Supporting information.

Assessment of chemical coverage of kinome space and its implications for kinase drug discovery.

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Table S1. Screening data for compounds 2-18 at 10μM.

Table S2. Kinases that bind over half of the 18 potential DFG-out conformation binding compounds.

Figure S1. Plot of compound structural similarity against SAR similarity.

Figure S2. Comparison of the ATP sites of AAK1 and LKB1.

Figure S3. Plots of kinase sequence similarity against SAR similarity.

Figure S4. Distribition of assays in the panel.

Figure S5. Validation of single-concentration %control data.

Figure S6. Illustration of calculation of SAR similarity matrices.

See also Supplementary_kinase_SARsim.txt, a text file containing 203x203 kinase vs kinase matrix showing SAR similarities and counts of compounds binding with different thresholds.

Table S1. *Affinity of compounds* ***2-18*** *(Fig. 4) at 10μM concentration, expressed as % control (see Experimental section: 0=potent binding, N=no effect detected). Two values (marked $^{+}$) were later found to have Kd>10μM. Kinases are ranked according to the Sugen phylogenetic tree. Counts of compounds binding to each kinase (Nc) and kinases binding to each compound (Nk) with %control thresholds of 1 and 10 are also shown.*

Part 1

	Compound																		
Kinase	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**Nc≤1**	**Nc≤10**
AKT1	N	N	5.6	N	N	N	N	N	N	N	N	N	N	N	N	N	N	3	20
AKT2	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	3	6
AKT3	N	N	N	0^{+}	N	N	N	N	N	N	N	N	N	N	N	3.8	N	4	18
PKCA	N	N	3.4	N	N	2.5	N	N	N	N	N	N	N	26.2	N	N	N	32	68
PKCH	N	21.65	N	N	N	19.2	N	N	N	N	N	N	N	20.9	N	0	N	10	40
PKN2	N	8	N	N	N	3	N	N	N	N	23.65	N	N	N	N	6.8	N	4	26
MSK1	N	N	N	N	9.4	0	N	N	N	N	N	N	N	N	N	N	N	3	12
MSK2	N	13.3	N	N	N	0	N	N	N	N	N	N	N	N	N	N	N	4	16
RSK1	N	10.9	N	N	N	0	22.4	N	N	N	N	N	N	N	N	4.1	N	4	36
RSK2	N	N	N	N	N	0	34.1	N	N	N	N	N	N	N	N	3.8	N	7	14
RSK4	N	20.25	N	N	N	0	N	N	N	N	N	N	N	N	N	N	N	5	10
PRKX	N	N	26.25	N	N	24.75	N	N	N	N	N	N	N	24.75	N	N	N	4	41
PKACB	N	N	16.15	N	N	7	N	N	N	N	N	N	N	N	N	32.2	N	14	53
PKG1	N	N	19.7	N	N	0.15	N	N	N	N	N	N	N	16.05	N	N	N	9	38
PKG2	14.1	N	N	N	N	0	N	N	N	N	N	3	N	11.3	N	N	N	16	48
MRCKA	8.1	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	16	44
DMPK1	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	2	9
NDR2	N	30.7	N	N	27.4	0	26.7	N	N	N	N	N	N	N	33.7	N	N	14	33
PDK1	12.6	15.5	N	N	10.3	5.8	29.1	N	N	N	24.6	N	N	N	N	N	N	1	10
YANK3	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	5.2	N	1	13
YANK2	N	N	N	N	N	15.4	N	N	N	N	N	18.9	N	N	N	2.8	N	3	33
CAMK1A	N	7.8	N	N	33.5	8.3	N	N	N	N	30.3	N	N	N	N	N	N	2	17
CAMK1D	33	2.1	N	N	N	0.7	N	N	N	N	16.9	N	N	N	N	N	N	4	26
CAMK1G	N	11.4	N	N	33.3	N	N	N	N	N	N	N	N	N	N	N	N	1	7
CAMK2A	26.1	28	33.8	N	N	0.5	N	N	N	N	N	N	N	19.5	31.7	N	N	5	35
CAMK2D	N	N	N	N	N	2	N	N	N	N	N	N	N	30.9	N	N	N	2	21
CAMK2B	24.7	N	N	N	N	4.6	N	N	N	N	N	N	N	12.2	30.1	N	N	9	32
CAMK2G	N	N	N	N	N	0.2	N	N	N	N	N	N	N	N	N	N	N	2	12
PHKG1	28.1	N	N	N	N	0.1	N	N	N	N	25.5	N	N	N	N	N	N	4	14
PHKG2	N	21.6	N	N	1.4	0	N	N	N	N	1.3	N	N	N	N	N	N	27	56
MNK2	1.4	24.8	N	N	N	2.1	N	16.1	N	N	8.5	N	N	2.1	2.5	19.4	N	83	188
STK33	24.1	N	N	N	3.2	0	N	10.9	N	N	2.6	N	N	N	N	N	N	6	29
AMPKA1	N	27.8	N	N	24	0	16	N	N	N	N	N	N	N	33.3	25.6	N	2	24
AMPKA2	N	25.4	N	N	25.75	0	4	N	N	N	N	N	N	N	N	14.35	N	8	33
BRSK2	N	30.3	N	N	32.75	0	8.7	N	N	N	N	6.55	N	N	N	0.1	N	7	27
MARK2	5.3	19.3	N	N	7.9	0.3	12.3	N	N	N	N	N	N	N	16.6	N	N	5	25
MARK1	N	N	N	N	15.5	0	17.5	N	N	N	N	N	N	N	N	31.3	N	8	21
MARK4	N	N	N	N	14.05	0	N	N	N	N	N	N	N	N	N	N	N	7	20
QIK	N	16.7	N	N	N	0.8	18	3.3	N	N	10.8	N	N	N	17.3	1.3	N	5	42
PIM1	0	N	N	N	N	12.8	N	N	N	N	N	21.1	N	N	N	N	N	21	44
PIM2	3.1	N	N	N	N	N	N	N	N	N	N	0.4	N	19.2	N	N	N	16	62
CAMKK2	3.7	N	N	N	N	0.1	N	N	N	N	2.8	35.4	N	N	N	N	N	10	33
CAMKK1	16.4	33.7	N	N	19.9	0.1	N	N	N	N	15.9	11	N	N	22.5	N	N	9	29
LKB1	0.5	0	N	N	0.5	1	0	25.7	25.1	N	1.4	3.7	N	N	27.7	N	N	73	132
AURC	12.5	1.7	N	N	0.9	0.5	3.4	N	N	N	2	29.7	N	N	N	32.9	N	26	79
AURB	30.85	4.7	N	N	0.15	0	0	17.2	N	N	26.7	N	N	N	N	N	N	37	98
AURA	N	13.2	N	N	9.1	0	0	8.7	N	N	32.7	N	N	N	N	N	N	15	69
PLK3	14	N	N	N	N	N	N	21.05	N	N	N	N	N	N	N	N	N	23	54
PLK1	4.05	N	N	N	N	1.55	N	N	N	N	30.9	N	N	9.5	N	N	N	18	47
PLK4	0.2	1.2	N	N	1.2	0	0	4.8	N	N	0.6	1.5	N	N	28.2	N	N	77	136
DAPK3	9.4	3.6	31.7	N	32.5	2.1	N	N	N	N	1.8	2.8	N	N	39	N	N	29	92
DAPK2	24	4.5	19	N	32	3.8	N	N	N	N	3.1	3.6	N	N	N	N	N	13	55
DRAK1	0.8	1.4	N	N	0.1	0	N	N	N	N	0.7	N	N	8.6	0.6	N	N	86	193
DRAK2	3.9	1.9	N	N	0.3	0.1	N	N	N	N	1.2	20.3	N	1.3	3.4	N	N	39	134
SKMLCK	1.9	17.4	N	N	0.8	20.7	0	16.8	N	N	N	0	N	23.5	5.7	N	N	26	82
CDK2	0.9	N	N	N	26.2	28.3	N	N	N	N	N	0.5	N	4.7	2.8	N	N	41	72
CDK5	10.4	N	N	N	8.5	16.8	N	N	N	N	N	17.2	N	N	0.6	N	N	27	63
PCTAIRE1	1.2	16.4	N	N	0	0	0.2	N	N	N	N	0	N	2.4	0	N	N	73	103
ERK1	29.6	13	N	N	N	10.8	N	32.2	N	N	N	N	N	N	N	N	N	14	47
ERK2	N	N	N	N	N	14	N	N	N	N	N	N	N	N	N	16.5	N	22	45
NLK	N	N	N	N	N	N	N	12.9	N	N	N	2.6	N	N	25.7	15.4	23.5	5	29
JNK1	N	5	N	N	20.1	0	N	23.3	N	N	N	N	N	34.8	N	1.3	5.1	54	104
JNK3	24.3	2	N	0.1	0.8	0	9.2	5.8	N	28.7	33.2	25.3	9.2	11.4	18.2	0	2.4	123	203
JNK2	N	N	N	39.1	30.6	0.1	N	N	N	N	N	N	N	N	N	10.2	0.4	19	54
P38A	N	N	N	N	N	N	N	22.2	0	0	N	N	N	N	N	28.2	0	17	36

Part 2

Kinase	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Nc≤1	Nc≤10
P38B	N	N	N	N	N	N	N	5.2	0	0	N	11.1	N	N	N	12.9	0	28	42
P38G	N	N	6.4	N	N	N	N	N	22.3	5.3	N	N	N	17.1	N	N	7.3	1	22
GSK3A	0.8	N	N	N	N	0.85	N	30.35	N	N	N	0	N	2	N	17.1	N	47	90
CLK1	0.7	N	N	N	N	0	N	N	N	N	N	N	N	0.7	28.1	N	N	87	218
CLK4	0.9	N	N	N	N	0	N	N	N	N	N	N	N	1.6	30.8	N	N	41	222
CLK2	0.9	26.7	N	N	11.5	0	N	8.5	N	N	N	6.2	N	0.2	24.6	N	N	102	207
CLK3	13.5	N	N	N	N	2.3	N	N	N	N	N	N	N	3.6	N	N	N	13	58
SRPK1	15.5	1.2	N	N	0.9	0	1.2	N	N	N	3.1	13.4	N	N	N	N	N	18	61
CK2A1	0.6	0	N	N	2.1	0	0	N	N	N	2.4	12.9	N	N	N	N	N	47	95
CK2A2	N	17.3	N	N	9.4	0	6.8	N	N	N	17.7	N	N	N	N	N	N	6	41
MAP3K5	N	15.6	N	N	N	1.4	N	N	N	N	N	N	N	N	N	N	N	0	8
MAP3K4	N	N	N	N	N	28.3	16.7	N	N	N	N	N	N	N	N	12.2	N	3	13
KHS1	N	N	N	N	21.8	0	0	5.4	N	N	24.4	N	N	N	N	0.1	N	29	62
KHS2	23.9	13.55	N	N	17.6	0.1	1.7	19.85	N	N	20	N	N	N	N	7.95	N	10	51
HPK1	9.6	9.2	N	N	3.2	0.5	0.5	16.1	N	N	1.1	N	N	N	N	0	N	33	73
HGK	8.9	19.5	N	N	10.2	0.25	17.5	1.75	N	N	N	21.4	N	N	N	26.1	2.85	6	59
TNIK	0.6	4.8	N	N	0.3	0	12.2	0.7	N	N	1.6	1.5	1.7	N	3.7	0.7	4.9	68	170
MST1	7.4	19.9	N	N	18.7	0	2	N	N	N	24.4	N	N	N	N	2.2	N	9	34
MST2	0.2	0.4	N	N	0	0	0.4	5.6	N	N	10.1	N	N	N	14.4	3.4	N	55	92
MST3	N	17.1	N	N	3.4	0.1	21.6	N	N	N	N	N	N	N	N	20.5	N	10	28
YSK1	N	N	N	N	24.15	0.4	N	N	N	N	N	N	N	N	N	2.05	N	5	18
MST4	N	7.8	19.5	N	4.4	17.2	N	N	N	N	N	N	N	N	N	15.45	N	13	35
SLK	3	6.9	N	N	N	0	1.1	16.5	N	N	0.1	2.6	N	N	N	0.1	N	61	145
LOK	13	33.5	N	N	4.8	0	0.2	17.4	N	2.25	0.1	22.5	N	N	N	0	1.1	58	99
PAK1	N	33.7	N	N	N	4.9	N	20.7	N	N	N	N	N	N	N	N	N	9	22
PAK3	N	N	N	N	29.2	0	25.9	N	N	N	N	N	N	N	N	N	N	8	20
PAK2	N	N	N	N	N	0[+]	N	6.6	N	N	N	N	N	N	N	N	N	13	24
PAK4	N	15.6	N	N	N	0.2	N	N	N	N	22.9	N	N	N	N	N	N	9	22
PAK5	N	18.5	N	N	N	0	N	32.4	N	N	29.9	N	N	N	N	N	N	14	29
PAK6	N	28.3	N	N	N	2.6	N	N	N	N	N	N	N	N	N	N	N	7	18
ULK3	8.3	2.1	27.5	N	6.3	0	3.9	8.5	N	N	11.7	N	N	N	N	N	N	40	93
FUSED	N	7.3	N	N	N	N	N	1.6	N	N	N	N	N	14.2	N	0	N	45	74
NEK2	0.3	N	N	N	N	0	N	N	N	N	N	N	N	N	13.1	N	N	34	54
NEK9	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	9	25
NEK6	N	N	N	N	34.6	N	N	N	N	N	N	N	N	N	N	N	N	18	28
NEK7	N	27.9	N	N	13.45	N	N	N	N	N	N	N	N	N	N	N	N	20	34
TLK1	N	27.55	N	N	31.65	0.75	32.9	N	N	N	N	0.1	N	N	N	N	N	9	22
TLK2	N	22.4	N	N	11.2	1.5	N	N	N	N	N	N	N	N	N	N	N	3	20
AAK1	0.2	0	N	N	1.1	0.1	1.8	N	N	N	0.2	1.5	N	13.8	33.3	N	N	89	193
BIKE	2.4	0.3	N	N	0.5	0	1.4	N	N	N	1.8	9.1	N	N	32.8	N	N	40	131
GAK	0.2	0.1	3	N	0.1	2.7	16.2	0.2	N	N	0	1.9	0	4.5	0.5	0.3	N	181	306
GCN2	1.7	0.2	N	N	3.3	0	1.8	N	N	N	3.9	N	N	N	23.25	N	N	54	96
MYT1	N	N	N	N	N	N	N	2.1	N	N	20.4	N	N	N	N	N	N	3	7
ALK1	11.7	N	N	N	N	0	N	0.3	N	N	N	17.45	N	N	N	3.3	N	7	32
ALK2	2.75	N	N	N	N	0.1	9.2	0.3	N	N	N	8.25	N	N	N	1.25	N	21	76
ALK4	N	N	N	N	N	2	N	3.5	N	N	N	N	5.45	N	N	3.1	N	4	33
TGFBR1	N	N	N	N	N	0	N	0	N	N	N	N	0	N	N	0.75	N	13	40
BMPR1A	N	N	N	N	N	4.35	N	0.85	N	N	N	N	N	N	N	0.5	N	9	22
ACTR2	N	15.4	N	N	N	22.7	N	0.7	N	N	N	4.2	20.4	N	5	30.3	N	10	41
ACTR2B	N	22.5	N	N	N	2.4	N	0	N	N	17.5	2.2	2.4	N	2.8	N	N	22	71
ABL	N	N	N	N	N	0.6	3.7	0.3	N	N	3.8	4.6	21.6	N	N	9.2	19	11	44
ARG	N	13.4	N	N	N	4.8	0	0	N	N	0.1	4.1	1.4	N	N	0.4	15.8	58	118
BTK	N	10.1	N	N	N	0	N	4	N	N	N	N	N	N	N	2.2	N	4	17
BMX	N	N	N	N	N	1.4	17.3	0	N	N	29.3	N	N	N	N	1.9	N	5	16
TXK	N	N	N	N	N	0	N	0	N	N	3.4	N	N	N	N	N	N	12	23
ITK	N	3.5	N	N	32.8	0.1	0.4	N	N	N	22.2	N	N	N	N	N	N	11	23
HCK	N	11.3	N	N	N	0	N	0.2	N	N	3.2	26.3	N	N	N	0.1	18.2	28	64
LYN	N	26.9	N	N	N	0.2	6.3	0.1	N	N	13.8	N	N	N	N	0.2	2.2	17	48
LCK	N	9.1	38.6	N	N	0	0.2	0.4	N	30.8	5.5	19.6	N	N	N	0.2	0.7	45	104
BLK	30.1	4.6	23.4	N	N	0	8.3	0.4	N	N	2.8	26.3	N	N	N	0.4	27.4	32	88
SRC	N	1.1	N	N	N	0	0.2	0	N	N	1	N	N	N	N	0	26.9	52	95
YES	N	16.6	N	N	N	0	3.7	0	N	N	11.7	27	N	N	N	0	21.4	30	65
FYN	N	15.8	N	N	N	0	10.4	0	N	N	5.2	N	N	N	N	0.4	17.4	21	59
FGR	N	10.4	N	N	N	0.1	6.8	0	N	N	2.7	20.7	N	N	N	0.7	N	23	66
FRK	N	N	N	N	N	0.5	38.7	0.4	N	N	16.5	N	N	N	N	1.3	0.7	19	49
BRK	N	29.2	N	N	N	1.8	N	0	N	N	11	N	N	N	N	0	N	26	43
CSK	N	8	N	N	N	0	N	0	N	N	N	N	N	N	N	0.2	30	27	38
FER	N	N	N	N	N	0	22.4	5	N	N	10.4	N	N	N	N	19.6	N	6	15
FES	N	N	N	N	N	0	31.9	3.3	N	N	23.2	N	N	N	N	5.7	N	8	19
FGFR2	N	7.9	N	N	9	0.1	4.3	N	N	N	N	N	N	N	N	N	N	8	46
FGFR3	N	11.1	N	N	8.1	0	4.3	N	N	N	N	N	N	N	N	N	N	13	42
FGFR1	N	8.7	N	N	13.9	0	1.7	N	N	N	N	N	N	N	N	N	N	10	36
FGFR4	N	N	N	N	N	0	N	17.6	N	N	N	N	N	N	N	N	N	10	22

Part 3

Kinase	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Nc≤1	Nc≤10
RET	N	4.8	N	N	7.5	0	0	0	N	N	2.2	N	N	N	N	1	1.4	55	90
KDR	N	26.6	N	N	0	0	2.9	18.5	N	N	N	N	N	N	33.7	18.8	N	15	41
FLT1	N	6.4	N	N	0.1	0.1	0.2	1.7	N	N	N	N	N	N	11.1	0.3	13.5	51	113
FLT4	16.3	3.7	N	N	26.1	0.1	6.4	0.8	N	N	20.3	N	N	N	N	4.6	25.4	43	88
FMS	23.5	0.6	14.3	N	0.6	0	7.9	1.1	N	N	0.9	N	N	N	11.4	0.6	0.4	58	124
KIT	N	0.7	29.2	N	0	0.1	0.7	0	N	1.5	3.5	21.9	N	N	0	0	0.1	117	182
PDGFRA	3.5	19.2	N	N	0.1	0.8	12.2	0.8	22.7	0.5	27.2	6.4	N	N	0	0	0.5	95	151
PDGFRB	3.5	1.4	19	N	0	0	4.5	0	30	0.1	0.4	5.3	N	N	0	0	0.1	121	190
FLT3	4.8	8.4	17	N	0.1	0	0.5	11	N	N	0.1	N	N	N	0.9	0.3	N	80	203
TIE2	N	34.7	N	N	N	0.4	0.4	2.5	N	N	N	N	N	N	N	2.7	N	17	42
ALK	N	11	N	N	28.2	0	22.2	N	N	N	2.2	N	N	N	N	N	N	16	51
LTK	N	N	N	N	N	0	24.3	N	N	N	8.1	N	N	N	N	N	N	6	34
ROS	N	N	N	N	N	0	N	N	N	N	N	N	N	N	N	N	N	1	16
INSR	N	13.5	N	N	N	0	0.4	N	N	N	32.9	N	N	N	N	N	N	8	16
IGF1R	N	19.8	N	N	N	0	0.1	N	N	N	34.1	N	N	N	N	N	N	9	21
IRR	N	13.95	N	N	N	0	0.15	N	N	N	N	N	N	N	N	N	N	9	20
TRKB	N	11.65	N	N	2.2	0	0.55	N	N	N	29.15	N	N	N	26.75	23.85	N	27	47
TRKC	N	27.95	N	N	6.65	0	0.1	N	N	N	N	N	N	N	30.7	N	N	22	33
TRKA	N	20.3	N	N	18.7	0	0.1	N	N	N	N	N	N	N	N	N	N	16	28
MUSK	N	N	N	N	N	0	0.45	N	N	N	N	N	N	N	27.95	N	N	16	35
AXL	0.5	33.2	N	N	11.4	0	0.2	N	N	N	1.1	N	N	N	N	2.7	N	42	86
MER	13.4	24.9	N	N	7.8	0	7.9	N	N	N	0.3	N	N	N	N	0.6	N	27	67
TYRO3	N	N	N	N	N	0.2	N	0	N	N	N	28.1	N	N	N	0.55	N	14	25
MET	N	N	N	N	N	0.3	0.6	N	N	N	15.8	N	N	29.8	N	2.3	N	13	45
ACK	N	2.1	N	N	N	0	20.2	1.2	N	N	3.4	N	N	N	N	22.8	N	12	40
TNK1	N	16.7	25.9	N	N	1	0	19.9	N	N	6.1	N	N	N	N	N	N	7	66
EGFR	N	N	N	N	N	21.2	N	1	N	N	15.9	N	N	N	N	0	N	29	49
ERBB2	N	20.2	N	N	N	N	N	N	N	N	6.9	N	N	N	N	0	N	11	24
ERBB4	N	N	N	N	N	34.7	N	9.1	N	N	27.8	N	N	N	N	0	N	15	28
SYK	N	10	N	N	N	1.3	12	1.2	N	N	0.3	16.8	N	N	N	N	N	6	41
ZAP70	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0	1
EPHA3	N	8.9	N	N	N	0	4.7	0	N	N	11.5	0.6	N	N	N	N	0	32	58
EPHA5	N	2.1	N	N	N	0	4	0	N	N	6.8	11.1	N	N	N	N	1.1	41	69
EPHA4	N	N	N	N	N	3.6	21	0	N	N	N	N	N	N	N	N	1.1	14	32
EPHA6	N	N	N	N	N	0	27.1	0	N	N	N	N	N	N	N	11.1	4.4	24	36
EPHA7	N	33.7	N	N	N	0	N	16	N	N	12.8	N	N	N	N	N	N	15	37
EPHB1	N	0	N	N	31.7	0	0.8	0	N	N	0.2	1.9	N	N	N	7.7	2.6	64	106
EPHB2	N	N	N	N	N	0.15	31.9	0	N	N	N	N	N	N	N	0	1.65	22	36
EPHB3	N	N	N	N	N	7.2	N	0	N	N	N	N	N	N	N	N	N	16	21
EPHB4	N	29.8	N	N	N	0.7	10.7	0	N	N	N	N	N	N	N	N	7.9	13	31
EPHA8	N	N	N	N	N	0.4	1.4	0	N	N	10.6	12.7	N	N	N	2	0	40	57
EPHA2	N	12.4	N	N	N	1.5	6.2	0.1	N	N	N	N	N	N	N	N	3.6	7	28
EPHA1	N	3.4	N	N	N	0.2	7.4	0	N	N	4.2	15.6	N	N	N	4.8	N	15	58
FAK	N	N	N	N	25.7	0	N	N	N	N	5.9	N	N	N	N	N	N	9	25
PYK2	N	27.3	N	N	N	0	14.7	16.2	N	N	N	N	N	N	N	N	N	11	25
JAK2	N	0.2	14	N	26.1	0.1	2.1	19.4	N	N	6.2	N	N	N	N	N	N	19	69
JAK1	N	0	N	N	7.4	1.8	N	N	N	N	N	N	N	N	N	N	N	35	63
TYK2	N	1.7	19.2	N	7.3	0	5	6.05	N	N	24.9	N	N	N	N	13.4	N	4	34
LIMK2	N	3.3	N	N	N	N	9.05	3.4	N	N	N	N	N	N	N	N	N	9	25
LIMK1	N	N	N	N	N	N	9.5	13.6	N	N	N	N	N	N	N	1.3	N	5	17
TESK1	28.1	12.2	7.7	N	N	10.8	16.2	N	N	N	N	N	N	N	N	17.5	N	6	19
HH498	N	9.3	N	N	N	7.6	N	0.1	N	24.9	N	N	N	N	N	N	6.4	9	35
MLK3	N	13.25	N	N	17.05	12.3	9.05	30.6	N	N	8.2	N	N	N	N	N	N	3	19
BRAF	2.9	28.4	N	N	N	N	N	N	N	14.25	N	24.5	N	N	N	N	N	13	24
RAF1	N	N	N	N	N	N	N	25.7	N	8.9	N	35.6	N	N	N	9.4	5.2	6	26
RIPK2	23.3	N	N	N	N	6.9	N	0	N	N	N	21.6	26.6	N	N	0	N	34	80
CK1a2	N	25.6	N	N	12.3	N	N	0.2	N	N	32.4	N	10.5	0	N	18.3	N	33	64
CK1d	16.3	7.7	N	N	0	N	N	0	N	N	9.1	19	0	0	19.6	0	N	148	221
CK1e	30.9	4.1	7.7	37.1	0	2.4	27.4	0	N	N	22.8	10.6	0	0	12.7	0	N	170	266
CK1g1	33.1	N	N	N	N	N	N	17.5	N	N	N	N	N	0	10.7	4.3	N	33	57
CK1g2	31.8	N	N	N	28.9	N	N	6.7	N	N	26.8	N	N	13.9	N	N	N	5	32
MPSK1	0	3	N	N	2.1	0	0.5	0.1	N	N	9.9	0	N	32.5	2.9	N	N	65	133
TTK	3.7	15.3	21.5	N	0.6	0	N	1.3	N	N	16	14.5	N	N	12.2	N	N	52	120
ADCK3	N	N	N	N	N	27.25	N	N	N	N	N	N	N	N	N	2	N	38	63
ADCK4	N	N	N	N	N	N	N	0	N	N	N	N	N	N	31.9	6.25	N	10	39
Nk≤1	17	12	0	2	23	126	32	48	2	4	14	8	4	6	8	39	11		
1< Nk ≤10	40	54	6	2	48	157	69	75	2	8	51	29	9	16	16	71	28		

Table S2. *Kinases that bind over half of the 18 potential DFG-out conformation binding compounds. The number of potential DFG-out binding componds that bound to each kinase with %control ≤10 is shown. The final column gives the fraction of potential DFG-out binding compounds bound at % control<10 divided by the fraction of all compounds bound at the same level. Compounds with a lower value in this final column have a high hit-rate against all compounds.*

Kinase	Group	n DFG cpds %control ≤10	Ratio DFG/All
MNK2	CAMK	9	1.5
AURB	Other	11	3.4
P38A	CMGC	9	7.6
P38B	CMGC	12	8.7
HPK1	STE	9	3.7
HGK	STE	9	4.6
TNIK	STE	10	1.8
SLK	STE	12	2.5
LOK	STE	16	4.9
HCK	TK	10	4.7
LYN	TK	12	7.6
LCK	TK	13	3.8
FRK	TK	13	8.1
RET	TK	16	5.4
FLT1	TK	14	3.8
FLT4	TK	13	4.5
FMS	TK	15	3.7
KIT	TK	17	2.8
PDGFRA	TK	16	3.2
PDGFRB	TK	16	2.6
FLT3	TK	12	1.8
TIE2	TK	10	7.2
MUSK	TK	10	8.7
AXL	TK	10	3.5
MER	TK	11	5.0
EPHA3	TK	12	6.3
EPHA5	TK	13	5.7
EPHA4	TK	13	12.3
EPHA6	TK	13	11.0
EPHB1	TK	13	3.7
EPHB2	TK	12	10.1
EPHB4	TK	9	8.8
EPHA8	TK	13	6.9
EPHA2	TK	9	9.8
HH498	TKL	10	8.7
RAF1	TKL	10	11.7

Figure S1 - *Plot of compound structural similarity (Daylight fingerprint) against compound SAR similarity. a) Tan10 metric, b) Tan1 metric. See Experimental section for definitions.*

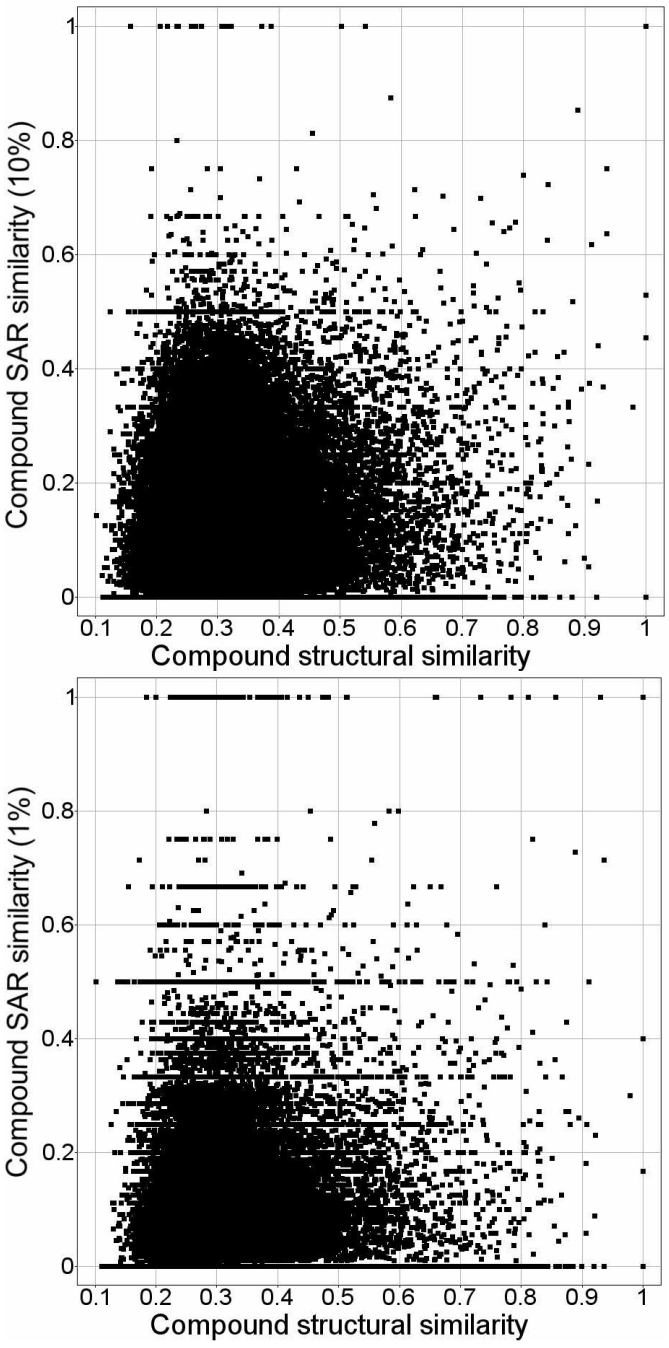


Figure S2 - *Comparison of 31 residues close to the ATP sites of AAK1 and LKB1. Residues are colour-coded by the properties shown in the Consensus column.*

AAK1	LKB1	Consensus	Comment
LEU52	LEU55	LEU	Above outer lipophilic pocket
ALA53	GLY56	SMALL	G in Gly-rich loop
GLY55	GLY58	GLY	G in Gly-rich loop
GLY56	SER59	SMALL	Turn in Gly-rich loop
PHE57	TYR60	AROMATIC	Turn in Gly-rich loop
ALA58	GLY61	SMALL	G in Gly-rich loop
VAL60	VAL63	VAL	Conserved Val above purine
GLY68	ALA76	SMALL	Conserved Ala above purine
LYS70	LYS78	LYS	Conserved Lys
GLU90	GLU98	GLU	Conserved Glu on C-helix
ILE91	ILE99	ILE	On C-helix
MET94	LEU102	ALIPHATIC	Back pocket on C-helix
VAL104	ILE111	ALIPHATIC	Back pocket
ILE124	MET127	ALIPHATIC	Back pocket
MET126	MET129	MET	Gatekeeper
ASP127	GLU130	NEGATIVE	Hinge inner H-bond acceptor
PHE128	TYR131	AROMATIC	Hinge
CYS129	CYS132	CYS	Hinge donor & outer H-bond acceptor
ARG130	VAL133	-	Outer hinge
GLY131	CYS134	SMALL	Outer hinge
GLY132	GLY135	GLY	Solvent front
GLN133	MET136	-	Solvent front & sugar pocket sidechain
VAL135	GLU138	-	Surface helix
ASN136	MET139	-	Surface helix
LYS178	LYS178	LYS	Gamma-phosphate region
GLU180	GLY180	-	Sugar pocket carbonyl
ASN181	ASN181	ASN	Mg binding
LEU183	LEU183	LEU	Outer hydrophobe below purine
CYS193	SER193	SMALL	Inner hydrophobe below purine
ASP194	ASP194	ASP	DFG Asp
PHE195	LEU195	HYDROPHOBIC	DFG Phe

Figure S3 - *Kinase sequence similarity (amino acid %identity over kinase domain) plotted against measures of kinase SAR similarity. a) Tanimoto similarity, %control threshold=1. b) As a, %control threshold=10. (c-d) are as (a-b), with unselective compounds (inhibiting 20 or more kinases with %control <1) removed.*

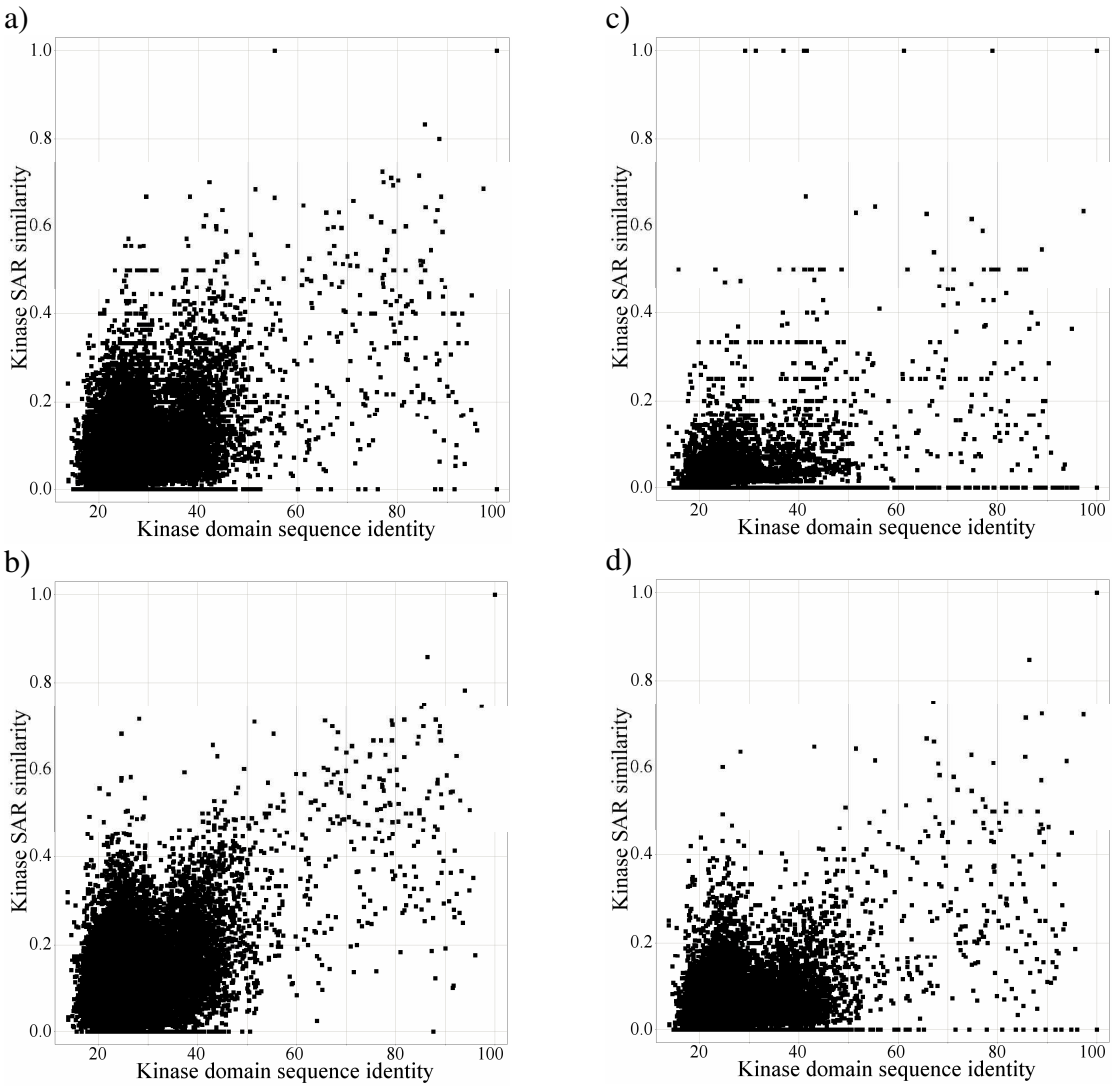


Figure S4 *– Distribution of kinases present in the assay panel plotted on the human kinome tree. Human Kinome provided courtesy of Cell Signaling Technology, www.cellsignal.com.*

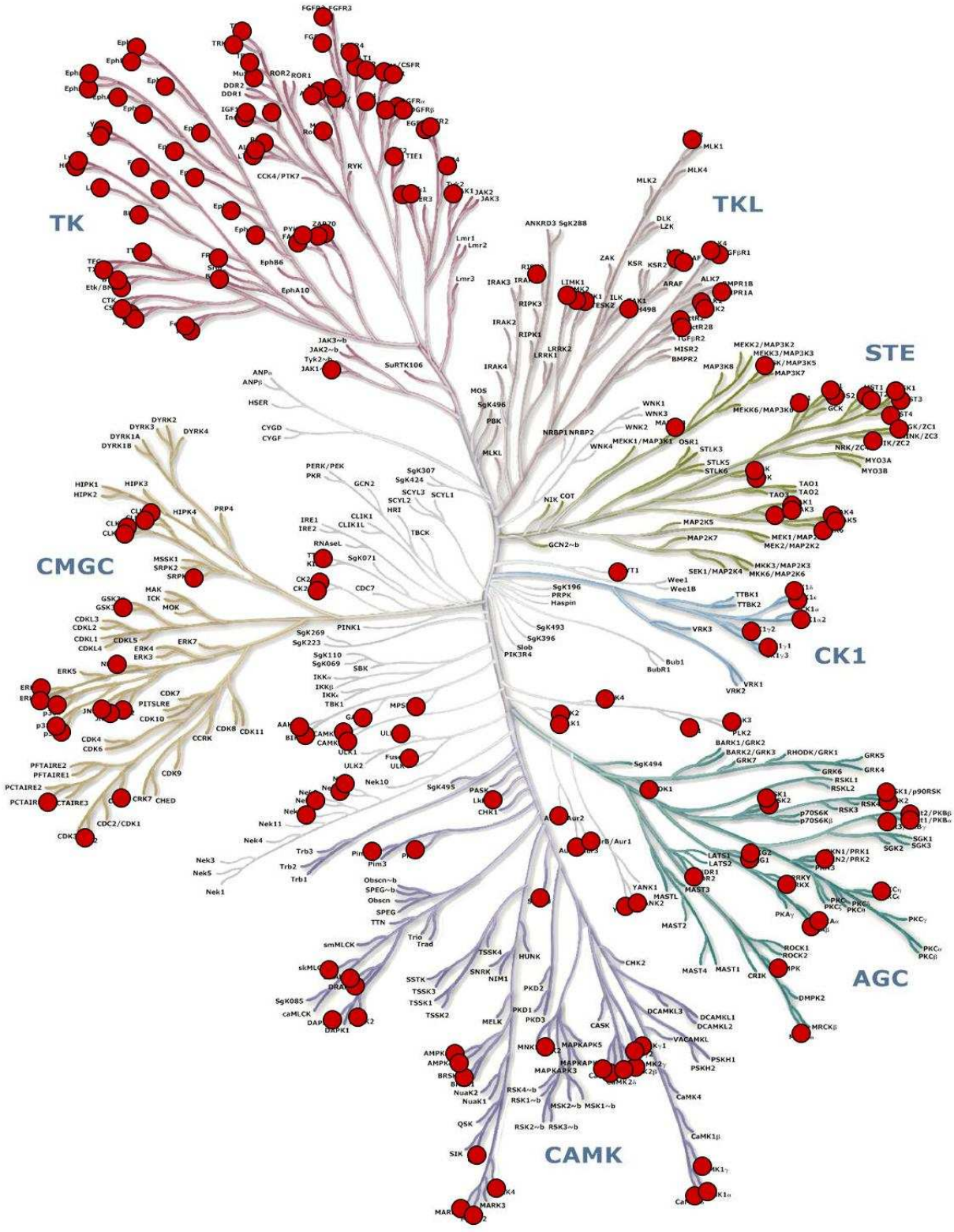
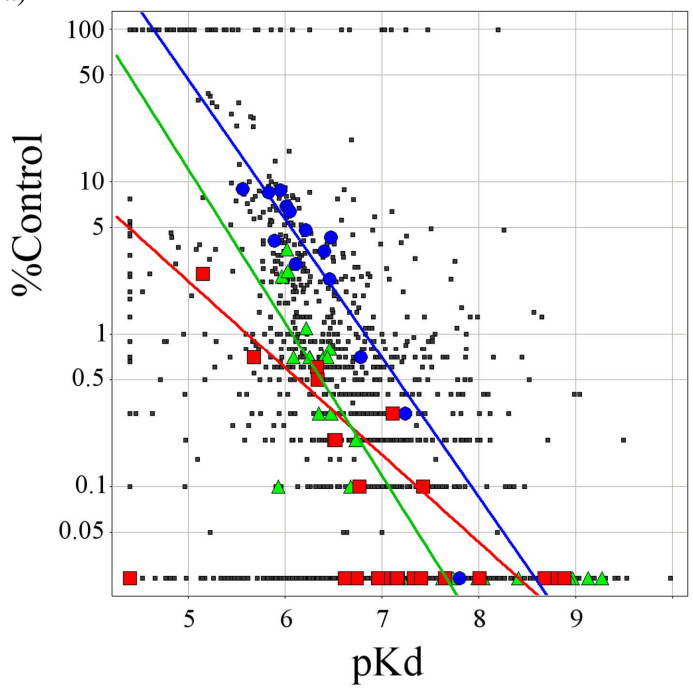


Figure S5 *– Validation of single-concentration %control data. a) Plot of %control vs. K_d over all assays (log scales). Blue circles show the correlation for Lck, red squares for KIT and green triangles for PDGFRβ. The lines of best fit through points in these assays with non-zero %control are shown. b) Plot of %control (human Lck) vs. pIC_{50} of murine Lck, as measured in a catalytic activity assay* [26].

a)



b)

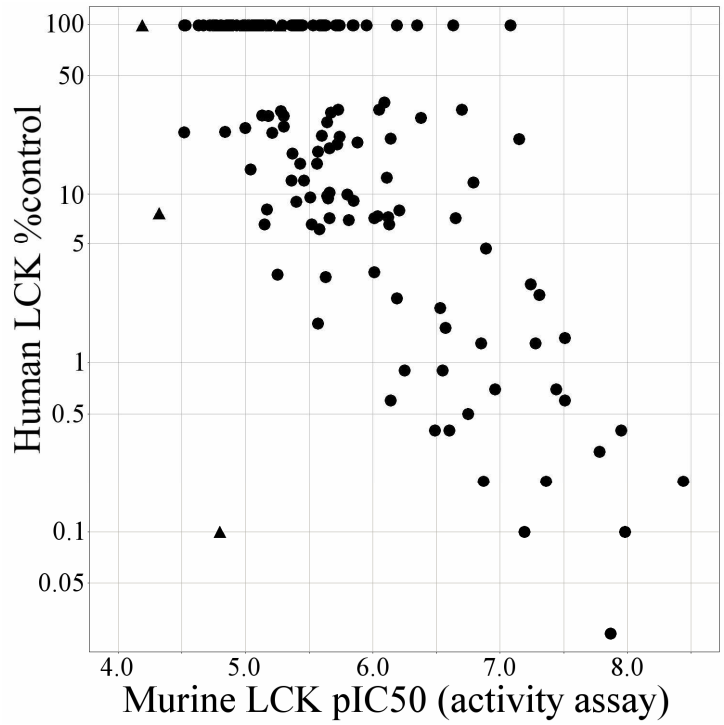


Figure S6 - *Illustration of the calculation of SAR similarity matrices for C compounds vs K kinases. The binding affinities are first converted to a binary C x K matrix (a). A C x C compound SAR similarity matrix (magenta arrows, b) and a K x K kinase similarity matrix (green arrows, c) are then produced using the Tanimoto coefficient, Nc/(Na+Nb-Nc) as defined in the figure.*

