

Table S11. List of PRISM Interaction Predictions for p53 Network. Out of 251 PRISM interaction predictions, 26 are present in Kohn's map, 59 are present in various PPI databases and 90 are present in STRING database. 104 interactions are validated totally.

PPI PREDICTIONS	INTERFACE	DATABASES
APC - E2F1	1gl2AD	
APC - CCNH	1vf6BD	
APC - TFDP1	1gl2AD	
APC - CCNA2	1jsuBC	
APC - JUN	1gl2AD	
APC - MAPK10	1pq1AB	
APC - BRCA1	1jsuBC	
APC - RFC5	1jsuBC	
APC - XRCC6	1rkeAB	
APC - CCNE1	1rkeAB	
APC - POLR2G	1cxzAB	
APC - RB1	1jsuBC	
APC - GTF2H1	1jsuBC	
APC - EP300	1g4yBR	
APC - LIG1	1jsuBC	
APC - PARP1	1jsuBC	
APC - EP300	1hx1AB	
APC - CCNB1	1jsuBC	KOHN'S MAP
APC - RPA1	1jsuBC	
APC - KAT2B	1rkeAB	
APC - MAX	1gl2AD	
APC - MDM2	1rkeAB	
APC - MYC	1gl2AD	MINT
APC - XRCC1	1jsuBC	
APC - HMGB1	1g4yBR	
APC - FOS	1gl2AD	
APC - MYC	1jsuBC	MINT
APC - RAD52	1pq1AB	
BAX - XRCC5	1nw9AB	
BAX - RAF1	1wmhAB	STRING
BAX - EP300	1rkeAB	STRING
CCNA2 - XRCC5	2ahmCG	
CCNA2 - EP300	1rkeAB	STRING
CCNB1 - RPA3	1quqCD	
CCNB1 - CCNE1	1gveAB	
CCND1 - MYC	1jsuBC	STRING
CCND1 - CDKN1B	1jsuBC	KOHN'S MAP

CCNE1 - RPA3	1quqCD	
CCNE1 - MAPK8	1w36CD	
CCNE1 - MNAT1	1gveAB	STRING
CCNE1 - CDK5	1unlAD	
CCNE1 - CASP3	1gveAB	STRING
CCNE1 - CDK5	1gveAB	
CCNE1 - EP300	1rkeAB	KOHN'S MAP
CCNE1 - CHEK1	1unlAD	
CCNH - MYC	1jsuBC	BIOGRID
CDK1 - CKS1B	1buhAB	KOHN'S MAP
CDK2 - PLK1	1rkeAB	INTACT
CDK2 - ABL1	1rkeAB	INTACT
CDK2 - APC	1rkeAB	
CDK2 - MAPK9	2btfAP	
CDK2 - SFN	1rkeAB	
CDK2 - CCNE1	1rkeAB	KOHN'S MAP
CDK2 - CCNE1	1unlAD	KOHN'S MAP
CDK2 - RB1	1nw9AB	KOHN'S MAP
CDK2 - TFDP2	1rkeAB	KOHN'S MAP
CDK2 - SKP2	1unlAD	KOHN'S MAP
CDK2 - EP300	1rkeAB	KOHN'S MAP
CDK2 - RPA3	1rkeAB	KOHN'S MAP
CDK2 - BAX	1rkeAB	STRING
CDK2 - E2F1	1e8oCD	KOHN'S MAP
CDK2 - CCNB1	1oiyBC	BIOGRID
CDK2 - CKS1B	1buhAB	KOHN'S MAP
CDK2 - XRCC5	1oiyBC	
CDK2 - MARK3	1oiyBC	INTACT
CDK4 - CDKN2D	1blxAB	BIOGRID
CDK4 - CSNK2A2	1buhAB	
CDK4 - XRCC5	1rkeAB	
CDK4 - CDKN2D	1e8oCD	BIOGRID
CDK4 - MYC	1jsuBC	NCI-NATURE PID
CDK4 - MAPK10	1buhAB	
CDK4 - KAT2B	1a9nAB	
CDK4 - ABL1	1gveAB	
CDK4 - CDK6	1buhAB	CELL-MAP
CDK6 - CKS1B	1buhAB	
CDK6 - CCNE1	1unlAD	STRING
CDK6 - RAD51	1unlAD	
CDK6 - RAF1	1wywAB	
CDK7 - CCND1	1xg2AB	STRING

CDK7 - RB1	1unlAD	STRING
CDK7 - RAD52	1lqbAB	
CDK7 - MYC	1jsuBC	STRING
CDK7 - HDAC1	1unlAD	
CDK7 - CDKN2D	1blxAB	
CDK7 - CKS1B	1buhAB	
CDKN1B - RAD52	1jsuBC	
CDKN1B - CCNE1	1jsuBC	BIOGRID
CDKN1B - WEE1	1jsuBC	STRING
CDKN1B - CDH1	1jsuBC	STRING
CDKN1B - CCNB1	1jsuBC	INTACT
CDKN1B - CCNA2	1jsuBC	KOHN'S MAP
CDKN1B - RB1	1jsuBC	PATHWAY COMMONS
CDKN2A - TP53	1lqbAB	BIOGRID
CDKN2A - CHEK1	1blxAB	
CDKN2D - MAPK8	1blxAB	
CDKN2D - CDH1	1rypMN	
CDKN2D - CDKN1B	1jsuBC	STRING
CDKN2D - CCNA2	1e8oCD	
CDKN2D - CCNB1	1e8oCD	
CDKN2D - CDK6	1blxAB	BIOGRID
CDKN2D - CHEK1	1blxAB	
CDKN2D - MAPK9	1blxAB	
CKS1B - MAPK10	1buhAB	
CRK - RPA3	1quqCD	
CSNK2A1 - CKS1B	1buhAB	
CSNK2A2 - CKS1B	1buhAB	
E2F1 - SFN	1e8oCD	
E2F1 - CDH1	1e8oCD	
E2F1 - RPA2	2c38SV	STRING
E2F1 - EP300	2ahmCG	KOHN'S MAP
E2F1 - NFKBIA	2ahmCG	STRING
E2F1 - EP300	1gl2AD	KOHN'S MAP
E2F1 - XRCC5	2ahmCG	
E2F1 - WEE1	1e8oCD	

E2F1 - MAX	1gl2AD	
E2F4 - XRCC5	1rkeAB	
EP300 - MAX	2ahmCG	BIOGRID
EP300 - ABL1	1rkeAB	MINT
ERCC1 - MYC	1jsuBC	
ERCC1 - EP300	1rkeAB	
ERCC1 - JUN	2ahmCG	
ERCC1 - RPA3	1quqCD	KOHN'S MAP
ERCC1 - MAX	2ahmCG	
ERCC1 - APC	1hx1AB	
ERCC1 - CDKN1B	1jsuBC	
ERCC4 - SKP2	2astBC	
ERCC4 - CDKN1B	1jsuBC	
FOS - E2F1	1gl2AD	STRING
FOS - RFC5	1gl2AD	
GADD45A - RAPIA	1c1yAB	
GADD45A - CDKN2D	1gveAB	
GADD45A - NFKB1	1gveAB	STRING
GADD45A - SFN	1gveAB	
GADD45A - BAX	1gveAB	STRING
GADD45A - MNAT1	1gveAB	
GADD45A - APC	1gveAB	
GADD45A - PLK1	1gveAB	
GADD45A - MAPK8	1lqbAB	STRING
GPIHBP1 - APC	1pq1AB	
GPIHBP1 - CDK2	1rkeAB	
GTF2H1 - CDKN1B	1jsuBC	
HDAC1 - XRCC5	1n62DF	STRING
HDAC1 - CDK1	1unlAD	BIOGRID
HDAC1 - CDK6	1unlAD	STRING
JUN - POLR2G	2ahmCG	
JUN - E2F1	1gl2AD	STRING
JUN - EP300	2ahmCG	BIOGRID
JUN - XRCC5	2ahmCG	
JUN - RAD51	2ahmCG	
JUN - SFN	2ahmCG	
JUN - MARK3	2ahmCG	
LIG3 - SFN	1e8oCD	

LIG3 - RAD23B	1tf0AB	
MAPK8 - RPA3	1lqbAB	
MAPK9 - E2F4	2btfAP	
MDM2 - CCNA2	1nw9AB	KOHN'S MAP
MYC - CCNE1	1jsuBC	STRING
MYC - RAD52	1pq1AB	
MYC - MAX	3ezeAB	KOHN'S MAP
MYC - CCNB1	1jsuBC	STRING
MYC - RB1	1jsuBC	BIOGRID
MYC - CDH1	1jsuBC	STRING
MYC - CCNA2	1jsuBC	STRING
MYC - CDKN1B	1jsuBC	INTACT
MYC - E2F1	1gl2AD	STRING
PARP1 - XRCC5	2ahmCG	BIOGRID
PARP1 - RAF1	1wmhAB	STRING
PARP1 - CDKN1B	1jsuBC	STRING
PARP1 - SKP2	3ezeAB	
PARP1 - CHEK1	1unlAD	MINT
PARP1 - CCNH	1jsuBC	
PARP1 - E2F1	2ahmCG	INTACT
PARP1 - NFKBIA	3ezeAB	STRING
PARP1 - CDH1	1jsuBC	
PARP1 - MYC	1jsuBC	STRING
PCNA - BRCA1	1xkpAC	NCI-NATURE PID
PCNA - CDKN1B	1pq1AB	STRING
PCNA - NFKB1	1h9sAB	PATHWAY COMMONS
PLK1 - RPA3	1quqCD	
PLK1 - CDH1	1lqbAB	STRING
POLR2D - CDK5	1gveAB	
POLR2G - MAPK9	2btfAP	
POLR2G - TFDP1	2btfAP	
POLR2G - RPA3	2btfAP	
POLR2G - E2F4	2btfAP	
RAD23B - TFDP2	1fxtAB	
RAD23B - CDKN1B	1jsuBC	
RAD51 - XRCC5	1rkeAB	STRING
RAD51 - SFN	3ezeAB	
RAD51 - SFN	1gveAB	
RAF1 - RAP1A	1clyAB	KOHN'S MAP
RAF1 - RAD52	1lqbAB	
RAF1 - SKP2	1wmhAB	

RAF1 - FEN1	1wywAB	
RAF1 - RAD51	1wmhAB	
RAP1A - CDH1	1clyAB	
RB1 - WEE1	1unlAD	
RB1 - PARP1	1gh6AB	STRING
RB1 - RAD23B	1tf0AB	
RELA - SFN	1rkeAB	STRING
RELA - BRCA1	1xkpAC	BIOGRID
RELA - NFKBIA	1oy3CD	BIOGRID
RFC1 - XRCC5	1nw9AB	BIOGRID
RFC5 - RAD51	1gveAB	
RFC5 - RAD51	1t08AB	
RFC5 - CDK6	1l0oBC	
RFC5 - MYC	1jsuBC	
RFC5 - PLK1	1gveAB	MINT
RFC5 - EP300	1rkeAB	
RFC5 - CSNK2A2	1gveAB	
RFC5 - XRCC6	1gveAB	INTACT
RFC5 - MAX	1gl2AD	
RFC5 - CDKN1B	1jsuBC	
RFC5 - MYC	1gl2AD	
RFC5 - XRCC6	1rkeAB	INTACT
RFC5 - CSNK2A1	1gveAB	
RFC5 - CCNE1	1gveAB	
RFC5 - E2F1	1gl2AD	
RPA1 - RPA2	1l1oEF	BIOGRID
RPA1 - XRCC5	1rkeAB	MINT
RPA1 - RPA3	1quqCD	BIOGRID
RPA1 - E2F1	1e8oCD	
RPA1 - CCNA2	1lqbAB	BIOGRID
RPA1 - CDKN1B	1jsuBC	
RPA2 - RPA3	1quqCD	BIOGRID
SKP1 - RPA3	1quqCD	
SKP1 - E2F1	2c38SV	
SKP2 - SKP1	2astAB	KOHN'S MAP
SKP2 - CCNE1	1gveAB	BIOGRID
SKP2 - CKS1B	2astBC	BIOGRID
SKP2 - SKP1	1fs2AD	KOHN'S MAP
SKP2 - CDK5	1unlAD	
TAF1 - ERCC4	1lkyAB	
TAF1 - RPA3	1quqCD	
TAF1 - CDK4	1blxAB	
TFDP1 - XRCC5	1rkeAB	

TFDP1 - EP300	1rkeAB	
TFDP2 - RB1	1j2jAB	KOHN'S MAP
TFDP2 - EP300	1rkeAB	
TFDP2 - E2F4	1cf7AB	KOHN'S MAP
TP53 - TP53BP2	1ycaAB	BIOGRID
XPA - CDKN1B	1jsuBC	
XRCC1 - CCNE1	1gveAB	
XRCC1 - EP300	1h9sAB	
XRCC1 - CDKN1B	1jsuBC	
XRCC1 - PLK1	1gveAB	
XRCC1 - MYC	1jsuBC	
XRCC1 - CDH1	1tueFG	
XRCC5 - ABL1	1rkeAB	KOHN'S MAP
XRCC6 - MDM2	1rkeAB	STRING
XRCC6 - MNAT1	1gveAB	

Table S12. PRISM Predictions for 15 Interactions with Available PDB Structures. There are 15 interaction predictions in the p53 P2IN, which have PDB structures in complex form. Out of these interactions, PRISM made 13 correct predictions.

PREDICTED INTERACTION	PREDICTION STATUS	PDB ID
CDK2 - CKS1B	CORRECTLY PREDICTED	1BUH
CDK2 - CCNE1	CORRECTLY PREDICTED	1W98
CDK2 - CCNB1	INCORRECT PREDICTION	2JGZ
CDKN1B - CCNA2	CORRECTLY PREDICTED	1JSU
CDKN2D - CDK6	CORRECTLY PREDICTED	1BLX
MYC - MAX	CORRECTLY PREDICTED	1NKP
RAF1 - RAP1A	CORRECTLY PREDICTED	1C1Y
RELA - NFKBIA	INCORRECT PREDICTION	1NFI
RPA1 - RPA2	CORRECTLY PREDICTED	1L1O
RPA1 - RPA3	CORRECTLY PREDICTED	1L1O
RPA2 - RPA3	CORRECTLY PREDICTED	1L1O
SKP1 - SKP2	CORRECTLY PREDICTED	2AST
SKP2 - CKS1B	CORRECTLY PREDICTED	2AST
TFDP2 - E2F4	CORRECTLY PREDICTED	1CF7
TP53 - TP53BP2	CORRECTLY PREDICTED	1YCS

Table S13. Protein List of Kohn's MIM. Kohn's molecular interaction map (MIM) has some nodes that do not have a protein counterpart, or some nodes correspond to multiple proteins. We updated Kohn's MIM's nodes by removing or expanding some of them.

KOHN'S ORIGINAL NODES	KOHN'S NODES UPDATED
14 3 3	SFN
Abl	ABL1
APC	APC
Bax	BAX
BRCA1	BRCA1
Casp3	CASP3
CycA	CCNA2
CycB	CCNB1
CycD	CCND1
CycE	CCNE1
CycH	CCNH
E-cad	CDH1
Cdk1	CDK1
Cdk2	CDK2
Cdk4-6	CDK4, CDK5, CDK6
Cdk7	CDK7
p16	CDKN2A
p19ARF	CDKN2A
Chk1	CHEK1
Cks1	CKS1B
Crk	CRK
E2F1-2-3	E2F1
E2F4	E2F4
ERCC1	ERCC1
XPF	ERCC4
Fos	FOS
HDAC1	HDAC1
DP1-2	TFDP1, TFDP2
JNK	MAPK8, MAPK9,
MAPK	MAPK8, MAPK9,
FEN-1	FEN1
C-TAK1	MARK3
HMG	HMGB1
HR23B	RAD23B
Jun	JUN
Mdm2	MDM2
Gadd45	GADD45A
Ligase 1	LIG1
Ligase 3	LIG3
Max	MAX
Myc	MYC
RPA	RPA1, RPA2, RPA3
CK2	CSNK2A1, CSNK2A2
p27	CDKN1B
p300	EP300
p36MAT1	MNAT1
p53	TP53
PARP	PARP1
pCAF	KAT2B
PCNA	PCNA
Plk1	PLK1

pRb	RB1
Rad51	RAD51
Rad52	RAD52
Raf1	RAF1
Ras	RAP1A
RF-C	RFC1
RPase 2	POLR2D
Skp1	SKP1
Skp2	SKP2
TAFII250	TAF1
TFIIH	GTF2H1
Wee1	WEE1
XPA	XPA
XRCC1	XRCC1
Ku70	XRCC6
Ku80	XRCC5
AP2	TFAP2A, TFAP2B,
ATM	ATM
Cdc25A	CDC25A
Cdc25C	CDC25B
C-EBP	CEBPA, CEBPB,
CK1d-k	CSNK1D, CSNK1E
CSB	ERCC6
HBP1	GPIHBP1
Dpase a	POLA1, POLA2
DMP1	DMTF1
Dpase b	POLB
Dpase d	POLD1, POLD2,
dsDNA	-
E2F6	E2F6
DNA-PK	PRKDC
Histones	-
Karp-1	KARP-1
E2F5	E2F5
p57	CDKN1C
p68	-
Paxillin	PXN
PKC	PRKCA, PRKCB
Rep fork	-
RHA	-
SL1	TAF1A
Sp1	SP1
ssb	-
ssDNA	-
U-glyc	UNG
Myt1	PKMYT1
p107	RBL1
p130	RBL2
XPB	ERCC3
XPC	XPC
XPD	ERCC2
p21	CDKN1A
TBP	TBP

Table S14. The Updated Interactions' List of Kohn's MIM. If a node was replaced with multiple proteins, the number of interactions automatically increased. We searched STRING database for validating the new edges and picked the ones, which were coming from high throughput experiments or databases.

INTERACTION	STRING PREDICTION METHOD	INTERACTION	STRING PREDICTION METHOD
TFAP2A ppi MYC	EXPERIMENTS	TFDP1 ppi E2F6	EXPERIMENTS
TFAP2B ppi MYC	EXPERIMENTS	TFDP2 ppi E2F6	EXPERIMENTS
TFAP2A ppi RB1	EXPERIMENTS	TFDP1 ppi RBL1	EXPERIMENTS
CSNK1D ppi TP53	EXPERIMENTS	TFDP2 ppi RBL1	EXPERIMENTS
CSNK1E ppi TP53	EXPERIMENTS	TFDP1 ppi RBL2	EXPERIMENTS
TP53 ppi PRKCA	EXPERIMENTS	TFDP2 ppi RBL2	EXPERIMENTS
PARP1 ppi POLA1	EXPERIMENTS	TFDP1 ppi CCNA2	DATABASES
PARP1 ppi POLA2	EXPERIMENTS	TFDP2 ppi CCNA2	DATABASES
PCNA ppi POLD1	EXPERIMENTS	TFDP1 ppi CDK2	DATABASES
PCNA ppi POLD2	EXPERIMENTS	TFDP2 ppi CDK2	DATABASES
PCNA ppi POLD3	EXPERIMENTS	TP53 ppi TFDP1	EXPERIMENTS
PCNA ppi POLD4	EXPERIMENTS	RB1 ppi TFDP1	EXPERIMENTS
RB1 ppi CEBPB	EXPERIMENTS	RB1 ppi TFDP2	EXPERIMENTS
RB1 ppi CEBPD	EXPERIMENTS	TP53 ppi MAPK8	EXPERIMENTS
RB1 ppi CEBPE	EXPERIMENTS	TP53 ppi MAPK9	EXPERIMENTS
RPA1 ppi POLA1	EXPERIMENTS	TP53 ppi MAPK10	EXPERIMENTS
RPA3 ppi POLA1	DATABASES	TP53 ppi RPA1	EXPERIMENTS
RPA3 ppi POLA2	DATABASES	CDK2 ppi RPA3	DATABASES
RPA2 ppi UNG	EXPERIMENTS	CCNA2 ppi RPA3	EXPERIMENTS
CDC25A ppi CDK4	DATABASES	TP53 ppi RPA1	EXPERIMENTS
CDC25A ppi	DATABASES	RAD51 ppi	EXPERIMENTS

CDK6		RPA1	
CDK4 ppi CCND1	EXPERIMENTS	RAD51 ppi RPA3	DATABASES
CDK4 ppi CDKN2A	EXPERIMENTS	RAD52 ppi RPA1	EXPERIMENTS
CDK4 ppi CDKN2A	EXPERIMENTS	RAD52 ppi RPA2	EXPERIMENTS
CDK6 ppi CDKN2A	EXPERIMENTS	RAD52 ppi RPA3	EXPERIMENTS
CDK7 ppi CDK4	EXPERIMENTS	RPA3 ppi RAD23B	DATABASES
CDK7 ppi CDK5	EXPERIMENTS	RPA1 ppi ERCC4	EXPERIMENTS
CCNH ppi CDK4	DATABASES	RPA3 ppi ERCC4	DATABASES
CCNH ppi CDK5	EXPERIMENTS	RPA3 ppi ERCC1	DATABASES
TFDP1 ppi E2F1	EXPERIMENTS	RPA3 ppi GTF2H1	DATABASES
TFDP2 ppi E2F1	EXPERIMENTS	XPA ppi RPA1	EXPERIMENTS
TFDP1 ppi E2F4	EXPERIMENTS	XPA ppi RPA3	DATABASES
TFDP2 ppi E2F4	EXPERIMENTS	XPA ppi RPA2	EXPERIMENTS
TFDP1 ppi E2F5	EXPERIMENTS	XPC ppi RPA3	DATABASES
TFDP2 ppi E2F5	EXPERIMENTS	TP53 ppi CSNK2A1	EXPERIMENTS

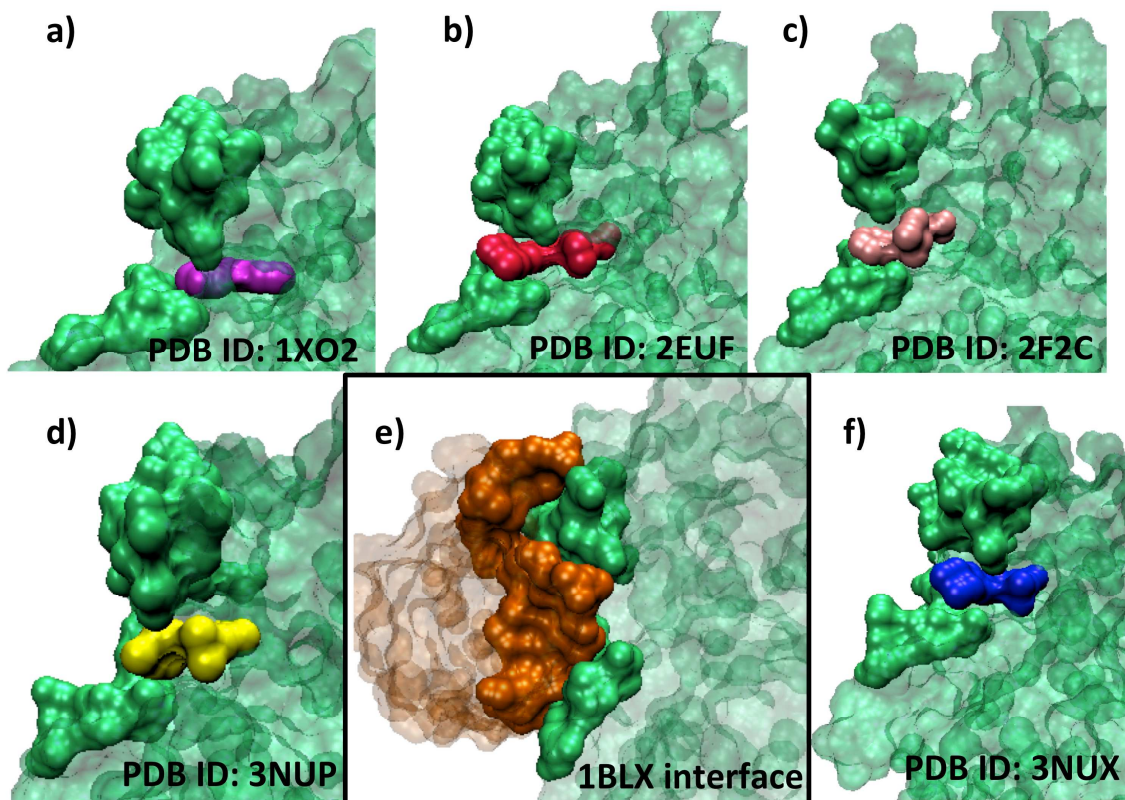


Figure S11. CDK6 binding site (one chain of CDK6–CDKN2D interface) highlighted on CDK6-drug complexes present in PDB. In each figure CDK6 structure is the transparent green body and the binding site on CDK6 is the opaque green one a) Fisetin-CDK6 complex b) PD-0332991-CDK6 complex, c) Aminopurvalanol-CDK6 complex, d) CHEBI: 792519-CDK6 complex, e) CDKN2D-CDK6 complex, f) CHEBI: 792520-CDK6 complex. The structures of CDK6 are not exactly the same in each PDB (please refer to Table S15 for the RMSD values of CDK6 structures), as a consequence we didn't perform a superimposition between CDK6-drug complexes and CDKN2D-CDK6 complex like we did in the Figure 5 of the main text.

Table SI5. RMSD values of CDK6 structures. We highlighted the RMSD values higher than 2.5 with red.

		CHAIN 2					
CHAIN 1	RMSD	1BLX_A	1XO2_B	2EUF_B	2F2C_B	3NUP_A	3NUX_A
	1BLX_A	-	2.67	2.8	2.82	0.78	0.92
	1XO2_B	2.67	-	0.88	1.06	1.69	1.77
	2EUF_B	2.8	0.88	-	0.9	1.68	1.78
	2F2C_B	2.82	1.06	0.9	-	1.95	1.98
	3NUP_A	0.78	1.69	1.68	1.95	-	0.4
	3NUX_A	0.92	1.77	1.78	1.98	0.4	-

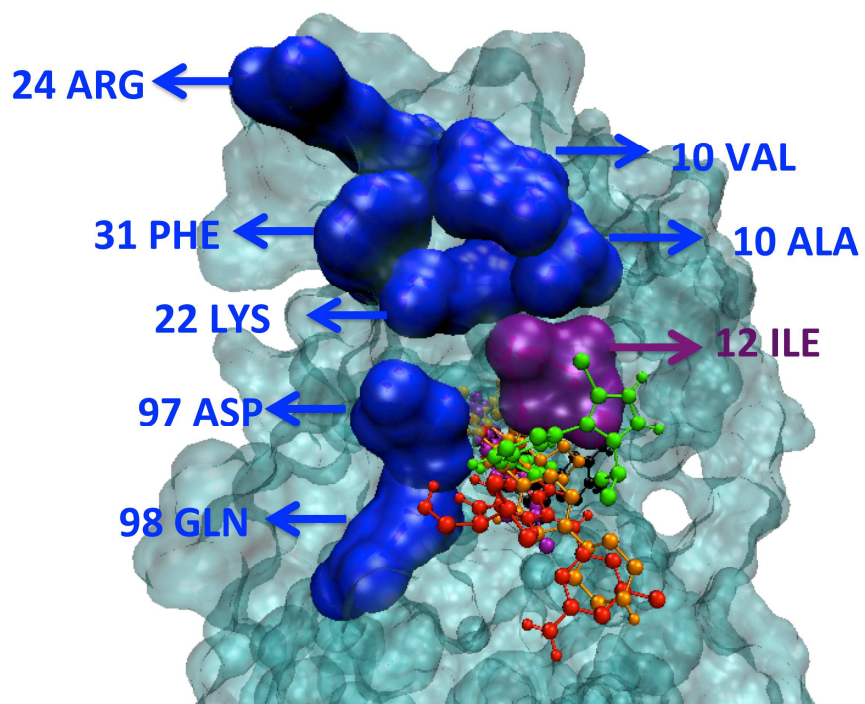


Figure SI2. The hotspots of CDK4 (dark blue surfaces), CDK4 structure (cyan transparent body) and the drugs (balls and sticks) docked on CDK4 can be seen all together in this figure. The drugs are close to hotspots 12 ILE, 98 GLN and 97 ASP.

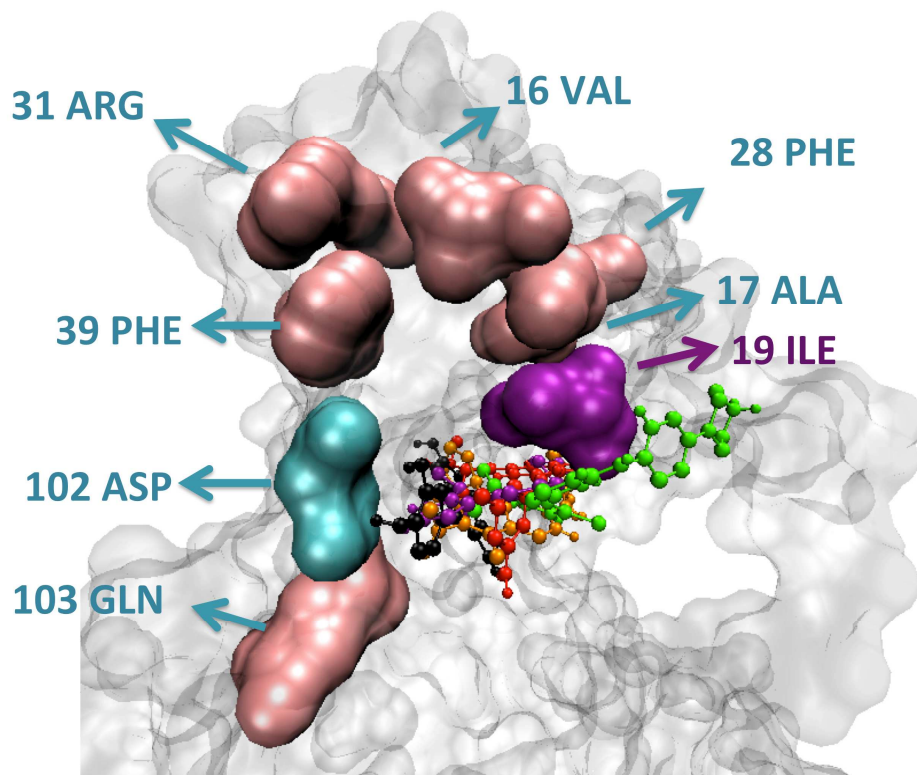


Figure SI3. The hotspots of CDK6 (pink surfaces), CDK6 structure (gray transparent body) and the drugs (balls and sticks) docked on CDK6 can be seen all together in this figure. The drugs are close to hotspots 19 ILE, 103 GLN and non-hotspot residue 102 ASP (cyan surface).

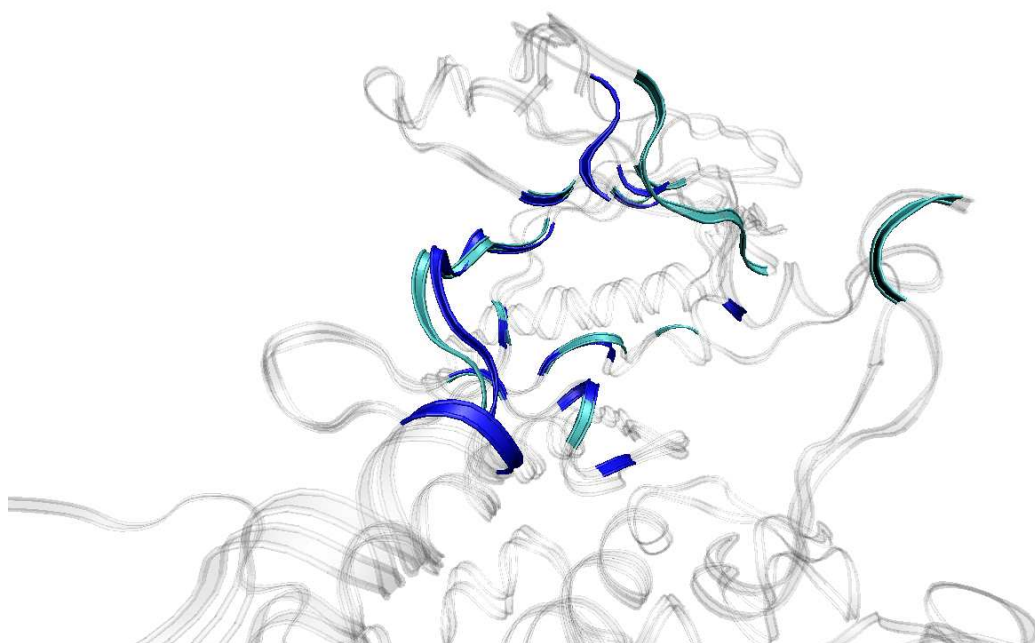


Figure SI4. Superimposition of pockets of CDK6 (cyan) and CDK4 (dark blue) using VMD visualization tool.

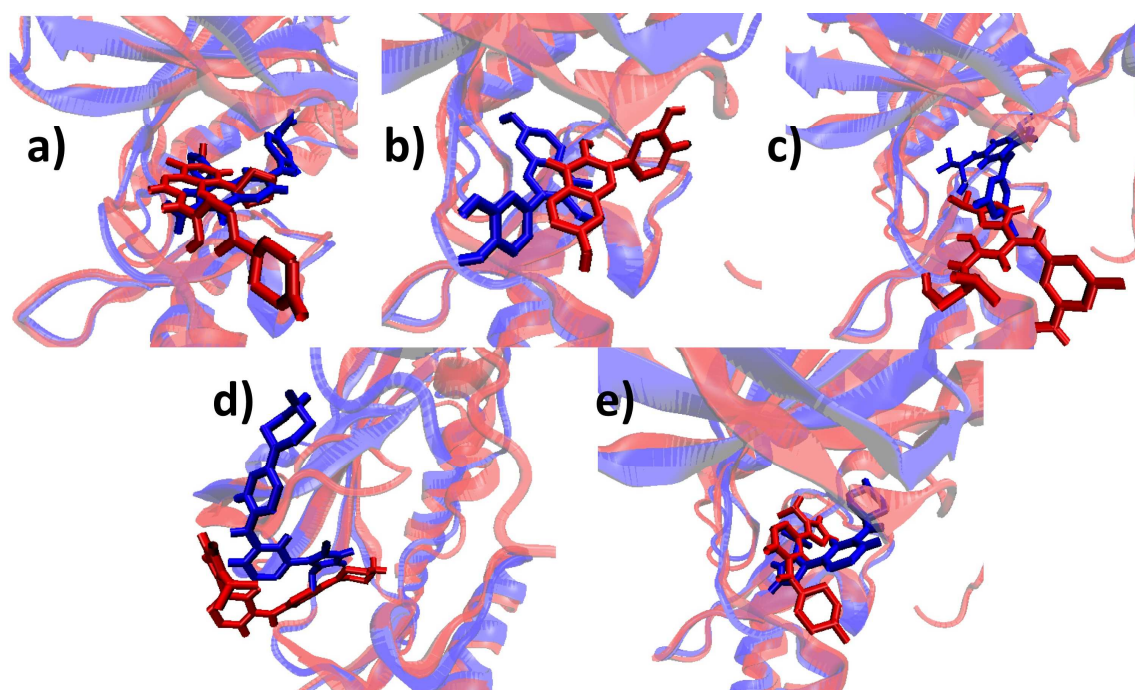


Figure S15. Superimposition of pockets of CDK6 (dark blue), CDK4 (red) and the drugs docked to them. The blue ligands are docked on CDK6 and the red ones are docked on CDK4. The ligands in the figures are: a) PD-0332991 b) Fisetin c) Aminopurvalanol d) CHEBI: 792520 e) CHEBI: 792519.