Journal of Applied Pharmaceutical Science Vol. 4 (11), pp. 047-053, November, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.4119
ISSN 2231-3354

The molecular docking of 1,4-naphthoquinone derivatives as inhibitors of Polo-like kinase 1 using Molegro Virtual Docker

Susi Kusumaningrum [1,2]*, Emil Budianto [1], Soleh Kosela [1], Wahono Sumaryono [2], Fifit Juniarti [2]

[1] Chemistry Department, Faculty of Mathematics and Natural Science, University of Indonesia, Depok Indonesia.
[2] Center of Pharmaceutical and Medical Technology, Agency for Assessment and Application of Technology, Jakarta, Indonesia.

ARTICLE INFO

Article history:
Received on: 11/07/2014
Revised on: 18/08/2014
Accepted on: 02/09/2014
Available online: 27/11/2014

Key words:
naphthoquinone, Polo like kinase-1, docking, molegro virtual docker

ABSTRACT

Polo-like kinase 1 (Plk1) is over expressed in many types of human cancers, and has been implicated as an adverse prognostic marker for cancer patients. Plk1 is localized to its intracellular anchoring sites via its polo-box domain (PBD). The PBD of Plk1 has a crucial role in proper subcellular localization and mitotic functions of Plk1. Plk1 is the preferential target for inhibition of the mitotic processing therefore it can be chosen as drug target for the treatment of cancer. The aim of the study is to find plk1 inhibitor potential from naphthoquinone derivatives through binding free energy analysis into plk1 using molecular docking. We conducted docking simulation to naphthoquinone derivatives as ligands into plk1 as receptor. The 3D structure of plk1 was downloaded from PDB (Code ID:3THB). The structure of ligands and protein were prepared using ChemBioDrawUltra 12.0. Docking process, the interaction and binding of ligands – protein were done and visualized using software Molegro Virtual Docking.(MVD). The results showed no hydrogen bonding and electrostatic interaction between compound NO11(modified naphthoquinone) with Plk1, but this compound have more steric interaction with Phe 133, Asp 194, Glu 101, Lys 82, Cys 133 and Glu 140 of Plk1. Moldock scores of compound NO11, is -134.73 kcal/mol. It is predicted that compound NO11 has potency as lead compound to find a new anticancer candidates for possible therapeutic agents.

INTRODUCTION

Cancer is the second leading causes of death in the world after heart disease. The number of cancer patients in the world increase approximately 6.25 million people per year (WHO). The prevalence rate in Indonesia is quite high, it is estimated that there are 100 cancer patients in every 100,000 population (Diananda, 2008; Indonesian Cancer Foundation, 2006). Besides surgery, hormone therapy and radiotherapy, chemotherapy is anaother alternative in cancer treatment. The aim of chemotherapy is to inhibit or halt the growth of cells oncogenes (cancer) in the patient's body. The working principle is the chemotherapy drugs attack specific phase or all phases of the mitotic division in cells that are replicating or expanding rapidly (cancer cells). Antimitotic form the basis of therapy for patients with multiple types of solid tumors and hematologic malignancies. However, by stabilizing (taxanes) or depolymerizing (vinca alkaloids) microtubules, current antimitotic affect both dividing and nondividing cells. An ideal next generation antimitotic should possess the following characteristics: target function(s) required in dividing cells but not nondividing cells; over-expression of the target in tumor with minimal expression in normal tissue; proven role for the target in inducing oncogenesis; robust pharmacodynamics (PD) marker(s) to monitor the inhibition of the target; and predictive marker(s) allowing enrichment of potentially responsive patient populations. One of the emerging next generation antimitotic targets is Polo-like kinase 1 (Plk1) (Degenhart, 2010; Reagan-Shaw and Ahmad, 2005; Strenhardt and Ulrich, 2006; Stebhardt, 2010). Plks is a family of kinases that perform several crucial functions in cell division. Five members of the Plk family (Plk1, Plk2, Plk3, Plk4 and

* *Corresponding Author*
Susi Kusumaningrum, Agency for the Assessment and Application of Technology (BPPT), Laboratory of Pharmaceutical & Medical Technology, LAPTIAB Building I No. 611 PUSPIPTEK Tangerang, Banten, Indonesia, Phone: +62-21-7560536 ext 7108, Fax: +62-21-7560536 ext 122, Email: susi.kusumaningrum@gmail.com

Plk5) have been discovered in human; all of which seem to have largely nonoverlapping functions during cell cycle. Plks consist of a kinase domain and two polo box regions. The two polo box regions fold together to form a polo box domain (PBD), a functional domain that can bind phosphorylated peptides. This priming phosphorylation is mainly provided by a cyclin-dependent kinase (Cdk)1 but there is also evidence that shows that at least Plk1 can create its own docking site through priming phosphorylation. This mechanism ensures targeted substrate recognition and recruitment of Plk1 to selected sites within the cell. (Bruinsma, 2012). Human Plk1 is a key regulator of multiple mitotic event and its overexpression is related to cell proliferation and carcinogenesis (Zhou, 2010). Naphthoquinone is one of secondary metabolites that are widespread in nature and found in large amounts in some families of plant kingdom such as Avicenniaceae, Bignoniaceae, Boraginaceae, Droseraceae, Ebenaceae, Juglandaceae, Nepenthaceae and Plumbagnaceae. Naphthoquinone also known as secondary metabolites of actinomycetes such as Streptomyces group, fungi/ mold (Fusarium, Marasmius, Verticillium), and in lichen and algae. The yellow or brown of naphthoquinone serves as a color pigmentation. In some plant families, such as Diospyros and Ebenaceae, it is found in the form of monomers, dimers or trimers (Babula, 2009). 1,4-Naphthoquinones are clinically important antitumor drugs containing a quinone moiety, such as anthracyclines, mitoxantrones and saintopin, which show excellent anticancer activity (Verma and Hanch, 2004; Verma,2006, Tandon *et al.*, 2004; Kayashima *et al.*, 2009). The National Cancer Institute (NCI), Bethesda, USA, is still playing an articular role in this field and identified that the quinone as an important pharmacophore for anticancer activity.

Some of naphthoquinone derivatives have been synthesized and evaluate in order to discover more potent anticancer agent. They were reported show cytotoxic activity. Traditional synthesis of new naphthoquinone derivatives and bioactive compounds can be carried out for optimization activity. However, those processes are high cost and also time consuming. On the other hand, screening of the small molecules from novel compounds represents an alternative process. Many studies have indicated that computational approaches, such as structural bioinformatics (Chou., 2004; Reindl, 2007) pharmacophore modeling are the best choice. Docking various ligands to the protein of interest followed by scoring to determine the binding affinity and to reveal the strength of interaction has become extensively used in virtual screening of large databases and lead optimization (Schneider & Bohm, 2002)

This paper reports screening of various naphthoquinone derivatives possessing benzolactam moiety bound directly or indirectly to ring system against Plk1 enzyme extracted from protein data bank, by utilizing the Molegro Virtual Docker Software. Various molecular structures of the ligands were docked and scored to identify the ligands that bind similar to reference ligand binding for Plk1 and to estimate the ligands binding affinity for its target.

MATERIAL AND METHODS

In this study, docking of 16 naphthoquinone derivatives, doxorubicin and poloxin against Plk1 have performed using MVD software. A single rigid crystal structure of an enzyme is used for docking studies from the 53 crystal structures of Plk1 held in the Protein Data Bank (PDB) (Duffey, 2012) accessed at the URL (http://www.rscb.org/pdb) under the criteria that they had reasonable resolution ($\leq$ 2.8 Å) and involved the non mutated pololike kinase enzyme from Homo sapiens, in the complex with small molecule ligands.

Twelve modified 1,4-Naphthoquinones, 5 derivate naphtoquinones, doxorubicin (chemotherapy drug), benzolactam (refference ligan) and poloxin (inhibitor Plk1) have been docked against Plk1 crystal structure and 10 independent runs were performed with the guided differential evolution algoritm, with each of these docking runs returning one solution (pose). The Moldock scoring function used by MVD is derived from the PLP scoring functions originaly proposed by Gehlhaar et al and extended later by Yang et al (Naeem, 2013).

The 10 solutions obtained from the 10 independent docking runs were re-ranked, in order to further increase the docking accuracy, by using a more complex scoring function. In the MVD, along with the docking scoring terms, a Lennard Jones 12-6 potential and sp2-sp2 torsion terms were also used (Naeem, 2013).

On the basis of pilot docking studies, the MolDock rerank scores were selected for ranking the inhibitor poses, and for all the pololike kinase 1 docking performed here, the poses selected as the best were taken as those with the highest MolDock re-rank score. Polo-like kinase-1 crystal structure was directly downloaded to the workspace of MVD from the PDB accessed at the URL: (http://www.rscb.org/pdb). The structure of naphtoquinone derivates have been drawn on ChemBioDrawUltra 12.0 software and imported to the MVD workspace in 'sdf' format. In order to make accurate predictions, it is important that the imported structures have been properly prepared, that is, the atom connectivity and bond orders are correct and partial atomic charges are assigned. PDB files often have poor or missing assignment of explicit hydrogens, and the PDB file format cannot accommodate bond order information. All necessary valency checks and H atom addition were thus performed using the utilities provided in MVD. The binding site specifies the region of interest where the docking procedure will look for promising poses (ligand conformations).

RESULT AND DISCUSSION

Molecular docking is an optimization problem, where the objective is to find the ligand binding mode with lowest potential energy. The process of docking involves sampling the coordinate space of the target binding site and scoring each possible ligand pose within that site, the highest scoring pose then taken as the predicted binding mode for that compound. There are many different docking programs now available and they differ in the

nature of the sampling algorithms they employ, in their manner of handling ligand and protein flexibility, in the scoring functions they use, and in the cpu time they required. In the studies reported here, MVD was used, because it showed higher docking accuracy when benchmarked against other available docking programs (MD: 87%, Glide: 82%, Surflex: 75%, FlexX:58%) and has been shown to be successful in several recent studies, but also for reasons of cost and user friendliness (Thomsen *et al.,* 2006).

MVD automatically identifies potential binding sites (also referred as cavities or active sites) by using its cavity detection algorithm. The cavities within a 30 x 30 x 30 Å3 cube centered at the experimentally known ligand position were used. The cavities that are identified by the cavity detection algorithm are then used by the guided differential evolution search algorithm to focus the search, to that specific area during the docking simulation. In the case of the crystal structures for pololike kinase 1 complexes, the program generally identified five different binding sites (Figure 1).

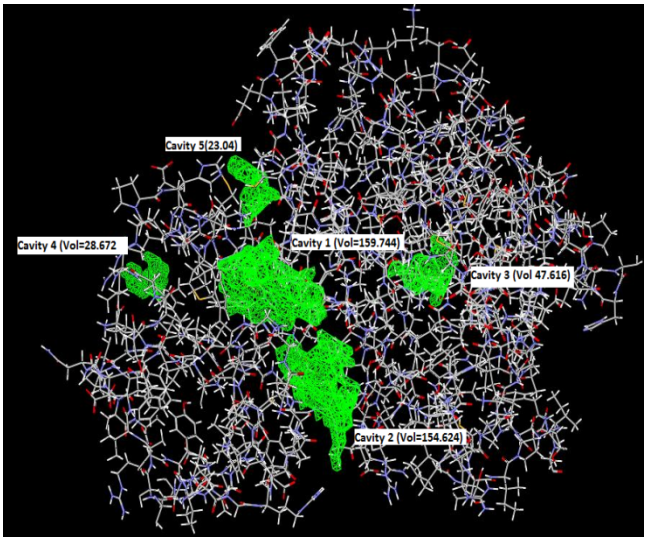


Fig. 1: The five cavity MVD-detected cavities in Plk1, and their calculated volumes (in Å) (PDB code 3THB (Diffey *et al.,* 2012), detected cavity green, carbon atoms grey, oxygen atoms red, nitrogen atoms blue.

From these five predicted cavities the one with the highest volume (159.744 Å; Duffey, 2012) was selected for consideration, as it includes the bound ligand. The best studied member of the Plk family is PLk1, which has been implicated in various essential cell-cycle-related processes including centrosome maturation, mitotic entry, checkpoint recovery, spindle assembly, sister chromatid . separation and cytokinesis (Bruinsma, 2012).

One application of molecular docking is to design pharmaceutical in silico by optimizing targeted lead candidates against protein. The lead candidates can be found using a docking algorithm that aims to identify the optimal binding mode of a small molecule (ligand) to the active site of macromolecular target. Twelve naphthoquinone ligands have been designed into oxime derivatives to obtain more potent compounds as inhibitors of Plk1. Furthermore docking of these ligand, five naphtoquinone derivatives, doxorubicin, benzolactam and poloxin were performed with the crystal structure of Plk1 and each ligand chosen the best position to determine the re-rank score. In each docking run, the best poses were selected on the basis of their MVD re-rank scores and the mean of the 5 re-rank scores was then computed as the final score for each compound. The MVD score and the re-rank scores of the best poses for each of the docking studies of naphthoqunone ligand, doxorubicin and benzolactam with plk1 are summarized in Table 1 and Table 2.

In general, the obtained score are between -57.7085 and -134.73 kcal/mol. Docking to Plk1 was also performed on poloxin. Moldock score of ligand NO11 is lower than benzolactam, doxorubicin and poloxin. Doxorubicin,known by its trade name Adriamycin or liposome-encapsulated form known as hydroxydaunorubicin with trade name Doxil is a drug used in cancer chemotherapy and derived by chemical semisynthesis from a bacterial species (Brayfield, 2013). Poloxin is a proven active compounds as an inhibitors of Plk1. By blocking PBD binding to its recognition motif, poloxin disrupted the human Plk1 sub-cellular localization and eventually arrested the cell cycle (Zhou, 2010; Lansing, 2007).

Moldock scores of compound NO11 (modified naphthoquinone), Doxorubicin and Poloxin are -134.73, -118.859 and -99.335 kcal/mol respectively. The molecular weight of the molecules modified naphthoquinones are between 158.153 to 424.448 with ClogP value between 1.93 to 7.21. Whereas the molecular weight of benzolactam and doxorubicin were 451.99 and 527.52 with ClogP value of 1.69 and 4.15. Modified naphthoquinone compounds have moldock score better than the original compound. Several modified naphthoquinone compounds (NO9, NO10 and NO11), even have the best score better than benzolaktam, doxorubicin and poloxin. This results indicates that the above mentioned molecules are predicted to be anticancer drug candidate The superposition of benzolactam, as observed in the cavity of the crystallographic structure of Plk1 and the best conformation obtained theoritically for naphthoquinone derivated are shown in Fig. 2. The result suggest that the sofware reproduced the appropiate conformation of benzolactam inside its binding site in the Plk1.

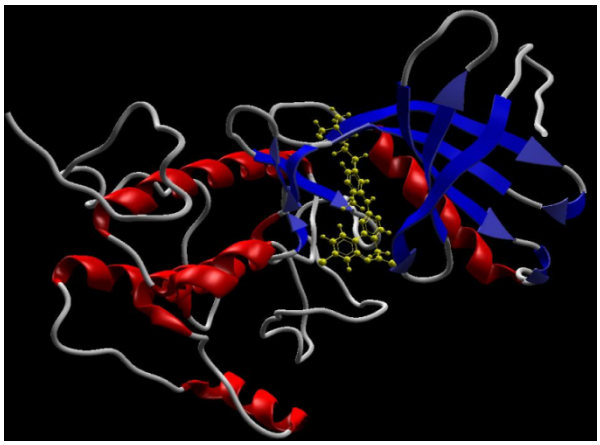


Fig. 2: Structural cartoon of pololike kinase 1 (PDB code 3THB, Duffey 1992), The α helices and β strands are represented as coils (red) and arrows (blue) respectively. Benzolactam is represented in ball and stick (yellow).

Table. 1: MVD and Re-rank score (kcal/mol) for 1,4-naphthoquinone and modified naphthoquinone when docked with polo like kinase crystal structure.

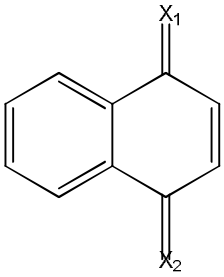
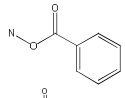
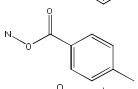
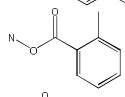
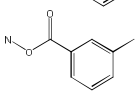
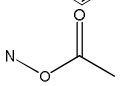
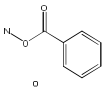
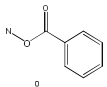
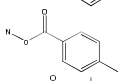
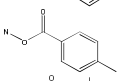
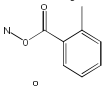
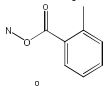
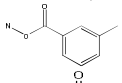
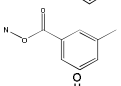
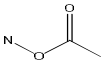
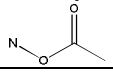
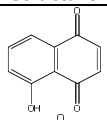
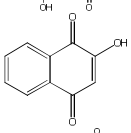
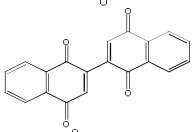
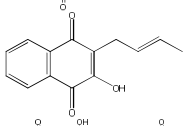
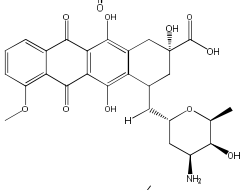
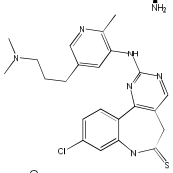
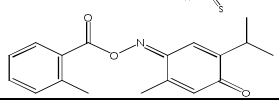
Structure	Compound	X1	X2	Moldock Score	Moldock Rerank Score
	**N**	O	O	-57.7085	-52.568
	NO-1	NOH	O	-62.6828	-55.3033
	NO-2		O	-98.9899	-79.5617
	NO-3		O	-98.0561	-70.3589
	NO-4		O	-102.774	-83.2676
	NO-5		O	-108.08	-81.7745
	NO-6		O	-77.2543	-67.9192
	NO-7	NOH	NOH	-67.565	-60.5387
	NO-8			-114.125	-97.5012
	NO-9			-132.774	-108.731
	NO-10			-121.731	-58.3122
	NO-11			-134.73	-109.495
	NO-12			-94.609	-81.8635

Table. 2: MVD and Re-rank score (kcal/mol) for derivates naphthoquinones, benzolactam and doxorubicin when docked with polo like kinase crystal structure.

Structure	Compound	Moldock Score	Rerank score
	**5HN**	-67.6119	-57.7854
	**2HN**	-64.9242	-55.5847
	**DHN**	-97.7074	-56.2726
	**Lapachol**	-96.6528	-73.7675
	**Doxorubicin**	-94.0242	-86.3942
	**Benzolaktam**	-118.859	-94.6529
	**Poloxin**	-99.335	-84.736

The best docking poses obtained on the basis of MVD re-rank score for modified naphthoquinone compound, benzolactam and doxorubicin of the crystal structures of plk1 are presented in Figure 3.

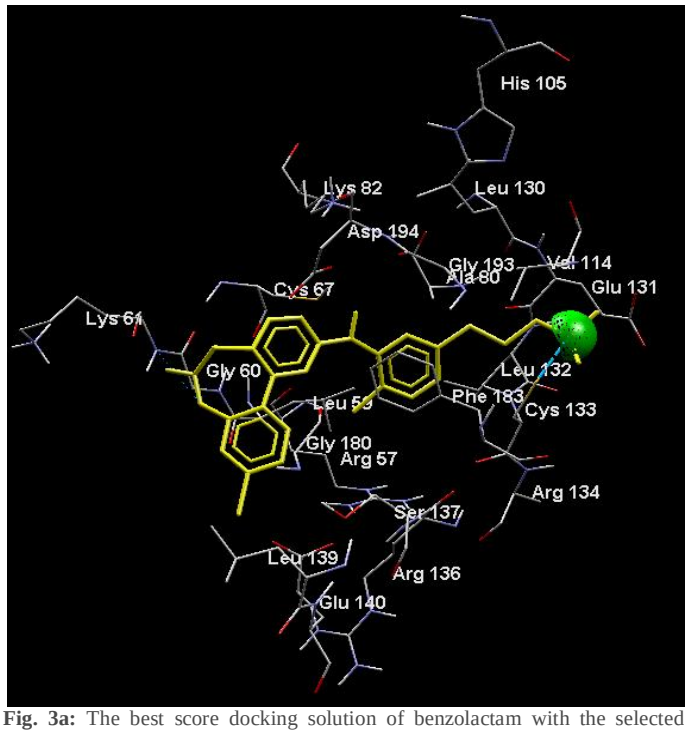


Fig. 3a: The best score docking solution of benzolactam with the selected crystal structure of plk1. Amino acids in the active site are presented in lines and ligand is presented in thick lines with fix colour. blue lines represent the hydrogen bonds between the ligand and the active site of plk1..

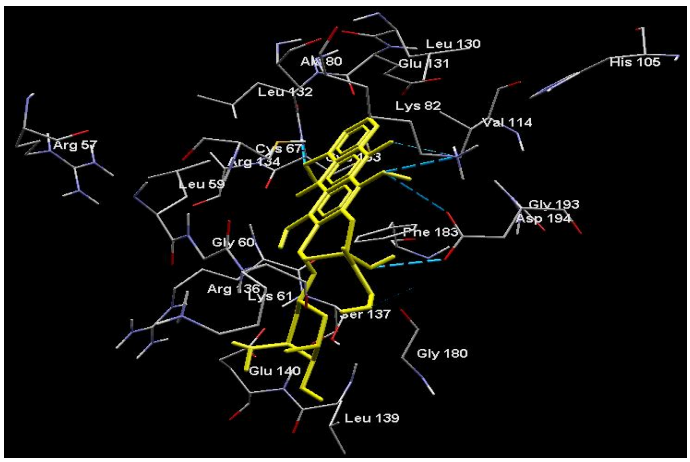


Fig. 3b: The best score docking solution ofdoxorubicin with the selected crystal structure of plk1. Amino acids in the active site are presented in lines and ligand is presented in thick lines with fix colour. blue lines represent the hydrogen bonds between the ligand and the active site of plk1.

Docking studies of Benzolactam with plk1 showed the presence of hydrogen bonding between these compounds with the proteins of plk1. It is revealed that the amine grup of benzolactam is bound in a hydrophobic cavity formed by Cys133.

The amine group of benzolactam also have electrostatic interaction with Glu131 of plk1 and steric interaction with Leu132, Glu131, Cys133, Val114,Gly60,Lys61 and Glu140. The docking results compound N (1.4- naphthoquinone) with plk1 reveals no electrostatic interactions but it have a hydrogen bonding and steric interaction between the ligand to receptor. The keton group of compound N have hydrogen bond interaction with Cys 133 of Plk1. The aromatic group and keton group of this compounds have steric interaction with Gly60 and Leu59 from Plk1 (Fig. 4, 5 & 6).

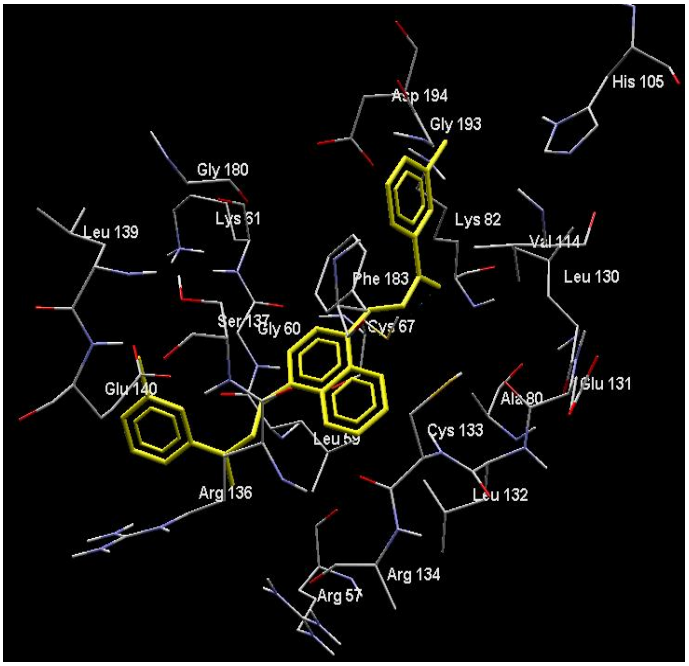


Fig. 3C: The best score docking solution of compound NO11 and with the selected crystal structure of plk1.Amino acids in the active site are presented in lines and ligand is presented in thick lines with fix colour. blue lines represent the hydrogen bonds between the ligand and the active site of plk1.

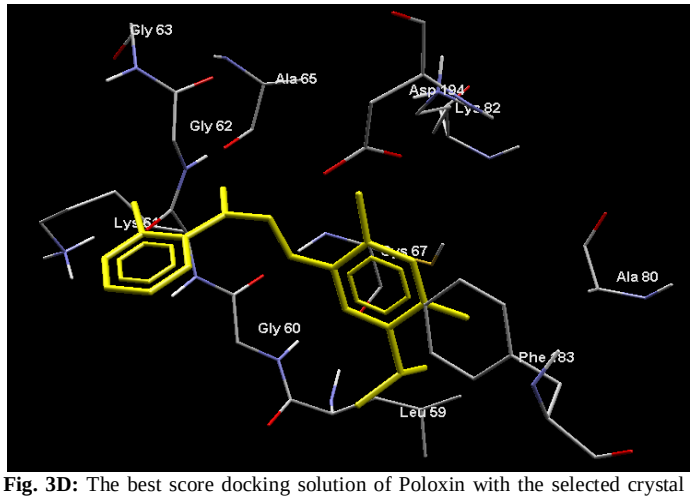


Fig. 3D: The best score docking solution of Poloxin with the selected crystal structure of plk1. Amino acids in the active site are presented in lines and ligand is presented in thick lines with fix colour. blue lines represent the hydrogen bonds between the ligand and the active site of plk1.

Compound N after modified into oxime compound (NO11) has a docking scores lower than the original compound. This means that the compound NO11 will have better activity than compound N. The docking results showed no hydrogen bonding and electrostatic interaction between compound NO11 with Plk1, but this

compound have more steric interaction. The aromatic groups of this compound have steric interaction with Phe 133, Asp 194, Glu 101, Lys 82, Cys 133 and Glu 140 from Plk1. One of the mechanism underlying inhibitors-targeted interactions proposed covalent modifications, as well as poloxin and thymoquinone (Reindl *et al.*, 2007) This was based on the onset time-dependency, and the fact that both inhibitors are Michael receptors with β-unsaturated carbons which hypothetically attack cystein residues on the PBD (Zhou, 2010).

Fig 7 showed the comparison of the binding of compound NO11, benzolactam, doxorubicin and poloxin in the active site of polo like kinase-1 (PDB ID: 3THB). It showed clear binding of compound NO11, benzolactam, doxorubicin and poloxin.

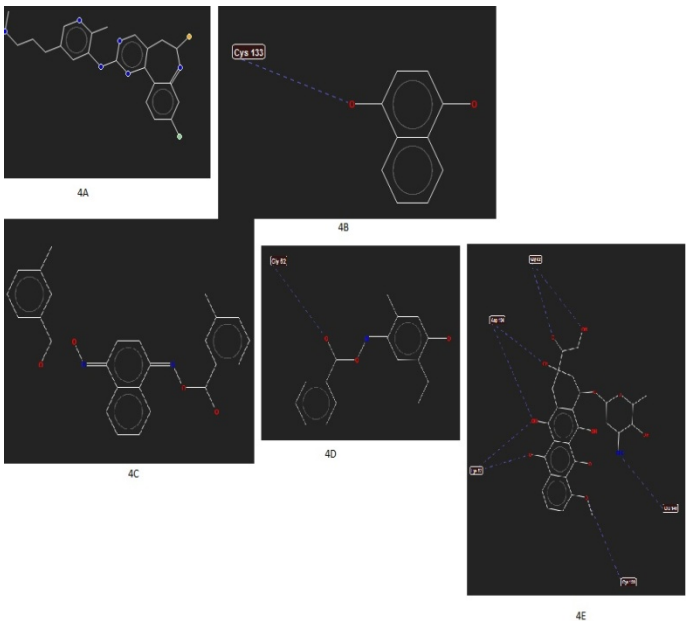


Fig. 4: Hidrogen bond interaction with plk1of benzolactam (4A), compound N (4B), compound NO11 (4C), Poloxin (4D) and doxorubicin (4E).

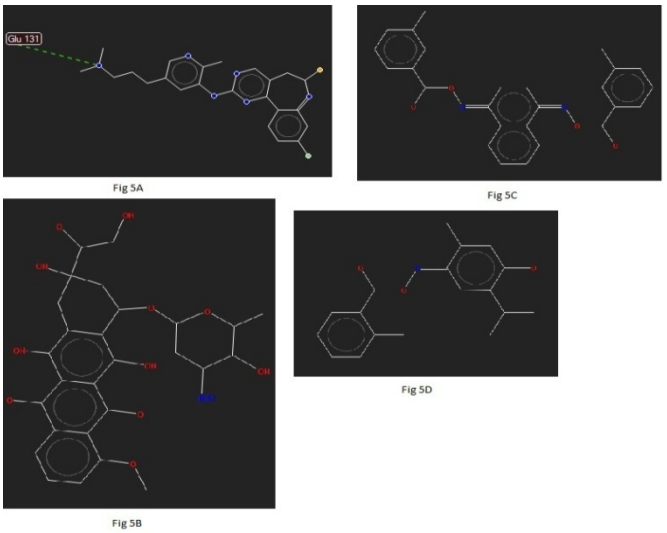


Fig. 5: Electrostatic interaction of benzolactam (5A), doxorubicin (5B), Compound NO11 (5C) and Poloxin(5D) Please delete note fig 5A, fig 5B, fig 5C, fig 5D; change with 5A, 5B, 5C, 5D.

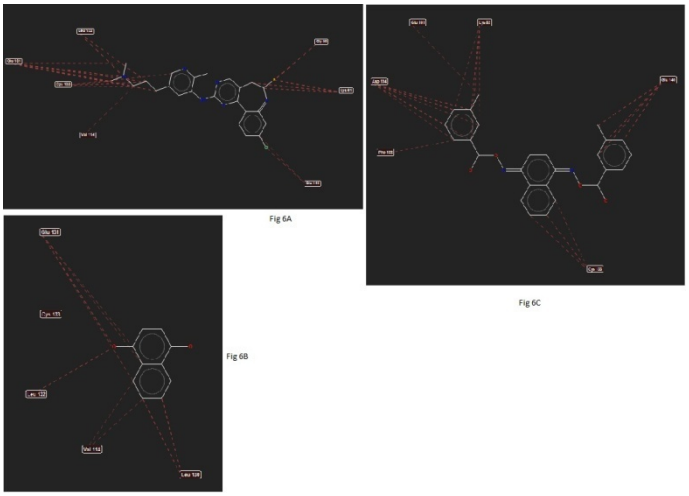
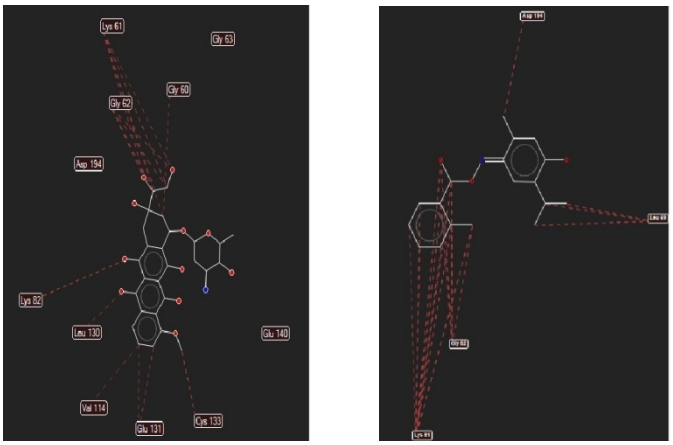
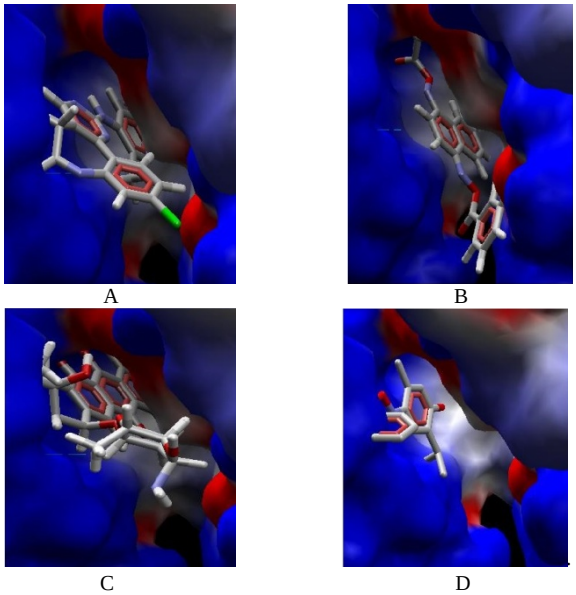


Fig. 6A-C: Steric interaction of benzolactam (a), compound N (b), doxorubicin compound NO11 (c).



D E

Fig. 6D-E: Steric interaction of doxorubicin (d) and Poloxin (e).



A B C D

Fig. 7: Binding of Benzolactam (a), Doxorubicin (b), Compound NO11(c) and Poloxin (d) in the active site of polo like kinase-1 (PDB ID 3THB). The anion binding pocket is blue and specificity pocket is red.

CONCLUSION

The docking studies as described above provide estimation on inhibitory activities of the docked ligand. The results showed that modified naphthoquinone compounds fits well in the active site of polo like kinase-1 and also interact with the residues in the active site which are important for their biological activity. Therefore modified naphthoquinone compounds could be a putative inhibitor of plk1 and might be used as anticancer drug candidates

REFERENCES

Babula P, Adam V, Havel L, Kizek L. Noteworthy Secondary Metabolite Naphthoquinones-their Occurance Pharmacological Properties an Analysis. Current Pharmaceutical Analysis, 2009; 5: 47-68.

Brayfield, A. ed. (19 December 2013). "Doxorubicin". *Martindale: The Complete Drug Reference*. Pharmaceutical Press. Retrieved 15 April 2014.

Bruinsma *et al.*, Switching Polo-like kinase-1 on and off in time and space. Trends in biochemical Sciences, 2012; 37: 12: 543-542.

Chou. Structural Bioinformatics and its Impact to Biomedical ScienceCurrent Medicinal Chemistry, 2004; 11: 2105-2134.

Diananda R, 2008, Mengenal seluk beluk kanker, Jogjakarta: Katahati hlm.103-124.

Degenhart and Lampkin. Targeting Polo-like Kinase in Cancer Therapy, Clin Cancer Res, 2010 16(2): 384-389.

Duffey MO, Vos TJ, Adams R , Alley J. Discovery of a Potent and Orally Bioavailable Benzolactam-Derived Inhibitor of Polo-Like Kinase 1 (MLN0905). *J. Med. Chem*, 2012; 55 (1): 197–208.

http://www.rscb.org/pdb [Accesed November 2011]

Itoigawa M, Ito C, Tan HTW, Okuda M, Tokuda H, Nishino H, Furukawa H. Cancer chemopreventive activity of naphthoquinones and their analogs from Avicennia plants. Cancer Letters, 2001; 174: 135-139.

Kayashima T, Mori M, Yoshida H, Mizushina Y. 1,4-Naphthoquinone is a potent inhibitor of human cancer cell growth and angiogenesis. Cancer Letter, 2009; 278: 34-40.

Lansing TJ, MCConnell RT. In vitro Biological Activity of Novel Small Molecule Inhibitor of Polo-Like Kinase I. Mol Cancer Ther, 2007:. 6(2): 450-459.

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26.

Llamazares S, Moreira A, Tavares A, et al. Polo encodes a protein kinase homolog required for mitosis in Drosophila. Genes Dev, 1991; 5:2153–65.

Lowery, D M, Lim D, Yaffe MB. Structure and function of Polo-like kinases. Oncogene, 2005; 24: 248-259.

Naeem S, Hylands P, and Barlow D. Docking Studies of Chlorogenic Acid against Aldose Reductase by using Molegro Virtual Docker Software. Journal of Applied Pharmaceutical Science, 2013; 3(01): 13-020.

Reindl W, Yuan J, Krämer A, Strebhardt K, Berg T. Inhibition of Polo-like Kinase 1 by blocking Polo Box Domain-Dependent protein-protein interaction. Chem & Bio, 2007; 15, 459-466.

Schneider G and Bohm HJ. Virtual Screening and Fast Automated Docking Methods. Drug Discov Today, 2002; 7(1): 64-70.

Strebhardt K and Ullrich A. Targeting polo-like Kinase 1 for cancer therapy. Nat. Rev.Cancer, 2006; 6: 321–330.

Stebhardt K. Multifaceted polo-like kinases: drug targets and antitargets for cancer therapy. Nature Review, 2010; 9: 643-660.

Tandon, KV, Singh RV and Yadav DB. Synthesis and evaluation of novel 1,4-naphthoquinone derivatives as antiviral, antifungal and anticancer agents. Bioorganic and Medicinal Chemistry Letters, 2004; 14: 2901-2904.

Thomsen R and Christensen MH. Moldock: A New Technique for High-Accuracy Molecular Docking. J.Med. Chem, 2006; 49: 3315-3321.

Verma RP & Hanch C. Elucidation of structure–activity relationships for 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones. Bioorganic & Medicinal Chemistry, 2004; 12: 5997–6009.

Verma R. Anti-Cancer Activities of 1,4-Naphthoquinones: A QSAR Study. Anti-Cancer Agents in Medicinal Chemistry, 2006; 6: 489-499.

Zhou Y, Jianhua C, Rehse PH. Thymoquionone and poloxin are slow-irreversible inhibitors of human Polo-like kinase 1 polo box domain. Journal of Medical College of PLA, 2010; 25: 136-142.

How to cite this article:

Susi Kusumaningrum, Emil Budianto, Soleh Kosela, Wahono Sumaryono, Fifit Juniarti. The molecular docking of 1,4-naphthoquinone derivatives as inhibitors of Polo-like kinase 1 using Molegro Virtual Docker. J App Pharm Sci, 2014; 4 (11): 047-053.