Identification of Novel CDK Inhibitors by Molecular Docking and Consensus Scoring Approach

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ABSTRACT
Cyclin Dependent Kinases go about as potential remedial focuses in cancer disease and several efforts are under way to find out more specific, potent and selective CDK inhibitors. In this paper, reported a computational molecular docking approach to screen approved drugs from DrugBank database. Docking and scoring of all compounds was done using Molegro Virtual Docker software, evaluated the binding affinities towards CDK-2, 4, 5 and 9 enzymes 2W9F, 2UZO, 1UNH and 3BLR resulted in variable dock scores. The resultant top 14 hits from a dataset of 1584 approved drugs were found to be more specific towards CDK inhibition. Further, re-scoring of 14 best docked poses followed by a consensus scoring approach retrieved top hits. In this study, tested three different scoring functions such as MolDock score of Molegro software, GOLD score and AutoDock. From the analysis, it was observed that Olmesartan and Telmisartan were reported to have high binding affinities with all CDKs tested.

Keywords
Cyclin-dependent kinases, Molecular docking, Consensus scoring, Binding affinity, DrugBank database, Olmesartan, Telmisartan, Protein Data Bank.

1. INTRODUCTION
Cell proliferation is a significant event that takes place due to the positive and negative signals which promote cell division and suppress the process [1]. The cell cycle is governed by a family of proteins, cyclin dependent kinases (CDKs). Cyclin dependent kinases are a gathering of serine/threonine kinases which assume a pivotal part in cell cycle control [2] and are included in diverse cellular processes, in regulation of cell division (CDKs1, 2, 3, 4, 6 and 7), transcription(CDKs7, 8 and 9) or support of the structure of the cytoskeleton (CDK5) [3]. Cyclin dependent kinases control the cell cycle movment working at the transition from G2 to M, G1 to S stages, and progression through S stage. During the procedure, a complex set of mechanisms, for example, cyclins, phosphorylations, and endogenous CDK inhibitors at different check points are included [4]. Cell cycle progresses by the activation of Cyclin and CDK complexes [5]. Cyclins act as check points which regulate the transition from one phase of cell cycle to another where certain mitogenic signals are required for their activities and progression. Moreover, CDKs 1, 2, 4 and 5 are found to be necessary to complete a cell cycle.

CDKs require cyclin subunits for activity. Activation of CDK2 results in rotation of N- and C-terminal domains leading to a slight widening of ATP cleft [6]. The movement of PSTAIRE helix and Glu51 and the subsequent reorganization leads to reshaping of the phosphate-binding site [7] in case of CDK-2. During mitosis CDKs phosphorylate many distinct proteins. These CDK substrates are phosphorylated at serine or threonine deposits that are perceived by the dynamic site of the CDK protein [8]. In most cases, the target serine (S) or threonine (T) residue is followed by a proline (P). The typical phosphorylation succession for CDKs is [S/T*]PX[K/R], where S/T* shows the phosphorylated serine or threonine, X represents to any amino acid and K/R represents the basic amino acid lysine (K) or arginine (R)[9].

All CDK inhibitors concentrated so far act by rivaling ATP for binding in the CDK ATP binding pocket [10]. CDK inhibitors raduce the kinase activites of the cyclin/CDK complexs, blocking the transition from G1 to S stages [11].It has been reported that CDK4/6 inhibitors displayed promising results in the treatment of breast cancer. Selective, ATP-competitive CDK4 inhibitors have been reported in literature [12-15] which are known to prevent phosphorylation and inactivation of Rb thereby inducing G1 stage leading to cell cycle arrest [16]. Success of few CDK4 inhibitors in early clinical phase trials has focused research to evaluate late-phase trials against breast cancer [17]. Based on the studies that explored various CDK bound inhibitors and their role in cell cycle progression and proliferation, CDK group of enzymes are thought to act as potential therapeutic targets in several proliferative diseases [8].

From literature it was identified that several drugs are known to act as anti-cancer agents, such as chemically synthesized and evaluated drugs or those which were obtained from plant sources such as natural products. However, there is a pressing need to discover novel, more potent and efficacious compounds as anti-cancer agents. Hence, in this paper presented a novel screening approach to identify potential anti-cancer agents against cell cycle enzymes, by screening approved drugs against enzymes participating in cell cycle process using computer-aided drug design procedures.

2. MATERIALS AND METHODS
2.1 Receptor X-ray Structure
The X-ray crystal structures of cell cycle regulator proteins (CDK-2, 4, 5 and 9; 2W9F, 2UZO, 1UNH and 3BLR) were recouped from Protein Data Bank (http://www.rcsb.org/pdb) and chosen as receptor models in virtual screening program. DrugBank database used as chemical compound library and employed three docking programs viz., Molegro Virtual Docker [18], GOLD [19] (Genetic Optimization for Ligand Docking) and AutoDock [20] for virtual ligand docking and a consensus scoring and ranking was employed to generate classes and the one with best rank was chosen.

2.2 Selection of Drugs from Drug Bank Database

The Drug Bank database is an one of a kind asset of drugs with detailed data on drug and complete drug target. The database contains nearly 7740 drug entries including 1584 FDA-approved small molecule drugs, 157 FDA-approved biotech (protein/peptide) drugs, and >6000 experimental drugs [21]. In the present study, 1584 approved drugs were selected for analysis.

2.3 Molegro Virtual Docker

Molegro Virtual Docker (MVD) is an integrated platform for predicting protein - ligand interactions. All default options including preparation of the molecules to determination of the potential binding sites of the target protein, and prediction of the binding modes of the ligands were employed. The MVD has been shown to yield higher docking accuracy than other state-of-the-art docking products [18].

2.4 Gold

The GOLD program uses a genetic algorithm (GA) and the binding site was defined as a spherical region which encompasses all protein atoms within 5.0 Å of each crystallographic ligand atom. Default settings were used for all calculations. For each of the 10 independent GA runs, a maximum number of 10000 GA operations were performed on a single population of 50 individuals. Operator weights for crossover, mutation, and migration were set to 100, 100 and 0.

To further speed up the calculation, the GA docking was stopped when the top three solutions were within 1.5 A° RMSD (Root Mean Square Deviation) of each other.

2.5 AutoDock

AutoDock requires receptor and ligand coordinates in MOL2 or PDB format. Nonpolar hydrogen atoms were removed from the receptor file and their partial charges were added to the corresponding carbon atoms. All docking runs were performed using the Lamarckian genetic algorithm and the best value was reported in kcal/mol. The standard docking protocol consisted of 10 independent runs per ligand, using an initial population of 50 randomly placed individuals, a maximum number of 2.5 x 10^5 energy evaluations, a mutation rate of 0.02, a crossover rate of 0.80, and an elitism value of 1. The probability of performing a local search on an individual in the population was 0.06, using a maximum of 300 iterations per local search. Results differing by less than 2 Å RMSD from each other were clustered together and represented as best docking energy [20].

2.6 Molecule Preparations

Although DrugBank database provides ligands in 3-D formats, an energy minimization routine was performed to generate three dimensional structures of all the molecules using corina make 3D option, derived charges and the geometries were optimized using cosmic module of Tsar Software. Water molecules were discarded from the PDB file, and missing side chains were reconstructed using WHAT-IF web interface (http://swift.cmbi.ru.nl/servers/html/index.html). Hydrogens were added and then the structure was converted to mol2 format using Mercury (http://www.ccdc.cam.ac.uk/products/mercury) (v. 1.4.2; Cambridge Crystallographic Data Centre (CCDC)).

2.7 Consensus Scoring and Ranking

Docking programs predict binding modes and energies of protein-ligand complex structures with reasonable accuracy and speed. Most of the docking programs are able to predict the nearer binding mode of a ligand, however, scoring functions play major role to differentiate correct poses from incorrect ones. As docking and scoring play important roles in drug design, it has been pointed out that the major weakness of docking programs lies in scoring functions. However, combinations of various scoring functions would reduce the errors in single scoring schemes and improve the probability of identifying true hits [22]. Thus, it has been demonstrated that consensus scoring was generally more effective than single scoring for molecular docking [23] and represented an effective way in getting improved hit rates in various virtual database screening studies [24].

In this study, tested three different scoring functions such as MolDock score of Molegro software, GOLD score implemented in GOLD 3.1, and Free energy score of AutoDock. Docking program Molegro Virtual Docker was used to dock DrugBank compounds and the generated ensemble of docked conformations were scored and applied to generate classes followed by ranking the best conformations. The best conformations of each ligand that were clustered using complete linkage analysis are saved in mol2 formats. These files are used to apply the remaining scoring functions. During ranking, signs of some scoring functions are changed to make certain that a lower score always indicates a higher affinity.

3. RESULTS AND DISCUSSION

The docking protocol was validated before screening DrugBank database. 2UZO protein bound ligand was docked into the binding pockets of all CDKs to obtain the docked pose and the RMSD (Root Mean Square Deviation) of all atoms between these two conformations is <2.0 ˚A indicating that the parameters for docking simulation are reasonable in reproducing the X-ray crystal structure. Therefore, DrugBank database was screened for all approved drugs, which were docked into each of the protein structures using default parameters of Molegro virtual docker. Table 1 shows the binding affinities and RMSD values of cell cycle proteins studied.The rationale behind selecting CDKs as potential cancer targets is based on published literature on these enzymes. Of all the cancer causing or participating proteins/enzymes such as CDKs, apoptotic proteins and others, it has been reported that the crucial phases of cell cycle can be arrested if any one of the CDKs are blocked in a way to reduce cell proliferation. Hence, it has been postulated by many authors that targeting CDKs would provide a higher chance or rate of inhibiting cell cycle process.

Table1: Mol dock scores of cell cycle regulator proteins

S.NO	PDB ID	Mol Dock Score(kcal/mol)			Average mol dock score (kcal/mol)	Average RMSD Value (°A)
		Run-1	Run-2	Run-3		
1	2W9F	145.5	147.78	146.3	146.51	0.67758
2	2UZO	126.54	123.25	125.63	125.15	1.06333
3	1UNH	113.91	111.66	114	133.19	0.11708
4	3BLR	114.24	112.32	114.63	114.06	0.17279

Docking of all 1584 approved drugs from DrugBank was carried out to evaluate best conformer based on the lowest docked energy (kcal/mol), in other words, it should possess highest affinity towards the binding site. Moreover, the virtual screening technique employed in this work recognized entirely diverse, yet specific drugs that bind in a comparable manner as seen with ATP binding in CDKs. Therefore, in the first step, virtual screening based on docking and scoring of DrugBank compounds resulted in few hits with dock scores reaching more than 200 kcal/mol. The result is given in Table-2.

Table 2: Docking results of MVD

Drug Name	2W9F dock score (kcal/mol)	2UZO dock score (kcal/mol)	1UNH dock score (kcal/mol)	3BLR dock score (kcal/mol)
Pentagastrin	158.351	149.198	145.323	156.789
Olmesartan	208.296	198.472	197.894	187.035
Teniposide	174.5	164.784	178.286	166.59
Verteporfin	200.02	223.223	185.378	213.67
Montelukast	175.412	167.435	155.934	163.284
candoxatril	165.536	154.91	155.38	169.491
Pemetrexed	162.825	138.96	159.865	148.055
Losartan	168.644	163.567	161.244	168.133
Candesartan	170.916	166.307	160.613	167.591
Eprosartan	181.317	167.877	161.587	177.815
Tiagabine	171.856	138.006	130.721	136.154
Repoglinide	167.581	150.842	142.284	138.795
Telmisartan	175.608	187.981	166.982	189.228
Atorvastatin	183.618	189.203	183.401	191.542

In the next step, re-scoring docking poses with independent functions was another valuable approach which gained prominence in recent studies [25].Therefore, re-scoring of best docked poses from MVD was done using GOLD and AutoDock. Results are presented in Table3.Further, a consensus scoring approach was implemented to evaluate best compounds from a set of 14 finalized drugs, which showed probable best docked poses against CDKs. Consensus scoring approaches combining multiple scoring functions were shown to work better in many [26]. Hence, the GOLD score, Molegro Score and AutoDock was applied to re-evaluate the 14 docked poses. Ranking was done individually by equally splitting the dock scores into three classes using Tsar Software (www.accelrys.com). The compounds in Class3 represent the highest class or top rank. Summation of all ranks (rank-sum) was considered as best technique rather taking average values [27]. The advantage of a sum over an average was that the contribution from the rank for each individual score can more easily be split out for illustrative purposes in the former instance [27]. The details are given in table-4.

Table 3: Dock scores comparison of top best compounds that exhibited high affinities with MVD.

Drug Name	GOLD (kcal/mol)				AutoDock (kcal/mol)			
	2W9F	2UZO	1UNH	3BLR	2W9F	2UZO	1UNH	3BLR
Pentagastrin	44.53	56.63	51.11	66.81	5.9	7.8	8	3.9
Olmesartan	60.26	63.88	54.01	60.03	8.5	8.7	7.8	5.7
Teniposide	33.31	42.63	38.35	9.72	7.3	8.7	8.6	5.2
Verteporfin	13.14	63.98	46.00	51.72	6.4	9.9	8.1	5.1
Montelukast	54.34	59.51	47.28	59.07	7.9	8.7	9.3	4.7
candoxatril	25.19	51.46	36.56	47.53	7.8	9.2	8.7	5
Pemetrexed	74.72	70.19	53.9	71	9	9.3	8.8	5.9
Losartan	59.11	64.09	48.68	72.82	7.4	9.1	8.2	8.6
Candesartan	53.51	64.83	49.45	67.02	7.6	8.8	8.8	8.5
Eprosartan	66.54	57.87	52.69	67.1	7.3	8.1	7.8	8.8
Tiagabine	57.11	49.58	39.72	59.06	7.2	7.3	7.7	7.4

Table 4: Ranks of scores obtained in Molegro, GOLD, AutoDock for CDKs(Top three best scores are underlined).

Drug Name	**M**	**G**	**A**	**Rank Sum**	**M**	**G**	**A**	**Rank Sum**	**M**	**G**	**A**	**Rank sum**	**M**	**G**	**A**	**Rank sum**
	2W9F				**2UZO**				**1UNH**				**3BLR**			
Pentagastrin	1	2	1	4	1	2	1	4	1	3	1	5	1	3	1	5
Olmesartan	3	3	3	9	3	3	2	8	3	3	1	7	2	3	1	6
Teniposide	1	2	2	5	1	1	2	4	3	1	2	6	2	1	1	4
Verteporfin	3	1	1	5	3	3	3	9	3	2	1	6	3	2	1	6
Montelukast	2	3	2	7	2	2	2	6	2	2	2	6	2	3	1	6
candoxatril	1	1	2	4	1	2	2	5	2	1	2	5	2	2	1	5
Pemetrexed	1	3	3	7	1	3	2	6	2	3	2	7	1	3	1	5
Losartan	1	3	2	6	1	3	2	6	2	3	1	6	2	3	3	8
Candesartan	1	2	2	5	1	3	2	6	2	3	2	7	2	3	3	8
Eprosartan	2	3	2	7	2	2	1	5	2	3	1	6	2	3	3	8
Tiagabine	1	3	2	6	1	1	1	3	1	1	1	3	1	3	2	6
Repoglinide	1	1	1	3	1	1	1	3	1	1	2	4	1	2	3	6
Telmisartan	2	3	3	8	2	3	3	8	2	3	3	8	3	3	3	9
Atorvastatin	2	2	1	5	2	1	2	5	3	1	1	5	3	2	3	8

M: Molegro Virtual Docker; G: GOLD; A: AutoDock

The best three drugs which reported to exhibit high binding affinity against all targets are considered and they are identified as:

- 2W9F:Olmesartan,Telmisartan,Eprosartan
- 2UZO: Olmesartan, Telmisartan, Verteporfin
- 1UNH: Olmesartan, Telmisartan, Candesartan
- 3BLR: Eprosartan, Telmisartan, Candesartan.

From the above data, it can be emphasized that Olmesartan and Telmisartan (Figure 1) would act as inhibitors against cell cycle proteins. Olmesartan, an angiotensin II receptor antagonist, chemically is (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl) -1H-imidazole-5-carboxylate, used for the treatment of high blood pressure. Considering the imidazole ring moiety at the centre, with tetrazole and dioxolyl groups as side chains on either arm of the structure, this scaffold should be studied in much detail owing to the interactions it makes with active site amino acid residues of tyrosine kinase enzymes participating in cancer pathways.

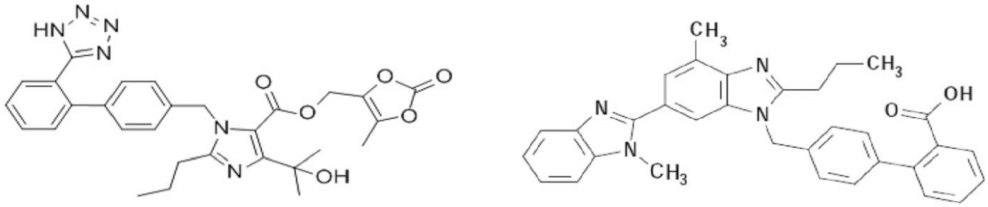

Figure 1. 2-dimensional structures of Olmesartan and Telmisartan

On the other hand, Telmisartan, an approved angiotensin II receptor antagonist has chemical structure, 2-(4-{[4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid. This chemical has two benzodiazoles and benzoic acid moieties making it more hydrophobic groups amenable to bind with hydrophobic amino acid residues of active site region of proteins. Hence, it would like to explore the characteristic features of these two compounds and screen proteins that are reported to be active in various cancer diseases. Moreover, experimental analysis involving cytotoxicity studies would shed some light in studying the capability of these drugs to act as possible anti-cancer agents.

4. CONCLUSION

The analysis reported in this paper identified a unique method of choice to screen DrugBank compounds which resulted in diverse, novel approved drugs as possible anti-cancer agents. The computer-aided drug design protocol implemented would be advantageous in exploring novel drugs that are identified using consensus scoring and ranking techniques, on one hand and they might also provide a new scaffold for further design and development of novel CDK inhibitors. Further, work is in progress to explore computational analysis on analogs of olmesartan and telmisartan to study the possible enhanced pharmacophoric features of these compounds.

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