Supplementary Data Table 1: X-ray Crystal Structure Data collection and Refinement Statistics (molecular replacement)

Data name	KSR2:MEK1:ADP	KSR2:MEK1:ANP: Trametinib	KSR2:MEK1:ANP: Cobimetinib	KSR2:MEK1:ANP: Selumetinib	KSR2:MEK1:ANP: PD0325901	KSR2:MEK1:ANP: APS-9-95-1	KSR1:MEK1:ANP	KSR1:MEK1:ANP: Trametinib	KSR1:MEK1:ANP: Cobimetinib	KSR1:MEK1:ANP: Selumetinib	KSR1:MEK1:ANP: PD0325901	KSR1:MEK1:ANP: APS-9-95-1
PDB code	7JUQ	7JUR	7JUS	7JUT	7JUU	7JUV	7JUW	7JUX	7JUY	7JUZ	7JV0	7JV1
Data collection												
Space group	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2	P 6_1 2 2
Cell dimensions												
a, *b*, *c* (Å)	139.03,139.03, 222.41	139.82,139.82, 221.58	140.04, 140.04, 220.60	139.10, 139.10, 218.98	138.95, 138.95, 222.10	138.74, 138.74, 221.83	137.71, 137.71, 218.91	137.47, 137.47, 221.80	136.20, 136.20, 218.57	137.37, 137.37, 216.55	137.66, 137.66, 220.89	137.05, 137.05, 221.28
α, β, γ (°)	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120	90 90 120
Resolution (Å)	50 - 3.22	50 - 2.82	50 - 2.99	50 - 3.09	50 - 3.19	50 - 3.35	50 - 2.88	50 - 3.34	50 - 3.1	50 - 3.21	50 - 3.63	50 - 3.62
R_{meas} (%)	9.9 (213.1)	13.7 (197.1)	8.0 (247.7)	10.2 (224.8)	10.2 (222.1)	9.3 (194.1)	10.7 (268.3)	9.0 (227.5)	9.3 (221.2)	7.9 (225.4)	12. 3 (187.2)	8.6 (190.7)
I / σI	20.86 (1.33)	15.87 (1.30)	22.26 (1.18)	20.90 (1.27)	17.70 (1.20)	11.90 (1.27)	18.75 (1.02)	17.57 (1.24)	20.4 (1.17)	(20.99) 1.09	15.10 (1.30)	16.46 (1.36)
$CC_{1/2}$	0.99 (0.51)	0.99 (0.52)	1.0 (0.51)	1.0 (0.51)	0.99 (0.48)	0.99 (0.59)	0.99 (0.51)	0.99 (0.48)	1.0 (0.51)	1.0 (0.54)	0.99 (0.54)	1.0 (0.49)
Completeness (%)	99.9 (100)	100 (100)	99.9 (100)	99.9 (99.9)	99.8 (100)	99.7 (100)	99.4 (100)	99.9 (100)	99.9 (100)	99.8 (99.9)	99.9 (100)	93.7 (95.3)
Redundancy	11.98 (12.37)	12.05 (12.42)	11.98 (12.43)	11.76 (11.15)	10.95 (11.38)	11.02 (11.58)	14.83 (15.52)	11.66 (12.35)	11.95 (12.41)	10.59 (11.01)	11.74 (12.28)	12.55 (12.98)
Refinement												
Resolution (Å)	3.22	2.82	2.99	3.09	3.19	3.35	2.88	3.34	3.1	3.21	3.63	3.62
No. reflections	21247	31247	28127	23585	21548	18480	28300	18630	22406	20359	14589	13697
R_{work} / R_{free} (%)	25.4 / 28.8	23.7 / 27.7	24.7 / 26.4	25.6 / 30.0	24.1 / 25.7	23.2 / 24.8	23.6 /27.8	26.4 / 28.3	24.7 / 25.7	25.3 / 27.1	24.5 / 25.9	27.7 / 30.3
No. atoms												
Protein	4670	4662	4651	4654	4645	4662	4679	4667	4668	4628	4652	4639
Ligand/Ion	55	101	94	89	90	103	64	100	94	89	89	102
Water	2	7	11	7	3	12	8	1	1	0	0	0
B-factors												
Protein	118.88	87.97	110.59	112.14	123.65	107.46	106.34	147.59	117.73	139.16	161.22	164.32
Ligand/Ion	108.17	83.89	110.08	110.7	118.76	106.73	104.18	156.83	124.17	146.06	173.31	184.11
Water	78.87	56.69	86.6	71.98	71.06	62.91	84.52	109.46	91.64	-	-	-
R.m.s. deviations												
Bond lengths (Å)	0.004	0.007	0.013	0.003	0.003	0.005	0.01	0.003	0.006	0.004	0.004	0.003
Bond angles (°)	0.994	1.085	1.813	0.605	0.574	0.965	1.242	0.86	1.089	0.67	0.882	0.88

* Values in parentheses are for highest-resolution shell.