Tropical Journal of Pharmaceutical Research March 2021; 20 (3): 505-510
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i3.9

Original Research Article

Determination of the anti-polo like kinase 1 potential of novel derivatives of thiophene using oncoinformatics approach

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Sent for review: 3 November 2020 *Revised accepted: 23 February 2021*

Abstract

Purpose: *To explore the anticancer mechanistic aspect of thiophene derivatives via targeting Polo like kinase 1 (PLK1).*
Methods: *The PLK1 enzyme is primarily expressed in cancer cells, and blocking its active site is one of the plausible ways to target cancer. Thus, in the present study, the thiophene derivatives were tested against PLK1 by molecular docking approach.*
Results: *Thiophene derivatives, named 8A, 8B and 14, exhibited better interactions with PLK1 active site than the positive control, doxorubicin. Molecular docking experiments revealed that 8A, 8B and 14 interacted efficiently with PLK1, and demonstrated binding energy and inhibition constant scores of '-8.02 kcal/mol and 1.33 μM', '-8.65 kcal/mol and 0.454 μM' and '-8.33 kcal/mol and 0.788 μM', respectively. In contrast, doxorubicin-PLK1 interaction had binding energy of -7.95 kcal/mol and inhibition constant of 2.75 μM.*
Conclusion: *These results predict that thiophene derivatives 8A, 8B and 14 might exert anticancer effect by inhibiting PLK1 activity. Although, wet lab experiments are required to validate the data, however, these results may pave the way for the development of novel PLK1 inhibitors for anticancer therapy.*

Keywords: *Anticancer therapy, Cancer cells, Molecular docking, Polo-like kinase 1, Thiophene derivatives*

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INTRODUCTION

Cancer is a major health concern globally, and a major cause of mortality in the United States [1]. Metastasis, recurrence and drug resistance are the factors that are associated with increased mortality rate. Conventional chemotherapeutic agents, such as, antimitotic and antimetabolites drugs [2] are not adequate to control the majority of cancers, and frequently direct to drug-resistant

and metastasis [3]. Therefore, the current situation has become more challenging, as the effectiveness of existing chemotherapy treatments is considerably decreasing. This has encouraged researchers to develop new drugs that can act on emerging cancer-specific targets, for instance polo-like kinase-1 (PLK1), which can be used as monotherapy as well as in combination with existing chemotherapy, for improved cancer treatment [4].

Antimitotics have been considered as the therapeutic option for the patient's with solid tumors, and PLK1 is one of the promising antimitotic targets [5]. The first polo-like kinase family member (i.e. Polo) was identified in *Drosophila melanogaster* [6]. Later, four PLK family members- PLK1, PLK2, PLK3 and PLK4 were recognized [7]. Out of all PLKs, the best-characterized one is PLK1, which is an antimitotic target expressed exclusively in dividing cells. Expression of PLK1 fluctuates during the progression of cell cycle, and peaks at M-phase of the cell cycle [8]. PLKs have various functions during mitosis, and PLK1 activity is vital for almost every mitosis step via its various phosphorylation and protein binding activities. PLK1 phosphorylates the cyclin B1 and Cdc25C to promote the mitotic entry [9].

PLK1 has emerged as a potent target enzyme for cancer drug development. The rationale behind development of PLK1 as a cancer target includes its overexpression in cancer, association with poor prognosis and ability to cause multi-nucleation [10,11]. In addition, increased PLK1 expression might help the cell to override G2 checkpoint arrest caused by DNA damage [12]. It has been reported that constitutive expression of PLK1 could lead to alter NIH 3T3 fibroblasts cells [13] and pro-apoptotic function of p53 protein as well [14].

Since PLK1 is linked to tumorigenesis, and can be targeted by various compounds or agents, it provides a potential route for the advancement of novel anticancer treatment. Earlier, one of the author's has explored the potency of novel thiophene derivatives (compounds named as 8A, 8B and 14) against various cancer cell lines, and found their potent activity against brain cancer, breast adenocarcinoma and non-small cell lung cancer cell lines [15]. However, the underlying mechanism of their anticancer effects still needs to be elucidated.

In continuance, to explore the mechanistic aspects, we predicted the potential of thiophene derivatives against cancer specific target, i.e., PLK1 in the present study.

EXPERIMENTAL

Ligand and protein preparations

The 3D structure of PLK1 (PDB ID: 2OWB) was retrieved from the Protein Data Bank. ChemDraw was used to design the structure of thiophene derivatives named as 8A, 8B and 14 that had been synthesized and tested against cancer cell lines by Dr. Amr S. Abouzied [15].

Calculation of physicochemical properties and toxicity risk prediction

Molinspiration property calculation tool (http://www.molinspiration.com/cgi-bin/properties) was employed to check the physicochemical properties of thiophene derivatives compounds. Various parameters such as topological polar surface area (TPSA), molecular weight, miLogP, the number of hydrogen bond donors, number of hydrogen bond acceptors, number of rotatable bonds, and violations of Lipinski's rule of five [16] were estimated using Molinspiration tool.

Further, Absorption (B) was calculated using Eq 1 [17]:

$$B\,(\%) = 109 - (0.345 \times TPSA) \quad \ldots\ldots\ldots (1)$$

Orisis datawarrior tool was used to predict the toxicity potential of thiophene derivatives. The prediction is based on relative analysis of thiophene derivatives with the pre-calculated set of previously explored structural molecules present in databases.

Molecular docking

The thiophene derivatives (compound 8A, 8B and 14) and control were docked with the PLK1 catalytic domain individually with Auto dock 4.2 tools following the method of Rizvi *et al* [18]. To target catalytic site of PLK1 enzyme, x, y, and z coordinate values were used as 0.069, 23.58 and 66.741, respectively, and Grid box dimension was set as 40Å × 40Å × 40Å with a spacing of 0.375Å. The figures were produced using Discovery Studio 2.5 (Accelrys).

Ligplot analysis

To determine the hydrogen and hydrophobic interactions between important amino acid residues of PLK1 with thiophene derivatives the 'thiophene derivatives-PLK1'complexes were analyzed by LIGPLOT^{+} Version v.2.1.

RESULTS

Physicochemical properties prediction

The physicochemical and drug-likeness properties of the thiophene derivatives (compounds 8A, 8B, and 14) was performed by Molinspiration property calculation tool. It was found that compounds 8A, 8B, and 14 were under the defined parameters of molecular weight (<500Da), hydrogen bond acceptor (≤10), and hydrogen bond donor (≤5) (Table 1) and none of the compounds violated the Lipinski's rule of five. The orisis software predicted the toxicity in the form of mutagenicity, tumorigenicity, irritability and reproductive effects (Table 2). Out of all the compounds tested, only compound 14 and doxorubicin predicted to have the irritability and reproductive effect, respectively.

Molecular docking and Ligplot analysis

Leu59, Gly60, Lys61, Cys67, Ala80, Leu130, Glu131, Leu132, Cys133, Arg134, Arg136, and Phe183 residues of PLK1 was found to interact with compound 8A (Figure 1a); while compound 8B was found to interact with Leu59, Gly60, Lys61, Gly62, Ala65, Lys66, Cys67, Ala80, Lys82, Val114, Glu131, Leu132, Cys133, Arg134, Arg136, Phe183, and Asp194 residues of PLK1 (Figure 2a). In addition, compound 14 was found to interact with Leu59, Gly60, Lys61 Gly62, Ala65, Cys67, Ala80, Val114, Leu130, Glu131, Leu132, Cys133, Arg134, Arg135, Arg136, and Phe183 residues of PLK1 (Figure 3a).

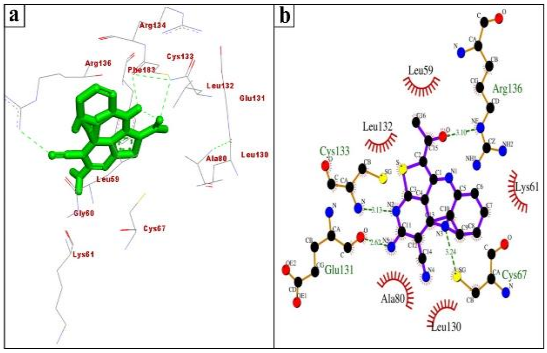

Figure 1: a) Molecular interaction of compound 8A (stick representation) with PLK1. **b)** Ligplot analysis of PLK1 showing the hydrogen bond (green dash line) and hydrophobic interaction (red arcs) with compound 8A

The free binding energy (ΔG) for compound 8A–PLK1, compound 8B–PLK1, and compound 14–PLK1 catalytic domain interactions were -8.02, -8.65, and -8.33 kcal/mol, respectively, while the inhibition constant (ki) values were 1.33, 0.454, and 0.788 μM, respectively (Table 3).

Table 1: Physicochemical parameters for the compounds

S. No.	Compound Name	Physiochemical parameters							
		% of Absorption*	Topological polar surface Area (Å)²	Molecular weight	miLogP**	Hydrogen bond donors	Hydrogen bond acceptors	Number of rotatable bonds	Lipinski's Violation
	Rule	**-**	**-**	**<500**	**≤5**	**<5**	**<10**	**≤10**	**≤1**
1	Compound 8A	68.34	117.83	323.38	2.98	5	6	3	0
2	Compound 8B	67.48	120.34	370.43	3.44	5	7	6	0
3	Compound 14	69.29	115.10	368.42	-4.55	2	7	6	0
4	Doxorubicin***	35.72	212.39	545.54	0.62	9	12	5	3

*Absorption was calculated as per Eq 1; **miLogP is the logarithm of compound partition coefficient between *n*-octanol and water. ***Doxorubicin is the anticancer control drug used for comparative analysis

Table 2: Toxicity risk assessment of compounds

Compound	Toxicity risk			
	Mutagenity	***Tumorigenicity***	***Irritability***	***Reproductive effect***
Compound 8A	None	None	None	None
Compound 8B	None	None	None	None
Compound 14	None	None	High	None
Doxorubicin*	None	None	None	High

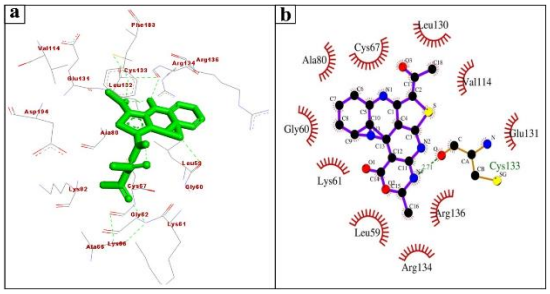

Figure 2: (a) Molecular interaction of compound 8B (stick representation) with PLK1. (**b)** Ligplot analysis of PLK1 showing the hydrogen bond (green dash line) and hydrophobic interaction (red arcs) with compound 8B

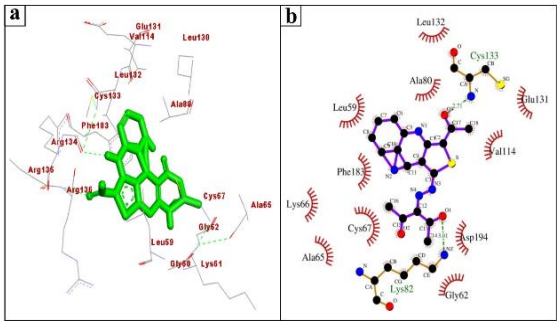

Figure 3: (a) Molecular interaction of compound 14 (stick representation) with PLK1. (**b)** Ligplot analysis of PLK1 showing the hydrogen bond (green dash line) and hydrophobic interaction (red arcs) with compound 14.

The amino acid residues Cys67, Glu131, Cys133, and Arg136 of PLK1 made hydrogen bond with compound 8A, while Cys133 was the common H-bond interacting amino acid residue of PLK1 with compound 8A, 8B, and 14 (Figure 1b, 2b, and 3b).

Doxorubicin is a chemotherapeutic agent in the treatment of different kinds of cancer, and in this study, it was used as the control compound. Leu59, Gly60, Lys61, Cys67, Ala80, Glu131, Leu132, Cys133, Arg134, Arg136, and Phe183 were the common interacting amino acid residues of PLK1 with doxorubicin, compounds 8A, 8B and 14 (Figures 1-3 and Figure 4). The ΔG and ki values for doxorubicin-PLK1 interaction were -7.95 kcal/mol and 2.75 μM, respectively (Table 3).

DISCUSSION

In the past few decades, promising anticancer compounds fails at different clinical trials stages as a result of inappropriate pharmacokinetic profiling. However, to reduce the failure rate, physicochemical profiling of new drug candidates has become an important part of drug discovery at present. These analyses involve assessment of various molecular descriptors that would help in prediction of drug-likeliness. There are various *in silico* tools available for calculating the molecular properties of a compound in order to assess its pharmacokinetic profile. In fact, these *in silico* tools have helped to overcome the issues related to failure of clinical trials [19].

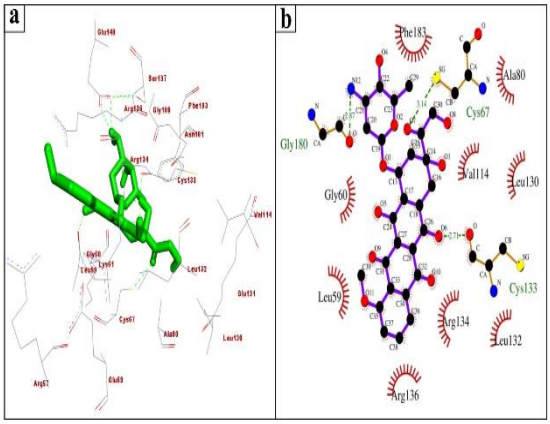

Figure 4: (a) Molecular interaction of Doxorubicin (stick representation) with PLK1. **(b)** Ligplot analysis of PLK1 showing the hydrogen bond (green dash line) and hydrophobic interaction (red arcs) with doxorubicin

Table 3: Binding energy of compounds with PLK1

Drug/ligand	Free binding energy (kcal/mol)	Inhibition constant (μM)
Compound 8A	-8.02	1.33
Compound 8B	-8.65	0.454
Compound 14	-8.33	0.788
Doxorubicin*	-7.95	2.75

*Doxorubicin is the anticancer control drug used for comparative analysis

Molinspiration tool was used in this study to screen the thiophene derivatives (compounds 8A, 8B, and 14) as drug candidates based on Lipinski's Rule of Five (Table 1). Lipinski's Rule of Five is based on the observation that the majority of oral drugs have a molecular weight ≤500, Log P value (logarithmic value of partition coefficient between *n*-octanol and water) ≤5, hydrogen bond donor sites <5, hydrogen bond acceptor sites <10 and rotatable bonds ≤10. Any compound which violates more than one of these rules has poor bioavailability. In this study, none of the tested compounds showed violation of Lipinski's Rule of Five except positive control doxorubicin. Thus, these compounds could be considered as potential drug candidates.

PLK1 is over-expressed in various cancer cells,

including breast cancer cells. Interestingly, PLK1 inhibition restrains cancer cells growth without affecting normal cells [20]. Therefore, it is regarded as an important therapeutic target in the management of various cancers. In this study, thiophene derivatives 8A, 8B and 14 strongly bound to the PLK1 catalytic site. Leu59, Gly60, Lys61, Cys67, Ala80, Glu131, Leu132, Cys133, Arg134, Arg136, and Phe183 were the common interacting residues of PLK1 catalytic site with the compound 8A, 8B, and 14. Interestingly, these residues of PLK1 enzyme have been reported to interact with the FDA approved anti-cancer drugs [21].

Amino acid residues, Leu59, Ala80, Val114, Leu132 and Cys133 of PLK1 have been reported to make hydrophobic interaction with natural compound (1,4-cyclohexylphenyl) ethanone [22]. Consistent with this, Leu59 and Ala80 residues of PLK1 were commonly involved in hydrophobic interaction with compound 8A, 8B and 14 (Figure 1b, 2b, and 3b). Moreover, both hydrogen bonds and hydrophobic interactions plays a vital role in the binding stability of ligand to its corresponding target protein [23].

The strength of binding between a ligand and protein is determined in terms of binding energy, and a higher (negative) energy represents the efficient binding of a ligand to the target protein or receptor [24]. Interestingly, this study shows that thiophene derivatives (compounds 8A, 8B, and 14) have better binding with PLK1 than the control drug (doxorubicin) in terms of the binding energy (Table 3), suggesting that these compounds might exert their anticancer effect by inhibiting PLK1 enzyme.

CONCLUSION

The molecular docking results predict that all the thiophene derivatives (compounds 8A, 8B, and 14) have better binding affinity towards PLK1 enzyme than the control drug (doxorubicin) with respect to Ki and ΔG values. Thus, the findings provide a predictive mechanistic insight into the mode of anticancer action of these thiophene derivatives, and might aid the further investigation of the exact mechanistic aspects of the anticancer potentials of the thiophene derivatives.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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