Supporting Information

A Proteometric Analysis of Human Kinome: Insight into Discriminant Conformation-Dependent Residues

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Table S1: List of the 444 kinase domain names used in the protein alignment.

Table S2: The first 5 z-scale components for the twenty natural amino-acids.[1]

Table S3: List of the 200 variables selected using the absolute regression coefficients of the PLS model. The variables are in decreasing order according to the absolute regression coefficients. In red are the variables kept after filtering on the total occurrence of the residue positions and on the gap proportions (gap percentage < 20%).

Figure S4: Aligned ABL1 sequence with the corresponding numbering used in the text. The residue positions selected by the model are in red.

Table S5: Comparison of the 29 residue positions found with the global statistical model including four Type-II kinase inhibitors with the residue positions found with each individual model built with one Type-II inhibitor.

Table S6: Residue selection from the dataset provided by Davis *et al.*[2] based on the best 200 variables selected by PLS regression. Only residue positions containing at least 2 z-scale descriptors and with less than 20% of gaps were kept. Asterisks symbolized the residue positions also found by applying the PLS model on the training set.

Table S7: Percentages of inhibition of Type-II inhibitors for each protein kinase. Non-bold rows represent the 263 protein kinases, used as training set for the PLS model and for which the activity was measured by Anastassiadis *et al.*[3] Bold rows represent protein kinases for which the activity was predicted by our statistical model. The rows in which the predicted activity is given in parentheses represent protein kinases that had been removed from the training set, and for which their activities were measured by Anastassiadis *et al.*[3] (see Method).

Figure S8: Residue selection from the PLS model established with the ponatinib datset. Only residue positions containing at least 2 z-scale descriptors and less than 20% of gaps were kept. We calculated three different rankings. Ranking sum_abs_coeff was obtained by summing the absolute coefficients of each residue position. Rank mean_diff was calculated according to the mean percentage difference for each residue at each position between protein kinases that bind the four Type-II inhibitors and those that do not bind the inhibitors. Rank max_diff was determined using the maximum difference for each residue. In bold are the positions we studied.

Figure S9: Representation of the C and R spines on the kinase domain of ABL1. The hydrophobic part of the R spine is shown as a red molecular surface, while the C spine is colored in yellow. The 29 selected residues identified by the PLS regression are represented in dark blue stick. The spines residues are atom-colored.

Figure S10: Representation of intermediate conformations of Phe of DFG motif (yellow) for protein kinases classified as DFG-out by MOE, with a Met as gatekeeper (PDB entries 1M7N,

1P4O, 2JIT, 2JIU, 2W5B, 2W5H, 3IKA and 4FZF). Phe conformations of DFG-out (green) and DFG-in (blue) of ABL1 crystal structures from PDB entries 2HYY and 2GQG respectively.

Table S1

AAK1	AATK	ABL1	ABL2	ACVR1	ACVR1B	ACVR1C	ACVR2A	ACVR2B
ACVRL1	ADRBK1	ADRBK2	AKT1	AKT2	AKT3	ALK	AMHR2	ANKK1
ARAF	AURKA	AURKB	AURKC	AXL	BLK	BMP2K	BMPR1A	BMPR1B
BMPR2	BMX	BRAF	BRSK1	BRSK2	BTK	BUB1	BUB1B	CAMK1
CAMK1D	CAMK1G	CAMK2A	CAMK2B	CAMK2D	CAMK2G	CAMK4	CAMKK1	CAMKK2
CCRK	CDC2	CDC2L2	CDC2L5	CDC2L6	CDC42BPA	CDC42BPB	CDC42BPG	CDC7
CDK10	CDK2	CDK3	CDK4	CDK5	CDK6	CDK7	CDK8	CDK9
CDKL1	CDKL2	CDKL3	CDKL4	CDKL5	CHEK1	CHEK2	CHUK	CIT
CLK1	CLK2	CLK3	CLK4	CRKRS	CSF1R	CSK	CSNK1A1	CSNK1A1L
CSNK1D	CSNK1E	CSNK1G1	CSNK1G2	CSNK1G3	CSNK2A1	CSNK2A2	DAPK1	DAPK2
DAPK3	DCLK1	DCLK2	DCLK3	DDR1	DDR2	DMPK	DYRK1A	DYRK1B
DYRK2	DYRK3	DYRK4	EGFR	EIF2AK1	EIF2AK2	EIF2AK3	EPHA1	EPHA2
EPHA3	EPHA4	EPHA5	EPHA6	EPHA7	EPHA8	EPHB1	EPHB2	EPHB3
EPHB4	ERBB2	ERBB4	ERN1	ERN2	FER	FES	FGFR1	FGFR2
FGFR3	FGFR4	FGR	FLT1	FLT3	FLT4	FRK	FYN	GAK
GCN2	GRK1	GRK4	GRK5	GRK6	GRK7	GSG2	GSK3A	GSK3B
HCK	HIPK1	HIPK2	HIPK3	HIPK4	HUNK	ICK	IGF1R	IKBKB
IKBKE	INSR	INSRR	IRAK1	IRAK3	IRAK4	ITK	JAK1	JAK2
JAK3	KALRN	KDR	KIAA1804	KIT	LATS1	LATS2	LCK	LIMK1
LIMK2	LMTK2	LMTK3	LRRK1	LRRK2	LTK	LYN	MAK	MAP2K1
MAP2K2	MAP2K3	MAP2K4	MAP2K5	MAP2K6	MAP2K7	MAP3K1	MAP3K10	MAP3K11
MAP3K12	MAP3K13	MAP3K14	MAP3K15	MAP3K2	MAP3K3	MAP3K4	MAP3K5	MAP3K6
MAP3K7	MAP3K8	MAP3K9	MAP4K1	MAP4K2	MAP4K3	MAP4K4	MAP4K5	MAPK1
MAPK10	MAPK11	MAPK12	MAPK13	MAPK14	MAPK15	MAPK3	MAPK4	MAPK6
MAPK7	MAPK8	MAPK9	MAPKAPK2	MAPKAPK3	MAPKAPK5	MARK1	MARK2	MARK3
MARK4	MAST1	MAST2	MAST3	MAST4	MASTL	MATK	MELK	MERTK
MET	MINK1	MKNK1	MKNK2	MLCK	MOS	RPS6KA5~d1	RPS6KA4~d1	MST1R
MST4	MUSK	MYLK	MYLK2	MYLK4	MYO3A	MYO3B	NEK1	NEK10
NEK11	NEK2	NEK3	NEK4	NEK5	NEK6	NEK7	NEK8	NEK9
NIM1	NLK	NRK1	NTRK1	NTRK2	NTRK3	NUAK1	NUAK2	OBSCN
OBSCN~b	OXSR1	PAK1	PAK2	PAK3	PAK4	PAK6	PAK7	PASK
PBK	PCTK1	PCTK2	PCTK3	PDGFRA	PDGFRB	PDIK1L	PDPK1	PFTK1
PFTK2	PHKG1	PHKG2	PIK3R4	PIM1	PIM2	PIM3	PINK1	PKDCC
PKMYT1	PKN1	PKN2	PKN3	PLK1	PLK2	PLK3	PLK4	PNCK
PRKAA1	PRKAA2	PRKACA	PRKACB	PRKACG	PRKCA	PRKCB	PRKCD	PRKCE
PRKCG	PRKCH	PRKCI	PRKCQ	PRKCZ	PRKD1	PRKD2	PRKD3	PRKG1
PRKG2	PRKX	PRKY	PRPF4B	PSKH1	PTK2	PTK2B	PTK6	RAF1
RAGE	RET	RIPK1	RIPK2	RIPK3	RIPK4	RIPK5	RNASEL	ROCK1
ROCK2	ROR1	ROR2	ROS1	RPS6KA1~d2	RPS6KA2~d2	RPS6KA3~d2	RPS6KA4~d2	RPS6KA5~d2
RPS6KA6~d2	RPS6KB1	RPS6KB2	RPS6KA1~d1	RPS6KA2~d1	RPS6KA3~d1	RPS6KA6~d1	RYK	SBK1
SBK2	SGK1	SGK110	SGK2	SGK3	SGK494	SIK3	SLK	SNF1LK
SNF1LK2	SNRK	SPEG	SPEG~b	SRC	SRMS	SRPK1	SRPK2	SRPK3
STK10	STK11	STK16	STK17A	STK17B	STK24	STK25	STK3	STK32A
STK32B	STK32C	STK33	STK35	STK36	STK38	STK38L	STK39	STK4
SYK	TAOK1	TAOK2	TAOK3	TBK1	TEC	TEK	TESK1	TESK2
TGFbR1	TGFbR2	TIE1	TLK1	TLK2	TNIK	TNK1	TNK2	TNNI3K
TP53RK	TRIO	TSSK1B	TSSK2	TSSK3	TSSK4	TSSK6	TTBK1	TTBK2
TTK	TTN	TXK	TYK2	TYRO3	UHMK1	ULK1	ULK2	ULK3
VRK1	VRK2	WEE1	WEE2	WNK1	WNK2	WNK3	WNK4	YES1
YSK4	ZAK	ZAP70						

Table S2

Residue	z1	z2	z3	z4	z5
Ala	0.24	-2.32	0.60	-0.14	1.30
Arg	3.52	2.50	-3.50	1.99	-0.17
Asn	3.05	1.62	1.04	-1.15	1.61
Asp	3.98	0.93	1.93	-2.46	0.75
Cys	0.84	-1.67	3.71	0.18	-2.65
Gln	1.75	0.50	-1.44	-1.34	0.66
Glu	3.11	0.26	-0.11	-3.04	-0.25
Gly	2.05	-4.06	0.36	-0.82	-0.38
His	2.47	1.95	0.26	3.90	0.09
Ile	-3.89	-1.73	-1.71	-0.84	0.26
Leu	-4.28	-1.30	-1.49	-0.72	0.84
Lys	2.29	0.89	-2.49	1.49	0.31
Met	-2.85	-0.22	0.47	1.94	-0.98
Phe	-4.22	1.94	1.06	0.54	-0.62
Pro	-1.66	0.27	1.84	0.70	2.00
Ser	2.39	-1.07	1.15	-1.39	0.67
Thr	0.75	-2.18	-1.12	-1.46	-0.40
Trp	-4.36	3.94	0.59	3.44	-1.59
Tyr	-2.54	2.44	0.43	0.04	-1.47
Val	-2.59	-2.64	-1.54	-0.85	-0.02

Table S3

variables	absolute_coefficients
res325z1	0.90
res325z4	0.81
res426z5	0.70
res662z2	0.68
res226z2	0.67
res101z3	0.65
res804z2	0.64
res391z4	0.63
res388z5	0.62
res105z4	0.61
res103z2	0.61
res108z1	0.60
res325z2	0.60
res799z5	0.60
res241z1	0.59
res785z1	0.59
res230z5	0.59
res177z3	0.58
res722z3	0.58
res734z2	0.57
res426z3	0.56
res666z5	0.56
res722z5	0.55
res187z5	0.54
res691z2	0.53
res729z5	0.53
res389z1	0.52
res799z3	0.52
res622z3	0.51
res371z3	0.50
res363z1	0.49
res118z3	0.49
res389z5	0.49
res665z3	0.49
res378z2	0.49
res625z1	0.49
res754z4	0.49
res366z1	0.48
res234z1	0.47
res675z4	0.47
res240z2	0.47
res331z5	0.47
res330z5	0.46
res404z2	0.46
res567z2	0.46
res372z2	0.46
res746z2	0.45
res675z3	0.45
res725z5	0.45
res384z3	0.45
res567z5	0.45
res414z1	0.44
res802z4	0.44
res426z4	0.44
res371z5	0.44
res402z5	0.44
res366z2	0.44
res295z1	0.44
res397z4	0.43
res622z1	0.43
res331z1	0.43
res372z3	0.43
res226z3	0.43
es375z2	0.42
res367z4	0.42
res325z3	0.42
res365z4	0.42
res724z1	0.42
res414z2	0.42
res521z1	0.42
res739z5	0.42
res808z2	0.42
res249z4	0.41
res570z1	0.41
res389z2	0.41
res778z4	0.41
res567z1	0.41
res384z4	0.41
res782z3	0.40
res577z1	0.40
res402z4	0.40
res778z3	0.40
res296z5	0.40
res785z3	0.40
res367z3	0.40
res493z2	0.39
res798z2	0.39
res778z5	0.39
res663z4	0.39
res239z3	0.39
res615z2	0.39
res371z1	0.39
res740z4	0.39
res491z5	0.39
res121z2	0.39
res809z5	0.38
res194z1	0.38
res98z4	0.38
res577z3	0.38
res236z1	0.38
res366z5	0.38
res389z4	0.38
res802z1	0.38
res738z1	0.38
res181z5	0.38
res527z5	0.38
res118z1	0.38
res324z3	0.38
res316z4	0.38
res248z5	0.38
res196z1	0.38
res801z2	0.38
res606z2	0.37
res367z5	0.37
res809z1	0.37
res368z1	0.36
res254z1	0.36
res606z4	0.36
res605z2	0.36
res100z3	0.36
res196z2	0.36
res119z1	0.36
res665z4	0.36
res227z2	0.35
res725z2	0.35
res424z3	0.35
res329z5	0.35

res385z1		0.35
res425z4		0.35
res114z5		0.35
res748z2		0.35
res392z1		0.35
res120z5		0.35
res295z3		0.35
res407z4		0.34
res806z1		0.34
res179z4		0.34
res785z5		0.34
res242z3		0.34
res751z4		0.34
res427z5		0.34
res187z1		0.34
res401z4		0.34
res584z3		0.34
res362z3		0.34
res296z2		0.34
res189z5		0.34
res119z3		0.34
res396z1		0.34
res615z1		0.34
res665z2		0.34
res492z2		0.34
res492z5		0.34
res808z5		0.34
res192z5		0.33
res806z4		0.33
res400z3		0.33
res393z5		0.33
res114z3		0.33
res493z3		0.33
res331z3		0.33
res569z5		0.33
res374z5		0.33
res370z5		0.33
res808z4		0.33
res450z1		0.33
res388z3		0.33
res444z3		0.33
res329z4		0.32
res579z5		0.32
res450z3		0.32
res331z2		0.32
res416z2		0.32
res606z5		0.32
res662z5		0.32
res239z4		0.32
res787z1		0.32
res386z4		0.32
res365z5		0.32
res409z4		0.32
res528z5		0.32
res493z1		0.32
res184z2		0.31
res409z2		0.31
res620z3		0.31
res795z5		0.31
res617z4		0.31
res610z3		0.31
res196z3		0.31
res410z5		0.31
res116z3		0.31
res735z5		0.31
res192z4		0.31

res358z2		0.31
res567z3		0.31
res416z5		0.31
res402z3		0.31
res226z4		0.31
res371z2		0.31
res743z5		0.31

Figure S4

>ABL1_Hsap (TK/Abl)

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- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - res60
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - I T M K H - K L G G G Q Y G E - V Y E G V W K K Y S - res120
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - L res180
T V A V K T L - K E D T M E - - - - - - - - - - - . - - - - - - - - - - - - - - - - - - V E E F L K E A A V M K E I K - res240
- - - - - - - - - H P N L V - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - Q L L G V C T R E P - res300
- - - - - - - - - - - - - - - P F Y I - I T E F - M T Y G - - - - - - - - - - - - - - - - - - - - - - - - N L L res360
D Y L R E - - - - - - - - - - - - - - - - - - - - C N R Q E V N A V V L L Y M A T Q I S S A M E Y L - E K - - - - - res420
- - - - K N F I H - - - - - - - - - - - R D L A A R N C L V - - - - - - - - - - - - - - - - - - - - - - - - - - res480
- - - - - - G E N H L V K V - - - - A D F G - - - - - - - - - - - - - - - - - L S R L M T - - - - - - - - - - - res540
- - - - - - - - - - - - - - - - - - - - - - G D T Y T A H A G - A K F P I K W T - - - - - - - - - - - - - - - res600
- - - - A P E - - - - - - - - S L A Y N K F - S I - - - - - K - S D V W A F G V L L W E I - - - - - - - - - - - - - res660
- A T Y G M S - - - - - P Y - - - - - - - - - - - - - P G I - - - - - - - - - - - - - - - - - - - - - - - - D L S Q res720
V - - - - Y E L L E K - D Y R M E R P E G - C P E K V Y E L - - - - - - - - - - - - - - - - - - - - - - - - M R A C res780
W Q W N P S D - - - - - R - P S - F A E I H Q A F - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - res840
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - res900
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - res960
- - - - - - - - - - - - - - - - res977
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Table S5

Residue position	Occurences imatinib	rank imatinib	Occurences masitinib	Rank masitinib	Occurences nilotinib	rank nilotinib	Occurences sorafenib	rank sorafenib
res426	5	1	4	2	4	2	2	17
res325	2	23	3	7	4	1	3	2
res192	2	4	3	4	1	75	2	14
res606	3	3	2	13	2	21	1	67
res785					3	3	3	3
res414	1	50			3	13	3	1
res402	1	57	1	81	3	7	3	5
res226			2	32	3	9	2	11
res675	2	13	2	18	2	22	1	41
res802	4	2	2	12				
res239			3	14			3	7
res187					3	14	2	18
res331	3	7	1	66	2	24		
res118	1	52			3	11	1	57
res799			2	29	2	35		
res665							3	4
res492			1	60	2	28		
res409					1	62	2	23
res365			1	72	1	73	1	69
res329					2	29		
res114	2	20	1	51				
res450							2	20
res778					1	52	1	73
res295	1	46	1	49				
res577	1	42	1	59				
res622							1	32
res296					1	53		

Table S6

Residue positions	Occurrence	Corresponding variables	Sum of absolute coefficients
res226*	4	res226z2, res226z1, res226z4, res226z3	0.05
res325*	4	res325z4, res325z1, res325z2, res325z3	0.05
res606*	3	res606z4, res606z2, res606z5	0.04
res187*	3	res187z5, res187z1, res187z3	0.04
res665*	3	res665z3, res665z4, res665z2	0.04
res499	3	res499z4, res499z1, res499z2	0.04
res785*	3	res785z1, res785z3, res785z4	0.03
res397	2	res397z4, res397z2	0.03
res804	2	res804z1, res804z2	0.03
res799*	3	res799z5, res799z3, res799z2	0.03
res414*	2	res414z1, res414z2	0.02
res675*	3	res675z4, res675z1, res675z3	0.02
res108	2	res108z1, res108z2	0.02
res625	2	res625z4, res625z1	0.02
res787	2	res787z4, res787z1	0.02
res742	2	res742z5, res742z3	0.02
res360	2	res360z4, res360z3	0.02
res327	2	res327z2, res327z5	0.02
res425	2	res425z1, res425z2	0.02
res402*	2	res402z5, res402z4	0.02
res330	2	res330z4, res330z5	0.02
res321	2	res321z3, res321z5	0.02
res524	2	res524z2, res524z5	0.02
res181	2	res181z2, res181z1	0.02
res111	2	res111z3, res111z5	0.02
res118*	2	res118z3, res118z1	0.02
res331*	2	res331z2, res331z5	0.02
res622*	2	res622z4, res622z1	0.02
res404	2	res404z3, res404z1	0.02
res194	2	res194z5, res194z1	0.02

Table S7

Kinase	Percentage of inhibition
AAK1	**38.3**
AATK	**-12.0**
ABL1	96.5
ABL1/E255K/	**93.0**
ABL1/F317I/	**94.0**
ABL1/F317L/	**94.0**
ABL1/H396P/	**94.0**
ABL1/M351T/	**89.9**
ABL1/Q252H/	**85.3**
ABL1/T315I/	**85.2**
ABL1/Y253F/	**94.0**
ABL2	95.1
ACVR1	1.3
ACVR1B	0.2
ACVR1C	**17.5**
ACVR2A	**-0.3**
ACVR2B	**8.9**
ACVRL1	-3.1
ADRBK1	4.2
ADRBK2	4.9
AKT1	6.9
AKT2	-2.5
AKT3	25.2
ALK	4.9
AMHR2	**-16.1**
ANKK1	**12.3**
ARAF	93.0
AURKA	21.1
AURKB	36.87 **(2.9)**
AURKC	12.8
AXL	35.23 **(44.1)**
BLK	42.5 **(68.7)**
BMP2K	**20.5**
BMPR1A	**1.7**
BMPR1B	**-3.7**
BMPR2	**-4.9**
BMX	6.7
BRAF	88.5
BRAF/V600E/	**86.3**
BRSK1	4.2
BRSK2	0.1
BTK	0.4
BUB1	**58.0**
BUB1B	**11.9**
CAMK1	-2.4
CAMK1D	12.3

Kinase	Percentage of inhibition
CAMK1G	1.6
CAMK2A	4.7
CAMK2B	5.0
CAMK2D	10.0
CAMK2G	1.4
CAMK4	1.4
CAMKK1	8.9
CAMKK2	2.5
CCRK	**-3.9**
CDC2	2.4
CDC2L2	**-6.8**
CDC2L5	**6.0**
CDC2L6	**-14.4**
CDC42BPA	14.8
CDC42BPB	2.9
CDC42BPG	**7.6**
CDC7	**46.1**
CDK10	**-12.9**
CDK2	5.3
CDK3/cyclinE/	**1.3**
CDK4	5.9
CDK5	8.3
CDK6	9.5
CDK7	-0.6
CDK8	**-9.7**
CDK9	5.3
CDKL1	**17.9**
CDKL2	**10.2**
CDKL3	**11.6**
CDKL4	**36.8**
CDKL5	**5.2**
CHEK1	9.1
CHEK2	0.9
CHUK	3.8
CIT	**10.6**
CLK1	26.2
CLK2	14.0
CLK3	6.4
CLK4	54.5
CRKRS	**4.5**
CSF1R	94.4
CSK	57.6
CSNK1A1	2.2
CSNK1A1L	**14.5**
CSNK1D	10.7
CSNK1E	7.6
CSNK1G1	7.6
CSNK1G2	11.1

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CSNK1G3	3.2	FGFR1	9.1
CSNK2A1	0.8	FGFR2	27.3
CSNK2A2	13.3	FGFR3	10.5
DAPK1	2.5	FGFR4	10.2
DAPK2	1.5	FGR	56.4
DAPK3	8.5	**FLT1**	49.5 **(50.3)**
DCLK1	**-4.0**	**FLT3**	90.8 **(62.0)**
DCLK2	-1.7	**FLT3/D835H/**	**62.0**
DCLK3	**-4.6**	**FLT3/D835Y/**	**62.0**
DDR1	**101.1**	**FLT3/K663Q/**	**62.0**
DDR2	98.2	**FLT3/N841I/**	**56.6**
DMPK	6.8	**FLT3/R834Q/**	**62.0**
DYRK1A	-1.7	FLT4	57.0
DYRK1B	7.2	FRK	83.8
DYRK2	1.1	FYN	62.7
DYRK3	8.6	**GAK**	**35.7**
DYRK4	-0.4	**GRK1**	**22.9**
EGFR	13.1	GRK4	10.8
EGFR/E746_A750del/	**8.4**	GRK5	5.0
EGFR/G719C/	**14.3**	GRK6	-2.6
EGFR/G719S/	**14.3**	**GRK7**	**-4.8**
EGFR/L747-T751del_Sins/	**8.4**	GSG2	33.5 (13.4)
EGFR/L747_E749del_A750P/	**8.4**	GSK3A	0.6
EGFR/L747_S752del_P753S/	**8.8**	GSK3B	6.3
EGFR/L858R/	**17.3**	HCK	53.4
EGFR/L861Q/	**14.3**	HIPK1	3.0
EGFR/S752-I759del/	**12.5**	HIPK2	12.2
EGFR/T790M/	**14.3**	HIPK3	14.3
EGFR/T790M_L858R/	**17.3**	**HIPK4**	**95.1**
EIF2AK1	**18.5**	**HUNK**	**-7.4**
EIF2AK2	**6.8**	**ICK**	**-3.1**
EIF2AK3	**-23.7**	IGF1R	11.6
EPHA1	36.8 **(64.5)**	IKBKB	17.2
EPHA2	89.2	IKBKE	10.7
EPHA3	59.2	INSR	1.0
EPHA4	88.0	INSRR	-1.5
EPHA5	77.4	IRAK1	6.7
EPHA6	58.0	**IRAK3**	**19.1**
EPHA7	19.3	IRAK4	19.8
EPHA8	71.6	ITK	1.8
EPHB1	89.4	**KALRN**	**-7.8**
EPHB2	98.5	KDR	63.1
EPHB3	94.4	**KIAA1804**	**24.7**
EPHB4	88.6	**KIT**	**71.8**
ERBB2	-2.7	**KIT/A829P/**	**74.8**
ERBB4	17.9	**KIT/D816H/**	**71.8**
ERN1	**23.7**	**KIT/D816V/**	**71.8**
ERN2	**12.4**	**LATS1**	**-4.7**
FER	6.4	**LATS2**	**-3.4**
FES	4.1	LCK	92.4

LIMK1	23.2	MAPKAPK3	2.2
LIMK2	**45.1**	MAPKAPK5	9.2
LMTK2	**-1.5**	MARK1	25.2
LMTK3	**-5.5**	MARK2	5.3
LRRK1	**7.6**	MARK3	6.2
LRRK2	18.9	MARK4	1.9
LTK	0.1	**MAST1**	**-16.1**
LYN	83.8	**MAST2**	**-18.6**
MAK	**8.7**	**MAST3**	**-13.1**
MAP2K1	-2.5	**MAST4**	**-9.4**
MAP2K2	10.3	**MASTL**	**20.7**
MAP2K3	**-6.8**	MATK	20.8
MAP2K4	**8.4**	MELK	15.2
MAP2K5	**30.0**	MERTK	11.8
MAP2K6	3.7	MET	4.2
MAP2K7	**-1.9**	**MET/M1250T/**	**12.3**
MAP3K1	**28.8**	**MET/Y1235D/**	**15.9**
MAP3K10	-1.9	MINK1	13.3
MAP3K11	1.7	MKNK1	24.9
MAP3K12	**-0.7**	MKNK2	29.7
MAP3K13	**8.9**	**MLCK**	**10.2**
MAP3K14	9.0	**MOS**	**26.0**
MAP3K15	**7.7**	MST1R	15.3
MAP3K2	-2.3	MST4	3.0
MAP3K3	-5.9	MUSK	8.9
MAP3K4	**11.4**	MYLK	7.4
MAP3K5	5.0	MYLK2	3.9
MAP3K6	**-11.7**	**MYLK4**	**4.2**
MAP3K7	10.8	**MYO3A**	**20.6**
MAP3K8	8.5	MYO3B	17.4
MAP3K9	-2.3	NEK1	25.0
MAP4K1	**-1.7**	**NEK10**	**-1.9**
MAP4K2	-2.5	NEK11	4.9
MAP4K3	**11.9**	NEK2	3.3
MAP4K4	27.8	NEK3	4.1
MAP4K5	**43.0 (14.4)**	NEK4	7.6
MAPK1	10.1	**NEK5**	**7.6**
MAPK10	9.2	NEK6	8.7
MAPK11	84.7	NEK7	4.5
MAPK12	7.0	**NEK8**	**1.2**
MAPK13	9.3	NEK9	4.6
MAPK14	76.7	**NIM1**	**14.1**
MAPK15	**-6.1**	NLK	0.9
MAPK3	-1.5	**NRK1**	**2.8**
MAPK4	**13.6**	NTRK1	23.9 **(12.5)**
MAPK6	**21.1**	NTRK2	14.6 **(9.8)**
MAPK7	**9.7**	NTRK3	34.5 **(1.6)**
MAPK8	7.9	NUAK1	1.2
MAPK9	5.2	NUAK2	1.6
MAPKAPK2	5.8	**OBSCN/b/**	**31.6**

OXSR1	4.4	PRKD2	11.3
PAK1	-4.0	PRKD3	10.6
PAK2	5.8	PRKG1	22.4
PAK3	-3.4	PRKG2	9.1
PAK4	11.1	PRKX	2.3
PAK6	-1.5	**PRKY**	**3.6**
PAK7	8.0	**PRPF4B**	**4.4**
PASK	1.1	**PSKH1**	**0.5**
PBK	2.5	PTK2	5.1
PCTK1	**1.5**	PTK2B	5.5
PCTK2	**12.0**	PTK6	29.6
PCTK3	**-11.4**	RAF1	98.6
PDGFRA	98.4	**RAGE**	**21.0**
PDGFRB	88.0	RET	98.2
PDIK1L	**11.5**	**RET/M918T/**	**91.6**
PDPK1	15.4	**RET/V804L/**	**88.6**
PFTK1	**-1.4**	**RET/V804M/**	**85.6**
PFTK2	**-0.9**	**RIPK1**	**15.6**
PHKG1	9.0	RIPK2	13.8
PHKG2	30.9 **(7.5)**	**RIPK3**	**45.2**
PIK3R4	**-17.6**	**RIPK4**	**15.0**
PIM1	13.6	RIPK5	7.6
PIM2	1.9	**RNASEL**	**38.3**
PIM3	26.3	ROCK1	-0.5
PINK1	**16.8**	ROCK2	4.9
PKDCC	**29.5**	**ROR1**	**16.1**
PKMYT1	**16.4**	**ROR2**	**48.0**
PKN1	1.1	ROS1	14.1
PKN2	5.8	**RPS6KA1/d2/**	**2.0**
PKN3	**8.7**	**RPS6KA2/d2/**	**21.1**
PLK1	3.0	**RPS6KA3/d2/**	**10.9**
PLK2	2.1	**RPS6KA4/d2/**	**4.7**
PLK3	0.7	**RPS6KA5/d2/**	**-11.9**
PLK4	**3.2**	**RPS6KA6/d2/**	**24.9**
PNCK	5.3	RPS6KB1	8.6
PRKAA1	**15.4**	RPS6KB2	0.0
PRKAA2	**11.1**	**RYK**	**7.8**
PRKACA	7.4	**SBK1**	**-10.2**
PRKACB	**9.1**	**SBK2**	**13.3**
PRKACG	-0.1	SGK1	4.8
PRKCA	16.5	**SGK110**	**36.2**
PRKCB	**16.2**	SGK2	-2.5
PRKCD	2.1	SGK3	4.4
PRKCE	3.6	**SGK494**	**15.6**
PRKCG	18.3	**SIK3**	**11.5**
PRKCH	-2.5	SLK	7.6
PRKCI	10.1	**SNF1LK**	**6.5**
PRKCQ	24.6	SNF1LK2	0.3
PRKCZ	13.0	**SNRK**	**-28.0**
PRKD1	2.1	**SPEG/b/**	**2.2**

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SRC	20.0	**TLK1**	**8.0**
SRMS	7.1	TLK2	21.6
SRPK1	1.9	**TNIK**	**15.0**
SRPK2	-1.5	**TNK1**	**26.5**
SRPK3	11.6	TNK2	17.4
STK10	27.6	TNNI3K	23.4
STK11	-2.2	**TP53RK**	**-0.3**
STK16	6.6	**TRIO**	**-3.1**
STK17A	7.6	TSSK1B	22.4
STK17B	**10.8**	TSSK2	26.5
STK24	-3.5	**TSSK3**	**8.9**
STK25	4.5	**TSSK4**	**17.0**
STK3	6.1	**TSSK6**	**-1.2**
STK32A	**21.2**	**TTBK1**	**31.1**
STK32B	**27.0**	**TTBK2**	**29.3**
STK32C	**10.9**	TTK	2.1
STK33	16.1	**TTN**	**11.6**
STK35	**15.4**	TXK	-1.3
STK36	**25.1**	TYRO3	8.3
STK38	4.1	**UHMK1**	**34.7**
STK38L	**-2.9**	ULK1	6.4
STK39	6.8	ULK2	-2.5
STK4	-0.4	ULK3	-2.8
SYK	-1.1	VRK1	3.3
TAOK1	21.5	**VRK2**	**-0.2**
TAOK2	63.1	WEE1	3.0
TAOK3	**36.5 (50.8)**	**WEE2**	**14.8**
TAOK3	36.5	**WNK1**	**5.3**
TBK1	3.3	WNK2	0.8
TEC	16.8	WNK3	0.8
TEK	2.8	**WNK4**	**11.6**
TESK1	**0.6**	**YES1**	49.3 (53.5)
TESK2	**-10.3**	YES1	49.3
TGFbR1	5.9	**YSK4**	**3.8**
TGFbR2	2.3	ZAK	83.3
TIE1	**5.2**	ZAP70	4.9

Table S8

| Residue position	Rank sum_abs_coeff	Rank Mean_diff	Rank Max_diff
res296	23	17	1
res426	27	10	2
res449	4	3	3
res325	2	6	4
res404	5	2	5
res184	106	4	6
res108	6	14	8
res450	1	1	9
res254	57	18	10
res746	89	20	11
res192	31	23	12
res492	3	7	13
res778	35	22	14
res491	55	16	16
res414	50	8	17
res250	11	15	19
res730	7	35	20
res252	54	12	21
res238	8	11	22
res572	14	29	23
res666	76	32	24
res327	12	19	25
res117	32	26	26
res100	26	34	28
res96	96	28	29
res226	10	39	30
res425	13	31	31
res233	37	36	32
res191	46	21	34
res97	30	45	35
res402	17	13	36
res779	24	25	37
res799	80	37	38
res390	15	24	39
res605	41	9	41
res112	93	33	44
res739	66	38	45
res320	29	49	46
res801	18	40	47
res741	42	48	48
res782	45	50	49
res621	51	47	50

Figure S9
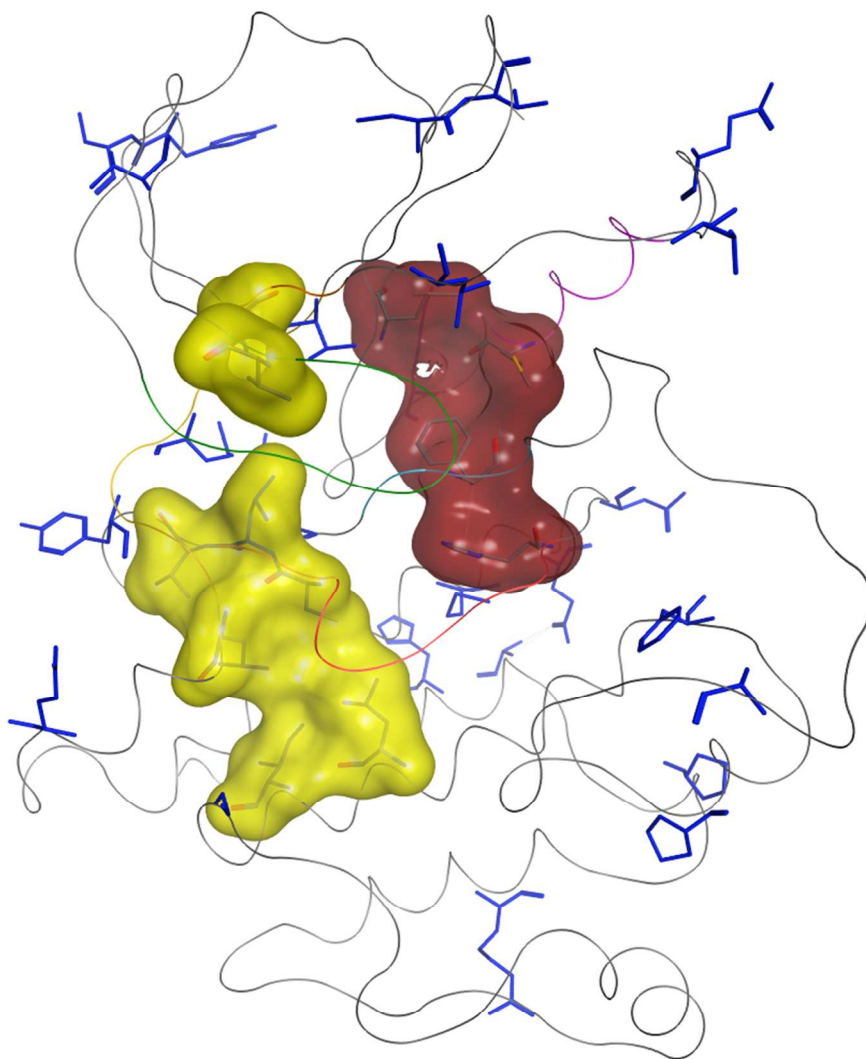
Figure S10
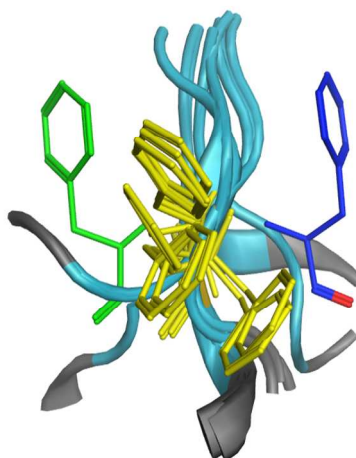
Bibliographie

1. Sandberg, M., Eriksson, L., Jonsson, J., Sjöström, M., Wold, S. (1998) New Chemical Descriptors Relevant for the Design of Biologically Active Peptides. A Multivariate Characterization of 87 Amino Acids. *J. Med. Chem. 41*, 2481-2491.

2. Davis, M. I., Hunt, J. P., Herrgard, S., Ciceri, P., Wodicka, L. M., Pallares, G., Hocker, M., Treiber, D. K., Zarrinkar, P. P. (2011) Comprehensive analysis of kinase inhibitor selectivity. *Nat. Biotechnol. 29*, 1046-1051.

3. Anastassiadis, T., Deacon, S. W., Devarajan, K., Ma, H., Peterson, J. R. (2011) Comprehensive assay of kinase catalytic activity reveals features of kinase inhibitor selectivity. *Nat. Biotechnol. 29*, 1039-1045.