Human gene name	Fly gene name	Fly geneID	Fly genotype
AAK1	Nak	CG10637	w[1118]; PBac{w[+mC]=WH}Nak[f04720]
ABL	Abl	CG4032	Abl[2]/TM6B, Tb[1]
ACVR1	sax	CG1891	y[1] w[*]; sax[5]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
ACVR2B	put	CG7904	ry[506] P{ry[+t7.2]=PZ}put[10460]/TM6B, Tb[1]
ADCK1	CG3608	CG3608	w[1118]; PBac{w[+mC]=WH}CG3608[f03261] CG4741[f03261]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
ADCK5	CG7616	CG7616	y[1] w[*]; P{w[+mC]=EP}CG7616[G14668]
AKT1	Akt1	CG4006	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Akt1[EY10012]/TM6B, Tb[1]
ALK	Alk	CG8250	w[1118]; Mi{ET1}Alk[MB06458]
ATM	tefu	CG6535	w[*]; P{ry[+t7.2]=neoFRT}82B tefu[atm-6] e[1]/TM6B, Tb[1]
ATR	mei-41	CG4252	mei-41[RT1] f[1]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
AURKA	aur	CG3068	aur[87Ac-3]/TM6B, Tb[1]
BMPR1A	tkv	CG14026	tkv[8] cn[1] bw[1] sp[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
BMPR2	wit	CG10776	bw[1]; wit[A12] st[1]/TM6B, Tb[1]
BRAF	phl	CG2845	phl[7]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
BRD3	fs(1)h	CG2252	w[67c23] P{w[+mC]=lacW}fs(1)h[G0495]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
BRSK1	sff	CG6114	w[1118]; Mi{ET1}sff[MB06603]
BUB1	Bub1	CG14030	w[1118]; PBac{w[+mC]=PB}Bub1[c04512]
CAMK1D	CaMKI	CG1495	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CaMKI[EY07197]
CAMK2D	CaMKII	CG18069	y[1] w[1118]; P{w[+mC] y[+mDint2]=EPgy2}CaMKII[EY14097]
CASK	CASK	CG6703	w[*]; Df(3R)caki[X-313], CASK[X-313]/TM6B, Tb[+]
CDC42BPA	gek	CG4012	P{ry[+t7.2]=PZ}gek[09373] cn[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
CDC7	CG5790	CG5790	w[1118]; PBac{w[+mC]=WH}CG5790[f04763]
CDC7	l(1)G0148	CG32742	w[67c23] P{w[+mC]=lacW}l(1)G0148[G0148]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
CDK1	cdc2	CG5363	cdc2[E1-23] b[1] pr[1] cn[1]
CDK11B	Pitslre	CG4268	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Pitslre[EY22469]/TM6B, Tb[1]
CDK12	Cdk12	CG7597	y[1] w[67c23]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}Cdk12[KG05512] ry[506]/TM6B, Tb[1]
CDK14	Eip63E	CG10579	w[*]; Eip63E[81]/TM6B, Tb[1]
CDK2	cdc2c	CG10498	w[*]; cdc2c[2]/TM6B, Tb[1]
CDK4/6	Cdk4	CG5072	w[1118]; P{w[+mC]=lacW}Cdk4[s4639]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
CDK8	Cdk8	CG10572	y[1] w[1118]; PBac{w[+mC]=5HPw[+]}Cdk8[A162]/TM6B, Tb[1]
CDK9	Cdk9	CG5179	w[1118]; PBac{w[+mC]=WH}Cdk9[f05537]
CHEK1	grp	CG17161	P{ry[+t7.2]=PZ}grp[06034] cn[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
CHUK	ird5	CG4201	P{ry[+t7.2]=Dipt2.2-lacZ}3, ird5[1] ca[1]/TM6B, Tb[1]
CIT	sti	CG10522	y[1]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}sti[KG01697] ry[506]/TM6B, Tb[1]
CSK	csk	CG42317	w;;FRT82B.dCskj1D8/TM6B, Tb[1]
CSNK1A1	Ckialpha	CG2028	w[67c23] P{w[+mC]=lacW}Ckialpha[G0492]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
CSNK1E	dco	CG2048	y[1] w[*]; P{w[+mC]=lacW}dco[j3B9]/TM6B, Tb[1]
CSNK1G3	gish	CG6963	y[1]; ry[506] P{y[+mDint2] w[BR.E.BR]=SUPor-P}gish[KG03891]/TM6B, Tb[1]
CSNK2A1	CkIIalpha	CG17520	y[1] w[*]; CkIIalpha[Tik]/TM6B, Tb[1]
DDR2	Ddr	CG33531	y[1] w[*]; Mi{y[+mDint2]=MIC}Ddr[MI04117]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
DGKE	Dgkepsilon	CG8657	cn[1] P{ry[+t7.2]=PZ}ox[1] Dgkepsilon[ox-1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
DGKZ	rdgA	CG42667	rdgA[KS60]
DYRK1B	mnb	CG42273	y[1] w[67c23] P{w[+mC] y[+mDint2]=EPgy2}mnb[EY14320] CG12985[EY14320]
DYRK4	smi35A	CG4551	y[1] w[*]; Mi{y[+mDint2]=MIC}smi35A[MI04771]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
EGFR	Egfr	CG10079	cn[1] Egfr[f2] bw[1] sp[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
EIF2AK3	PEK	CG2087	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}PEK[EY09578]
EPHB1	Eph	CG1511	y[1]; Mi{y[+mDint2]=MIC}Eph[MI05205]
ERN1	Ire1	CG4583	w[1118]; PBac{w[+mC]=WH}Ire1[f02170]/TM6B, Tb[1]
ETNK1	eas	CG3525	w[1118] eas[alaE13]
FER	Fps85D	CG8874	w[*]; P{w[+mC]=lacW}Fps85D[X42]/TM6B, Tb[1]
FGFR	htl	CG7223	w[*]; htl[AB42]/TM6B, Tb[1]
FGFR	btl	CG32134	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}btl[EY01638]/TM6B, Tb[1]
FLT1	Pvr	CG8222	w[1118]; PBac{w[+mC]=PB}Pvr[c02195]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
FRK	Src42A	CG44128	w[1118]; Src42A[myri]
FYN, SRC	Src64B	CG7524	w[1118]; PBac{w[+mC]=PB}Src64B[c04709]/TM6B, Tb[+]
GAK	aux	CG1107	w[*]; aux[L7]/TM6B, Tb[1]
GRK5	Gprk2	CG17998	ry[506] P{ry[+t7.2]=PZ}Gprk2[06936] CG11337[06936]/TM6B, Tb[1]
GSK3A	sgg	CG2621	sgg[M11] w[*] f[36a]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
GSK3B	gskt	CG31003	y[1] w[*]; Mi{y[+mDint2]=MIC}gskt[MI04964]/TM6B, Tb[1]
GUCY2D	CG34357	CG34357	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CG34357[EY21024]/TM6B, Tb[1]
HIPK2	hipk	CG17090	w[1118]; P{w[+mGT]=GT1}hipk[BG00855]/TM6B, Tb[1]
ILK	Ilk	CG10504	mwh[1] Ilk[1] red[1] e[4]/TM6B, Tb[1]
INSR	InR	CG18402	ry[506] P{ry[+t7.2]=PZ}InR[05545]/TM6B, Tb[1]
IRAK4	pll	CG5974	e[1] pll[2] ca[1]
JAK	hop	CG1594	hop[2]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
JNK	bsk	CG5680	bsk[1] cn[1] bw[1] sp[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO

Supplementary Table 1: Kinase-mutated flies.

Gene names, corresponding CG numbers, and fly genotypes are shown for each kinase. Human orthologs of fly genes were predicted by DIOPT (http://www.flyrnai.org/cgi-bin/DRSC_orthologs.pl).

Human gene name	Fly gene name	Fly geneID	Fly genotype
KDR	Cad96Ca	CG10244	w[1118]; P{w[+mC]=XP}Cad96Ca[d07355]/TM6B, Tb[1]
KSR	ksr	CG2899	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}ksr[EY01688] Hcs[EY01688]/TM6B, Tb[1]
LATS1	wts	CG12072	w[*]; wts[x1] P{ry[+t7.2]=neoFRT}82B/TM6B, Tb[1]
LIMK1	LIMK1	CG1848	y[1] w[67c23] P{w[+mC] y[+mDint2]=EPgy2}LIMK1[EY08757]
LKB1	Lkb1	CG9374	w[1118]; P{w[+mC]=EP}Lkb1[G5285]
LRRK1	Lrrk	CG5483	w[*]; Lrrk[ex1]/TM6B, Tb[1]
MAP2K4	Mkk4	CG9738	w[1118]; PBac{w[+mC]=RB}Mkk4[e01485]/TM6B, Tb[1]
MAP2K6	lic	CG12244	y[1] w[67c23] P{y[+m8]=Mae-UAS.6.11}lic[GG01785]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
MAP2K7	hep	CG4353	w[*] hep[r75]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
MAP3K13	wnd	CG8789	y[1] w[*]; Mi{PT-BM.2}wnd[MI00494-BM.2]/TM6B, Tb[1]
MAP3K15	Pk92B	CG4720	y[1] w[*]; Mi{y[+mDint2]=MIC}Pk92B[MI02915]/TM6B, Tb[1]
MAP3K4	Mekk1	CG7717	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Mekk1[EY11461]
MAP3K7	Tak1	CG18492	w[*] Tak1[179]
MAP3K7	Takl1	CG31421	w[1118]; PBac{w[+mC]=PB}Syp[c04375] Takl1[c04375]/TM6B, Tb[1]
MAP3K7	Takl2	CG4803	w[1118]; P{w[+mC]=XP}Takl2[d10454]
MAP3K9	slpr	CG2272	w[1118] Mi{ET1}slpr[MB03655]
MAP4K3	hppy	CG7097	w[*]; P{w[+mW.hs]=FRT(w[hs])}G13 P{w[+mC]=lacW}hppy[SH1261]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
MAP4K4	msn	CG16973	w[*]; msn[102] P{ry[+t7.2]=neoFRT}80B/TM6B
MAPK1	rl	CG12559	y[1] w[*]; Mi{y[+mDint2]=MIC}rl[MI07033]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
MAPK11	p38c	CG33338	y[1] w[67c23]; ry[506] P{y[+mDint2] w[BR.E.BR]=SUPor-P}p38c[KG05834]/TM6B, Tb[1]
MAPK14	Mpk2	CG5475	w[*]; P{ry[+t7.2]=neoFRT}82B Mpk2[1]
MAPK14	p38b	CG7393	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}p38b[EY11174]
MAPK15	Erk7	CG32703	y[1] w[*] Mi{y[+mDint2]=MIC}Erk7[MI05843]
MAPKAPK3	MAPk-Ak2	CG3086	w[*] P{w[+mC]=EP}MAPk-Ak2[G265]
MARK3	par-1	CG8201	y[1] w[67c23]; P{w[+mC]=lacW}par-1[k06323]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
MAST1	CG6498	CG6498	w[1118]; Mi{ET1}CG6498[MB04862]
MASTL	gwl	CG7719	w[1118]; P{w[+mC]=EP}gwl[EP515]/TM6B, Tb[1]
MEK	Dsor1	CG15793	y[1] w[*] Dsor1[LH110] P{w[+mW.hs]=FRT(w[hs])}101/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
MKNK1	Lk6	CG17342	w[1118]; Lk6[2]/TM6B, Tb[1]
MST4	GckIII	CG5169	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}GckIII[EY05076]
MTOR	Tor	CG5092	y[1] w[*]; Tor[DeltaP] P{ry[+t7.2]=neoFRT}40A/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
MUSK	Nrk	CG4007	y[1] w[*]; P{w[+mC]=EP}Nrk[G2759] CG34439[G2759]
MYLK2	Strn-Mlck	CG44162	w[1118]; PBac{w[+mC]=PB}Strn-Mlck[c02860]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
MYLK3	sqa	CG42347	w[1118]; PBac{w[+mC]=WH}sqa[f01512]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
MYO3A	ninaC	CG5125	w[*]; ninaC[5]
NCK1	dock	CG3727	P{ry[+t7.2]=PZ}dock[04723] cn[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
NEK11	png	CG11420	y[1] png[1058] w[*]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
NIM1	CG4629	CG4629	y[1] w[*]; Mi{y[+mDint2]=MIC}CG4629[MI02585]
NLK	nmo	CG7892	w[*]; nmo[DB] P{ry[+t7.2]=neoFRT}80B/TM6B, Tb[1]
NPR1	CG3216	CG3216	w[1118]; Mi{ET1}CG3216[MB07455]
NPR1	Gyc76C	CG42636	y[1] w[1118]; PBac{w[+mC]=5HPw[+]}Gyc76C[A377]
NPR2	CG31183	CG31183	y[1] w[*]; Mi{y[+mDint2]=MIC}CG31183[MI02001]
NPR2	Gyc32E	CG33114	y[1] w[67c23]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}Gyc32E[KG06014]
NRBP1	Madm	CG1098	w[1118]; P{w[+mC]=EP}Madm[EP3137]/TM6B, Tb[1]
NUAK1	CG43143	CG43143	y[1] w[*]; Mi{y[+mDint2]=MIC}CG43143[MI04137]/TM6B, Tb[1]
PAK1	Pak	CG10295	Pak[6]/TM6B, Tb[1]
PAK3	Pak3	CG14895	y[1] w[*]; P{y[+m8]=Mae-UAS.6.11}Pak3[LA00012]
PAK7	mbt	CG18582	y[1] w[67c23] P{w[+mC] y[+mDint2]=EPgy2}mbt[EY08341]
PASK	Pask	CG3105	y[1] w[*]; Mi{y[+mDint2]=MIC}Pask[MI04252]
PDK3	Pdk	CG8808	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Pdk[EY01879]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PDPK1	Pdk1	CG1210	w[1118]; P{w[+mGT]=GT1}Pdk1[BG02759]
PIK3C2A	Pi3K68D	CG11621	w[1118]; Mi{ET1}Pi3K68D[MB08286] CG14131[MB08286]
PIK3CA	Pi3K92E	CG4141	w[1118]; Mi{ET1}Pi3K92E[MB06212]/TM6B, Tb[1]
PIK3R4	ird1	CG9746	y[1] w[*]; Mi{y[+mDint2]=MIC}ird1[MI05805]/TM6B, Tb[1]
PINK1	Pink1	CG4523	w[*] Pink1[B9]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
PITPNM2	rdgB	CG11111	y[1] w[67c23] P{w[+mC] y[+mDint2]=EPgy2}rdgB[EY20869] CG32625[EY20869]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
PKN2	Pkn	CG2049	P{ry[+t7.2]=PZ}Pkn[06736] cn[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PLK1	polo	CG12306	w[*]; P{w[+mC]=PTT-GC}polo[CC01326]/TM6B, Tb[1]
PLK4	SAK	CG7186	w[1118]; PBac{w[+mC]=PB}SAK[c06612]/TM6B, Tb[1]
PRKAA2	SNF1A	CG3051	SNF1A[1]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
PRKACA	Pka-C1	CG4379	Pka-C1[H2]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PRKACG	CG12069	CG12069	w[1118]; Mi{ET1}CG12069[MB10013]/TM6B, Tb[1]
PRKAR2A	Pka-R2	CG15862	y[1] w[*]; Mi{y[+mDint2]=MIC}Pka-R2[MI00092]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PRKCA	inaC	CG6518	w[*]; inaC[2]
PRKCA	Pkc53E	CG6622	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Pkc53E[EY14093]
PRKCD	Pkcdelta	CG42349	w[1118] PBac{w[+mC]=RB}Pkcdelta[e04408]

Supplementary Table 1, continued.

Human gene name	Fly gene name	Fly geneID	Fly genotype
PRKCE	Pkc98E	CG1954	w[1118]; PBac{w[+mC]=WH}Pkc98E[f06221]/TM6B, Tb[1]
PRKCI	aPKC	CG42783	y[1] w[67c23]; P{w[+mC]=lacW}aPKC[k06403]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PRKD1	PKD	CG7125	y[1] w[67c23]; Mi{ET1}PKD[MB00674]
PRKG1	CG4839	CG4839	y[1] w[*]; Mi{y[+mDint2]=MIC}CG4839[MI08552]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PRKG1	for	CG10033	y[1] w[*]; P{w[+mC]=UASp-YFP.RabX2.S21N}for[02]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PRKG2	Pkg21D	CG3324	w[1118]; Mi{ET1}Pkg21D[MB04805]
PRKX	Pka-C3	CG6117	y[1] w[*]; Mi{y[+mDint2]=MIC}Pka-C3[MI04599]/TM6B, Tb[1]
PRPF4B	CG7028	CG7028	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CG7028[EY11156]
PTK2	Fak	CG10023	y[1] w[67c23]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}Fak[KG00304]
PTK7	otk	CG8967	w[1118]; P{w[+mC]=EP}otk[EP2017]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
PXK	CG8726	CG8726	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CG8726[EY21837]
PXK	Slob	CG43756	w[*]; PBac{GAL4D,EYFP}Slob[PL00361] Myo28B1[PL00361] cn[1] bw[1]; PBac{GAL4D,EYFP}PL00361 P{w[+mW.hs]=FRT(w[hs])}2A P{ry[+t7.2]=neoFRT}82B
RET	Ret	CG14396	y[1] w[*]; Mi{y[+mDint2]=MIC}Ret[MI07200]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
RIOK3	CG3008	CG3008	y[1] w[1118]; P{w[+mC]=EP}CG3008[G18059]
ROCK1	rok	CG9774	y[1] w[1118] rok[2] P{ry[+t7.2]=neoFRT}19A/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
ROS1	sev	CG18085	w[1118] sev[14]; P{w[+mW.hs]=sev2}ch21
RPS6KA3	S6kII	CG17596	w[*] P{w[+mC]=EP}S6kII[G1845] CG17600[G1845]
RPS6KA5	JIL-1	CG6297	y[1]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}JIL-1[KG02848] ry[506]/TM6B, Tb[1]
RPS6KB1	S6k	CG10539	P{ry[+t7.2]=PZ}S6k[07084] ry[506]/TM6B, Tb[1]
RYK	dnt	CG17559	y[1] w[67c23]; P{y[+t7.7] w[+mC]=wHy}dnt[DG04604]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
RYK	drl	CG17348	w[1118]; drl[exc21]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
RYK	Drl-2	CG3915	w[1118]; P{w[+mGT]=GT1}Drl-2[BG02105]
SBK1	CG11221	CG11221	y[1] w[*]; Mi{y[+mDint2]=MIC}CG11221[MI03008]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
SBK2	CG4945	CG4945	w[1118]; PBac{w[+mC]=WH}CG4945[f02115]
SCYL1	yata	CG1973	y[1] w[67c23]; P{y[+t7.7] w[+mC]=wHy}yata[DG08312]/TM6B, Tb[1]
SCYL2	CG1951	CG1951	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CG1951[EY00129]
SCYL2	CG34356	CG34356	y[1] w[*]; Mi{y[+mDint2]=MIC}CG34356[MI08649]/TM6B, Tb[1]
SCYL3	CG1344	CG1344	w[1118]; P{w[+mC]=EP}CG1344[EP2646]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
SGK494	Pk17E	CG7001	y[1] w[67c23] P{w[+mC] y[+mDint2]=EPgy2}Pk17E[EY06723]
SIK2	Sik2	CG4290	P{w[+mC]=EP}Sik2[G366] w[*]
SIK3	Sik3	CG42856	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Sik3[EY14354]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
SMG1	nonC	CG32743	w[*] P{w[+mC]=EP}nonC[G1076]
SPEG	Unc-89	CG33519	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Unc-89[EY15484]
SPHK1	Sk2	CG32484	y[1] w[67c23]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}Sk2[KG05894] ry[506]
SRPK2	SRPK	CG8174	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}SRPK[EY03876]
SRPK3	srpk79D	CG11489	w[1118]; PBac{w[+mC]=PB}srpk79D[c00270]
STK10	slik	CG4527	y[1]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}slik[KG04837]
STK17A	Drak	CG32666	y[1] P{y[+mDint2] w[BR.E.BR]=SUPor-P}Drak[KG03058]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
STK3	hpo	CG11228	y[d2] w[1118] P{ry[+t7.2]=ey-FLP.N}2; P{ry[+t7.2]=neoFRT}42D hpo[KC202]/CyO, P{w[+mC]=GAL4-Kr.C}DC3, P{w[+mC]=UAS-GFP.S65T}DC7
STK32B	CG32944	CG32944	w[*]; P{w[+mW.hs]=FRT(w[hs])}2A PBac{GAL4D,EYFP}CG32944[PL00206] P{ry[+t7.2]=neoFRT}82B
STK36	fu	CG6551	fu[mH63]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
STK38	trc	CG8637	ru[1] jv[1] trc[1] ca[1]/TM6B, Tb[1]
STK39	fray	CG7693	y[1] w[*]; Mi{y[+mDint2]=MIC}fray[MI03454] CG7694[MI03454]/TM6B, Tb[1]
STYK1	CG3277	CG3277	y[1] w[*]; Mi{y[+mDint2]=MIC}CG3277[MI06697]
SYK	shark	CG18247	P{ry[+t7.2]=neoFRT}43D shark[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
TAF1	Taf1	CG17603	w[1118]; P{w[+mC]=EP}Taf1[EP421]/TM6B, Tb[1]
TAOK1	Tao	CG14217	w[1118] P{w[+mC]=EP}Tao[EP1455]
TBK1	ik2	CG2615	y[1] w[*]; ik2[5] dp[ov1] bw[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
TEC	Btk29A	CG8049	y[1] w[67c23]; P{w[+mC]=lacW}Btk29A[k00206]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
TESK2	cdi	CG6027	ry[506] cdi[R47]/TM6B, Tb[1]
TGFBR1	babo	CG8224	w[*]; babo[32]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
TIE1	Tie	CG7525	y[1] w[*]; Mi{y[+mDint2]=MIC}Tie[MI02904]/TM6B, Tb[1]
TIE1	tor	CG1389	vas[1] tor[1] cn[1] bw[1] sp[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
TLK2	tlk	CG34412	y[1] w[67c23] P{w[+mC] y[+mDint2]=EPgy2}Tlk[EY14954]/FM7c, P{w[+mC]=2xTb[1]-RFP}FM7c, sn[+]
TNK1	Ack-like	CG43741	w[1118]; Mi{ET1}Ack-like[MB05119]
TNK2	Ack	CG14992	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Ack[EY09374]
TRIB2	trbl	CG5408	y[1]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}trbl[KG02308] ry[506]/TM6B, Tb[1]
TRRAP	Nipped-A	CG33554	Nipped-A[NC186] cn[1] bw[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
TSSK1B	CG14305	CG14305	w[1118]; P{w[+mC]=EPg}CG14305[HP30350] CG14304[HP30350]
TTBK1	Asator	CG11533	y[1] w[67c23]; ry[506]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}Asator[KG05051]
TTK	ald	CG7643	w[*]; P{w[+mGS]=GSV1}ald[EP-M50.2]/TM6B, Tb[1]
TTN	bt	CG32019	w[1118]; bt[l-b]/ln(4)ci[D], ci[D] pan[ciD]
ULK1	Atg1	CG10967	w[1118]; P{ry[+t7.2]=PZ}Atg1[00305] ry[506]/TM6B, Tb[1]
ULK3	CG8866	CG8866	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CG8866[EY18321]/TM6B, Tb[1]
VRK3	CG8878	CG8878	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}CG8878[EY10775] Hen1[EY10775]
WEE1	wee	CG4488	w[1]; wee[ES1] cn[1]/CyO, P{w[+mC]=2xTb[1]-RFP}CyO
WNK1	Wnk	CG7177	y[1] w[67c23]; P{w[+mC] y[+mDint2]=EPgy2}Wnk[EY10165]/TM6B, Tb[1]

Supplementary Table 1, continued.

Chromosome X

Drugs			Gene symbol		*ptc>Ret*^{M955T} viability (%)			s.e.		
–	soraf	L15	Human	Fly	–	soraf	L15	–	soraf	L15
				control	3	18	20	1	1	4
Pro-target for sorafenib										
*	M		*SGK494*	*Pk17E*	19	67	43	4	5	18
Pro-targets for LS1-15										
*		M	*GSK3*	*sgg*	13	29	69	2	14	13
*		M	*NEK11*	*png*	26	35	63	8	4	7
*		M	*TLK2*	*tlk*	35	42	59	2	6	9
*		M	*ROS1*	*sev*	17	30	54	4	8	8
*		W	*BRD3*	*fs(1)h*	31	38	47	6	10	7
*		W	*CSNK1A1 (CK1a)*	*CkIalpha*	37	14	43	3	10	1
*		W	*PINK1*	*Pink1*	33	19	42	5	4	7
		W	*DYRK1A*	*mnb*	2	29	36	1	5	1
Pro-targets for both sorafenib and LS1-15										
*	S	S	*BRAF*	*phl*	100	90	96	0	7	4
*	S	S	*STK36 (FU)*	*fu*	76	93	88	9	7	13
*	S	S	*PRKAA2 (AMPK)*	*SNF1A*	29	86	81	3	9	10
*	M	M	*MEK*	*Dsor1*	78	55	80	6	3	20
*	M	M	*JAK*	*hop*	45	63	78	9	11	9
*	W	M	*TAOK1*	*Tao*	24	46	75	12	17	3
*	M	M	*MAP2K6 (MKK6)*	*lic*	36	54	75	10	8	13
*	W	M	*ROCK1*	*rok*	32	42	67	15	2	7
	M	M	*STK17A (DRAK1)*	*Drak*	14	64	65	9	9	6
*	M	M	*MAP2K7 (MKK7)*	*hep*	20	55	58	6	2	5
*	M	W	*ATR*	*mei-41*	10	61	39	3	6	1
	W	W	*CDC7*	*l(1)G0148*	0	24	21	0	4	1

Supplementary Table 2: Pro-targets of sorafenib [1] and LS1-15 [4].

A list of genes of which heterozygosity led to statistically significant increase in the survival of *ptc>dRet*^{M955T} flies in the presence of **1** or **4**. *ptc>dRet*^{M955T} flies were crossed to kinase-mutant flies, and the number of *ptc>dRet*^{M955T},*mutant*$^{-/+}$ adults was divided by that of total pupae to calculate percent viability. Viabilities of kinase-proficient controls differ between data sets for different chromosomes due to swapped genders of parent flies in the crosses (Supplementary Figs. 3b-h). W, M, and S indicate statistically significantly weak, modest, and strong effects, respectively: for genes on the X chromosome, weak (21-50% viability), moderate (51-80% viability), and strong effects (81-100% viability), respectively, and for genes on 2nd, 3rd, and 4th chromosomes, weak (51-70% viability), moderate (71-90% viability), and strong effects (91-100% viability), respectively. s.e., standard error for three experimental replicates. Asterisks: statistically significant change in % viability in the absence of drug treatment. –, soraf, and L15 indicate vehicle-, sorafenib [**1**]-, and LS1-15 [**4**]-treated flies, respectively.

Chromosomes 2, 3 and 4

Drugs				Gene symbol		*ptc>Ret*^{M955T} viability (%)			s.e.		
−	soraf	L15		Human	Fly	−	soraf	L15	−	soraf	L15
					control	28	48	52	3	5	9
Pro-targets for sorafenib											
	M			*KSR2*	*ksr*	51	78	69	8	2	13
	M			*STK24 (MST3)*	*GckIII*	61	73	67	12	7	10
*	M			*IKBKB*	*ird5*	47	89	57	5	2	9
*	M			*STK39 (PASK)*	*fray*	54	71	52	3	8	6
	M			*ABL1, ABL2*	*Abl*	18	79	42	6	3	6
	M			*MAP3K4 (MTK1)*	*Mekk1*	12	72	38	4	5	5
Pro-targets for LS1-15											
*		S		*LATS1 (WARTS)*	*wts*	70	58	96	10	4	4
		M		*KDR*	*Cad96Ca*	44	46	89	13	5	1
		M		*PRKCA*	*Pkc53E*	55	51	87	11	5	2
		M		*TNK1*	*Ack-like*	42	55	87	6	4	2
*		M		*ADCK5*	*CG7616*	84	63	86	3	7	3
*		M		*CDK2*	*cdc2c*	78	54	85	4	3	7
		M		*CSNK1G3*	*gish*	58	51	83	12	10	1
*		M		*CAMK1D*	*CaMKI*	56	43	83	4	3	3
*		M		*RYK*	*Drl-2*	53	58	83	13	5	2
*		M		*RPS6KA5 (MSK1)*	*JIL-1*	75	32	83	5	11	5
*		M		*CDK1*	*cdc2*	58	56	82	7	16	1
*		M		*PAK1*	*Pak*	65	30	81	3	5	2
*		M		*FER*	*Fps85D*	72	50	81	2	13	7
		M		*NPR1*	*CG3216*	37	39	80	2	10	4
*		M		*SYK*	*shark*	63	48	80	13	7	10
		M		*PTK7*	*otk*	41	64	80	8	2	8
*		M		*CDK4/6*	*Cdk4*	50	53	79	6	12	3
*		M		*TRIB2*	*trbl*	38	44	77	6	6	7
*		M		*RYK*	*dnt*	33	60	75	3	6	2
*		M		*LKB1*	*Lkb1*	61	61	74	8	7	2
*		M		*MASTL (GWL)*	*gwl*	61	38	74	7	5	8
*		M		*ACVR1*	*sax*	35	52	73	1	2	2
*		M		*VRK3*	*CG8878*	43	46	73	2	2	1
*		M		*CIT*	*sti*	58	43	72	9	8	4
*		M		*PLK4*	*SAK*	64	39	72	7	5	6
*		M		*CDK12*	*Cdk12*	66	47	72	2	2	6
*		M		*NLK*	*nmo*	69	45	71	3	0	7
		W		*MTOR*	*Tor*	43	46	70	9	9	5
*		W		*CASK*	*CASK*	48	53	68	3	9	3
		W		*PLK1*	*polo*	39	24	68	9	12	5
*		W		*RPS6KB1 (p70S6K)*	*S6k*	61	39	66	9	7	1
		W		*MINK1*	*msn*	42	34	66	6	4	1
*		W		*DDR2*	*Ddr*	49	37	65	6	12	4
		W		*ATM*	*tefu*	29	61	62	4	2	1

Supplementary Table 2, continued.

Chromosomes 2, 3 and 4 (continued)

Drugs			Gene symbol		*ptc>Ret*^{M955T} viability (%)			s.e.		
–	soraf	L15	Human	Fly	–	soraf	L15	–	soraf	L15
				control	28	48	52	3	5	9
Pro-targets for both sorafenib and LS1-15										
*	S	S	*TGFBR1 (ALK5)*	*babo*	98	96	100	2	2	0
*	M	S	*LRRK1*	*Lrrk*	94	87	98	2	3	1
*	M	S	*MAP4K3 (GLK)*	*hppy*	95	89	97	1	5	1
*	M	S	*MUSK*	*Nrk*	77	79	95	5	5	3
*	W	S	*DYRK4*	*smi35A*	64	70	95	10	8	3
*	S	S	*PKN*	*Pkn*	88	93	94	2	2	3
*	M	S	*SRPK*	*SRPK*	77	89	94	7	11	4
*	M	S	*PRKD1*	*PKD*	83	84	94	4	3	1
	M	S	*PRKG1*	*CG4839*	60	74	93	14	2	2
*	M	S	*TNK2*	*Ack*	70	71	93	1	6	4
*	M	S	*ILK*	*Ilk*	85	78	93	1	5	6
	M	S	*CDC42BPA*	*gek*	47	81	92	8	2	1
*	W	S	*CHEK1*	*grp*	78	67	92	5	4	3
	M	S	*MAP3K13 (LZK)*	*wnd*	33	82	92	5	5	4
*	M	S	*SRPK*	*srpk79D*	88	87	92	6	4	4
*	M	S	*FRK*	*Src42A*	88	80	91	6	9	5
*	M	S	*JNK*	*bsk*	76	88	91	6	3	5
*	M	S	*EPH*	*Eph*	72	64	91	2	4	3
*	W	S	*AKT1*	*Akt1*	51	69	91	7	3	2
*	M	M	*PRKACA (PKA)*	*Pka-C1*	56	71	90	4	4	7
*	M	M	*TTN*	*bt*	78	82	90	6	4	4
*	M	M	*BUB1*	*Bub1*	45	80	90	4	13	2
*	W	M	*SPHK2 (SK2)*	*Sk2*	67	68	89	1	8	7
*	M	M	*CSNK1E*	*dco*	90	72	89	8	8	6
*	M	M	*CDK9*	*Cdk9*	48	81	89	4	8	2
*	W	M	*RET*	*Ret*	73	69	88	3	4	6
*	M	M	*FLT1*	*Pvr*	69	71	88	4	9	2
*	M	M	*EGFR*	*Egfr*	86	76	88	1	4	1
*	M	M	*NPR2*	*Gyc32E*	61	76	87	8	4	4
*	W	M	*SIK3*	*Sik3*	43	67	86	3	4	4
*	M	M	*STK3 (MST2)*	*hpo*	66	76	86	3	8	6
	M	M	*SCYL2*	*CG1951*	31	71	86	8	14	1
*	M	M	*SCYL3*	*CG1344*	67	73	86	7	9	2
*	W	M	*PRPF4B*	*CG7028*	57	65	86	4	5	2
*	M	M	*STK32B (YANK2)*	*CG32944*	60	80	86	4	6	2
*	W	M	*NUAK1*	*CG43143*	62	69	84	4	7	6
*	W	M	*TESK2*	*cdi*	82	66	83	6	12	12

Supplementary Table 2, continued.

Chromosomes 2, 3 and 4 (continued)

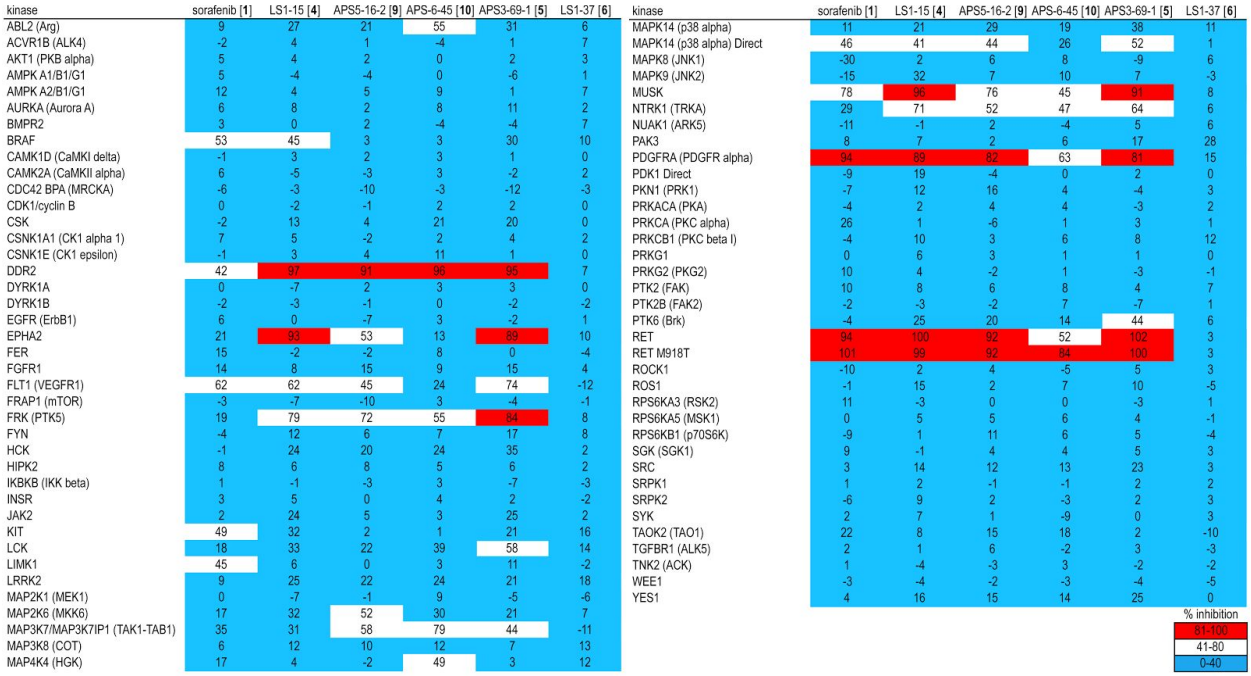
Drugs			Gene symbol		*ptc>Ret*^{M955T} viability (%)			s.e.		
–	soraf	L15	Human	Fly	–	soraf	L15	–	soraf	L15
				control	28	48	52	3	5	9
*	M	M	*CDK8*	*Cdk8*	84	78	83	4	5	4
	W	M	*RIOK3*	*CG3008*	49	69	83	9	2	3
*	M	M	*MYLK*	*Strn-Mlck*	61	85	83	2	4	2
	M	M	*PDK3*	*Pdk*	16	71	83	4	16	6
*	M	M	*PRKG1*	*for*	55	73	82	4	14	2
	M	M	*PRKG2*	*Pkg21D*	41	73	82	7	3	4
*	S	M	*CSNK2A1*	*CkIIalpha*	69	93	82	4	7	7
*	S	M	*MAPK11 (p38b)*	*p38c*	63	93	81	6	7	3
*	M	M	*SPEG*	*Unc-89*	68	78	81	1	9	10
*	M	M	*STK10 (LOK)*	*slik*	68	83	81	3	4	1
*	M	M	*CAMK2D*	*CaMKII*	72	78	81	6	9	8
*	M	M	*BMPR2*	*wit*	78	74	81	1	2	1
*	M	M	*PTK2 (FAK)*	*Fak*	58	81	80	2	3	7
*	M	M	*CDK14*	*Eip63E*	72	73	80	6	6	6
*	W	M	*MARK3*	*par-1*	67	70	79	6	7	10
	M	M	*WEE1*	*wee*	18	78	78	5	9	4
*	M	M	*PIK3CA*	*Pi3K92E*	59	72	78	5	7	3
*	W	M	*PIK3C2A*	*Pi3K68D*	49	63	78	8	10	6
*	M	M	*TRRAP*	*Nipped-A*	66	82	78	12	2	4
*	M	M	*MAP2K4 (MKK4)*	*Mkk4*	56	75	78	4	6	12
*	W	M	*ULK1 (ATG1)*	*Atg1*	79	61	78	8	1	1
*	W	M	*MAPK14 (p38a)*	*Mpk2*	82	51	78	1	1	2
	W	M	*MAPK11 (p38b)*	*p38b*	39	69	77	4	3	6
*	W	M	*SCYL1*	*yata*	91	70	77	7	13	4
	W	M	*CDC7*	*CG5790*	31	61	76	9	13	3
*	W	M	*GRK5*	*Gprk2*	64	70	73	5	2	5
*	W	M	*TTBK1 (BDTK)*	*Asator*	60	67	72	9	7	4
*	M	M	*MYLK2*	*sqa*	47	77	72	5	6	4
	W	M	*NPR1*	*CG10738*	45	64	71	5	6	2
*	M	W	*MAPK1 (ERK)*	*rl*	53	71	69	4	5	10
	M	W	*PRKCI*	*aPKC*	35	78	68	7	2	1
	M	W	*NIM1*	*CG4629*	29	79	68	2	2	10
*	M	W	*SRC, LCK, HCK*	*Src64B*	70	74	67	2	3	2
	M	W	*SBK2*	*CG4945*	25	76	67	9	1	0
*	M	W	*GAK*	*aux*	56	71	67	3	5	7
	M	W	*AAK1*	*Nak*	42	77	66	5	7	5
*	W	W	*PRKX*	*Pka-C3*	49	70	66	5	3	4
*	M	W	*BTK*	*Btk29A*	60	81	63	2	4	4
	M	W	*SBK1*	*CG11221*	31	86	56	5	7	6

Supplementary Table 2, continued.

Drugs			Gene symbol		*ptc>Ret^{M955T}* viability (%)			s.e.		
−	soraf	L15	Human	Fly	−	soraf	L15	−	soraf	L15
				control	3	18	20	1	1	4
Anti-targets for LS1-15										
		S	*SMG1*	*nonC*	3	31	2	3	10	2
		M	*LIMK1*	*LIMK1*	1	22	8	1	9	4
Anti-targets for both sorafenib and LS1-15										
*	S	S	*MAPK15 (ERK7)*	*Erk7*	0	0	0	0	0	0
	M	S	*MAP3K7 (TAK1)*	*Tak1*	3	8	2	3	4	2
*	M	S	*RPS6KA3 (p90RSK)*	*S6kII*	0	8	4	0	7	4
Chromosomes 2, 3 and 4										
				control	28	48	52	3	5	9
Anti-target for sorafenib										
	M		*CSK*	*csk*	43	22	58	11	5	6
Anti-targets for LS1-15										
*		M	*STK38*	*trc*	3	34	14	1	12	2
*		M	*MYO3A*	*ninaC*	14	48	25	2	3	4
*		W	*MAP3K15 (ASK3)*	*Pk92B*	16	40	36	4	8	1
Anti-targets for both sorafenib and LS1-15										
*	S	S	*PDPK1*	*Pdk1*	0	0	0	0	0	0
*	S	S	*HIPK2*	*hipk*	0	0	0	0	0	0
*	S	S	*TTK*	*Mps1*	1	0	0	1	0	0
*	S	S	*MKNK1*	*Lk6*	0	0	0	0	0	0
	S	M	*PAK3*	*Pak3*	14	6	20	8	4	2

Supplementary Table 3: Anti-targets of sorafenib [1] and LS1-15 [4].

A list of genes whose heterozygosity caused statistically significant decrease in % viability of *ptc>dRet^{M955T}* flies in the presence of drugs. Same legend as Supplementary Table 2 except for W, M, and S for genes on the X chromosome (weak [11-17% viability], moderate [6-10% viability], and strong [0-5% viability] effects, respectively} or 2nd, 3rd, and 4th chromosomes (weak [30-47% viability], moderate [10-29% viability], and strong effects [0-9% viability], respectively).



kinase	sorafenib [1]	LS1-15 [4]	APS5-16-2 [9]	APS-6-45 [10]	APS3-69-1 [5]	LS1-37 [6]
ABL2 (Arg)	9	27	21	55	31	6
ACVR1B (ALK4)	-2	4	1	-4	1	7
AKT1 (PKB alpha)	5	4	2	0	2	3
AMPK A1/B1/G1	5	-4	-4	0	-6	1
AMPK A2/B1/G1	12	4	5	9	1	7
AURKA (Aurora A)	6	8	2	8	11	2
BMPR2	3	0	2	-4	-4	7
BRAF	53	45	3	3	30	10
CAMK1D (CaMKI delta)	-1	3	2	3	1	0
CAMK2A (CaMKII alpha)	6	-5	-3	3	-2	2
CDC42 BPA (MRCKA)	-6	-3	-10	-3	-12	-3
CDK1/cyclin B	0	-2	-1	2	2	0
CSK	-2	13	4	21	20	0
CSNK1A1 (CK1 alpha 1)	7	5	-2	2	4	2
CSNK1E (CK1 epsilon)	-1	3	4	11	1	0
DDR2	42	97	91	96	95	7
DYRK1A	0	-7	2	3	3	0
DYRK1B	-2	-3	-1	0	-2	-2
EGFR (ErbB1)	6	0	-7	3	-2	1
EPHA2	21	93	53	13	89	10
FER	15	-2	-2	8	0	-4
FGFR1	14	8	15	9	15	4
FLT1 (VEGFR1)	62	62	45	24	74	-12
FRAP1 (mTOR)	-3	-7	-10	3	-4	-1
FRK (PTK5)	19	79	72	55	84	8
FYN	-4	12	6	7	17	8
HCK	-1	24	20	24	35	2
HIPK2	8	6	8	5	6	2
IKBKB (IKK beta)	1	-1	-3	3	-7	-3
INSR	3	5	0	4	2	-2
JAK2	2	24	5	3	25	2
KIT	49	32	2	1	21	16
LCK	18	33	22	39	58	14
LIMK1	45	6	0	3	11	-2
LRRK2	9	25	22	24	21	18
MAP2K1 (MEK1)	0	-7	-1	9	-5	-6
MAP2K6 (MKK6)	17	32	52	30	21	7
MAP3K7/MAP3K7IP1 (TAK1-TAB1)	35	31	58	79	44	-11
MAP3K8 (COT)	6	12	10	12	7	13
MAP4K4 (HGK)	17	4	-2	49	3	12

kinase	sorafenib [1]	LS1-15 [4]	APS5-16-2 [9]	APS-6-45 [10]	APS3-69-1 [5]	LS1-37 [6]
MAPK14 (p38 alpha)	11	21	29	19	38	11
MAPK14 (p38 alpha) Direct	46	41	44	26	52	1
MAPK8 (JNK1)	-30	2	6	8	-9	6
MAPK9 (JNK2)	-15	32	7	10	7	-3
MUSK	78	96	76	45	91	8
NTRK1 (TRKA)	29	71	52	47	64	6
NUAK1 (ARK5)	-11	-1	2	-4	5	6
PAK3	8	7	2	6	17	28
PDGFRA (PDGFR alpha)	94	89	82	63	81	15
PDK1 Direct	-9	19	-4	0	2	0
PKN1 (PRK1)	-7	12	16	4	-4	3
PRKACA (PKA)	-4	2	4	4	-3	2
PRKCA (PKC alpha)	26	1	-6	1	3	1
PRKCB1 (PKC beta I)	-4	10	3	6	8	12
PRKG1	0	6	3	1	1	0
PRKG2 (PKG2)	10	4	-2	1	-3	-1
PTK2 (FAK)	10	8	6	8	4	7
PTK2B (FAK2)	-2	-3	-2	7	-7	1
PTK6 (Brk)	-4	25	20	14	44	6
RET	94	100	92	52	102	3
RET M918T	101	99	92	84	100	3
ROCK1	-10	2	4	-5	5	3
ROS1	-1	15	2	7	10	-5
RPS6KA3 (RSK2)	11	-3	0	0	-3	1
RPS6KA5 (MSK1)	0	5	5	6	4	-1
RPS6KB1 (p70S6K)	-9	1	11	6	5	-4
SGK (SGK1)	9	-1	4	4	5	3
SRC	3	14	12	13	23	3
SRPK1	1	2	-1	-1	2	2
SRPK2	-6	9	2	-3	2	3
SYK	2	7	1	-9	0	3
TAOK2 (TAO1)	22	8	15	18	2	-10
TGFBR1 (ALK5)	2	1	6	-2	3	-3
TNK2 (ACK)	1	-4	-3	3	-2	-2
WEE1	-3	-4	-2	-3	-4	-5
YES1	4	16	15	14	25	0

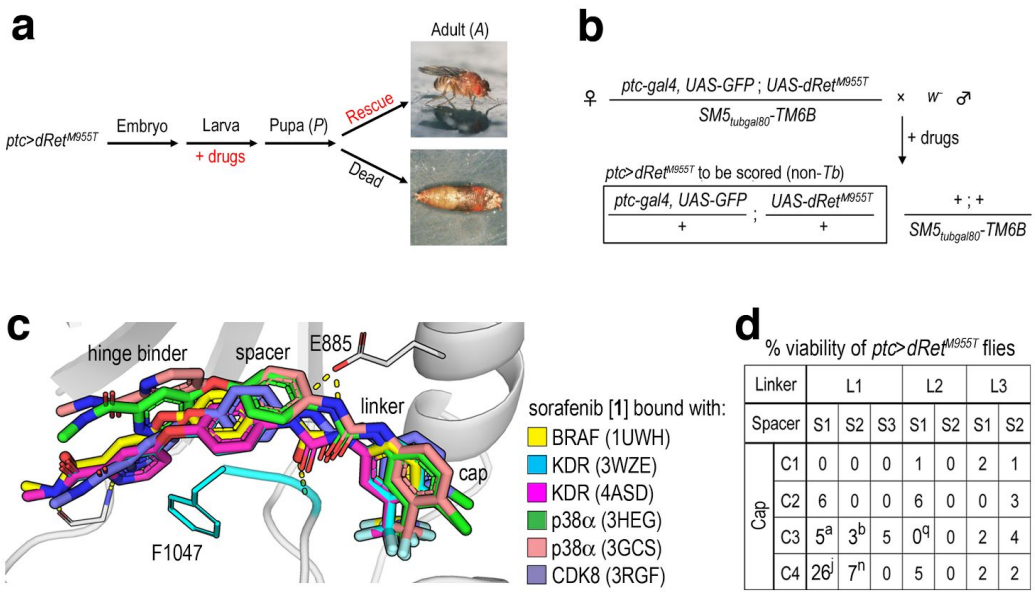
Supplementary Table 4: *In vitro* inhibition data for kinases.

Percent *in vitro* inhibition of human kinase activities by TCIs. Red, greater than 80% inhibition. White, 41-80% inhibition. Blue, less than 40% inhibition.

Category	Parameter	Description
Assay	Type of assay	Whole organism
	Target	Kinases
	Primary measurement	Fly viability
	Key reagents	Semi-defined fly medium (BDSC), DMSO (SIGMA-Aldrich)
	Assay protocol	See "Fly assays" in Methods
	Additional comments	
Library	Library size	31 FDA drugs and 30 in-house chemicals
	Library composition	FDA-approved drugs and drug candidates
	Source	Selleck, LC laboratories, Tocris Bioscience, and in-house
	Additional comments	
Screen	Format	Fly culture vials
	Concentration(s) tested	1 to up to 800 μM in 0.1% DMSO
	Plate controls	not applicable
	Reagent/ compound dispensing system	not applicable
	Detection instrument and software	not applicable
	Assay validation/QC	not applicable
	Correction factors	not applicable
	Normalization	not applicable
	Additional comments	
Post-HTS analysis	Hit criteria	Rescue of lethality compared with DMSO control or sorafenib
	Hit rate	not applicable
	Additional assay(s)	Validation using cultured human MTC cells
	Confirmation of hit purity and structure	Validated by LC-MS and ^{1}H NMR (See "Synthetic Methods and Compound Characterization")
	Additional comments	

Supplementary Table 5: Small molecule screening data.

Figure S1



Linker		L1			L2		L3	
Spacer		S1	S2	S3	S1	S2	S1	S2
Cap	C1	0	0	0	1	0	2	1
	C2	6	0	0	6	0	0	3
	C3	5[a]	3[b]	5	0[q]	0	2	4
	C4	26[j]	7[n]	0	5	0	2	2

Supplementary Fig. 1: Determining the effects of inhibitors in *Drosophila* MTC model.

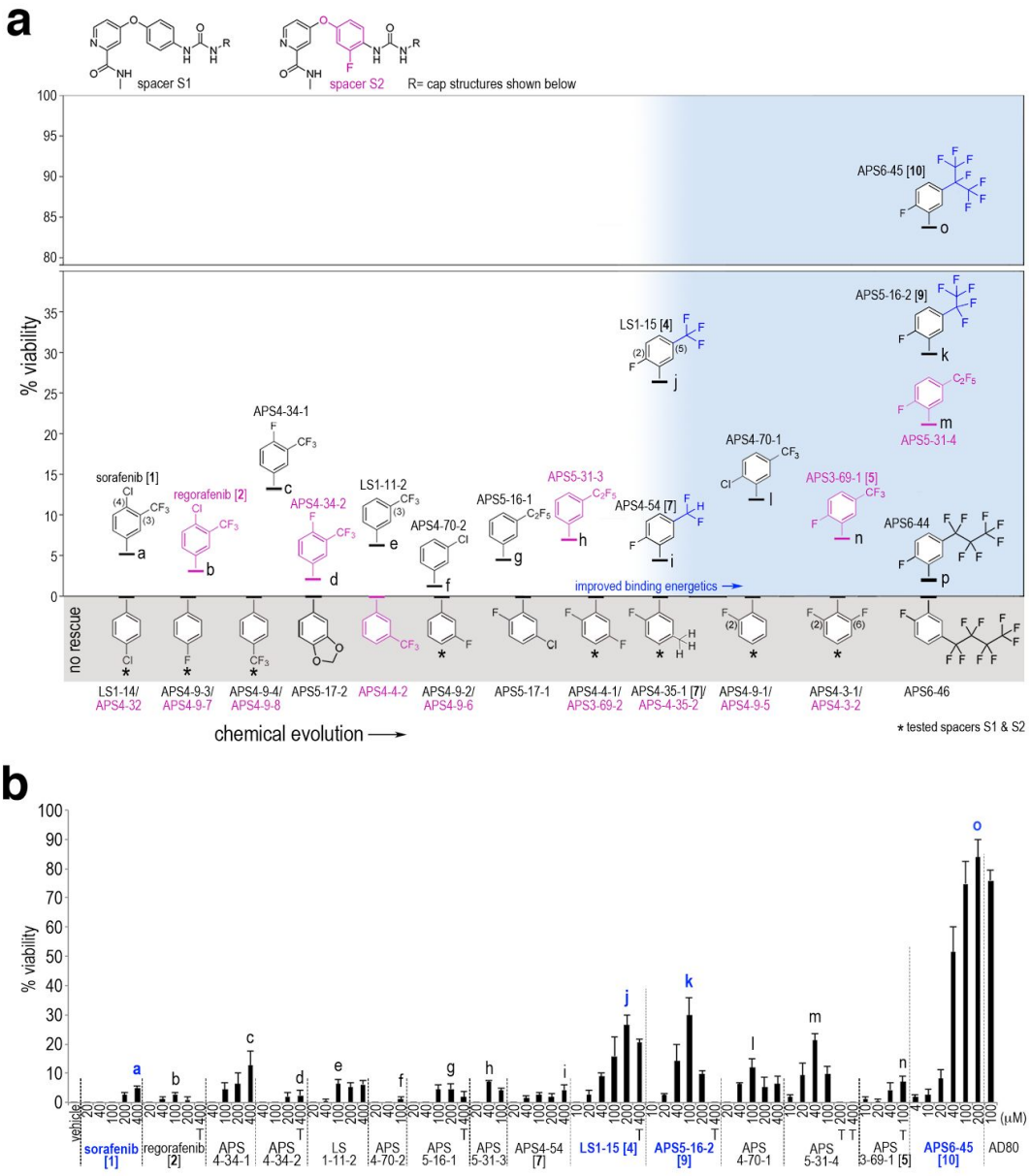
a, Scheme showing quantitative 'rescue-from-lethality' *Drosophila* platform used for drug and compound screening. In *ptc>dRet*^{M955T} flies, the *patched* (*ptc*) promoter drives an oncogenic mutant isoform of *Drosophila Ret* (*dRet*^{M955T}) in several tissues, directing lethality prior to emergence as adults. Larvae consume candidate drugs; drug efficacy is quantified by dividing the number of rescued adults (*A*) by the number of total pupae (*P*).

b, Scheme showing preparation of *ptc>dRet*^{M955T} flies. In *ptc-gal4*,*UAS-GFP*;*UAS-dRet*^{M955T}/*SM5*$_{tub\text{-}gal80}$*-TM6B* flies, *tubulin* promoter-driven GAL80 suppressed GAL4 activity to suppress *dRet*^{M955T} expression. For drug screening, these flies were crossed with w^- flies to create non-*Tb*, oncogenic *ptc-gal4*,*UAS-GFP*;*UAS-dRet*^{M955T} (*ptc>dRet*^{M955T}) flies that were morphologically distinguishable from *Tb* control flies at the pupal stage. Fly progenies were treated with or without drugs, and raised at 25°C.

c, The conformations of **1** when bound to various kinases in the DFG-out (*i.e.* inactive) conformation (gray); PDB ID of the shown structures is listed in parentheses. For example, when bound to BRAF, **1** (yellow version) interacts with the hinge region of the ATP-binding pocket and a conserved glutamate residue from the C-helix (E885) using hinge binder and linker regions, respectively. The cap group of **1** occupies the DFG-out pocket, which is created by movement of the phenylalanine (F1047) from the DFG-in (*i.e.* active) conformation.

d, Rescue of *ptc>dRet*^{M955T} flies by TCIs. The chemical structures for tested compounds within the matrix is denoted based on linker (L1-L3), spacer (S1-S3), and caps (C1-C4) as shown in Fig. 2a. Lower case letters correspond to viability data as shown in Supplementary Figs. 2a and 2b. LS1-15 [**4**] (**j**) rescued viability significantly better than sorafenib [**1**] (**a**) and regorafenib [**2**] (**b**).

Figure S2

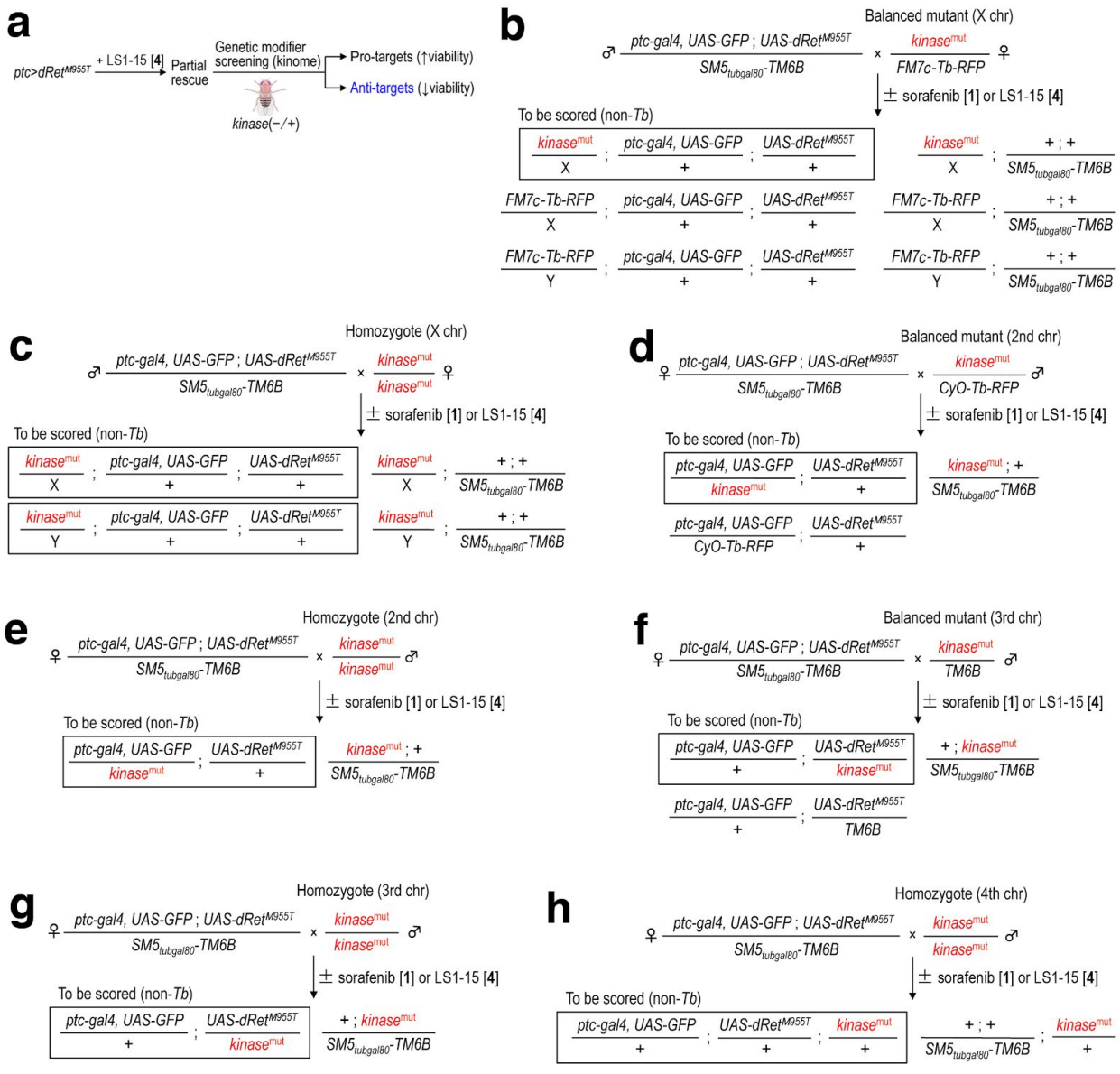


Supplementary Fig. 2: Extended description of the terminal cap group SAR.

a, Rescue of *ptc>dRet*^{M955T} flies by TCIs. Additional, specific compound designations correspond to the synthetic procedures in the Methods section, and those highlighted in magenta posses spacer S2; see also Fig. 4a. APS5-16-2 carrying the $–C_2F_5$ group within the cap showed significant rescue (**k**), whereas APS6-45, with the *–iso*C_3F_7 substitution, shows the strongest efficacy (**o**) exceeding AD80. The lowercase letters (**a**-**o**) correspond to the dosing plots shown in **b**.

b, Dose response to TCIs. T, toxic dose for flies. Error bars, standard errors in triplicate.

Figure S3

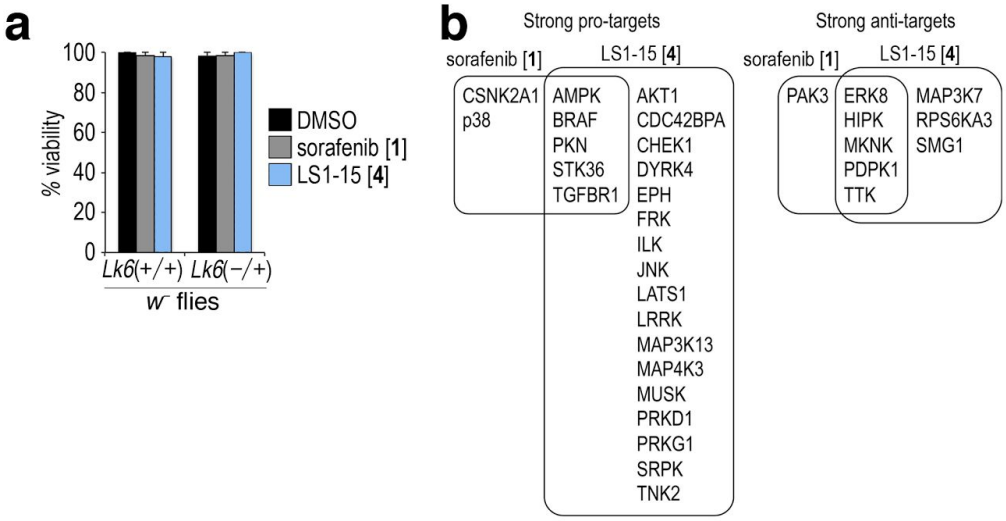


Supplementary Fig. 3: Determining the effects of heterozygosity of kinase genes in *Drosophila* MTC model.

a, Scheme showing screening approach to identify genetic modifiers of **4** efficacy in *ptc>dRet*^{M955T} flies. Fly kinome genes were identified as "pro-targets" or "anti-targets" if—as whole animal heterozygotes (*ptc>dRet*^{M955T},*gene*$^{-/+}$)—they increased or decreased, respectively, the efficacy of **4**.

b-h, Generating experimental flies. *ptc>dRet*^{M955T} flies are crossed with flies mutant for a kinase gene on either X (**b, c**), 2nd (**d, e**), 3rd (**f, g**), or 4th (**h**) chromosomes, and their progenies were raised on fly food with or without drugs at 23°C. Mutant alleles in parent flies are either balanced with *Tb* allele (**b, d, f**), or homozygous (**c, e, g, h**).

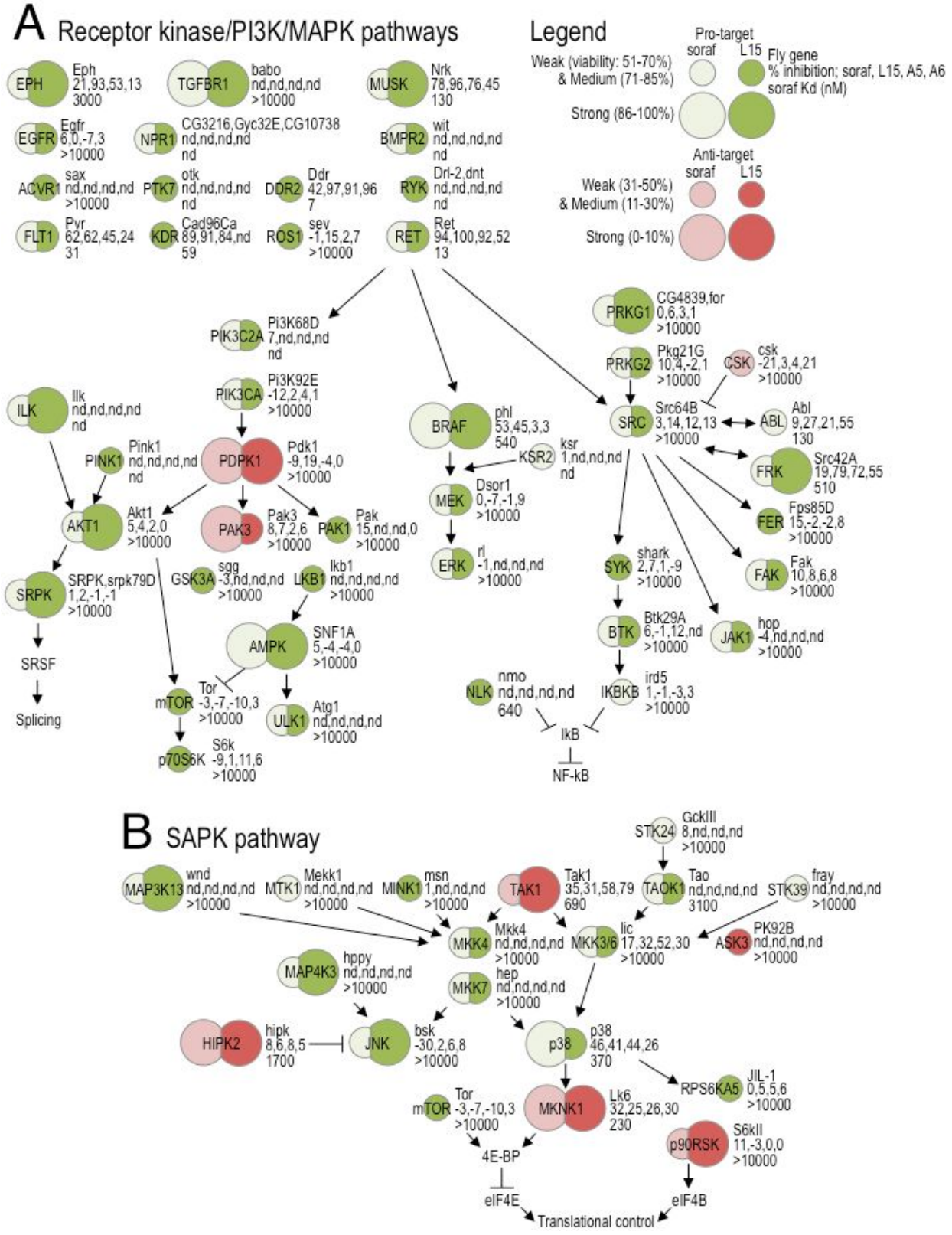
Figure S4



Supplementary Fig. 4: Shared and specific pro-targets and anti-targets.

a, *Lk6* heterozygosity had no effect on viability of control flies. Control (w^-) or *Lk6* heterozygous (w^-;$Lk6^{-/+}$) larvae were treated with or without drugs, and cultured at 23°C. Percent viability was determined using numbers of pupae and adults. Error bars, standard errors in triplicate.

b, Venn diagrams showing pro-targets and anti-targets for **1** and/or **4**. Shown are strong pro-targets and strong anti-targets in which heterozygosity gave rise to > 91% and < 9% viability to *ptc>dRet*^{M955T} flies, respectively, in the presence of compounds at 23°C.


A Receptor kinase/PI3K/MAPK pathways
Legend
Pro-target
soraf
L15
Fly gene
% inhibition; soraf, L15, A5, A6
soraf Kd (nM)
Weak (viability: 51-70%)
& Medium (71-85%)
Strong (86-100%)
Anti-target
soraf
L15
Weak (31-50%)
& Medium (11-30%)
Strong (0-10%)
EPH
Eph
21,93,53,13
3000
TGFBR1
babo
nd,nd,nd,nd
>10000
MUSK
Nrk
78,96,76,45
130
EGFR
Egfr
6,0,-7,3
>10000
NPR1
CG3216,Gyc32E,CG10738
nd,nd,nd,nd
nd
BMPR2
wit
nd,nd,nd,nd
nd
ACVR1
sax
nd,nd,nd,nd
>10000
PTK7
otk
nd,nd,nd,nd
nd
DDR2
Ddr
42,97,91,96
7
RYK
Drl-2,dnt
nd,nd,nd,nd
nd
FLT1
Pvr
62,62,45,24
31
KDR
Cad96Ca
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59
ROS1
sev
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RET
Ret
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13
PRKG1
CG4839,for
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PRKG2
Pkg21G
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>10000
CSK
csk
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>10000
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Pi3K68D
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nd
PIK3CA
Pi3K92E
-12,2,4,1
>10000
ILK
Ilk
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nd
BRAF
phl
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540
SRC
Src64B
3,14,12,13
>10000
ABL
Abl
9,27,21,55
130
KSR2
ksr
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nd
PINK1
Pink1
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nd
PDPK1
Pdk1
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>10000
FRK
Src42A
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510
MEK
Dsor1
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FER
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Akt1
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Pak3
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PAK1
Pak
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ERK
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FAK
Fak
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BTK
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JAK1
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>10000
AMPK
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SRSF
Splicing
mTOR
Tor
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>10000
ULK1
Atg1
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NLK
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640
IKBKB
ird5
1,-1,-3,3
>10000
IkB
NF-kB
p70S6K
S6k
-9,1,11,6
>10000
B SAPK pathway
STK24
GckIII
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>10000
MAP3K13
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MTK1
Mekk1
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MINK1
msn
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TAK1
Tak1
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690
TAOK1
Tao
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3100
STK39
fray
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>10000
MKK4
Mkk4
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>10000
MKK3/6
lic
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ASK3
PK92B
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MAP4K3
hppy
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MKK7
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HIPK2
hipk
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JNK
bsk
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p38
p38
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JIL-1
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mTOR
Tor
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>10000
MKNK1
Lk6
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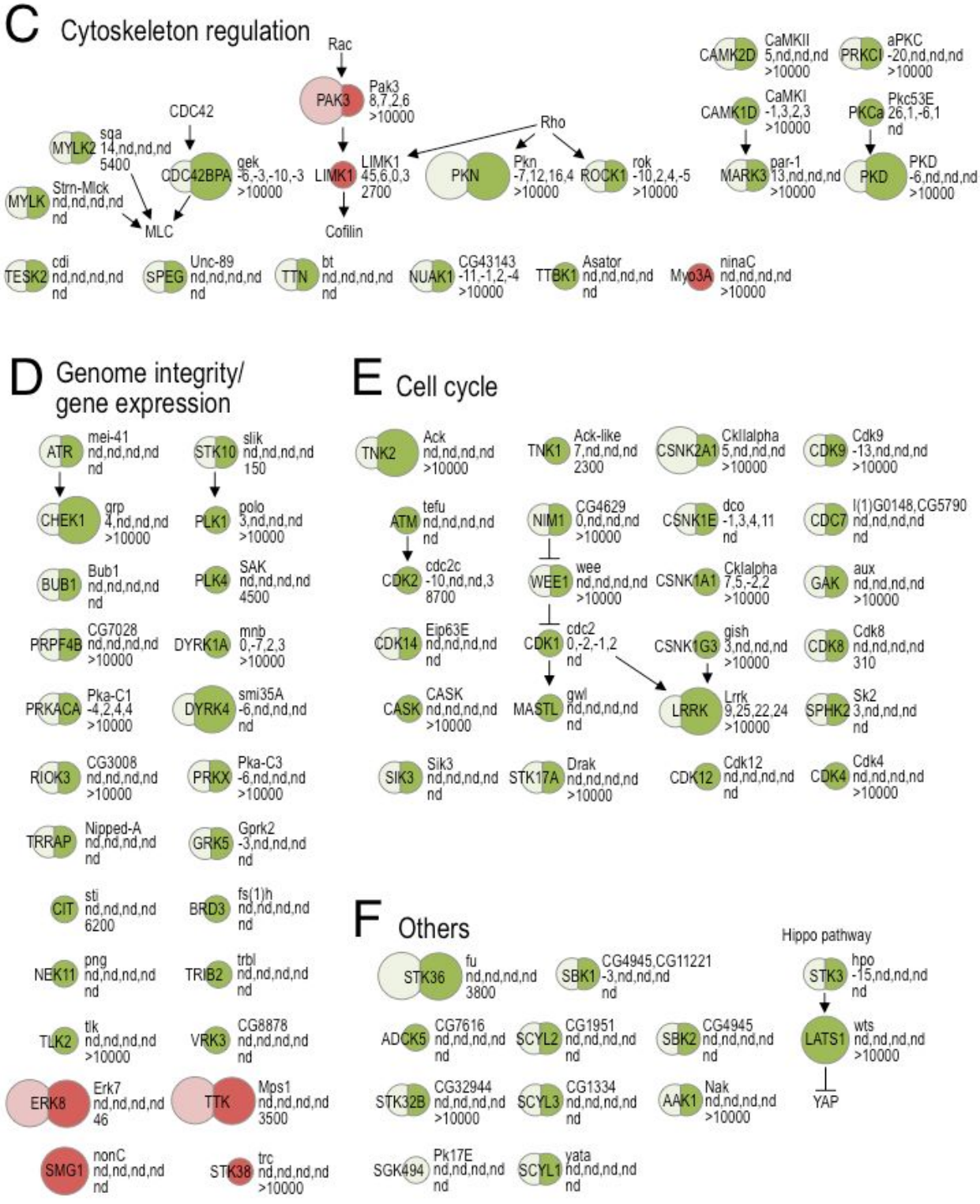
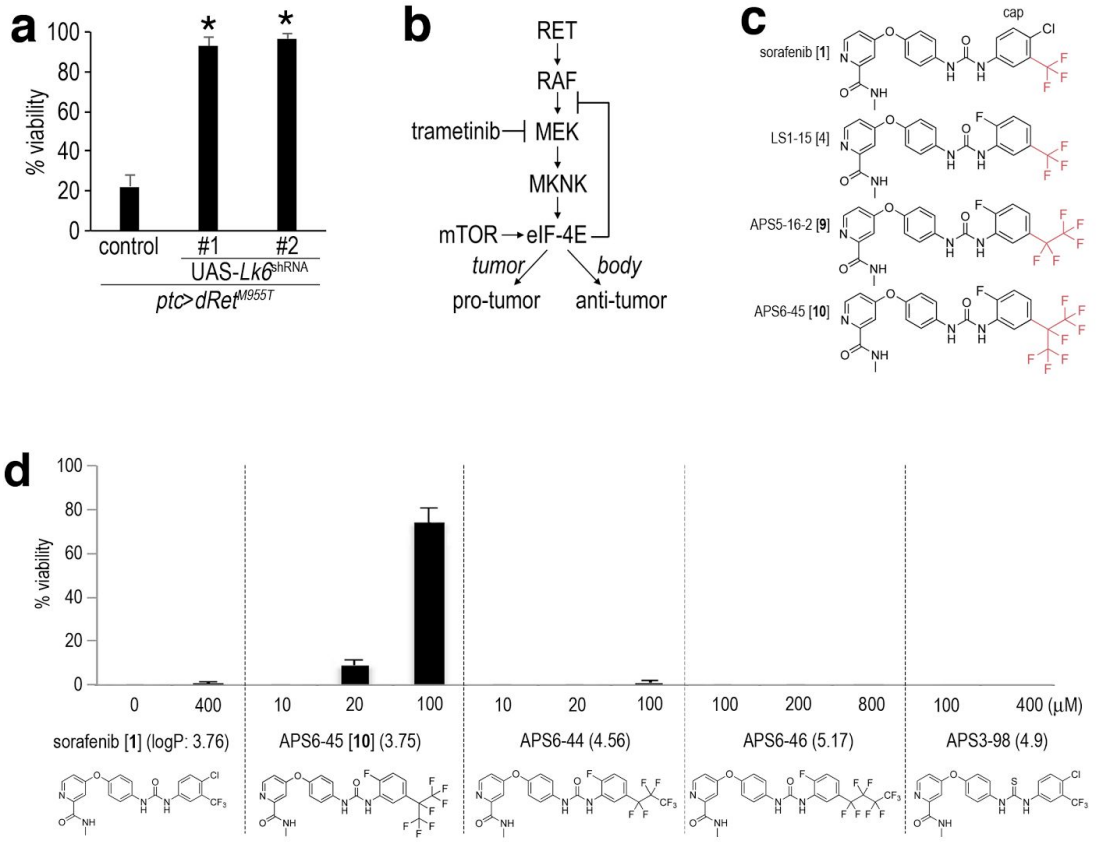
4E-BP
eIF4E
eIF4B
Translational control


C Cytoskeleton regulation
Rac
PAK3
Pak3 8,7,2,6 >10000
CDC42
MYLK2 sqa 14,nd,nd,nd 5400
CDC42BPA gek -6,-3,-10,-3 >10000
MYLK Strn-Mlck nd,nd,nd,nd nd
MLC
LIMK1 LIMK1 45,6,0,3 2700
Cofilin
Rho
PKN Pkn -7,12,16,4 >10000
ROCK1 rok -10,2,4,-5 >10000
CAMK2D CaMKII 5,nd,nd,nd >10000
PRKCI aPKC -20,nd,nd,nd >10000
CAMK1D CaMKI -1,3,2,3 >10000
PKCa Pkc53E 26,1,-6,1 nd
MARK3 par-1 13,nd,nd,nd >10000
PKD PKD -6,nd,nd,nd >10000
TESK2 cdi nd,nd,nd,nd nd
SPEG Unc-89 nd,nd,nd,nd nd
TTN bt nd,nd,nd,nd nd
NUAK1 CG43143 -11,-1,2,-4 >10000
TTBK1 Asator nd,nd,nd,nd nd
Myo3A ninaC nd,nd,nd,nd >10000
D Genome integrity/ gene expression
ATR mei-41 nd,nd,nd,nd nd
CHEK1 grp 4,nd,nd,nd >10000
BUB1 Bub1 nd,nd,nd,nd nd
PRPF4B CG7028 nd,nd,nd,nd >10000
PRKACA Pka-C1 -4,2,4,4 >10000
RIOK3 CG3008 nd,nd,nd,nd >10000
TRRAP Nipped-A nd,nd,nd,nd nd
CIT sti nd,nd,nd,nd 6200
NEK11 png nd,nd,nd,nd nd
TLK2 tik nd,nd,nd,nd >10000
ERK8 Erk7 nd,nd,nd,nd 46
SMG1 nonC nd,nd,nd,nd nd
STK10 slik nd,nd,nd,nd 150
PLK1 polo 3,nd,nd,nd >10000
PLK4 SAK nd,nd,nd,nd 4500
DYRK1A mnb 0,-7,2,3 >10000
DYRK4 smi35A -6,nd,nd,nd nd
PRKX Pka-C3 -6,nd,nd,nd >10000
GRK5 Gprk2 -3,nd,nd,nd nd
BRD3 fs(1)h nd,nd,nd,nd nd
TRIB2 trbl nd,nd,nd,nd nd
VRK3 CG8878 nd,nd,nd,nd nd
TTK Mps1 nd,nd,nd,nd 3500
STK38 trc nd,nd,nd,nd >10000
E Cell cycle
TNK2 Ack nd,nd,nd,nd >10000
ATM tefu nd,nd,nd,nd nd
CDK2 cdc2c -10,nd,nd,3 8700
CDK14 Eip63E nd,nd,nd,nd nd
CASK CASK nd,nd,nd,nd >10000
SIK3 Sik3 nd,nd,nd,nd nd
TNK1 Ack-like 7,nd,nd,nd 2300
NIM1 CG4629 0,nd,nd,nd >10000
WEE1 wee nd,nd,nd,nd >10000
CDK1 cdc2 0,-2,-1,2 nd
MASTL gwl nd,nd,nd,nd nd
STK17A Drak nd,nd,nd,nd >10000
CSNK2A1 CkIIalpha 5,nd,nd,nd >10000
CSNK1E dco -1,3,4,11 nd
CSNK1A1 CkIalpha 7,5,-2,2 >10000
CSNK1G3 gish 3,nd,nd,nd >10000
LRRK Lrrk 9,25,22,24 >10000
CDK12 Cdk12 nd,nd,nd,nd nd
CDK9 Cdk9 -13,nd,nd,nd >10000
CDC7 l(1)G0148,CG5790 nd,nd,nd,nd nd
GAK aux nd,nd,nd,nd >10000
CDK8 Cdk8 nd,nd,nd,nd 310
SPHK2 Sk2 3,nd,nd,nd nd
CDK4 Cdk4 nd,nd,nd,nd >10000
F Others
STK36 fu nd,nd,nd,nd 3800
ADCK5 CG7616 nd,nd,nd,nd nd
STK32B CG32944 nd,nd,nd,nd >10000
SGK494 Pk17E nd,nd,nd,nd nd
SBK1 CG4945,CG11221 -3,nd,nd,nd nd
SCYL2 CG1951 nd,nd,nd,nd nd
SCYL3 CG1334 nd,nd,nd,nd nd
SCYL1 yata nd,nd,nd,nd nd
SBK2 CG4945 nd,nd,nd,nd nd
AAK1 Nak nd,nd,nd,nd >10000
Hippo pathway
STK3 hpo -15,nd,nd,nd nd
LATS1 wts nd,nd,nd,nd >10000
YAP

Supplementary Fig. 5: Pro-targets and anti-targets of sorafenib [1] and LS1-15 [4].

Pro-targets and anti-targets of **1** and **4** were grouped into receptor kinase/phosphoinositide 3-kinase (PI3K)/MAPK (**A**), stress (**B**), cytoskeleton (**C**), genome integrity/gene expression (**D**), cell cycle (**E**), or other signaling pathways (**F**) according to their functions. Pale green and dark green circles indicate pro-targets of **1** and **4**, respectively, whereas pink and red circles indicate anti-targets of **1** and **4**, respectively. Small and large circles indicate weak/medium and strong modifiers of compound efficacy in *ptc>dRet*^{M955T} flies, respectively. Percent inhibition of each kinase by TCIs and Kd value by **1** (ref. [10]) are also shown. Soraf, sorafenib [**1**]; L15, LS1-15 [**4**]; A5, APS5-16-2 [**9**]; A6, APS6-45 [**10**].

Figure S6



Supplementary Fig. 6: Derivatives of sorafenib [1].

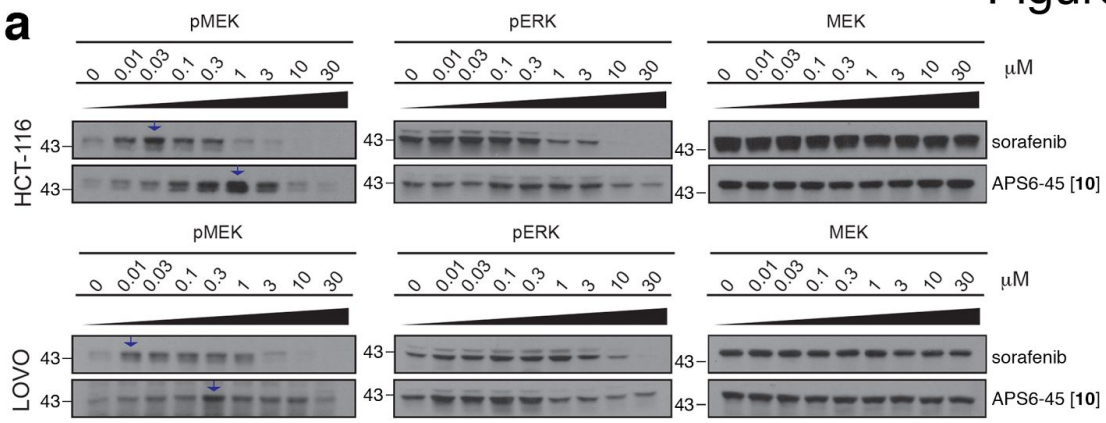
a, *Lk6* knockdown specifically in *dRet*^{M955T} cells increases the viability of *ptc>dRet*^{M955T} flies. Two different sequences (#1 and #2) were driven by the *ptc* promoter to knock down *Lk6* expression. Error bars, standard errors in triplicate. Asterisks, $p < 0.05$ in Student's *t*-test as compared with no-shRNA control.

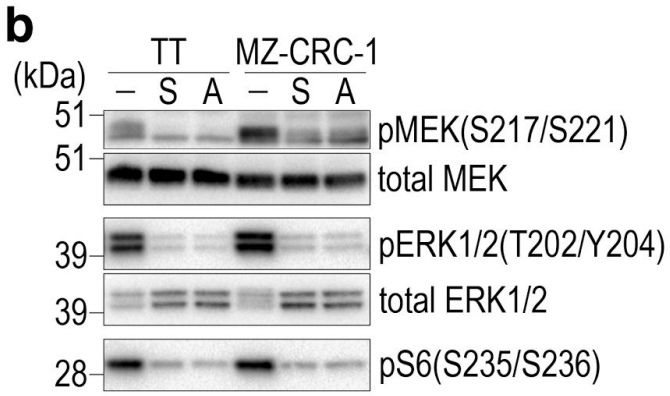
b, A model of MKNK inhibition of RAS/MAPK pathway signaling.

c, The TCIs **9** and **10** possess extended perfluoroalkyl group substitutions relative to **1** and **4** (red).

d, Comparing efficacy and logP values (parentheses) for **1** and several of the TCIs, demonstrating poor correlation between the two parameters.

Figure S7





c

Compound	MTD (mg/kg/day)	PK						
		Dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (μM)	AUC_{0-24} (μM・h)	$AUC_{0-\infty}$ (μM・h)	$MRT_{0-\infty}$ (h)
APS6-45 [**10**]	160 <	20	5.6	2.0	9.7	123.7	131.8	9.3

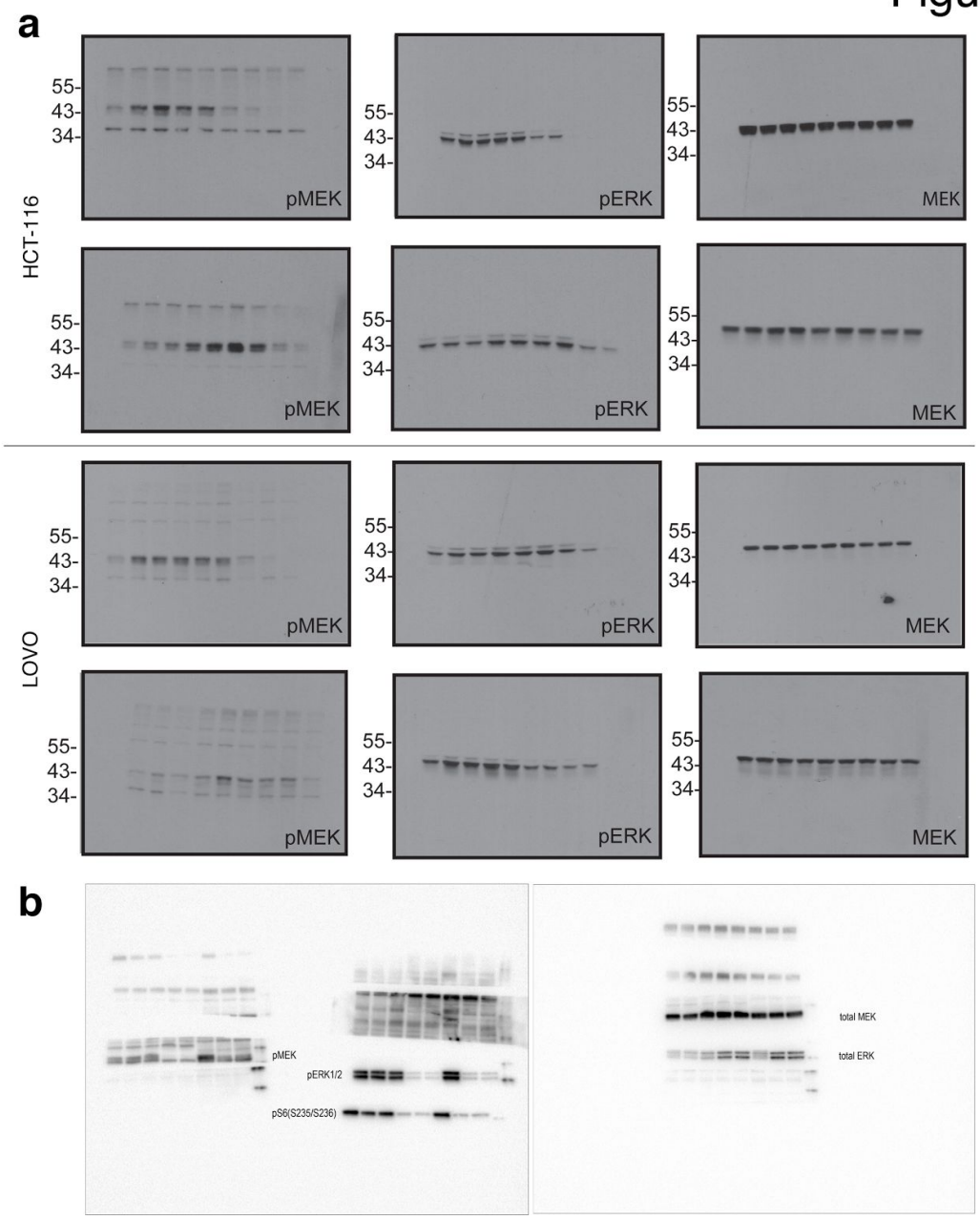
Supplementary Fig. 7: Effects of APS6-45 [10] on Ras/MAPK signaling in human cancer cells.

a, Human cancer cell lines HCT-116 and LOVO were treated with the indicated doses of **1** and **10**, and the effects on Ras/MAPK signaling were measured by western blot using pMEK(S217/S221) and pERK(T202/Y204) antibodies. Peak transactivation of BRAF by **1** (ref. [38]) and **10** are indicated by arrows. Uncropped images are in Supplementary Fig. 8a.

b, 10 inhibited Ras pathway activity in human MTC cells. TT and MZ-CRC-1 were treated with vehicle (–), 1 μM of sorafenib [**1**] (S), or 1 μM of APS6-45 [**10**] (A) for 1 h, and cell lysates were analyzed for activity of the Ras/MAPK pathway effectors MEK, ERK, and S6. Uncropped images are in Supplementary Fig. 8b.

c, Maximum tolerated dose (MTD) and pharmacokinetics (PK) of **10** in mice. For PK test, mice were dosed with 20 mg/kg of **10** orally.

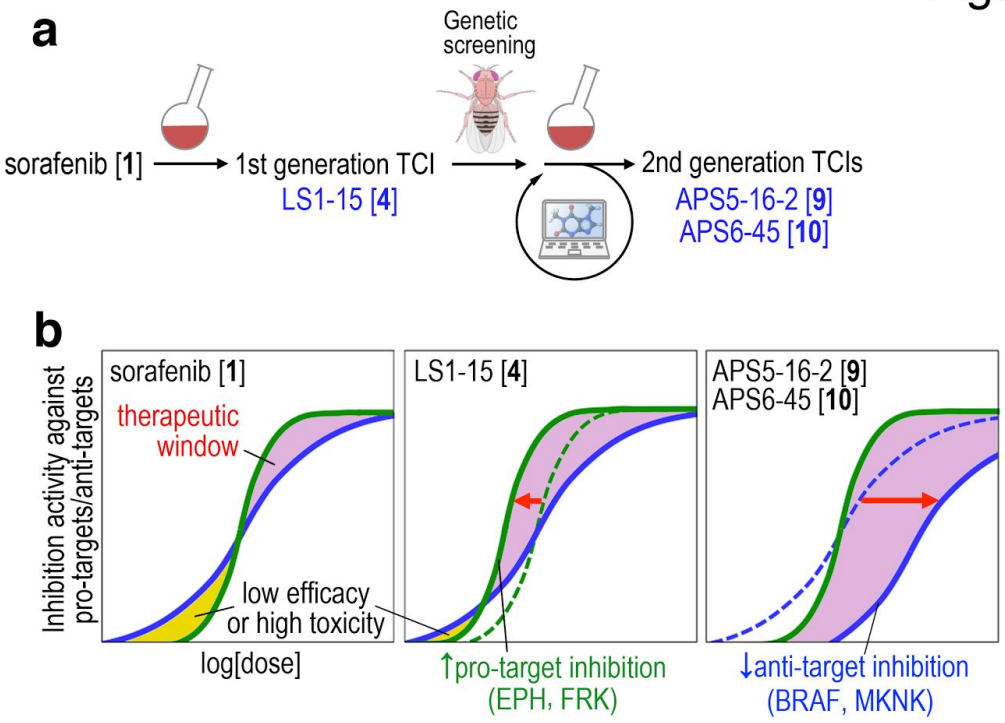
Figure S8



Supplementary Fig. 8: Uncropped western images.

a and b, Original images for Supplementary Figs. 7a and 7b, respectively.

Figure S9



Supplementary Fig. 9: Optimizing polypharmacology.

a, Scheme showing stepwise derivatization of TCIs. The first set of TCIs includes combinations between spacers/linkers/caps generated by medicinal chemistry. Drug screening experiments with *ptc>dRet*^{M955T} flies identified **4** as the best derivative; subsequent genetic screening revealed pro-targets and anti-targets for **1** and **4**. Computation compared physicochemical features between compounds such as intramolecular steric hindrance and modifications of the cap to prevent its binding to anti-targets, pointing to novel chemical spaces **9** and **10**.

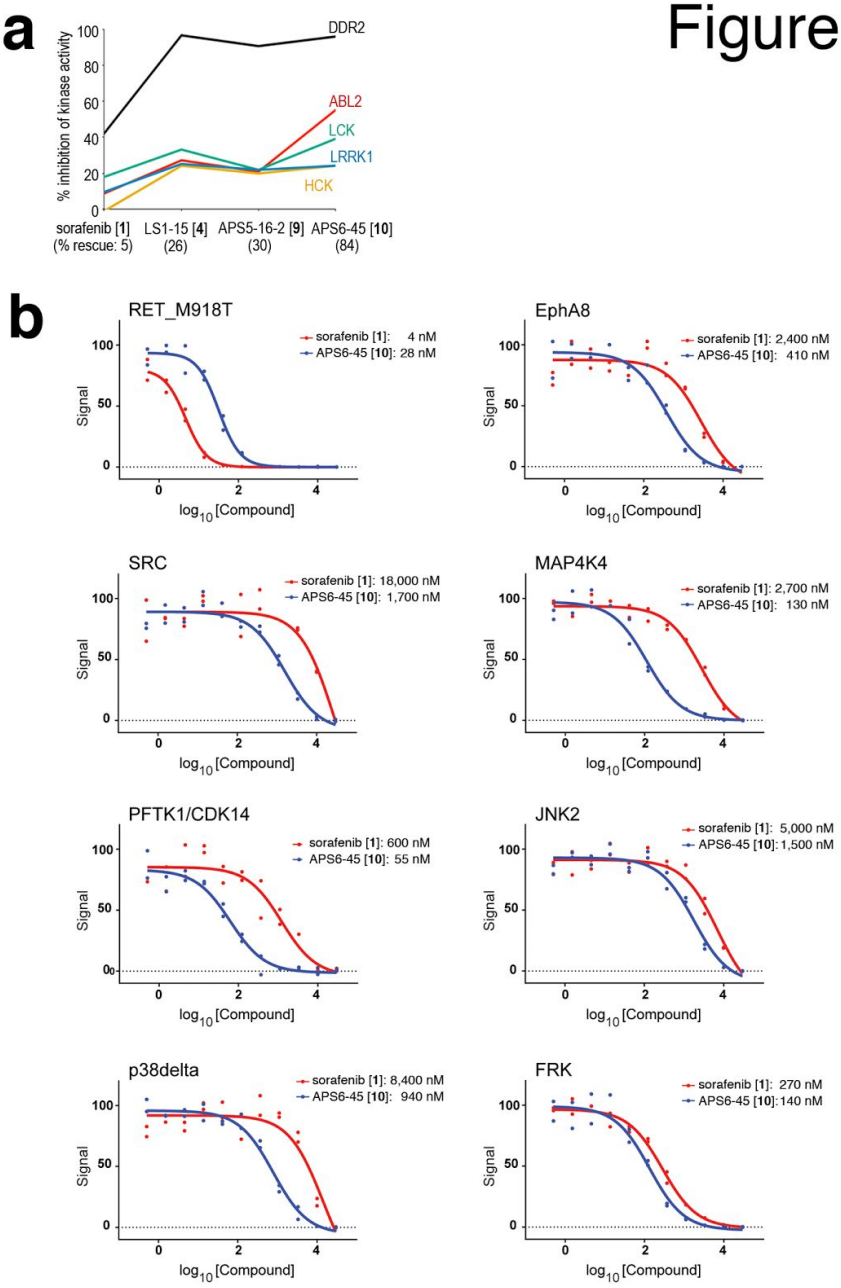
b, Models for mechanism of action of each TCI.

(Left) **1** inhibits pro-targets such as RET (green). At low dose, however, such inhibition is not sufficiently potent to overcome anti-targets such as BRAF (yellow). Such unwanted effects are reduced but not abolished at higher concentration; in addition, inhibition of anti-targets (blue) further limits the therapeutic window (pink).

(Middle) **4** inhibits additional pro-targets EPH and FRK, generating a larger therapeutic window than **1**. **4** at low dose is still limited by toxicity because it activates BRAF as **1** does.

(Right) **9** and **10** displayed reduced binding potency to BRAF, thus preventing activation of these anti-targets even at low dose. Other anti-targets such as MKNK are also kept uninhibited, leading to a wider therapeutic window than **1**.

Figure S10

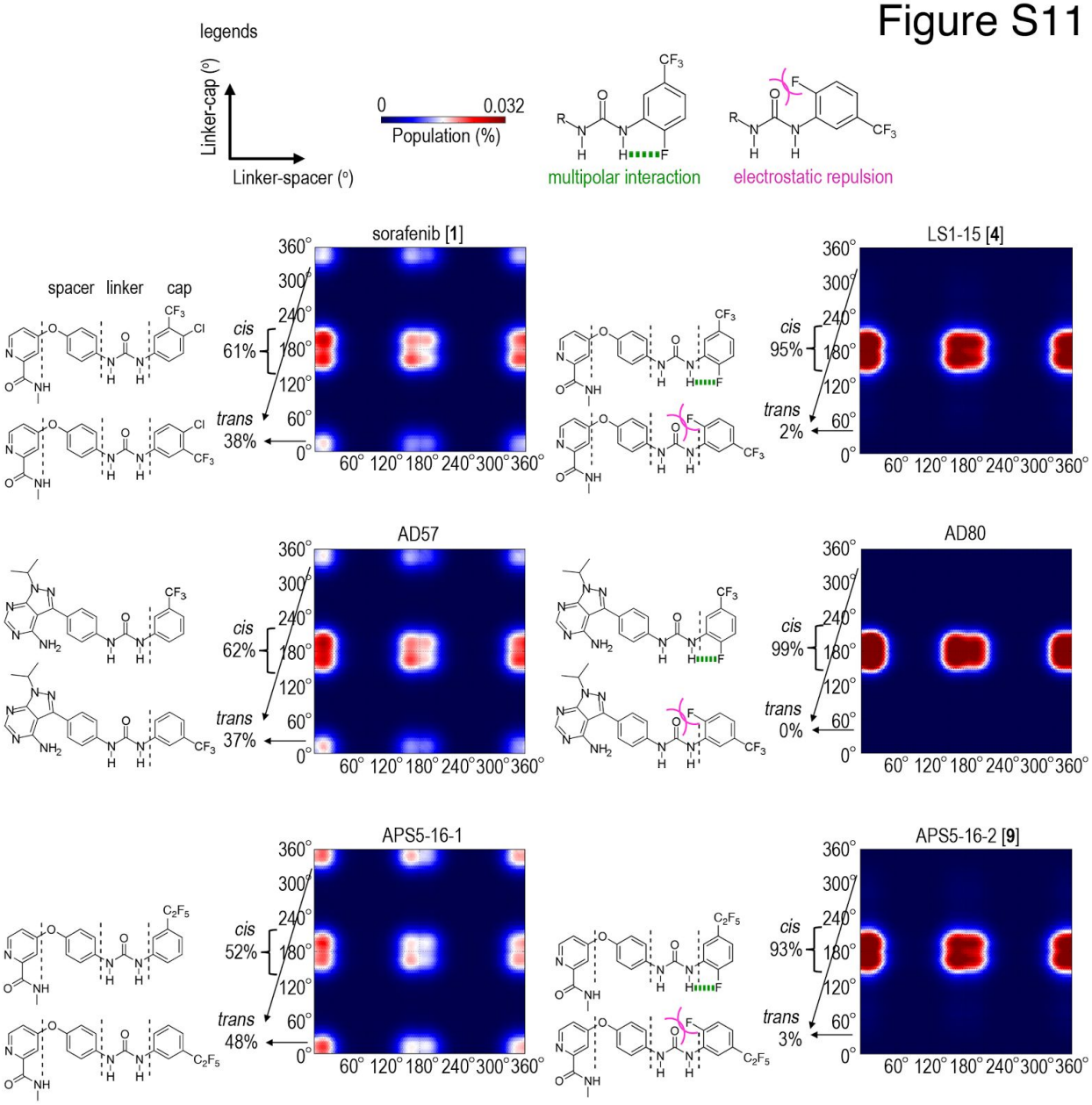


Supplementary Fig. 10: Increased activity of APS6-45 [10] against pro-targets of sorafenib [1].

a, Distinct inhibition of pro-target kinases by TCIs. Percent inhibition of kinase activities were determined by *in vitro* assays. Percent rescue of *ptc>dRet*^{M955T} flies by each compound is shown (parentheses). Note that LRRK1 is a strong pro-target, whereas ABL2, DDR2, HCK, and LCK are weak to moderate pro-targets (Supplementary Table 2).

b, Kd values determined by multi-point assays for **1** and **10** against pro-target kinases of **1**.

Figure S11



Supplementary Fig. 11. Computing physicochemical features for TCIs.

Torsional energy of the linker/cap and linker/spacer is converted into relative conformational population of the compounds, represented in a heatmap. Since most TCIs do not have a substituent on the spacer region, linker/spacer is symmetric at 180°. **1**, APS5-16-1, and AD57 have two predominant conformational populations, the *cis*- and the *trans*- conformers, likely due to the rotation of the linker/cap. Conversely, **4**, **9**, and AD80 strongly favor the *cis*- over the *trans*- conformation, likely due to the multipolar interaction between the urea amide hydrogen and fluorine (green broken line), and strong electrostatic repulsion between the fluorine and the urea carbonyl oxygen in the *trans*- conformation (magenta arcs).

Supplementary Dataset 1: *In vitro* inhibition of kinases by APS6-45 [10].

Percent *in vitro* activity remaining for human kinases was determined in the presence of 10 μM of **10**.

Supplementary Dataset 2: Numbers of samples.