APPENDIX FIGURES AND TABLE

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Appendix Figure S1: Dose-response analyses for the individual drugs



Legend: HCT116 cells were treated with increasing concentrations of NEN and the individual drugs as indicated. Graphs shows the ratio of toxicity and viability measured after a 24h treatment (N=3). The concentrations used for determination of cytotoxicity effects throughout the study were NEN 1.2 μ M; Domperidone (Domp), Imipramine (Imi), Desipramine (Desi) and Amitriptyline (Ami), each 30 μ M; Clomipramine (Clomi) 20 μ M.

Appendix Figure S2: GO gene set enrichment analysis (GSEA) of transcriptome data



Legend: GO gene set enrichment analysis (GSEA) of microarray data from HCT116 cells upon double treatment with NEN (1.2µM) and Domperidone (30µM) for 16 hours vs. vehicle control treatment (N=3).

Appendix Figure S3: Heat map of differentially expressed genes (DEGs) from the transcriptome analysis



Legend: Differentially expressed genes determined from the microarray analysis of HCT116 cells upon treatment with vehicle control (Ctrl), NEN (1.2μ M), Domperidone (Dom, 30μ M) or double treatment with NEN and Domperidone for 16 hours. Genes showing synergistic induction upon double treatment in comparison to single on control treatment are shown.

Appendix Figure S4A: Induction of ISR proteins upon drug treatments



Appendix Figure S4B: Induction of ISR proteins upon drug treatments



Appendix Figure S4A and for B

Legend:

A Immunoblot analysis including corresponding densitometric quantifications of CHOP, ATF4, phosphorylated (p-) and t-) eIF2alpha (eIF2a) of HCT116 and U87 cells treated as indicated for 16h or 24h, respectively (NEN 1.2 μ M; Domperidone (Domp), Imipramine (Imi), Desipramine (Desi), each 30 μ M; Clomipramine (Clomi) 20 μ M).

B Immunoblot analysis including corresponding densitometric quantifications of CHOP, ATF4, phosphorylated (p-) and t-) eIF2alpha (eIF2a) of BxPC3 and U87 cells treated as indicated for 24h (NEN 1.2 μ M; Domperidone (Domp), Imipramine (Imi), Desipramine (Desi), each 30 μ M; Clomipramine (Clomi) 20 μ M).

Data information: Data are presented as mean (SD) (N=3) and were analyzed twoway ANOVA with Tukey post-hoc test. * p< 0.05; ** p< 0.01;*** p< 0.001; **** p < 0.0001.

Appendix Figure S5: WikiPathways gene set enrichment analysis (GSEA) of transcriptome data



Legend: Wikipathway gene set enrichment analysis (GSEA) of microarray data from HCT116 cells upon double treatment with NEN (1.2µM) and Domperidone (30µM) for 16 hours vs. vehicle control treatment (N=3).

Appendix Figure S6: Heat map of CLEAR network gene expression from the transcriptome analysis



Legend: Expression of genes defining the CLEAR network as reported in Palmieri et al. (2011, Hum Mol Genet 20: 3852-3866, Table 2) from the microarray analysis of HCT116 cells upon treatment with vehicle control (Ctrl), NEN (1.2 μ M), Domperidone (Dom, 30 μ M) or double treatment with NEN and Domperidone for 16 hours. Of the 127 gene, 16 were missing from the expression matrix (probably filtered out due to low expression or they were missing from the Affymetrix chip).



Double treatment vs Control

• P • P & Log2 FC

Total = 857 genes

Legend: Volcano blot of differentially expressed genes determined from the microarray analysis from HCT116 cells upon double treatment with NEN (1.2μ M) and Domperidone (30μ M) for 16 hours vs. vehicle control treatment (N=3). UPP1 is highlighted as one of the strongest upregulated genes upon combined drug treatment.

Appendix Figure S8: Induction of UPP1 upon drug treatments



Legend:Immunoblot analysis including corresponding densitometric quantifications of UPP1 in HCT116, BxPC3 and U87 cells treated as indicated for 16h (HCT116) or 24h (BxPC3, U87) (NEN 1.2 μ M Domepridone (Domp), Imipramine (Imi), Amitiptylin (Ami), 30 μ M each, and Clomipramine 20 μ M). Protein bands were normalized to vinculin (loading control) and were analyzed by one-way ANOVA and Tukey post-hoc test. * p<0.05; **p<0.01; ***p<0.001; **** p<0.0001.

APPENDIX TABLE S1

Statistical tests and exact p-values

Figure	Test and post hoc	p-value	Groups for post hoc	Adjusted p-
panel	test	(main test)	comparisons	values for
				multiple
				comparisons
Figure 1A	two-way ANOVA	< 0.0001	NEN:Ctrl vs. NEN:2-DG	0.0001
	with Tukey post-		FCCP:Ctrl vs. FCCP:2-DG	0.0337
	hoc test			
Figure 1D	<u>HCT116:</u>			
	two-way ANOVA	< 0.0001	Ctrl:Domp vs. NEN:Domp	< 0.0001
	with Tukey post-		Ctrl:Imi vs. NEN:Imi	< 0.0001
	hoc test		Ctrl:Ami vs. NEN:Ami	< 0.0001
			Ctrl:Desi vs. NEN:Desi	< 0.0001
			Ctrl:Clomi vs. NEN:Clomi	< 0.0001
	<u>U87:</u>			
	two-way ANOVA	< 0.0001	Ctrl:Ctrl vs. NEN:Ctrl	0.0332
	with Tukey post-		Ctrl:Domp vs. NEN:Domp	< 0.0001
	hoc test		Ctrl:Imi vs. NEN:Imi	< 0.0001
			Ctrl:Ami vs. NEN:Ami	0.0001
			Ctrl:Desi vs. NEN:Desi	< 0.0001
			Ctrl:Clomi vs. NEN:Clomi	< 0.0001
	<u>BxPC3:</u>			
	two-way ANOVA	< 0.0001	Ctrl:Domp vs. NEN:Domp	< 0.0001
	with Tukey post-		Ctrl:Imi vs. NEN:Imi	< 0.0001
	hoc test		Ctrl:Ami vs. NEN:Ami	< 0.0001
			Ctrl:Desi vs. NEN:Desi	0.4315 (ns)
			Ctrl:Clomi vs. NEN:Clomi	< 0.0001
Figure 1E	<u>HCT116:</u>			
	one-way ANOVA	< 0.0001	Ctrl vs. NEN	0.0002
	with Tukey post-		Ctrl vs. N + D	< 0.0001
	hoc test		Ctrl vs. N + D + zVAD	< 0.0001
			Ctrl vs. Staurospor.	< 0.0001
			N + D vs. N + D + zVAD	0.0007
	1107		N + D vs. Staurospor.	0.0052
	<u>087:</u>	0.0075		0.0000
	Kruskal-Wallis and	0.0075	Ctri vs. N + D	0.0206
	Dunn s post-noc		Domp vs. N + D	0.0050
	test			

Figure 2A	HCT116; CHOP:			
	(upper left graph)	< 0.0001	Ctrl vs. N+D	< 0.0001
	one-way ANOVA		NEN vs. N+D	< 0.0001
	with Tukey post-		Domp vs. N+D	< 0.0001
	hoc test			
	(upper right graph)			
	Kruskal-Wallis and	< 0.0001	Ctrl vs. NEN	0.0355
	Dunn's post-hoc		Ctrl vs. NEN+Imi	0.0049
	test		Ctrl vs. NEN+Ami	0.0003
			Ctrl vs. NEN+Desi	0.0001
			Ctrl vs. NEN+Clomi	0.0004
	HCT116: ATF4:			
	(lower left graph)			
	one-way ANOVA	< 0.0001	Ctrl vs. N+D	< 0.0001
	with Tukey post-		NEN vs. N+D	< 0.0001
	hoc test		Domp vs. N+D	0.0004
	(lower right graph)			
	Kruskal-Wallis and	< 0.0001	Ctrl vs. NEN+Imi	0.0088
	Dunn's post-hoc		Ctrl vs. NEN+Ami	0.0017
	test		Ctrl vs. NEN+Desi	0.0003
			Ctrl vs. NEN+Clomi	0.0011
Figure 2C		< 0.0001	Ctrl:Crtl-siRNA vs_N+D:Crtl-	
rigure ze	with Tukey nost-	0.0001	siRNA	< 0.0001
	hoc test		N+D·Crtl-siRNA vs	× 0.0001
			$N+D$ si ΔTEA	0.1369 (ns)
			N+D:Crtl_siRNA vs	0.1305 (113)
				< 0.0001
Figure 2D			GADD34	< 0.0001
rigure 2D	with Tukey post-	<0.0001		<0.0001
	hoc test	<0.0001		0.0001
		СНОР		0.0001
			Ctrlvs N+D	< 0.0001
				< 0.0001
		ATE4		< 0.0001
		<u>A114</u>		0 0002
				0.0002
Figure 25		< 0.0001		0.00+0
I Igule ZE	with Tukey post	< 0.0001	NEN:Domparidono	< 0.0001
	has tost		NEN:Domparidana ya	< 0.0001
	noc test			< 0.0001
		<0.0001		< 0.0001
Figure ZF	with Tukov post			< 0.0001
	with rukey post-			
				< 0.0001
				< 0.0001
				< 0.0001
				< 0.0001
				< 0.0001
				< 0.0001
1	1	1		< 0.0001

Figure 3A	TFE3: (left graph):			
0	one-way ANOVA	<0.0001	Ctrl vs. NEN	< 0.0001
	with Tukey post-		Ctrl vs. Domp	0.0118
	hoc test		Ctrl vs. N+D	<0.0001
			NEN vs. N+D	< 0.0001
			Domp vs. N+D	< 0.0001
	TEE3 (right graph):			
	one-way ANOVA	<0.0001	Ctrl vs. NEN+Imi	0.0052
	with Tukey post-		Ctrl vs. NEN+Ami	0.0482
	hoc test		Ctrl vs. NEN+Desi	<0.0001
			Ctrl vs. NEN+Clomi	<0.0001
	CD68 (left graph):			
	one-way ANOVA	<0.0001	Ctrl vs. NFN	0.0002
	with Tukey post-		Ctrl vs. Domp	<0.0001
	hoc test		Ctrl vs N+D	<0.0001
	CD68 (right graph)			10.0001
	$\frac{\text{ODOO}(\text{Hight graph)}}{\text{ODO-WAY}} \Delta NOV\Delta$	<0.0001	Ctrl vs_NEN+Imi	<0.0001
	with Tukey post-		Ctrl vs. NEN+Ami	<0.0001
	hoc test		Ctrl vs. NEN+Desi	<0.0001
			Ctrl vs. NEN+Clomi	<0.0001
Figure 3B	Lamp1 (top papel):			\0.0001
ligure 50	Kruskal-Wallis with	<0.0001	Ctrlvs NEN	0 0008
	Dunn's nost-hoc	0.0001	Ctrl vs. NEN+Domp	<0.0000
	tost		NEN vs. NEN+Domp	0.0001
	lest		Domp vs. NEN+Domp	<0.0001
	IC3 (middle nanel)			<0.0001
		<0.0001	Ctrlvs NEN	<0.0001
	with Tukey post-	<0.0001	Ctrl vs. NEN+Domp	<0.0001
	hoc test		NEN vs. Domp	0.0001
	noc test		NEN vs. NEN+Domp	<pre>0.0408</pre>
			Domp vs. NEN+Domp	<0.0001
	n62 (lower papel):			<0.0001
	Kruskal-Wallis with	<0.0001	Ctrlvs NEN	0 0008
	Dunn's nost-hoc	<0.0001	NEN vs. Domp	<0.0000
	tost		Domp vs. NEN+Domp	<0.0001
Figure 3C	IC3-II/I protein			<0.0001
ligure Se	ratio:			
		<0.0001	Ctrl vs. NEN	0 0387
	with Tukey post-	0.0001	Ctrl vs. NEN+Domp	<0.0001
	hoc test		NEN vs. NEN+Domp	<0.0001
	n62 levels:			10.0001
		<0.0001	Ctrl vs. NEN+Domp	<0.0001
	with Tukey nost-		NEN vs. NEN+Domp	0.0002
	hoc test			0.0002
Figure 3D	Kruskal-Wallis with	<0.0001	Ctrl vs. NFN	0.0461
inguic 50	Dunn's nost-hoc	10.0001	Ctrl vs. NEN+Domp	0.0007
	test			0.0007
Figure 4R	LIPP1 left granh			
		<0.0001	Ctrl vs. Domp	0 0002
	with Tukey nost-	\$0.0001	Ctrl vs N+D	0.0002
	hor test		NEN vs. N+D	<0.0002
		1		\$0.0001

			Domp vs. N+D	<0.0001
	UPP1, right graph:			
	one-way ANOVA	<0.0001	Ctrl vs. NEN+Imi	<0.0001
	with Tukey post-		Ctrl vs. NEN+Ami	<0.0001
	hoc test		Ctrl vs. NEN+Desi	<0.0001
			Ctrl vs. NEN+Clomi	<0.0001
Figure 4C	two-way ANOVA	0.0016	Ctrl:siCtrl vs. N+D:siCtrl	0.0024
	with Tukey post-	(treatment)	N+D:siCtrl vs.	
	hoc test	0.0137 (KD)	N+D+ISRIB:siCtrl	0.0041
			N+D:siCtrl vs.	
			N+D:siTFE3/MITF	0.0071
Figure 4D	two-way ANOVA	<0.0001	siCtrl:Ctrl vs. siCtrl:N+D	<0.0001
	with Tukey post-		siCtrl:N+D vs. siUPP1:N+D	
	hoc test			<0.0001
Figure 4E	3D Toxicity (left			
	graph):			
	two-way ANOVA	<0.0001	sictri:Ctri vs.	.0.0001
	with Tukey post-		siCtri:NEN+Domp	<0.0001
	noc test		SILTRINEN+DOMP VS.	0.0001
	2D Tovisity (right	-0.0001	SIUPP1:NEN+Domp	0.0001
	ZD TOXICITY (right	<0.0001	SICTICTIVS.	<0.0001
			SIOPPT:NEN+DOMP	<0.0001
	two-way ANOVA		siupp1:NENLDomp	<0.0001
	hoc tost		SIGPPENENTDOMP	<0.0001
Figure 4H			siCtrl·NEN+lmi vs	
inguic 411	with Tukey post-		sil IPP1 ·NFN+Imi	0 0003
	hoc test		siCtrl·NEN+Ami vs	0.0000
			siUPP1:NEN+Ami	<0.0001
			siCtrl:NEN+Desi vs.	
			siUPP1:NEN+Desi	0.0004
Figure 5A	DHODH, Left graph:	<0.0001	Ctrl vs. NEN	0.0067
0	Kruskal-Wallis with		Ctrl vs. N+D	0.1246
	Dunn's post-hoc			
	test			
	DHODH, right			
	graph:		Ctrl vs. NEN	<0.0001
	one-way ANOVA		Ctrl vs. Imi	<0.0001
	with Tukey post-		Ctrl vs. NEN+Imi	<0.0001
	hoc test		Ctrl vs. Ami	<0.0001
			Ctrl vs. NEN+Ami	<0.0001
			Ctrl vs. NEN+Desi	<0.0001
			Ctrl vs. Clomi	0.0061
			Ctrl vs. NEN+Clomi	<0.0001
		-0.0004		
Figure 5B		<0.0001	Ctri+Jnki:Ctri vs.	-0.0001
	with Tukey post-		NEN:Domp+A//	<0.0001
	noc test			

			NEN:Domp vs.	<0.0001
			NEN:Domp+A77	
			NEN:Domp+A77 vs.	<0.0001
			NEN+Jnki:Domp+A77	
Figure 5D	<u>Left graph:</u>			
	two-way ANOVA	<0.0001	NEN:Imipramine vs.	
	with Tukey post-		NEN:Imi+A77	<0.0001
	hoc test		NEN:Desipramine vs.	
			NEN:Desi+A77	<0.0001
			NEN:Amitriptyline vs.	
			NEN:Ami+A77	<0.0001
	Right graph:			
	two-way ANOVA	10.0001	Ctri:Clomi+A/7 vs.	.0.0001
	with Tukey post-	<0.0001	NEN:Clomi+A//	<0.0001
	noc test		NEN:CIOMI VS.	.0.0001
		0.0000	NEN:CIOMI+A77	<0.0001
Figure 6C	two-way ANOVA	0.0002	Ctri:Ctri VS. Ctri:NEN+Domp	<0.0001
	with Tukey post-		Ctri:NEN+Domp vs.	0.0004
	nocitest		0.3%CD:NEN+Domp	0.0004
			1 5% CD:NEN+Domp	<0.0001
				<0.0001
			0.01%CD:NEN+Domp	0 0007
				0,0007
			0.06%CD:NEN+Domp	0 0004
Figure 6D	two-way ANOVA	<0.0001	Ctrl:NEN+Domp vs	0,0004
inguic ob	with Tukey post-	10.0001	CD:NEN+Domp	<0.0001
	hoc test		Ctrl:NFN+Imi vs	
			CD:NEN+Imi	0.0009
			Ctrl:NEN+Ami vs.	
			CD:NEN+Ami	<0.0001
			Ctrl:NEN+Desi vs.	
			CD:NEN+Desi	<0.0001
			Ctrl:NEN+Clomi vs.	
			CD:NEN+Clomi	<0.0001
Figure 6E	CHOP:			
	one-way ANOVA	<0.0001	Ctrl vs. N+D	<0.0001
	with Tukey post-		N+D vs. N+D+CyD	<0.0001
	hoc test			
	<u>TFE3:</u>			
	one-way ANOVA			
	with Tukey post-	0.0030	Ctrl vs. N+D	0.0014
	hoc test			
	CDC0.			
		10 0001		10,0001
	one-way ANOVA	<0.0001		<0.0001
	with Tukey post-		N+D VS. N+D+CYD	0.0323
	not test			
	NPC1:			

	one-way ANOVA with Tukey post- hoc test	0.0001	Ctrl vs. N+D N+D vs. N+D+CyD	<0.0001 0.0078
	<u>UPP1:</u> one-way ANOVA with Tukey post- hoc test	<0.0001	Ctrl vs. N+D N+D vs. N+D+CyD	<0.0001 <0.0001
	<u>DHODH:</u> one-way ANOVA with Tukey post- hoc test	0.0038	Ctrl vs. N+D	0.0082
Figure 7A	<u>PDO-42 (left):</u> one-way ANOVA with Tukey post- hoc test	<0.0001	Ctrl vs. NEN 1,2+A Imi30 vs. NEN1,2 + I Desi30 vs. NEN1,2+D NEN2,5 vs. NEN2,5+C20	0.0001 0.0001 <0.0001 0.0041
	PDO-48 (right): one-way ANOVA with Tukey post- hoc test	0.0003	Ami vs. NEN 1,2+A Desi vs. NEN1,2+D NEN 1,2 vs. NEN1,2+C NEN 2,5 vs. NEN 2,5+A NEN 2,5 vs. NEN 2,5+1 NEN 2,5 vs. NEN 2,5+D NEN 2,5 vs. NEN 2,5+C	0.0331 0.0456 0.0257 0.0016 0.0003 0.0001 <0.0001
Figure 7B	<u>PDO-42:</u> one-way ANOVA with Tukey post- hoc test	<0.0001	Upper left graph: Ctrl vs. N+A Ctrl vs. N+A+Paclitaxel 2nM Ctrl vs. N+Paclitaxel 20nM Ctrl vs. N+A+Paclitaxel 20nM Lower left graph: Ctrl vs. N+I+Paclitaxel 2nM Ctrl vs. N+I+Paclitaxel 20nM Ctrl vs. N+I+ Paclitaxel 20nM Ctrl vs. Pacli 200	0.0372 <0.0001 0.0016 <0.0001 0.0010 0.0019 0.0005 <0.0001 0.0003
	PDO-48: one-way ANOVA with Tukey post- hoc test	<0.0001	Upper right graph Ctrl vs. N+A+Paclitaxel 2nM Ctrl vs. Pacli 20 Ctrl vs. N+Paclitaxel 20nM Ctrl vs. N+A+Paclitaxel 20nM Ctrl vs. Pacli 200 Lower left graph: Ctrl vs. Pacli 20	0.0154 0.0006 <0.0001 <0.0001 <0.0001 0.0008

			Ctrl vs. N+Paclitaxel 20nM	<0.0001
			Ctrl vs. N+I+ Paclitaxel	
			20nM	<0.0001
			Ctrl vs. Pacli 200	<0.0001
Figure	<u>BxPC3 (upper</u>	< 0.0001	NEN:Ctrl vs. NEN:2-DG	<0.0001
EV1A	<u>graph):</u>		NEN:Ctrl vs. NEN:2-DG	<0.0001
	two-way ANOVA		FCCP:Ctrl vs. FCCP:2-DG	<0.0001
	with Tukey post-			
	hoc test			
	U87 (lower graph):			
	two-way ANOVA	< 0.0001	NEN:Ctrl vs. NEN:2-DG	< 0.0001
	with Tukey post-		NEN:Ctrl vs. NEN:2-DG	<0.0001
	hoc test		FCCP:Ctrl vs. FCCP:2-DG	<0.0001
Figure	one-way ANOVA	< 0.0001	Ctrl vs. 2-DG	<0.0001
EV1B	with Tukey post-		Ctrl vs. NEN+2-DG	<0.0001
	hoc test		NEN vs. 2-DG	<0.0001
			NEN vs. NEN+2-DG	<0.0001
			2-DG vs. NEN+2-DG	<0.0001
Figure	one-way ANOVA	< 0.0001	Ctrl 1% vs. NEN 10%	<0.0001
EV1C	with Tukey post-		NEN 10% vs. NEN 1%	<0.0001
	hoc test			
Figure	HCT116, upper			
EV1D	graph:			
	two-way ANOVA	< 0.0001	Ctrl:Domp vs. NEN:Domp	<0.0001
	with Tukey post-		Ctrl:Imi vs. NEN:Imi	<0.0001
	hoc test		Ctrl:Ami vs. NEN:Ami	< 0.0001
			Ctrl:Desi vs. NEN:Desi	<0.0001
			Ctrl:Clomi vs. NEN:Clomi	<0.0001
	BxPC3, lower			
	graph:			.0.0001
	two-way ANOVA	< 0.0001	Ctrl:Imi vs. NEN:Imi	<0.0001
	with Tukey post-		Ctrl:Ami vs. NEN:Ami	<0.0001
	noc test		Ctrl:Desi vs. NEN:Desi	<0.0001
Figuro	UCT116 uppor		Ctrictoffil vs. NEN.Cloffil	<0.0001
FIGULE FV/1F	graph:			
		< 0.0001	Ctrl·Ctrl vs NFN·Ctrl	<0.0001
	with Tukey post-	< 0.0001	Ctrl:Domp vs_NEN:Domp	<0.0001
	hoc test		Ctrl:Imi vs. NFN·Imi	<0.0001
			Ctrl:Ami vs. NFN:Ami	<0.0001
			Ctrl:Desi vs. NEN:Desi	<0.0001
			Ctrl:Clomi vs. NEN:Clomi	< 0.0001
	U87, lower graph:			
	two-way ANOVA	< 0.0001	Ctrl:Domp vs. NEN:Domp	<0.0001
	with Tukey post-		Ctrl:Imi vs. NEN:Imi	<0.0001
	hoc test		Ctrl:Ami vs. NEN:Ami	<0.0001
			Ctrl:Desi vs. NEN:Desi	<0.0001

			Ctrl:Clomi vs. NEN:Clomi	<0.0001
Figure	one-way	< 0.0001	Ctrl vs. Staurosp	<0.0001
EV1F	ANOVA+Welch's			
	correction with			
	Dunnet's post hoc			
	test			
Figure	one-way ANOVA		Ctrl vs. NEN+Imi	0.0096
EV2A	with Dunnet's post		Ctrl vs. NEN+Ami	0.0002
	hoc test		Ctrl vs. NEN+Desi	<0.0001
			Ctrl vs. NEN+Clomi	<0.0001
Figure	HCT116, left graph:			
EV2C	two-way ANOVA	<0.0001	CHOP:Ctrl vs. CHOP:NEN	0.0003
	with Tukey post-		CHOP:Ctrl vs.	
	hoc test		CHOP:NEN+Domp	<0.0001
			ATF4:Ctrl vs.	
			ATF4:NEN+Domp	0.0007
			p-/t-elF2a:Ctrl vs.	0.0000
			p-/t-elF2a:NEN+Domp	0.0006
			p-/t-elf2a:NEN vs.	0.0005
			p-/t-eiF2a:NEN+Domp	0.0005
	graph:			
		<0.0001		0.0010
	with Tukey post-	<0.0001	CHOP:Ctrl vs. CHOP.INEN	0.0010
	hoc test		CHOP:NEN+Ami	<0.0001
	not test		CHOP:NEN vs	<0.0001
			CHOP:NEN+Ami	0.0062
			CHOP: Ami vs	0.0002
			CHOP:NEN+Ami	<0.0001
			ATF4:Ctrl vs.	
			ATF4:NEN+Ami	<0.0001
			ATF4:NEN vs.	
			ATF4:NEN+Ami	<0.0001
			ATF4:Ami vs.	
			ATF4:NEN+Ami	0.0002
			p-/t-elF2a:Ctrl vs. p-/t-	
			eIF2a:NEN+Ami	<0.0001
			p-/t-elF2a:NEN vs. p-/t-	
			elF2a:NEN+Ami	<0.0001
			p-/t-eIF2a:Ami vs. p-/t-	
			elF2a:NEN+Ami	<0.0001
	<u>U87, right graph:</u>			
	two-way ANOVA	<0.0001	CHOP:Ctrl vs.	
	with Tukey post-		CHOP:NEN+Ami	<0.0001
	hoc test		CHOP:NEN vs.	.0.0001
			CHOP:NEN+AMI	<0.0001
				10 0001
				<0.0001
			ATE4:Ctrl vs. ATE4:NEN	<0.0001
			ATEA:UTEN:	<0.0001
				~0.0001

			ATF4:NEN vs.	-0.0001
			ATF4:NEN+AMI ATF4:Ami vs	<0.0001
			ATF4:NEN+Ami	<0.0001
			p-/t-elF2a:Ctrl vs. p-/t-	
			elF2a:NEN+Ami	<0.0001
			p-/t-eIF2a:NEN vs. p-/t-	
			elF2a:NEN+Ami	0.0266
			p-/t-elF2a:Ami vs. p-/t-	
			elF2a:NEN+Ami	0.0012
Figure	Unpaired t test		Left graph:	
EV2D	with Welch's		Ctrl vs. siATF4	0.0015
	correction		<u>Right graph:</u>	0.0001
			Ctrl vs. siChop	0.0064
Figure	two-way ANOVA	<0.0001	Ctrl:NEN+Imi vs.	0.000
EV2E	with Tukey post-		ISRIB:NEN+Imi	<0.0001
	hoc test		Ctrl:NEN+Ami vs.	-0.0001
			ISRIB:NEN+Ami	<0.0001
				<0.0001
			Ctrl·NEN+Clomi vs	<0.0001
			ISBIB:NEN+Clomi	0.0020
Figure	two-way ANOVA	<0.0001	Ctrl:NEN+Domp vs.	0.0020
EV2F	, with Tukey post-		ISRIB:NEN+Domp	<0.0001
	hoc test		Ctrl:NEN+Imi vs.	
			ISRIB:NEN+Imi	<0.0001
			Ctrl:NEN+Ami vs.	
			ISRIB:NEN+Ami	<0.0001
			Ctrl:NEN+Desi vs.	
			ISRIB:NEN+Desi	<0.0001
			Ctrl:NEN+Clomi vs.	0.0017
Figure			ISRIB:NEN+CIOMI	0.0017
FIGULE	<u>IVITE, lett graph:</u>	0.0006	Ctrlvs NEN	0 0009
EVSA	with Tukey post-	0.0000	Ctrlvs Domp	0.0009
	hoc test		Ctrl vs. N+D	0.0024
	MITE, right graph:			0.0012
	one-way ANOVA	0.0001	Ctrl vs. NEN+Clomi	0.0220
	with Tukey post-			
	hoc test			
	<u>SQSTM1, left</u>			
	<u>graph: one-way</u>	<0.0001	Ctrl vs. NEN	0.0031
	ANOVA with Tukey		Ctrl vs. Domp	<0.0001
	post-hoc test		Ctrl vs. N+D	<0.0001
			NEN vs. N+D	< 0.0001
	COCTN11 wight		Domp vs. N+D	0.0004
	graph: one-way	<0.0001	Ctrl vs. NEN±lmi	<0.0001
	<u>Braph.</u> one-way	V.0001	Ctrl vs. NEN+Ami	0.0007

	ANOVA with Tukey		Ctrl vs. NEN+Desi	<0.0001
	post-hoc test		Ctrl vs. NEN+Clomi	<0.0001
	NPC1, left graph:	0.0098	Ctrl vs. Domp	0.0077
	one-way ANOVA		Ctrl vs. N+D	0.0405
	with Tukey post-			
	hoc test			
	NPC1, right graph:	<0.0001	Ctrl vs. NEN+Imi	<0.0001
	one-way ANOVA		Ctrl vs. NEN+Ami	<0.0001
	with Tukey post-		Ctrl vs. NEN+Desi	<0.0001
	hoc test		Ctrl vs. NEN+Clomi	<0.0001
Figure	LC3-II/I protein			
EV3C	ratio:			
	one-way ANOVA	<0.0001	Ctrl vs. NEN	0.0007
	with Tukey post-		Ctrl vs. NEN+IMI	<0.0001
	hoc test		NEN vs. NEN+IMI	<0.0001
	p62 levels:			
	one-way ANOVA	<0.0001	Ctrl vs. NEN	0.0402
	with Tukey post-		Ctrl vs. NEN+IMI	0.0003
	hoc test		NEN vs. NEN+IMI	0.0030
Figure	LC3-II/I protein			
EV3D	<u>ratio:</u>			
	one-way ANOVA	<0.0001	Ctrl vs. NEN	0.0005
	with Tukey post-		Ctrl vs. NEN+AMI	<0.0001
	hoc test		NEN vs. NEN+AMI	<0.0001
	p62 levels:			
	one-way ANOVA	<0.0001	Ctrl vs. NEN	0.0551 (ns)
	with Tukey post-		Ctrl vs. NEN+AMI	0.0006
	hoc test		NEN vs. NEN+AMI	0.0077
Figure	one-way ANOVA	<0.0001	Ctrl vs. N+D	<0.0001
EV4A	with Tukey post-		NEN vs. N+D	<0.0001
	hoc test		Domp vs. N+D	<0.0001
Figure	UPP1, left graph:			
EV4C	one-way ANOVA	<0.0001	Ctrl vs. NEN	0.0123
	with Tukey post-		Ctrl vs. Domp	0.0006
	hoc test		Ctrl vs. N+D	<0.0001
			NEN vs. N+D	0.0003
			Domp vs. N+D	0.0050
	<u>UPP1, middle</u>			
	graph:			
	one-way ANOVA	0.0017	Ctrl vs. N+Ami	0.0017
	with Tukey post-		NEN vs. N+Ami	0.0079
	hoc test		Ami vs. N+Ami	0.0053
	UPP1, right graph:			
	one-way ANOVA	0.0002	Ctrl vs. N+Imi	0.0003
	with Tukey post-		NEN vs. N+Imi	0.0010
	hoc test		Ami vs. N+Imi	0.0011

Figure EV4F	two-way ANOVA	<0.0001	siCtrl:NEN+Domp vs.	
C	, with Tukey post-		siUPP1:NEN+Domp	0.0034
	hoc test		siCtrl:NEN+Imi vs.	
			siUPP1:NEN+Imi	0.0211
			siCtrl:NEN+Ami vs.	
			siUPP1:NEN+Ami	0.0135
			siCtrl:NEN+Desi vs.	
			siUPP1:NEN+Desi	0.0196
			siCtrl:NEN+Clomi vs.	
			siUPP1:NEN+Clomi	0.1278 (ns)
Figure	<u>PDO-B42:</u>		<u>Upper left graph:</u>	
EV5A	one-way ANOVA	<0.0001	Ctrl vs. N+D+Paclitaxel	
	with Tukey post-		2nM	0.0053
	hoc test		Ctrl vs. N+Paclitaxel 20nM	0.0275
			Ctrl vs. N+D+ Paclitaxel	
			20nM	<0.0001
			Ctrl vs. Pacli 200	0.0203
			Lower left graph:	
			Ctrl vs. N+C+Paclitaxel 2nM	0.0113
			Ctrl vs. N+C+Paclitaxel	
			20nM	<0.0001
	<u>PDO-48:</u>			
	one-way ANOVA	<0.0001	<u>Upper right graph:</u>	
	with Tukey post-		Ctrl vs. Pacli 20	0.0068
	hoc test		Ctrl vs. N+Paclitaxel 20nM	<0.0001
			Ctrl vs. N+D+Paclitaxel	
			20nM	<0.0001
			Ctrl vs. Pacli 200	<0.0001
			<u>Lower right graph:</u>	
			Ctrl vs. N+C+Paclitaxel 2nM	0.0010
			Ctrl vs. Pacli 20	0.0024
			Ctrl vs. N+Paclitaxel 20nM	<0.0001
			Ctrl vs. N+C+Paclitaxel	
			20nM	<0.0001
			Ctrl vs. Pacli 200	<0.0001
Figure	Left graph, CHOP:	0.0149		0.0216
EVOD	with Duppet's pest	0,0148	NENLYC NENLA~	0,0510
	with Dunnet's post		NEN VS. NEN+AIII	0,0578 (115)
	Niddle graph		AITH VS. NENTAITH	0,0545
	<u>iviluule grapii,</u>	0.0061	Ctrlvc NEN+Ami	0 0307
		0.0001		0.0307
	with Duppot's post		Amilyo NENITAMI	0.1237
	hoc test		AIIII VS. INLINTAIIII	0.0104
	Right granh PLIMA	0.0039	Ctrl vs NEN+Ami	0.0058
		0,0000	NEN vs. NEN+Ami	0 1306
	with Dunnet's nost		Ami vs. NFN+Ami	0 1430
	hoc test			0,1700