Docking Studies on a Series of Polo-like Kinase 4 Inhibitors

Ru DING1,a, Juan LIU2,b, Rong TAN3,c, Yuan LIU4,d, Ping YI1,e*

1State Key Laboratory of Functions and Applications of Medicinal Plants, Guizhou Medical University, 3491 Baijin Road, Guiyang 550014, PR China
2Graduate School, Guizhou Medical University, University Town, Guian New District, Guiyang 550025, PR China
3Pharmacy Affiliated Hospital of Guizhou Medical University, Guiyang 550001, PR China
4Center for Disease Control and Prevention of Guizhou Province, Guiyang 550003, PR China

a541888827@qq.com, b870383821@qq.com, c355153975@qq.com,
d1363405389@qq.com, eyiping2100@aliyun.com
*Corresponding author

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Abstract. Polo-like kinase 4 (PLK4), a mitotic kinase was regarded as a potential target for cancer therapy. A novel series of PLK4 competitive kinase inhibitors have been docked into the active site of Polo-like kinase 4 (PDB code 4JXF) by using CCDC GOLD, furthermore, the binding modes for the inhibitors generated by MOE2015 may explain the mechanism of kinase selectivity.

Introduction

The Polo-like kinase (PLK) family of serine/threonine kinases has an important role in regulating mitosis [1]. There are five members known to the researchers. Among PLK1, 2, 3, 4 and 5, PLK1 is the most studied one. Several PLK1 inhibitors have been taken into the clinic [2]. However, PLK4 enzyme received little attention. It has been shown that treating breast cancer cells with PLK4 RNAi stops centriole duplication and leads to cell death and furthermore normal breast cells are not affected. These findings proved PLK4 as a target for anticancer research [3].

In recent years, a number of Polo-like kinase(PLK) inhibitors have appeared in the patent and primary literatures. Among them, Peter B. Sampson, Henry W. Pauls and his colleagues synthesized a series of (1R,2S)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3’-indolin]-2’-one based skeleton derivatives as potent(Fig. 1), selective PLK4 inhibitors. Forthmore, An X-ray crystal structure of a similar analogue inhibitor in complex with PLK4 have been determined which provide important information about the interaction with the residues of the binding site [4, 5].

In this study, we applied this receptor-based technique to a set of 49 PLK4 inhibitors which have been recently developed [4, 5]. In order to fast recognize the inhibitor that we discussed, the numbers of the inhibitors from the original papers have unchanged in current study. The crystal structure of the catalytic domain of PLK4 enzyme together with an automatic docking program was used to determine the molecular alignment of the ligands. The model obtained by this way yielded a high correlation between the experimentally determined binding affinity
and the calculated molecular interaction fields. Encouraged by these results the receptor-based model should now be used for the screening and prediction of novel inhibitors for PLK4 enzyme.

Figure 1. (1R,2S)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3’-indolin]-2’-one based skeleton,

Computational Details

Biological Data and Molecular Structures

The 3D structures of these compounds were constructed using the molecular modeling software package SYBYL-X 2.1. Partial atomic charges were calculated by the MMFF94 method, and energy minimizations were performed using the Tripos force field with a distance-dependent dielectric and the Powell conjugate gradient algorithm (convergence criterion of 0.001 kcal/mol Å). All compounds were generated in the protonation state under physiological condition.

Molecular Docking

To locate the appropriate binding orientations and conformations of the inhibitors interacting with PLK4, a powerful computational searching method was needed. The advanced molecular docking program GOLD (version 5.3), with a powerful genetic algorithm (GA) method for conformational search and docking programs, was employed to generate an ensemble of docked conformations. Atomic coordinates for PLK4 complex with the ligand ((1R,2S)-2-{3-[(E)-2-{4-{[(dimethylamino)methyl]phenyl}ethenyl]-2H-indazol-6-yl}]-5’-meth oxyspiro[cyclopropane-1,3’-indol]-2’(1’H)-one) that was used for our modeling study have been deposited in the Brookhaven Protein DataBank with a resolution of 2.4 Å (PDB ID: 4JXF) [5]. The original ligand was removed from the coordinated set of PLK4, the ligands were scored based on the fitness function ‘GoldScore’. GOLD was run to save up to 10 top-ranked docking solutions for the ligands.

Results and Discussion

In a preliminary docking study, we tested whether GOLD is able to correctly reproduce the position of the co-crystallized inhibitor. Docking of inhibitor into the PLK4 binding site, using default settings and with considering the co-crystallized water molecules, showed good agreement with the experimentally derived binding mode (RMSD 0.809 Å).
Due to the structural similarity of the analyzed data set with the co-crystallized inhibitor, it is likely that all active compounds show the same orientation at the binding pocket of the PLK4. We employed default settings of the GOLD program to end up with a consistent alignment of all 49 derivatives as described in detail in the Methods Section. 49 conformational binding modes for each ligand were generated at the active site. Moreover, it was observed that the orientations of all 49 inhibitors as extracted from the GOLD docking are quite similar. When they were superimposed, a small but distinct shift of the scaffold was found. In order to explain activity selection mechanism between PLK4 enzyme and the inhibitors, we choose high activity compound 56b to illuminate the results. Fig. 2 which was generated by MOE2015, represents the interaction model of the docked inhibitor 56b with PLK4 enzyme. Hydrogen bonds are depicted by dashed lines. When the hydrogen bond is formed with the residue sidechain, the arrow is drawn in green. Hydrogen bonds to the residue backbone are drawn in blue, with an additional dot drawn at the residue attachment point. Inhibitor 56b binds to the active sites and makes several interactions with the hinge-binding region of the enzyme. Three key hydrogen bonds are found between the co-crystallized structure (PDB code: 4JXF) and the most inhibitors: Hydrogen bonding of the indazole to Glu90 and Cys 92 of the hinge region; H-bond from the indolinone moiety to the side chain of Lys41. Near the R3 substituent region, the hydrophilic N,N-dimethyl-1-phenylmethanaminium R3 substituent of inhibitor 56b have several hydrogen bonding interactions of the nearby water molecules, which form a H-bond net. Maybe this is the reason why inhibitor 56b have higher affinity than most other inhibitors. As shown in Fig. 2, there are 4 default color schemes for residues. Hydrophobic residues are all colored with a green interior, whereas polar residues are colored in light purple. Basic residues are further annotated by a blue interior ring, and acidic residues with a red ring. Water molecules are drawn without interior color, and metals are colored grey. Solvent accessible surface area of the ligand is plotted directly onto the atoms in the form of a blue smudge. Hydrophobic residues Leu18, Phe23, Val26, Ala39, Leu73, Met91, Leu142, Leu143 and Leu161 have hydrophobic interaction with the skeleton of the inhibitor56b, polar residues Asn102, Gly19, Thr159, Gln160, Arg135, Tyr100, Ser140, Asp154, Gly95, Asn341, His91, Arg28 and Thr238 have polar interaction with polar substituent of inhibitor 56b. Other inhibitors have the similar interactions with the PLK4 enzyme [6-8].
Summary

In summary, docking analyses have been performed on 49 compounds using molecular docking method. Satisfactory models were obtained to explain the activities of the structures. The receptor sites will guide the design of novel structures which demonstrate optimal binding to and inhibition of PLK4.

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References


