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Structural Analysis of Noncovalent Interactions in CDK2 Inhibitor Complexes

Vijina Chakkyarath*

Department of Bioinformatics, Bharathiar University, Coimbatore, Tamil Nadu, India.

***Corresponding author:** Vijina Chakkyarath, Department of Bioinformatics, Bharathiar University, Coimbatore, Tamil Nadu, India; E-mail: vbioinfo2009@gmail.com

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Abstract

A huge number of ATP site directed, small molecular inhibitors have been synthesized and tested for finding their biological activity against different types of kinases more than the past three decades. Cyclin dependent kinases are also one of the significant targets for drug discovery. Three dimensional structures of 6 CDK2 ATP complexes and 50 CDK2 inhibitor complexes have taken from PDB and IC_{50} values available for 23 of these complexes. As binding to ATP site and the biological activity may be dependent on the different noncovalent interactions such as hydrogen bonds, hydrophobic bonds and electrostatic, Vaanderwaals such as other interactions. In the present work we have analyzed these interactions in the CDK2-ATP complexes as well as CDK2 inhibitor complexes. Based on these interactions we have developed multiple regression models to account for the experimentally observed IC_{50} values. We have made extensive analysis of the amino acids ATP contacts amino acids inhibitor contacts. Also the extend of similarity between the various ligands has been quantified using 2D and 3D analysis methods.

Keywords: Noncovalent interactions; Vaanderwaals; Cyclin-dependent kinases; Ligand; CDK2 inhibitor

Introduction

Kinases are become one of the most important classes of drug target with around 30 different kinase are being developed and investigated for cancer treatment [1]. Cyclin-Dependent Kinases (CDKs) are protein kinases with a cyclin subunit and it is essential for enzymatic activity [2]. It is present in all type of eukaryotes, and is having crucial roles in signaling pathways to control normal human cell functions and active merely when linked with a regulatory partner. Eukaryotic cells contain at most nine CDKs, and those are, CDK1, 2, 3, and 4, are openly involved in regulation of cell cycle [3-5]. CDKs are dependable for regulating cell division cycle, helping to make sure that the genome is replicated once per cell cycle and it is required for timing and order of cell division [6-8]. CDK2 is a major constituent of the CDK complex, and it is responsible for the transition of G1/S phase and it is a monomer comprised of a polypeptide chain consisting of 298 amino acid residues with mainly α-helix elements as well as a β-sheet terminus [9].

The activation CDK involves two-step process and that requires phosphorylation and cycline binding in the T loop [10,11]. Over-activity or insufficient activity of CDKs or is linked with several tumors, for this reason it became an important target in anticancer and antiviral drug discovery [12]. CDK2 inhibitors show exciting potential activity as tumor suppressors. The inhibitors of kinases interact with the backbone motif and are the part of binding site [8]. Finn, et al., in their article provides the most recent approaches of targeting this essential cell cycle regulatory mechanism in the perspective of breast cancer therapy [13].

Nonbonding interactions among proteins and ligands play essential roles in important biological processes mainly signal transduction and enzymatic reactions. Understanding these interactions is important for designing synthetic inhibitors. In this work, we focus on non-covalent interactions of 6 CDK2 ATP complexes and 50 CDK2 inhibitor complexes and discussed structural analysis of these interactions in 56 CDK complexes. Analyzing Structural information can be helpful for understanding these complexes at the molecular level.

Materials and Methods

The crystallographic data of 56 CDK complexes taken from the Protein Data bank (PDB) forms the source of present study. Amoung them 50 complexes belong to the small molecular inhibitors of CDK2 and 6 are ATP complexes [14]. The PDB ID for the proteins used in the present study along with the amino acid contacts are given in corresponding tables.

Analysis of protein ligand interactions

Each of the CDK2 complex structures were analyzed using the Java tool provided at the protein data bank website, which gives the details about different types of contacts such as bridged hydrogen bonds, hydrophobic bonds, hydrophilic bonds and other interactions [15]. The cutoff limits for the bridged hydrogen bonds is the distances between the ligand atoms and all H_2O atoms in the structure and returns all the distances that are less than 5 A, for hydrophilic bonds the distances between potential H-bonds donors or accepters and returns all the distances that are within the range of set to 2.7 A for the limit and the upper limit is set to 3.3 A. For hydrophobic bonds the distances between C-C and returns all the distances that are within the range of lower limit is set to. 9 A, and the upper limit is set to 3.9 A, for other interactions the distances between the ligand atoms and protein atoms which are not between potential h-bonds donor or acceptors or C-C within the range of the lower limit is set to. 9 A and the upper limit is set to 3.9 A.

2D similarity

Here 2D comparison have done using the tool super ligands [16].This program will search for ligands similar to a given ligand and also compare two ligands by computing the Tanimoto coefficient. Here 23 small molecular inhibitors which have similar IC_{50} values have been taken for analysis.

3D superposition

In the similar way 3D superposition among the ligands has been done using the tool Super ligands. This program comparing all instances of two PDB ligands by performing a three dimensional and giving best fitting pair of ligands. The results section of this program shows number of atoms of structure 1, number atoms of structure 2, and number of superposed atoms, number of superposed atoms same type root mean square distance and superposed structure. Here root mean square values of 23 small molecular inhibitors of CDK have been chosen.

Single correlation and regression analysis

A correlation is a number between -1 and +1 that measures the degree of association between two variables. Positive value for the correlation implies a positive association and negative value implies a negative association or inverse association. In statistics regression analysis examines the relation of a dependent variable to specified independent variables. The mathematical model of their relationship is the regression equation. Uses of regression include curve fitting, modeling of casual relationships, and testing scientific hypothesis about relationship between variables. In the present work regression analysis were carried out for four processes.

- Interaction with binding energy values.
- Back check prediction value.
- Jack knife test.
- Amino acid ligand interactions.

Results and Discussions

Analysis of protein ligand interactions

A dataset of three dimensional structures of six CDK2 ATP complexes and 50 CKD2 inhibitor complexes are taken from PDB with reference to and IC_{50} values are available for 23 out of 50 CDK2 inhibitor complexes and are retrieved from Binding database [17,18]. The details of 6CDK2-ATP complexes and 50 CDK2 inhibitor complexes are listed in Table 1. 23 CDK2 inhibitor complexes out 50 that have IC_{50} values are listed in Table 2.

PDBID	R	Sub-type	Cyclin	SMI	PI	ATP	References
1b38	2	CDK2	-	-	-	Yes	Brown, et al.
1b39	2.1	CDK2	-	-	-	Yes	Brown, et al.
1fi n	2.3	CDK2	CyclinA	-	-	Yes	Jeffrey, et al.
1fq1	3	CDK2	-	-	-	Yes	Song, et al.
1hck	1.9	CDK2	-	-	-	Yes	Schulze-Gahmen, et al.
1jst	2.6	CDK2	CyclinA	-	-	Yes	Russo, et al.
1AQ1	2	CDK2	-	Yes	-	-	Lawrie, et al.
1CKP	2.05	CDK2	-	Yes	-	-	Gray, et al.
1D18	2.2	CDK2	-	Yes	-	-	Shewchuk, et al.
1PXO	1.96	CDK2	-	Yes	-	-	Wang, et al.
1E1V	1.95	CDK2	-	Yes	-	-	Arris, et al.
1E1X	1.85	CDK2	-	Yes	-	-	Arris, et al.
1E9H	2.5	CDK2	CyclinA3	Yes	-	-	Davies, et al.
1FVT	2.2	CDK2	-	Yes	-	-	Davis, et al.
1FVV	2.8	CDK2	CylinA	Yes	-	-	Davis, et al.
1G5S	2.61	CDK2	-	Yes	-	-	Dreyer, et al.
1GIH	2.8	CDK2	-	Yes	-	-	Ikuta, et al.
1GII	2	CDK2	-	Yes	-	-	Ikuta, et al.
1GIJ	2.2	CDK2	-	Yes	-	-	Ikuta, et al.
1GZ8	1.3	CDK2	-	Yes	-	-	Gibson, et al.
1H0V	1.9	CDK2	-	Yes	-	-	Gibson, et al.
1H0W	2. 10	CDK2	-	Yes	-	-	Davies, et al.

1H1P	2. 10	CDK2	-	Yes	-	-	Davies, et al.
1H1Q	2.5	CDK2	-	Yes	-	-	Davies, et al.
1H1R	2	CDK2	-	Yes	-	-	Davies, et al.
1H1S	2	CDK2	-	Yes	-	-	Davies, et al.
1JSV	1.96	CDK2	-	Yes	-	-	Davies, et al.
1H07	1.85	CDK2	-	Yes	-	-	Beattie, et al.
1KE5	2.2	CDK2	-	Yes	-	-	Bramson, et al.
1KE6	2	CDK2	-	Yes	-	-	Bramson, et al.
1KE7	2	CDK2	-	Yes	-	-	Bramson, et al.
1KE8	2	CDK2	-	Yes	-	-	Bramson, et al.
1KE9	2	CDK2	-	Yes	-	-	Bramson, et al.
1OGU	2.6	CDK2	CyclinA	Yes	-	-	Sayle, et al.
1OI9	2. 10	CDK2	CyclinA	Yes	-	-	Hardcastle, et al.
1OIQ	2.31	CDK2	-	Yes	-	-	Anderson, et al.
1OIR	1.91	CDK2	-	Yes	-	-	Anderson, et al.
1OIT	1.6	CDK2	CyclinA	Yes	-	-	Anderson, et al.
1OIU	2	CDK2	CyclinA	Yes	-	-	Hardcastle, et al.
1OIY	2.4	CDK2	CyclinA	Yes	-	-	Hardcastle, et al.
1P2A	2.5	CDK2	-	Yes	-	-	Liu, et al.
1PF8	2.51	CDK2	-	Yes	-	-	Moshinsky, et al.
1PKD	2.3	CDK2	CyclinA	Yes	-	-	Johnson, et al.
1PXI	1.95	CDK2	-	Yes	-	-	Wu, et al.
1PXJ	2.3	CDK2	-	Yes	-	-	Wu, et al.
1PXK	2.8	CDK2	-	Yes	-	-	Wu, et al.
1PXL	2.5	CDK2	-	Yes	-	-	Wu, et al.
1PXM	2.53	CDK2	-	Yes	-	-	Wang, et al.
1PXN	2.5	CDK2	-	Yes	-	-	Wang, et al.
1PXP	2.3	CDK2	-	Yes	-	-	Wang, et al.
1PYE		CDK2	-	Yes	-	-	Hamdouchi, et al.
1R78	2	CDK2	-	Yes	-	-	Luk, et al.
1URW	2	CDK2	-	Yes	-	-	Byth, et al.
1H08	1.8	CDK2	-	Yes	-	-	Beattie, et al.
1HOO	1.6	CDK2	-	Yes	-	-	Beattie, et al.
1HO1	1.79	CDK2	-	Yes	-	-	Beattie, et al.

Table 1: CDK2 inhibitor complexes.

PDBID	IC_{50}	PDBID	IC_{50}
1E1V	17000	1KE6	5.7
1E1X	2200	1KE7	8.9
1GII	78	1KE8	1000
1GIJ	25000	1KE9	660
1H00	38000	1OGU	34
1H01	1000	1OIR	32
1H1Q	970	1OIT	3
1H1R	2300	1P2A	12
1H1S	5.4	1PYE	324
1H07	3000	1R78	3
1H08	300	1URW	3
1KE5	560		

Table 2: List of 23 CDK2 inhibitor complexes with IC_{50} values.

2D similarity

Here 23 small molecular inhibitor which have IC_{50} value has been taken for analysis. Here we compared all 23 ligands with each other that have different activity. 23 small inhibitors with their hetro ID and 2D similarity values are shown in Table 3. Using this percentage values we can say that how much one ligand structure shows similarity with another ligand. Ligands that show best (maximum Tanimoto coefficients) are shown in bold [20]. The similarity and activity values of two ligand molecules are not always related. If the two molecules are of the same type, as the similarity increases the activity value may also show similar values. From the Table 3, for the same type of molecules 1H1Q and 1H1R have activity values 970 and 2300 respectively and they also show similarity of 97.76% but here it is also seen in the table that the different types of molecules such as 1H01 and 1KE8 having same activity value (1000, 1000) shows only 42% similarity [21].

Amino acids	Total number	Number of occurrence	Percentage
I 10	6	6	100
G 11	6	3	50
E 12	6	4	67
G 13	6	6	100
T 14	6	4	67
Y 15	6	3	50
G 1 6	6	2	33
V 18	6	5	83
A3 1	6	5	83
K33	6	5	83
V64	6	5	83
F80	6	3	50
E8 1	6	6	100
F82	6	6	100
L83	6	6	100

D86	6	4	67
D 127	6	2	33
F 146	6	1	17
K89	6	1	17
K 129	6	4	67
G 147	6	1	17
Q 13 1	6	4	67
N 132	6	5	83
L 134	6	5	83
D 145	6	5	83
A 149	6	1	17

Table 3: Representation of percentage of occurrence in various amino acid residues in ATP complexes.

3D superposition

In a similar manner 3D superposition also has been done for 23 CDK2 complexes which already have IC_{50} values. Here root mean square values of 23 small molecule inhibitors of CDK have been chosen. The activity is more in case of molecules having minimum root mean square value [22-30]. Ligands that shows best (minimum RMS deviations) are shown in bold for example in Table 4 the ligand 1H1Q and 1H1R having activity values 970 and 2300 shows minimum RMS deviation.

Amino acids	Total number	Number of occurrence	Percentage
I 10	50	47	94
G 11	50	15	30
E 12	50	20	40
G 13	50	12	24
T 14	50	1	2
V18	50	34	68
A31	50	43	86
K33	50	28	56
V64	50	29	58
F80	50	42	84
E81	50	47	94
F82	50	41	82
L82	50	1	2
H82	50	2	4
L83	50	48	96
V83	50	2	4
H84	50	30	60
T89	50	1	2
Q85	50	21	42

K89	50	19	38
N132	50	14	28
K88	50	1	2
D86	50	35	70
Q131	50	20	40
L134	50	47	94
A 144	50	18	36
D145	50	39	78
F146	50	10	20
L298	50	1	2

Table 4: Representation of percentage of occurrence in various amino acid residues in small molecule inhibitors.

Comparison of contacts maps of two related molecules

Contacts map of two related complexes which have similar IC_{50} values are drawn here using the JAVA tool provided at the PDB site. Using contact maps we can find various amino acids residues that are in contacts with sugar molecules, bases adenine moieties and also extract various information about ligands and proteins interactions. Here we analyzed various nonlocal interactions present in the ligand [31]. Here two small molecule inhibitors of cyclin dependent kinase which have similar IC_{50} are compared. It is seen that various contacts are represented using various colors green for hydrophilic, pink for hydrophobic, blue for bridged hydrogen bond and white color for other contacts. In 1H1Q amino acid residues such as I10, E12, G13, V18, A31, V64, F80, E81, F82, 83, H84, Q85, K89, N82, 83, H84, Q85, K89, D86, Q82, 83, H84, Q85, K89, Q131, L134, A144, D145 are making contacts with small molecular inhibitors. In 1H1R amino acids residues such as I10, E12, A31, V64, F80, E81, F82, L83, H84, Q85, K89, N132, D86, Q131, L134 AND D145 are making contacts with small molecular inhibitor. In H1Q7 bridged hydrogen bonds, hydrophilic bonds, 22 hydrophobic bonds 28 other interactions are present. In 1H1R 22 bridged hydrogen bonds, 1 hydrophilic bond 34 hydrophobic bonds and 37 other interactions present. The comparison results shows that the relative molecules which have similar IC_{50} values have almost similar number of hydrophilic bonds, number of hydrophobic bonds and other nonlocal interactions but in case of bridged hydrogen bonds variation can be seen.

Contacts with the aminoacid residues

The ATP binding pocket: Aminoacid-ATP interaction: In Table 4 the amino acids that interact with the various atoms of ATP are iven. This table reveals that the residues I10, G13, E81, F82, and L83 are making contacts with ATP in all the ATP-CDK2 complexes. Further in five out of six complexes the residues V18, A31, K33, V64, N132, L134 and D145 are also making interactions with ATP. Four additional contacts are observed from residues E12, T14, D86, K129 and Q131. The interacting residues further grouped on the basis of the interactions with the adenine, ribose and phosphate moieties of ATP. They are represented in this Table in various colors: Green color represents the sugars, blue for bases red for phosphate and brown for other contacts [32]. From the results we can that I10, A31, K33, V64, E81, F82, L82, L83, H84, D86, L134 are making contacts with the adenine moieties of ATP. Quite interestingly out of eleven residues seven are hydrophobic which imply that the adenine moiety is in hydrophobic environment. Residues G13, T14, K129, Q131, N132, and D145 are making contacts with the phosphate group [33].

The small molecule inhibitor complexes

In Table 5 amino acids that interact with small molecular inhibitors are given. The Table results reveals that the residues I10, A31, E81, F80, F82,L83 and l34 are making contacts with small molecular inhibitors. Further we can see that G11, E12, V18, V64, H84, K89, D86, F145 are making contacts with small molecular inhibitors in a partial manner. As described in Table 4 here also interacting residues are further classified on the basis of interactions with the adenine and ribose phosphate moieties. Color representation is similar to that the Table 4. In addition brown color represents new contacts. From the results we could observe that the small molecular inhibitors interact with the CDK2 in a manner similar to its natural ligand ATP. In addition new contacts with residues E8, K9, F80, Q85, N132, Q131, A144 and D145 are making contacts with some of the complexes. Differences and similarities in these interactions are expected to provide a rational for the varied IC_{50} values [34,35].

Amino acids residues	Inhibitor	ATP
I10	94	100
G11	30	50
E12	40	67

G13	50	100
T14	2	67
Y15	0	50
G16	0	33
V18	68	83
A31	86	83
K33	56	83
V64	58	83
F80	84	50
E81	94	100
F82	82	100
L83	96	100
H84	60	67
D86	70	33
K89	38	17
D127	0	17
Q131	40	67
N132	28	17
L134	94	67
A144	36	83
D145	78	83
F146	20	83

Table 5: Combination of percentage of ATP complexes and small molecular inhibitors with various amino acid residues.

Representation of percentage of occurance in various aminoacid residues in ATP and SMI complexes

The percentage of occurrence of various amino acids in the binding pocket of ATP complexes are represented in Table 5. We observed that the residues such as I10, G13 and E81, F82, and L83 are having maximum number of percentage of occurrence.

The percentage of occurrence of various amino acids in the binding pocket of small molecule inhibitors is represented in Table 6. A similar correlation in the small molecule inhibitor shows that have maximum percentage of occurrence compare to other amino acid residues.

S. no.	PDBID	Ligand name	No. of bridged hydrogen bonds	No. of hydrophilic bonds	No. of hydrophobic bonds	Other	Total
1	1B38	ATP	57	13	7	43	120
2	1B39	ATP	61	13	7	43	124
3	1FIN	ATP	33	4	8	19	64
4	1FQ1	ATP	-----	8	6	37	51
5	1HCK	ATP	45	15	7	47	114
6	1JST	ATP	9	9	10	56	84

Table 6: Ligand protein interactions in CDK2-ATP complexes.

Combination of percentage of ATP complexes and small molecular inhibitors with various aminoacid residues

Combination of percentage of ATP complexes and small molecular inhibitors with various amino acid contacts shown in Table 7. A graph displays the percentage of occurrence of amino acid in ATP complexes and small molecular inhibitor complexes.

S. no	PDBID	No. of bridged hydrogen bonds	No. of hydrophilic bonds	No. of hydrophobic bonds	Other	Total
1	1AQ1	55	4	22	28	109
2	1CKP	15	1	19	26	61
3	1D18	13	2	22	25	62
4	1DM2	20	5	10	22	57
5	1FVT	8	4	19	33	64
6	1FVV	9	4	26	39	78
7	1G5S	-----	4	22	17	43
8	1GIH	-----	1	9	22	32
9	1GII	11	2	13	23	49
10	1GIJ	28	2	9	29	68
11	1GZ8	43	3	13	23	82
12	1H00	28	1	18	32	79
13	1H0V	31	4	8	16	59
14	1H0W	3	1	13	13	30
15	1H1P	-----	------	-----	25	25
16	1H1Q	7	1	22	28	58
17	1H1R	21	1	34	37	93
18	1H1S	45	4	16	36	101
19	1JSV	39	3	9	26	77
20	1H07	45	4	16	36	101
21	1H08	50	4	14	27	95
22	1KE5	27	2	16	24	69
23	1KE6	20	4	16	31	71
24	1KE7	12	5	10	36	63
25	1KE8	13	3	22	31	69
26	1KE9	15	2	14	10	41
27	1OGU	21	1	16	32	70
28	1OI9	3			5	8
29	1OIR	18	3	11	19	51

Table 7: Ligand protein interactions with CDK2-SMI complexes.

Conservation plot of amino acids contacts

Conservation plot of amino acid interactions CDK2-ATP complexes: In Figure 1 conservation plot of ATP-CDK2 complexes have shown. The amino acids that interact with ATP are taken in the X-axis and percentage of conservation is taken as Y-axis. Graph has drawn using Table 5 [36]. From the Figure we can observe residues such as I10, G13, F82 have more conservation that is 100 percent

conservation. Below that V18, A31, K33, V64, N131, L134 and D147 are seen. Here we can also say that F146, K89, G147 and A149 have lowest conformation.

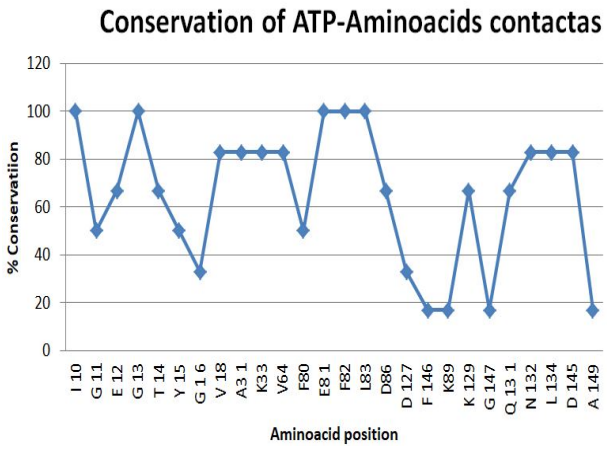

Figure 1: Conservation plot of ATP-amino acids contacts.

Conservation plot for amino acids interactions CDK2-inhibitor complexes

In Figure 2 conservation of CDK2 inhibitor complexes is shown. The amino acids that interact with inhibitor complexes are taken in the x-axis and percentage of conservation is taken as Y-axis [37]. Graph has been drawn using the Table 6. Here I10, E81, L83, L134 have highest value that is highest 100. A31, F80, F82, and D145 has nearer to the value 80 and T14, L82, H82, V83, T89, K88, L298 have lowest values nearer to zero.

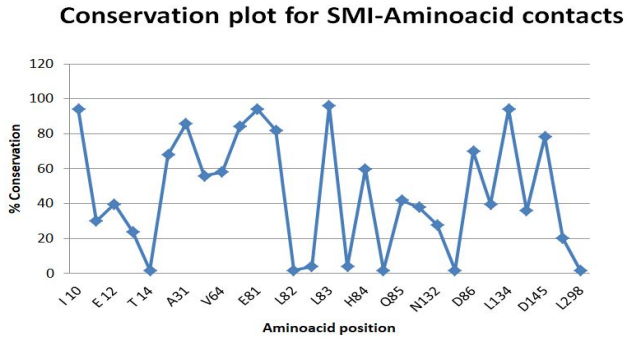

Figure 2: Conservation plot of SMI-amino acids contacts.

Conservation plot of ATP-CDK2 contacts *vs.* inhibitor CDK2 contacts

In Figure 3 conservation of ATP-CDK2 complexes *vs.* CDK2-inhibitor complexes is shown. The amino acids that interact with ATP and SMI complexes are taken in the X-axis and percentage of conservation is taken as y-axis. Here two values that is conservation of ATP-CDK values combined with conservation of SMI CDK values. Here we can observe that in both case I10, G13, E81, F81, F82 have maximum values [38]. In ATP-CDK lowest value is H84 and A144. But in SMI- CDK T14, Y15, G16, and D127 have lowest values. In ATP-CDK maximum value is 100 but in SMI-CDK maximum value is 94.

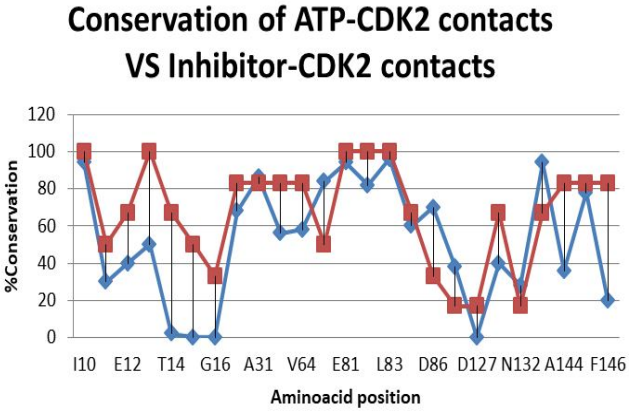

Figure 3: Conservation plot of ATP-CDK2 contacts *vs.* inhibitor-CDK2 contacts.

Ligand-protein interactions in CDK2-ATP complexes

First we considered the interactions of the natural ligand ATP in different CDK2-ATP complexes using the software in the PDB. Using this tool number of hydrogen bonds, hydrophobic bonds, hydrophilic bonds and the other bonds are found and shown in Table 8. Here we can see that hydrogen bonds present in five molecules out of six. Hydrophobic bonds, hydrophilic bonds and the other bonds are present in all six complexes [39]. In this Table interactions of 1B38 are seen to similar to 1B39 only hydrogen bond is different but we see the total interactions of these molecules it seems to be almost similar. In the case of 1FIN and 1FQ1 number of bonds seems to be different but when we compare the total interactions it is almost similar.

Dependent variables	No. of BHB	No. of hydrophilic bonds	No. of hydrophobic bonds	Other	Total
IC_{50}	0.034802	0.391765	0. 13696237	0.090143	-0.0096
$LogIC_{50}$	0.030922	-0.69087	0.060849	-0.08489	-0.03881
$1/IC_{50}$	0. 145977	0.666331	0.028395	0.214466	0.245536

Table 8: Single correlation coefficients with IC_{50}, Log IC_{50} and $1/IC_{50}$.

Ligand protein interactions in CDK2-small molecule inhibitor complexes

Here we analyzed the various ligand protein interactions in CDK2-Small molecule inhibitor complexes. 50 CDK 2 small molecule

inhibitor were analyzed and the results are shown in Table 9. Here we can see all the molecule such as 1G5S, 1GIH, 1H 1P 1PF8 hydrogen bond is absent. Hydrophilic bonds are absent in molecules such as 1H 1P, 1OI9, 1OIU, and 1OIY. Hydrophobic bonds are absent in molecules such as 1HIP, 1O 19 1OIU, and 1OIY but 1H 1P all these three bonds are absent [40].

PDBID	IC_{50}	LogIC_{50}	1/C	No. of BHB	No. of hydrophilic bonds	No. of hydrophobic bonds	Other	Total
1E1V	17000	4.230449	5.88E-05	20	1	16	24	61
1E1X	2200	3.342423	0.000455	28	3	10	20	61
1GII	78	1.892095	0.012821	11	2	13	23	49
1GIJ	25000	4.39794	0.00004	28	2	9	29	68
1H00	38000	4.579784	2.63E-05	28	1	18	32	79
1H01	1000	3	0.001	60	1	21	26	108
1H1Q	970	2.986772	0.001031	7	1	22	28	58
1H1R	2300	3.361728	0.000435	21	1	34	37	93
1H1S	5.4	0.732394	0. 185185	45	4	16	36	101
1H07	3000	3.477121	0.000333	45	4	16	36	101
1H08	300	2.477121	0.00333	50	4	14	27	95
1KE5	560	2.748188	0.001786	27	2	16	24	69
1KE6	5.7	0.755875	0. 175439	20	4	16	31	71
1KE7	8.9	0.94939	0. 11236	12	5	10	36	63
1KE8	1000	3	0.001	13	3	22	31	69
1KE9	660	2.819544	0.001515	15	2	14	10	41
1OGU	34	1.531479	0.029412	21	1	16	32	70
1OIR	32	1.50515	0.03125	18	3	11	19	51
1OIT	3	0.477121	0.333333	36	4	20	32	92
1P2A	12	1.079181	0.083333	9	5	18	20	52
1PYE	324	2.510545	0.003086	11	2	26	33	72
1R78	3	0.477121	0.333333	4	6	20	24	54
1URW	3	0.477121	0.333333	57	4	17	33	111

Table 9: Multiple regression analysis tables.

Single correlation coefficients with IC_{50}, log IC_{50} and $1/IC_{50}$

23 small inhibitors of kinase inhibitors that have IC_{50} values have been selected to compute single correlation coefficient. Correlation coefficient is generally used to find the relation between the two molecules [41]. It is of two types positive and negative. Here correlation analysis of IC_{50}, log IC_{50} and $1/IC_{50}$ was carried out. Number of brigdes hydrogen bonds, number of hydrophilic bonds, number of hydrophobic bonds, other bonds and total number of interactions are selected as dependent variables. First correlation coefficient of IC_{50} with various combinations such as number of bridged hydrogen bonds, number of hydrophilic bonds, number of hydrophobic bonds, other interactions and total of these interactions has found. In case of dependent variables with number of hydrogen bonds seen that two values got almost similar values with IC_{50} and log IC_{50} but in case of $1/IC_{50}$ is different and is seen as greater than other values [42]. In case of dependent variables with number of hydrophilic bonds are seen that two values are negative that is we can say that it is a negative correlation and the other value is positive and we can say as positive correlation. So again here also $1/IC_{50}$ values with various combinations got greater value. In case of dependent variables with number of hydrophobic bonds, it is seen that one is negative correlation other two is positive correlation. Here also $1/IC_{50}$ values with various combinations got high value compared with other variables [43]. In case of dependent variables with other interactions IC_{50} and $1/IC_{50}$ got positive correlation but log IC_{50} got negative correlation [44]. Here also $1/IC_{50}$ values show greater correlation. Then correlation coefficients of total of these interactions were analyzed. Here first two values show negative correlation and third one showing positive here also $1/IC_{50}$ values with various

combinations got greater value compared to IC_{50} and Log IC_{50} values. In general we can say single correlation is high in case of $1/IC_{50}$ compared to IC_{50} and log IC_{50}.

Multiple regression analysis

Multiple regression and Pearson coefficients were done using 23 CDK inhibitors that have IC_{50} values. Number of bridges hydrogen bonds, number of hydrophilic bonds, number of hydrophobic bonds, other bonds and total number of interactions are selected as dependent variables [45]. Log values and reciprocal of IC_{50} values were calculated. Relationship between five sets of parameters and the IC_{50} values, log IC_{50} values and $1/IC_{50}$ were analyzed by computing correlation coefficients and by multiple regression analysis. The 23 CDK inhibitors that have been used for multiple regression analysis is shown in Table 10.

Various combination	Correlation coefficient
12	0.393499
13	0. 136962137
14	0.090143
15	0.009601
123	0.462561
124	0.090143
125	0.009601
135	0.009601
145	0. 129561752
1234	0.522186
1235	0.009601
1245	0. 129561752
1345	0.21842
12345	0.522186

Table 10: Regression analysis table with IC_{50}.

- Number of hydrogen bonds.
- Number of hydrophilic bonds.
- Number of hydrophobic bonds.
- Other bonds.
- Total.

given time two or more interactions were considered together. The results are given in Table 11. When two interactions were considered number of hydrogen bonds and number of hydrophobic bonds gave the maximum correlation of 0.39. The above procedure was repeated for log IC_{50} and $1/IC_{50}$ and the results are precised in Table 12.

Multiple regression analysis of small molecule inhibitor interaction *vs.* biological activity

Multiple analysis of the role of the different interactions such as IC_{50}, Log IC_{50} and $1/IC_{50}$ *vs.* biological activity was carried out. At a

Various combination	Correlation coefficient
12	0.701756
13	0.060185
14	0.084893
15	0.038813
123	0.701756
124	0.084893

125	0.038813
135	0.038813
145	0.088108
1234	0.70176
1245	0.088108
1345	0. 131050295
12345	0.70176

Table 11: Regression analysis table with LogIC_{50}.

- Number of hydrogen bonds.
- Number of hydrophilic bonds.
- Number of hydrophobic bonds.
- Other bonds.
- Total.

Various combination	Correlation coefficient
12	0.68138
123	0.715931
124	0.214466
125	0.245536
145	0.254938
1234	0.717425
1235	0.245536
1245	0.254938
1345	0.263815
12345	0.717425

Table 12: Regression analysis table with 1/IC_{50}.

- Number of hydrophilic bonds.
- Number of hydrophobic bonds.
- Other bonds.
- Total.

Prediction of IC_{50} values based on interactions

We have made an attempt to predict the IC_{50} value using the concept on interaction. We setup regression equations for the 23 small molecule inhibitor complexes with IC_{50} value and interaction obtained with minimum distance of separation respectively. Aback check test was carried out to verify the self-consistency of the analysis; it entails calculating coefficients of multiple regressions using 23 small molecule inhibitor and computing their active IC_{50} values by resubstituting the values. Here calculation is done using log IC_{50} and 1/IC_{50} for good results [46]. The calculated predictive value and the log IC_{50} values are given in the Table 13. We found an agreement between log IC_{50} values and predictive value experimental observation as seen in Figure 4. From the results it is observed that the predictive value is compared with the IC_{50} value which gives similarity value more or less than 1. 1E1X, 1E1V, 1GII, 1GIJ, 1H08 are showing less than 1. 1KE5, 1KE9 and 1PYE show similar values. 1OGU and 1H07 are showing difference greater than 1.

PDBID	IC_{50}	LogIC_{50}	No. of BHB	No. of hydrophilic bonds	No. of hydrophobic bonds	Other	Total	Back check
1E1V	17000	4.230449	20	1	16	24	61	3.461787
1E1X	2200	3.342423	28	3	10	20	61	2.401971
1GII	78	1.892095	11	2	13	23	49	2.905079
1GIJ	25000	4.39794	28	2	9	29	68	3.050602

1H00	38000	4.579784	28	1	18	32	79	3.416404
1H01	1000	3	60	1	21	26	108	3.398465
1H1Q	970	2.986772	7	1	22	28	58	3.26172
1H1R	2300	3.361728	21	1	34	37	93	2.941842
1H1S	5.4	0.732394	45	4	16	36	101	1.63112
1H07	3000	3.477121	45	4	16	36	101	1.63112
1H08	300	2.477121	50	4	14	27	95	1.703302
1KE5	560	2.748188	27	2	16	24	69	2.851035
1KE6	5.7	0.755875	20	4	16	31	71	1.583326
1KE7	8.9	0.94939	12	5	10	36	63	1. 111215
1KE8	1000	3	13	3	22	31	69	2.022434
1KE9	660	2.819544	15	2	14	10	41	2.891583
1OGU	34	1.531479	21	1	16	32	70	3.459479
1OIR	32	1.50515	18	3	11	19	51	2.353705
1OIT	3	0.477121	36	4	20	32	92	1.500674
1P2A	12	1.079181	9	5	18	20	52	0.884951
1PYE	324	2.510545	11	2	26	33	72	2.527774
1R78	3	0.477121	4	6	20	24	54	0. 190581
1URW	3	0.477121	57	4	17	33	111	1.628374

Table 13: Predictive value table of log IC_{50}.

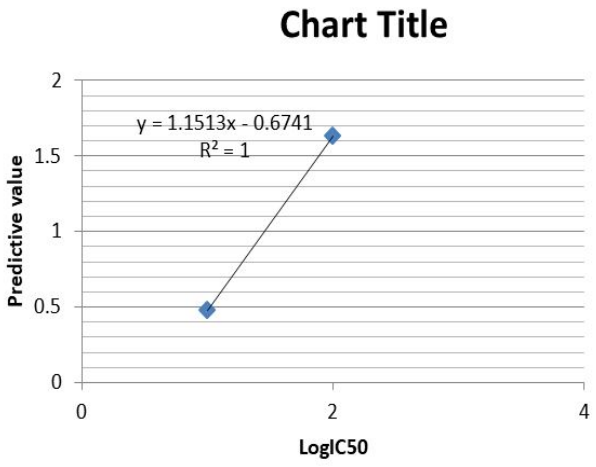

Figure 4: Predictive value graph of log IC_{50}.

Predictive value graph for logIC_{50}

Here predictive values are taken as X-axis and Log IC_{50} values are taken as Y-axis. Here 1R78, 1P2A, 1KE7, 1PYE, 1KE5, 1KE9, 1H1Q, 1H1R are matching. When comparing the LogIC_{50} values of these molecules it is seen that the activity values are almost similar. Using these values straight line graphs have been drawn as in Figure 4.

Jack knife test

We have also performed the jack knife test (leave one out of rule) for all those 23 complexes to examine the validity of the present method and the results and are included in Table 14. Third test validate the present method by determining the coefficients of multiple regression (n-1) data and then computing the IC_{50} values of the omitted complex. We found an agreement between the IC_{50} values and Jack knife value plotted in Figure 5.

PDBID	IC_{50}	LogIC_{50}	No. of BHB	No. of hydrophilic bonds	No. of hydrophobic bonds	Other	Total	JKV
1E1V	17000	4.230449	20	1	16	24	61	3.346952
1E1X	2200	3.342423	28	3	10	20	61	2.237571
1GII	78	1.892095	11	2	13	23	49	3.06734

1GIJ	25000	4.39794	28	2	9	29	68	2.660123
1H00	38000	4.579784	28	1	18	32	79	3.226579
1H01	1000	3	60	1	21	26	108	3.666906
1H1Q	970	2.986772	7	1	22	28	58	3.321855
1H1R	2300	3.361728	21	1	34	37	93	2.57461
1H1S	5.4	0.732394	45	4	16	36	101	1.818512
1H07	3000	3.477121	45	4	16	36	101	1.246213
1H08	300	2.477121	50	4	14	27	95	1.518566
1KE5	560	2.748188	27	2	16	24	69	2.859292
1KE6	5.7	0.755875	20	4	16	31	71	1.66765
1KE7	8.9	0.94939	12	5	10	36	63	1.224553
1KE8	1000	3	13	3	22	31	69	1.902066
1KE9	660	2.819544	15	2	14	10	41	2.935676
1OGU	34	1.531479	21	1	16	32	70	3.901542
1OIR	32	1.50515	18	3	11	19	51	2.498339
1OIT	3	0.477121	36	4	20	32	92	1.636851
1P2A	12	1.079181	9	5	18	20	52	0.810898
1PYE	324	2.510545	11	2	26	33	72	2.531933
1R78	3	0.477121	4	6	20	24	54	0.002181
1URW	3	0.477121	57	4	17	33	111	2.006258

Table 14: Jack Knife test value table of $LogIC_{50}$.

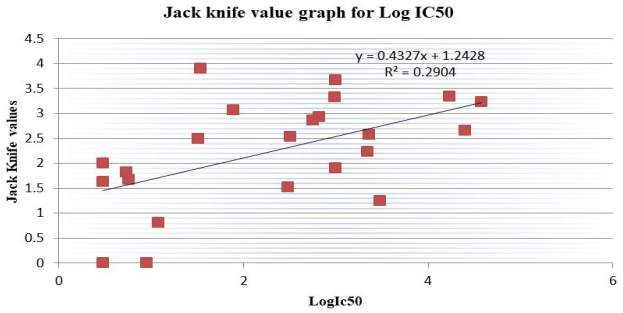

Figure 5: Jack Knife value graph for $logIC_{50}$.

From the result we can observe that the similarities between the Jack knife value and IC_{50} value are more or less than 2. In Table 15 1R78, 1URW, 1OIT, 1OGU, 1H07, 1H08, and 1GII are showing more two differences. 1H01, 1H1Q, 1KE9, 1P2A, 1PYE, 1OIR etc. are showing less two differences.

PDBID	$LogIC_{50}$	1/C	Hydrophobic residues	Neutral residues	Negatively charged residues	Positively charged residues
1E1V	4.230449	20	8	4	3	1
1E1X	3.342423	28	8	1	3	1
1GII	1.892095	11	9	1	3	2
1GIJ	4.39794	28	6	1	3	2
1H00	4.579784	28	6	1	3	3

1H01	3	60	5	1	4	2
1H1Q	2.986772	7	8	2	4	2
1H1R	3.361728	21	7	3	4	2
1H1S	0.732394	45	9	3	3	2
1H07	3.477121	45	9	2	3	2
1H08	2.477121	50	8	1	2	1
1KE5	2.748188	27	6	2	1	2
1KE6	0.755875	20	10	1	3	2
1KE7	0.94939	12	10	2	3	3
1KE8	3	13	9	1	4	2
1KE9	2.819544	15	9	0	2	2
1OGU	1.531479	21	8	2	4	2
1OIR	1.50515	18	6	2	3	2
1OIT	0.477121	36	6	1	3	1
1P2A	1.079181	9	7	1	2	1
1PYE	2.510545	11	7	2	2	1
1R78	0.477121	4	9	4	3	0
1URW	0.477121	57	7	1	3	2

Table 15: Multiple regression analysis for the Log IC_{50} and $1/IC_{50}$.

Multiple regression analysis of aminoacid ligand interaction

Representation of aminoacid ligand interaction in small molecule inhibitor complexes: From the Table 16 the amino acid ligand interactions has been calculated from the contact map by using the hydrophobic bonds, neutral, positive charge and negative charge. Here we can observe that the hydrophobic interactions are more in the case of 1KE6 and 1KE7 and less in the case of 1H01. Neutral residues are more in the case of 1E1V and 1R78 and in the case of 1KE9 it is absent. Negatively charged residues are almost equal in all the complexes except in case of 1KE5. Positively charged residues are high in case of 1H00 and 1R78 it is absent.

Single regression analysis result				
Dependent variables	**Hydrophobic residues**	**Neutral residues**	**Negatively charged residues**	**Positively charged residues**
$LogIC_{50}$	-0.28809	-0.05182	0.080357	0.211428
$1/IC_{50}$	0.123239	0.154196	0.004804	-0.30999

Table 16: Single regression result of amino acid ligand interaction.

Multiple regression result of amino acid ligand interaction

Here we did the multiple regression analysis for the log IC_{50} and $1/IC_{50}$ values. Here log IC_{50} showing maximum correlation (0.366175) than the $1/IC_{50}$ (0.341989) but almost similar (Table 17).

Multiple regression analysis result	
Dependent variables	
$LogIC_{50}$	0.366175
$1/IC_{50}$	0.341989

Table 17: Multiple regression result of amino acid ligand interaction.

Conclusion

Understanding the structural basis of small molecular ligand binding to enzyme can pave way for design of novel inhibitors, lead modification and eventually in structure based drug discovery. Keeping this in mind, in the present work we have analyzed 50 cyclin dependent kinase (which has a key role in cell signaling) small molecule inhibitor complexes and 6 CDK2-ATP complexes. 23 CDK2 small molecule inhibitor complexes that have IC_{50} values out of 50 CDK2 inhibitor complexes are also taken for various types of analysis. As binding to the ATP site and biological activity may be dependent on the different non-covalent interactions such as hydrogen bonds, hydrophobic bonds hydrophilic bonds and electrostatic vaanderwaals such as other interactions. Here we have analyzed these interactions in the CDK2-ATP complexes as well as the CDK2 inhibitor complexes. The 2D and 3D similarity analysis of 23 CDK2 small molecule inhibitor that have IC_{50} values enabled us to relate structural similarity with biological activity. Further from various noncovalent interactions we have developed multiple regression models to accounts for the experimentally observed IC_{50} values and to predict biological activity based on the different non-covalent interactions.

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