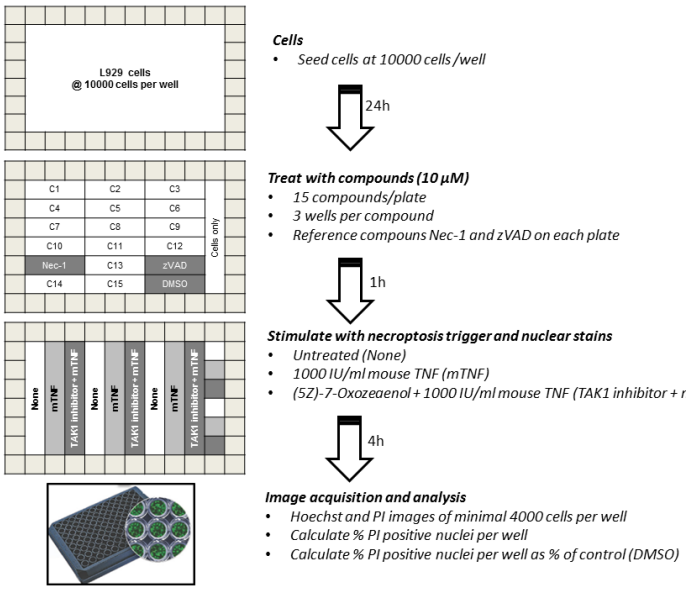
Supplementary Figures

Supplementary Figure S1.

A



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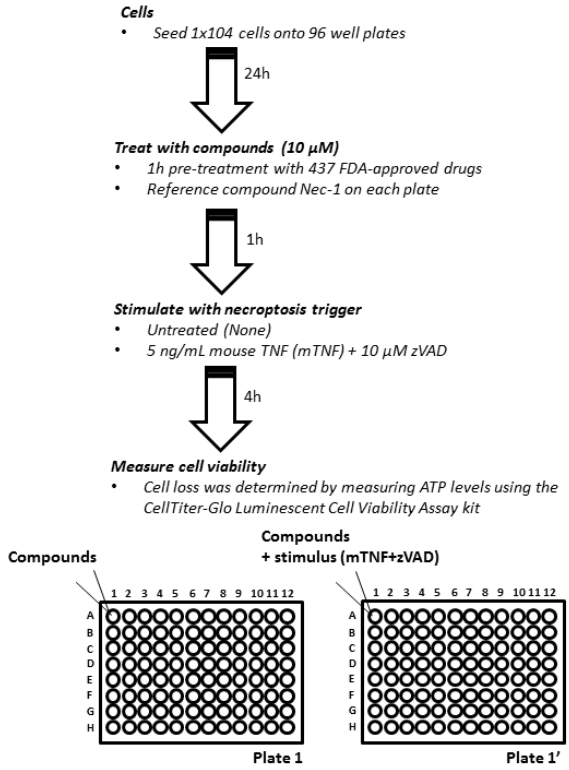
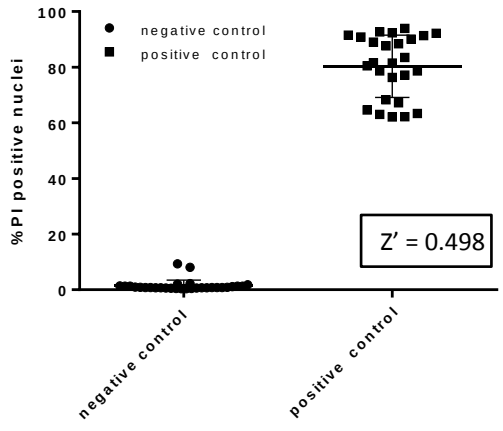


Supplementary Figure S2.

A



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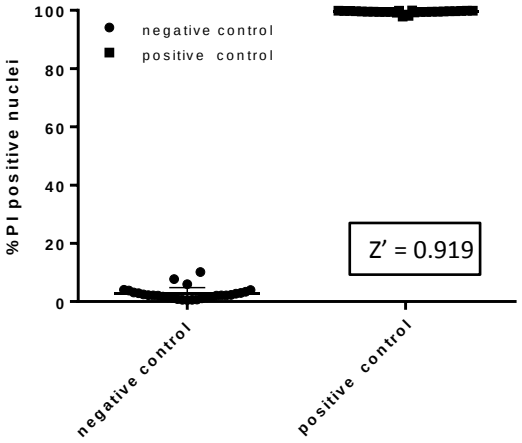
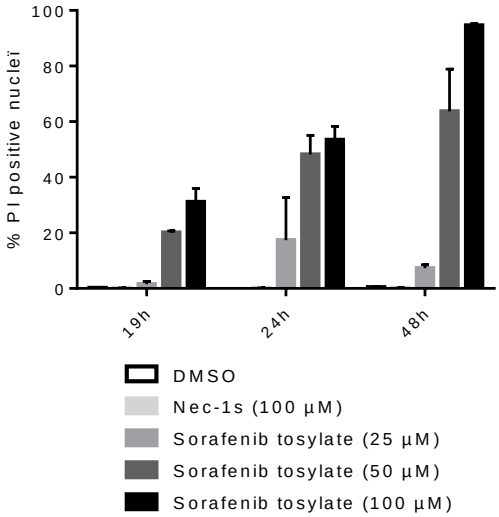
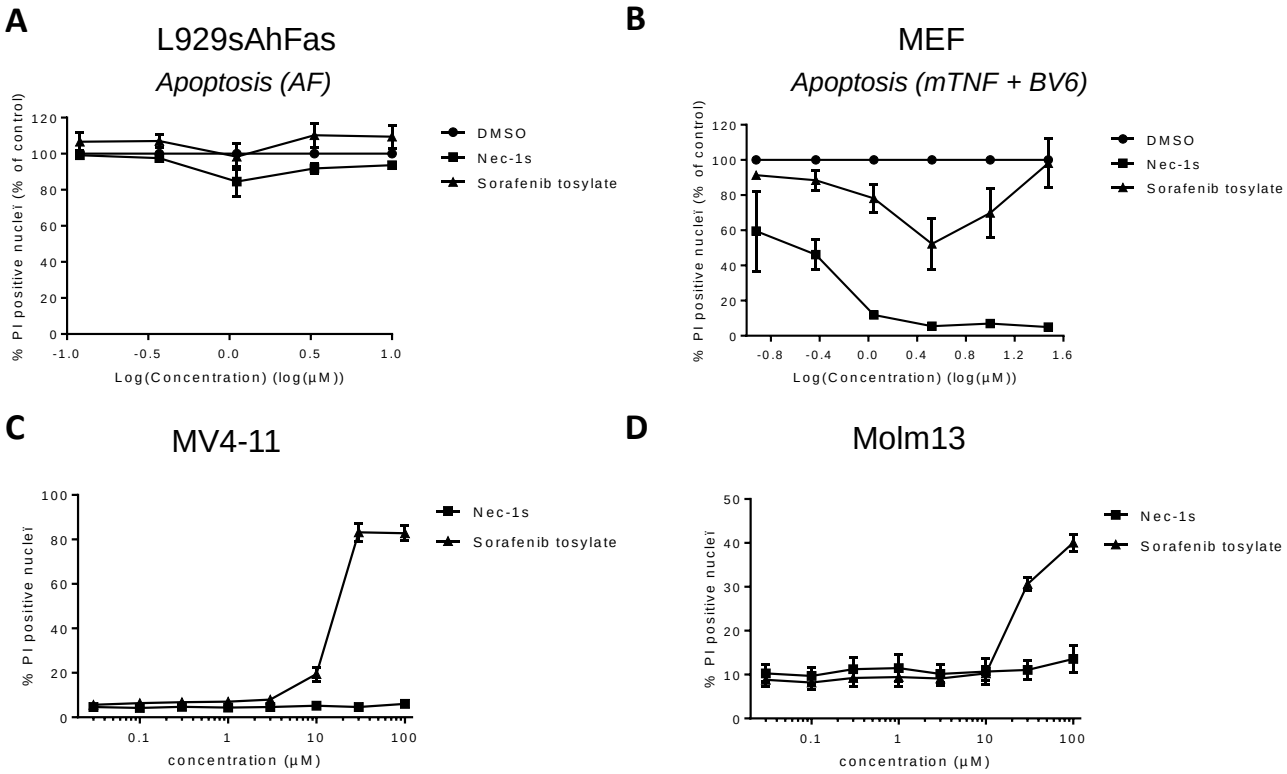


Supplementary Figures

Supplementary Figure S3.

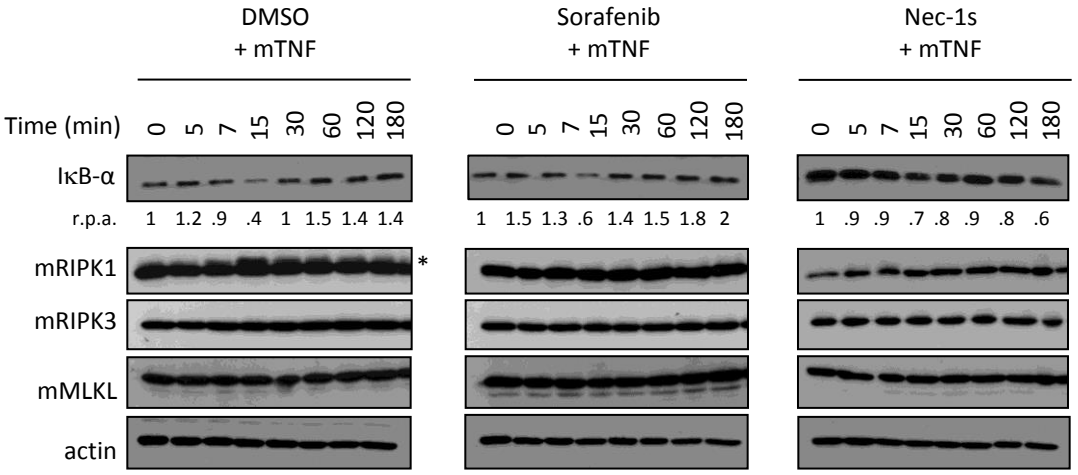


Supplementary Figure S4.

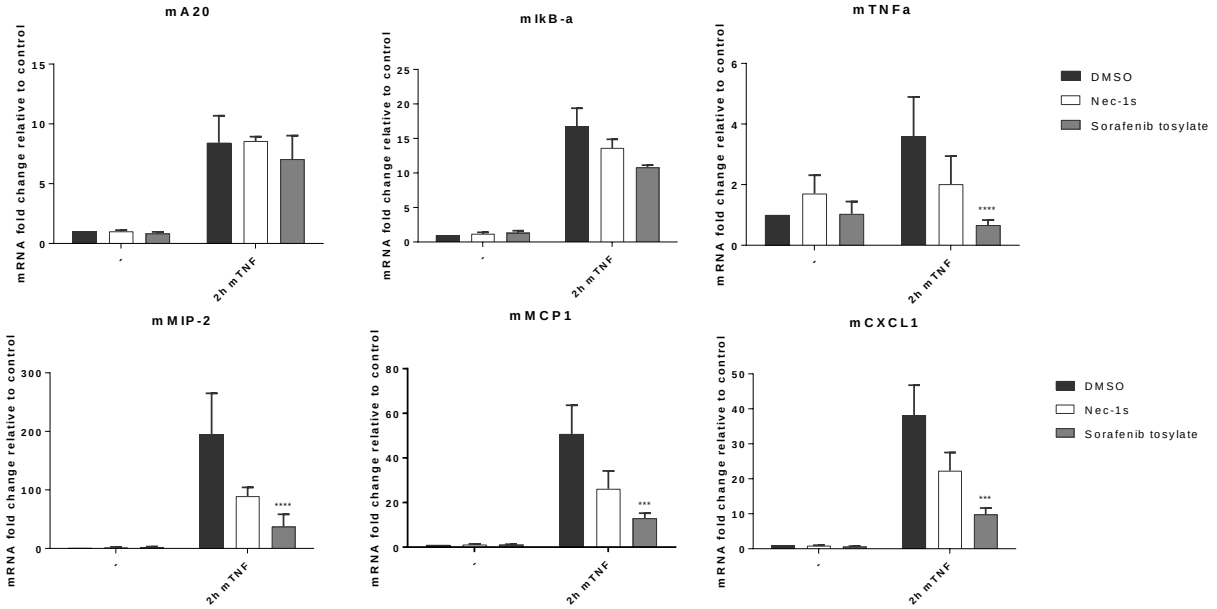


Supplementary Figures

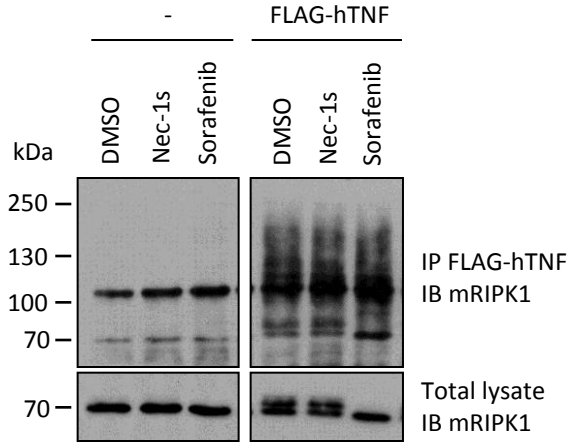
Supplementary Figure S5.



Supplementary Figure S6.



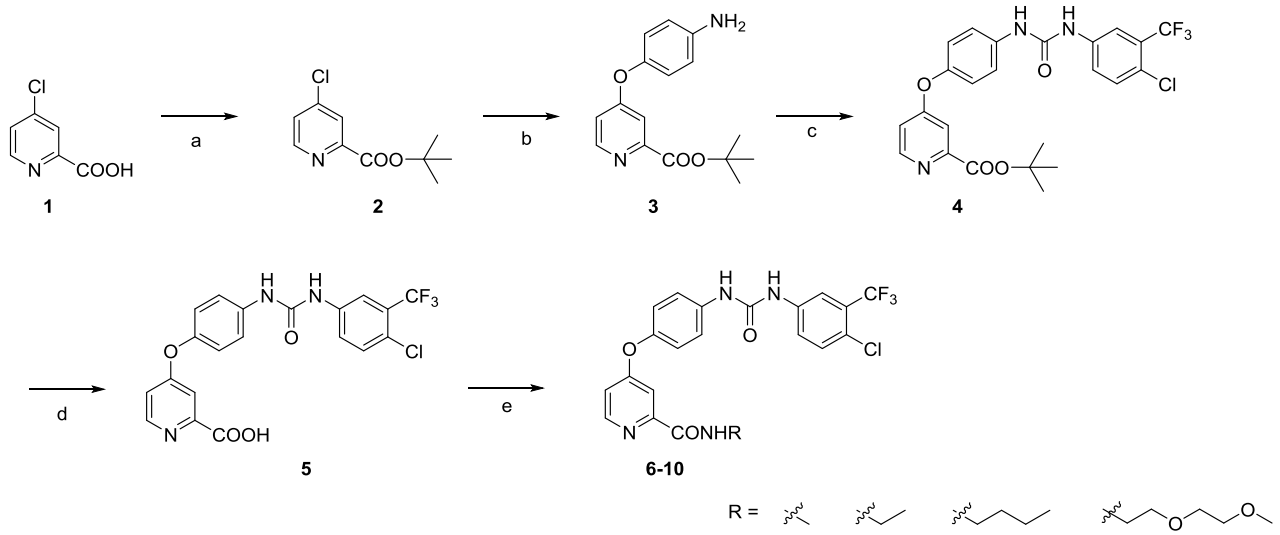
Supplementary figure S7.

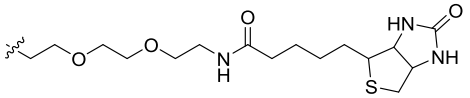


Supplementary Figures

Supplementary Figure S8.

A

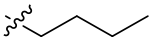
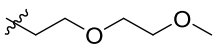
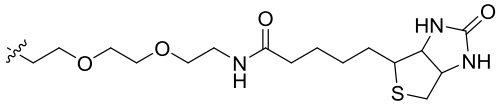




Reagents and conditions:

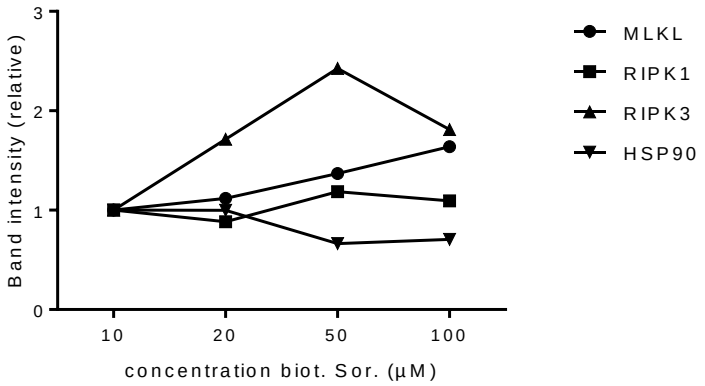
a: 1. $SOCl_2$, DMF, reflux, 2h;
2. *tert.*-BuOH, pyridine, DCM, -40°C to 50°C, 16h;
b: 1. *p*-aminophenol, *tert.*-BuOK, DMF, rt, 0.5h;
2. *tert.*-butyl 4-chloropicolinate, K_2CO_3, 80°C, 2h;
c: 4-chloro-3-(trifluoromethyl)phenylisocyanate, DCM, rt, 16h;
d: TFA, triethylsilane, DCM, 50°C, 16h
e: Primary amine analogue, HATU, DIPEA

B

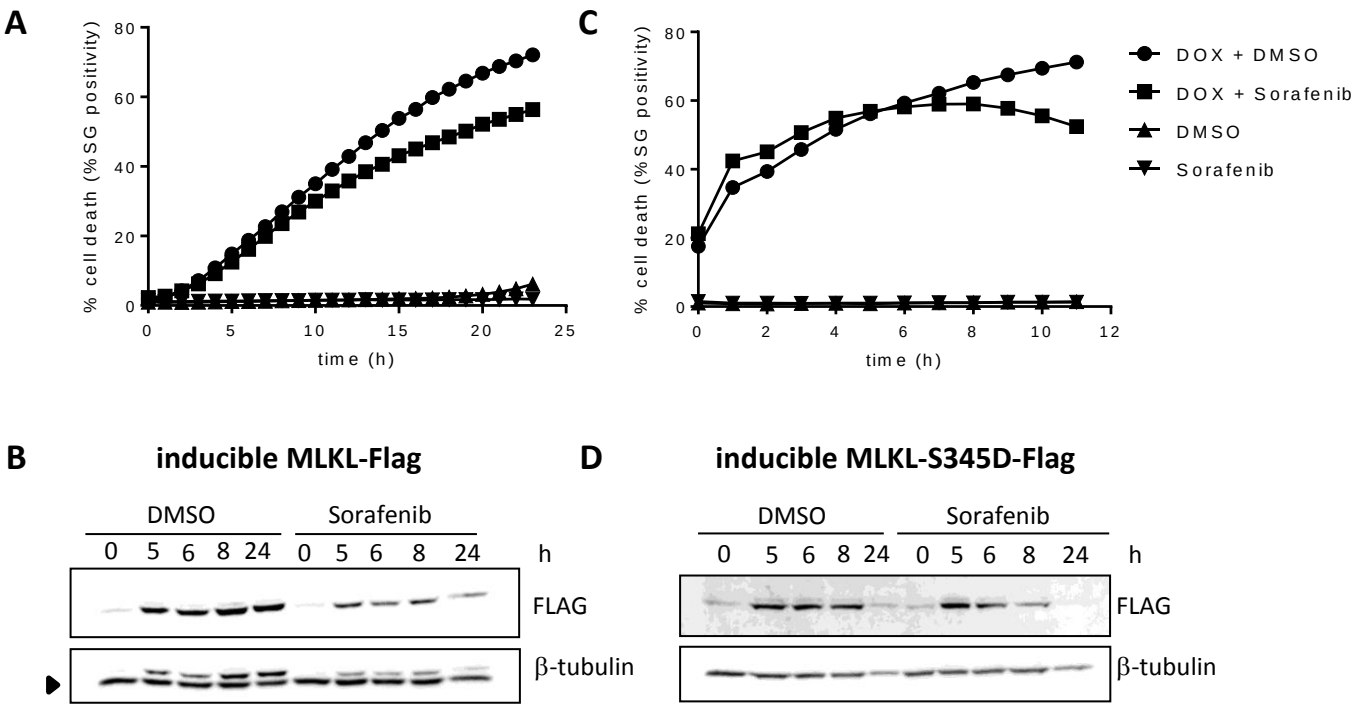
Compound	R	IC_{50} (µM)	
		-1h	-24h
6		1.29	1.42
7		2.24	>10
8		4.65	>10
9		1.50	n/a
10		n/a	>10

Supplementary Figures

Supplementary Figure S9.

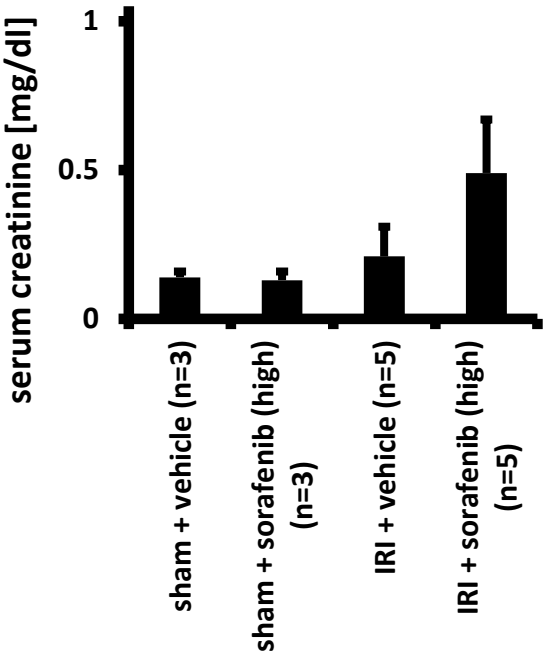


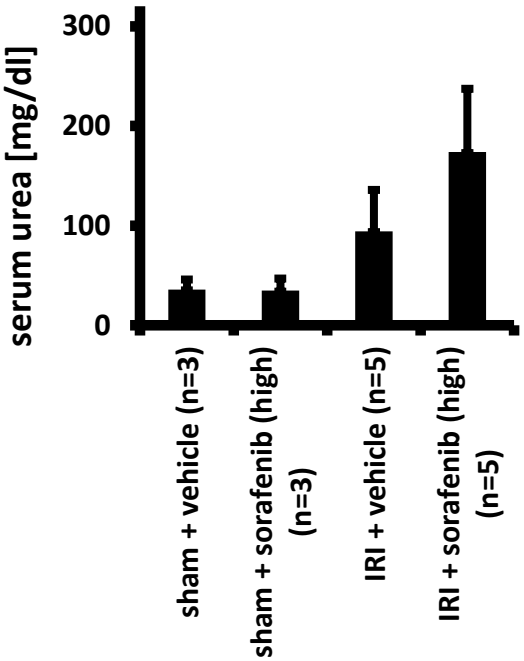
Supplementary Figure S10.



Supplementary Figures

Supplementary Figure S11.





Target family	Compound	Known targets	Cell death *TNF (POC)*	Validation screen *IC50 (μM) (TNF)*	Cell death *TNF/Taki (POC)*
Serine/threonine protein kinases					
RAF	Sorafenib tosylate	C-RAF*, B-RAF*, B-rafV600E*, PDGFRβ, VEGFR 1/2/3, c-Kit, FGFR1, RET, Flt3	41.5	3.25	11.8
Mitogen-actived protein kinases (MAP kinases)					
MEK	PD-98059	MEK1*, MEK2*, HPGD	70.9	NA	98.9
	U-0126	MEK1*, MEK2*, AP-1, STK33	69.7	NA	98.7
Receptor tyrosine kinases					
EGFR	AG-494	EGFR (Erb-B2)*, PDGFR, CDK2, POL E, JMJD2E	58.6	32.26	95.8
VEGFR	SU 4312	VEGFR1/2 (Flk1, Flg)*, PDGFR-β, NOS, ALDH1A1	69.6	26.41	96.8
PDGFR	AG-1296	PDGFRβ*, FGFR, c-Kit	77.6	33.24	93.6
	TYRPHOSTIN 9	PDGFR*, CRAC channel, EGFR	41.8	4.45	95.8
Non-receptor tyrosine kinases					
BCR-ABL	Imatinib mesylate	BCR-ABL*, c-Kit, RET, TrkA, MCSF-1R, PDGFRα/β, DDR1, ABL1	63.9	NA	96.1
JAK	AG-490	JAK1/2*, EGFR (Erb-B2)*, POL E, HADH2	74.2	87.27	97.3

Supplementary table 1. A selection of compounds from the screening assay on L929 cells that protect against necroptosis. Table with a selection of compounds (10 μM) from the cellular screening assay on L929sAhFas cells (Figure 1A-B). Compounds (10 μM) with < 80% cell death (POC) were respectively classified as protective compounds. POC = percent of control. * = primary target. Compound targets were identified using PubChem databank and DrugBank databank. Protective compounds were validated by analysis of a dose response and IC50 calculation. NA = not applicable in the condition of this validation assay.

Target family	Compound	Known targets	cell death *TNF (POC)*	cell death *TNF/Taki (POC)*
Serine/threonine protein kinases				
GSK	Kenpaullone	GSK-3β*, CDK1/Cyclin B, CDK2/cyclin A; E, CDK5/p25, c-Src, CK2, ERK1/2, Lck	162.2	99.9
Mitogen-actived protein kinases (MAP kinases)				
ERK	5-Iodotubercidin	ERK2*, PKA, ADK, CSNK1A1 & CSNK2A1, IRK	228.6	100.9
Receptor tyrosine kinases				
PDGFR	SU11652	PDGFRβ*, Flk-1(VEGFR2), FGFR1, Kit family members, EGFR	194.4	104.0
Non-receptor tyrosine kinases				
Src	PP2	P56lck*, p59fynT*, Hck*, c-Src*, TGF-β1R, CSK, EGFR	127.4	100.2

Supplementary table 2. A selection of compounds from the screening assay on L929 cells that sensitize for necroptosis. Table with a selection of compounds from the cellular screening assay on L929sAhFas cells (FIgure 1A-B). Compounds with > 120% cell death (POC) were classified as sensitizing compounds. POC = percent of control. * = primary target. Compound targets were identified using PubChem databank and DrugBank databank.

Target family	Compound	Known targets	cell death *TNF (POC)*	cell death *TNF/Taki (POC)*
Serine/threonine protein kinases				
PI3K	3-Methyladenine	class I & II & III PI3K* (a.o. Vps34)	88.7	101.5
	LY 294002	PI3Kα,β,δ*, CK2, PIM1, BET	85.7	99.2
	Wortmannin	PI3K*, PI4K, DNA-PK, ATM, MLCK, ATR	99.4	100.8
	Quercetin·2H2O	PI3K*, PIPK, F-ATPase, cAMP & cGMP PDE, PKC, activator of SIRT1, FAS, RECQ1, HADH2	90.4	98.5
Akt/PKB	Triciribine	Akt-1/2/3*, DNA synthesis inhibition, HIV-1	83.6	98.0
	BML-257	AKT1 translocation inhibitor*, HCV NS5B RdRp	91.3	99.7
GSK	Indirubin	GSK-3β*, CDK1/Cyclin B, CDK2/cyclin A;E, CDK4/cyclin D1, CDK5/p35, AHR ligand	91.7	99.1
IRAK	AG-126	IRAK*, ALDH1A1	94.7	99.4
MLCK	ML-7·HCl	MLCK*, PKC, PKA	90.2	99.4
	ML-9·HCl	MLCK*, PKA, PKC, hGEM, hPIM1	84.8	99.8
ROCK	Rockout	ROCK1*, ROCK2*, PRK2, MSK-1, PKA	106.0	99.0
	Y-27632·2HCl	ROCK1 (p160ROCK)*, ROCK2, Prkce, PKC, PKA, PRK2	93.3	98.6
Mitogen-actived protein kinases (MAP kinases)				
p38	SB-202190	p38α *, p38β*, EGFR	110.1	96.3
	SB-203580	p38α/β/β2*, SAPK3/4, RAF1, JNK2-α1-2/β1-2, ALK 5	107.6	99.6
RAF	GW 5074	c-Raf1*, CDK1/2, c-src, ERK2, MEK, p38, Tie2, VEGFR2, c-fms	90.0	99.1
	ZM 336372	c-Raf*, B-RAF	81.9	99.4
Receptor tyrosine kinases				
EGFR	Tyrphostin AG112	EGFR*, PLK1/3, ULK3, STK17A(DRAK1), MNK1, MEKK3, MNK2, BMX(ETK)	89.4	98.7
	BML-265	EGFRK*	118.4	99.6
	Erbstatin analog	EGFRK*	83.3	99.4
	Lavendustin A	EGFRK*, $p60^{c\text{-}src}$, $p56^{lck}$, c-erb B-2, PKA/C	85.9	100.0
	RG-14620	EGFRK*	95.9	99.8
	TYRPHOSTIN 23	EGFRK*, L3MBTL1, ALDH1A1, JMJD2E	88.9	100.0
	TYRPHOSTIN 25	EGFRK*, HADH2, POLK, JMJD2E	90.0	100.0
	TYRPHOSTIN 46	EGFRK*, $p56^{lck}$, PDGFR, POL K, HADH2, JMJD2E	97.8	99.8
	TYRPHOSTIN 47	EGFRK*, PDGFR, $p210^{bcr\text{-}abl}$, POL B/E/I, ALDH1A1, JMJD2E	93.0	100.1
	TYRPHOSTIN 51	EGFRK*	116.5	100.6
	TYRPHOSTIN AG 1478	EGFRK*, MNK1, $p60^{c\text{-}src}$, v-Abl, FBPase	84.2	98.7
	AG-825	HER2*, HER1, PDGFR	80.1	99.4
VEGFR	SU1498	VEGFR2 (Flk1)*, HER2 kinases, PDGFR	91.7	99.2
PDGFR	AG-370	PDGFR*	86.0	99.7
	TYRPHOSTIN AG 1295	PDGFRβ*, VEGFR2, Flt3	93.6	100.1
IRK	HNMPA	IRK*	80.3	100.2
Non-receptor tyrosine kinases				
BTK	LFM-A13	BTK*, Plk1	93.5	100.1
	Terreic acid	BTK*, MurA	103.9	99.1
Src	PP1	P56lck*, p59fynT*, Hck*, c-Src*, TGF-β1R, EGFRK, JAK2, ZAP-70	113.7	100.0
JAK	ZM 449829	JAK3*, EGFR, JAK1, CDK4	87.3	99.6
tyrosine kinases	Genistein	tyrosine kinases*, topoisomerase-II, CLK1, EGFR, hERα/β, hAOX	86.1	99.3
	TYRPHOSTIN AG 1288	tyrosine kinases*, guanylyl cyclase	81.1	99.7

Supplementary table 3. A selection of compounds, from the screening assay on L929 cells, that have no effect on necroptosis. Table with a selection of compounds from the cellular screening assay on L929sAhFas cells (figure 1A-B). Compounds with < 80% cell death (POC) and > 120% cell death (POC) were respectively classified as protective or sensitizing compounds. POC = percent of control. * = primary target. Compound targets were identified using PubChem databank and DrugBank databank.

				IC50 (μM)	
Species	**Cell type**	**Pathway**	**Stimulus**	**Sorafenib**	**Nec-1s****
Murine	**L929sAhFas**	**Necroptosis**	**mTNF**	1.27 ± 0.90	0.24 ± 0.12
		Apoptosis	**Anti-Fas**	-	-
	MEF	**Necroptosis**	**mTNF + BV6 + zVAD**	3.48 ± 1.59	0.63 ± 0.25
		Apoptosis	**mTNF + BV6**	2.20 ± 0.47*	0.38 ± 0.05*
Human	**Jurkat FADD$^{-/-}$**	**Necroptosis**	**hTNF**	14.37 ± 1.85	0.32 ± 0.11
	HT29	**Necroptosis**	**hTNF + BV6 + zVAD**	11.51 ± 3.17	0.11 ± 0.02
	MV4-11	**Necroptosis**	**BV6 + zVAD**	-	0.15 ± 0.01
	Molm13	**Necroptosis**	**BV6 + zVAD**	≤ 0.03	0.28 ± 0.17

Supplementary table 4. Sorafenib inhibits TNF-induced RIPK1-dependent cell death in both murine and human cell lines. Summary table of IC50 values (μM) of figure 2 for inhibition of necroptosis/apoptosis in both murine and human cell lines. Data were normalized to DMSO-treated control cells and represent the mean value ± S.E.M. of three independent experiments (* = duplicates). Toxic concentrations were removed from the analysis. ** = in HT-29 cells, Nec-1 was used in stead of Nec-1s.