2	Lck	4
	Fyn	5
	Hck	5
	c-Src	33
SU6656	Yes	20
	Lyn	130
	Fyn	170
	c-Src	280
Bosutinib	c-Src	1.2
Lck inhibitor	Lck	1
	c-Src	70

Table S9. Cell viability ratios following inhibition of autophagy.

Compound	Concentration (μ M)	Ratio of MCF10A <i>CDH1</i> ^{+/−} to MCF10A viability
STF-62247	0.2	0.93
	0.39	1.08
	0.78	0.93
	1.56	0.86
	3.13	0.89
	6.25	0.89
	12.5	0.72
	25	0.63
	50	0.64

Table S10. IC₅₀ values from inhibition of autophagy.

Compound	Cell line	IC ₅₀ (μM)
STF-62247	MCF10A	≥50
	MCF10A <i>CDH1</i> ^{-/-}	23.82

Table S11. MCF10A cell viability ratios following treatment with drug combinations.

Drug combination	Concentration (μ M)	Ratio of MCF10A <i>CDH1</i> ^{-/-} to MCF10A viability
PF-543/chloroquine	0.2/0.2	0.89
	0.39/0.39	0.89
	0.78/0.78	0.83
	1.56/1.56	0.81
	3.13/3.13	0.67
	6.25/6.25	0.64
	12.5/12.5	0.75
	25/25	1.19
PF-543/chlorpromazine	0.2/0.1	0.97
	0.39/0.2	0.91
	0.78/0.39	0.93
	1.56/0.78	0.86
	3.13/1.56	0.73
	6.25/3.13	0.59
	12.5/6.25	0.64
	25/12.5	0.78
PF-543/atorvastatin	0.2/0.31	0.90
	0.39/0.63	0.83
	0.78/1.25	0.85
	1.56/2.5	0.82
	3.13/5	0.75
	6.25/10	0.76
	12.5/20	0.93
	25/40	0.87

Table S12. NCI-N87 cell viability ratios following treatment with candidate synthetic lethal compounds.

Compound	Concentration (μ M)	Ratio of NCI-N87 <i>CDH1</i> ^{+/−} to NCI-N87 viability
PF-543	0.2	1.00
	0.39	1.02
	0.78	1.05
	1.56	0.98
	3.13	1.04
	6.25	1.00
	12.5	0.93
	25	1.16
	50	1.17
PP1	0.16	1.12
	0.31	1.21
	0.63	1.23
	1.25	1.30
	2.5	1.40
	5	1.16
	10	0.92
	20	0.91
Chlorpromazine	0.39	1.01
	0.78	1.04
	1.56	0.96
	3.13	0.94
	6.25	0.93
	12.5	0.86
	25	0.77
	50	0.90
Chloroquine	0.39	0.98
	0.78	1.01
	1.56	0.99
	3.13	1.00
	6.25	0.96
	13	0.92
	25	0.92
	50	0.94

Table S13. IC₅₀ values for candidate synthetic lethal compounds in NCI-N87 isogenic cells.

Compound	Organoid line	IC ₅₀ (μM)
PF-543	NCI-N87	33.71
	NCI-N87 <i>CDH1</i> ^{-/-}	35.88
PP1	NCI-N87	1.50
	NCI-N87 <i>CDH1</i> ^{-/-}	3.52
Chlorpromazine	NCI-N87	42.63
	NCI-N87 <i>CDH1</i> ^{-/-}	35.39
Chloroquine	NCI-N87	≥50
	NCI-N87 <i>CDH1</i> ^{-/-}	≥50

Table S14. Gastric organoid viability ratios following treatment with candidate synthetic lethal compounds.

Compound	Concentration (μ M)	Ratio of <i>Cdh1</i> ^{-/-} organoid to <i>Cdh1</i> ^{+/+} organoid viability
PF-543	0.39	0.48
	0.78	0.52
	1.57	0.38
PP1	6.5	0.53
	13	0.54
	26	0.44
Chlorpromazine	6.25	0.35
	12.5	0.53
	25	0.70
Chloroquine	12.5	0.40
	25	0.39
	50	0.49

Table S15. IC₅₀ values for candidate synthetic lethal compounds in *Cdh1*^{+/+} and *Cdh1*^{fl/fl} gastric organoids.

Compound	Organoid line	IC ₅₀ (μM)
PF-543	<i>Cdh1</i> ^{+/+} organoids	1.84
	<i>Cdh1</i> ^{fl/fl} organoids	0.38
PP1	<i>Cdh1</i> ^{+/+} organoids	27.42
	<i>Cdh1</i> ^{fl/fl} organoids	9.75
Chlorpromazine	<i>Cdh1</i> ^{+/+} organoids	7.24
	<i>Cdh1</i> ^{fl/fl} organoids	0.02
Chloroquine	<i>Cdh1</i> ^{+/+} organoids	31.76
	<i>Cdh1</i> ^{fl/fl} organoids	0.84

Table S16. Mammary organoid viability ratios following treatment with candidate synthetic lethal compounds.

Compound	Concentration (μM)	Ratio of <i>Cdh1^{fl/fl}</i> organoid to <i>Cdh1^{fl/fl}</i> organoid viability
PF-543	0.39	0.62
	0.78	0.74
	1.57	0.52
PP1	6.5	1.01
	13	0.99
	26	0.77
Chlorpromazine	6.25	1.09
	12.5	0.70
	25	0.56
Chloroquine	12.5	1.22
	25	1.09
	50	0.57

Table S17. IC₅₀ values for candidate synthetic lethal compounds in *Cdh1*^{+/+} and *Cdh1*^{fl/fl} mammary organoids.

Compound	Organoid line	IC ₅₀ (μM)
PF-543	<i>Cdh1</i> ^{+/+} organoids	46.76
	<i>Cdh1</i> ^{fl/fl} organoids	19.94
PP1	<i>Cdh1</i> ^{+/+} organoids	42.51
	<i>Cdh1</i> ^{fl/fl} organoids	24.86
Chlorpromazine	<i>Cdh1</i> ^{+/+} organoids	133.13
	<i>Cdh1</i> ^{fl/fl} organoids	66.10
Chloroquine	<i>Cdh1</i> ^{+/+} organoids	167.49
	<i>Cdh1</i> ^{fl/fl} organoids	87.03