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Identification of novel and selective non-peptide inhibitors targeting the polo-box domain of polo-like kinase 1

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ABSTRACT

A series of non-peptide inhibitors targeting the polo-box domain (PBD) of polo-like kinase 1 (Plk1) was designed based on the potent and selective minimal tripeptide Plk1 PBD inhibitor. Seven compounds were designed, synthesized and evaluated for fluorescence polarization (FP) assay. The most promising compound **10** bound to Plk1 PBD with IC_{50} of 3.37 μM and had no binding to Plk2 PBD or Plk3 PBD at 100 μM. Molecular docking study was performed and possible binding mode was proposed. MM/GBSA binding free energy calculation were in agreement with the observed experimental results. These novel non-peptide selective Plk1 PBD inhibitors provided new lead compounds for further optimization.

1. Introduction

Polo-like kinase 1 (Plk1) is a serine/threonine protein kinase which acts as a key regulator in multiple stages of mitotic progression [1]. Plk1 modulates the transition through the G2/M checkpoint by influencing the activation of the CDC25C phosphatase and cyclin B1 [2]. The overexpression of Plk1 is required for the viability of broad spectrum of cancer cells and interference with Plk1 function induces cell apoptosis in most cancer cells [3]. Therefore Plk1 has been considered as an attractive anti-cancer drug target for anticancer drug development.

Five Plks in mammalian cells have been identified (Plk1-5) so far. Among them, Plk1-4 consists of an N-terminal catalytic domain and a C-terminal domain having 1 or 2 highly conserved sequences, termed polo-box domains (PBDs) [4]. A large body of evidence suggests that PBD directs the N-terminal catalytic domain for specific subcellular localization through interacting with phosphoserine/phosphothreonine (pS/pT)-containing motifs. Moreover, the subcellular targeting binding site in PBD forms a compact and druggable interface [5].

Plk1, Plk2 and Plk3 are three closely related members while Plk4 is a distantly related kinase with apparently different expression patterns and physiological functions [3,4]. In contrast to the role of Plk1 in cell proliferation and tumorigenesis, the two most closely related kinases, Plk2 and Plk3, seem to have a role in checkpoint-mediated cell-cycle arrest to ensure genetic stability and prevent oncogenic transformation [3–5]. Thus, the development of Plk1-specific inhibitors could be important for anti-Plk1 cancer therapy.

For a long period, several potent orthosteric Plk1 inhibitors targeting the ATP-binding catalytic domain have been reported [3]. However, the ATP-binding sites of the catalytic domains of protein kinases are closely related, these efforts suffered from a lack of selectivity. Rigosertib (ON01910) was reported as a Plk1 allosteric inhibitor, which showed potent Plk1 inhibitory activity and antitumor activity [6–8]. However, it has an inhibitory effect on multiple target (Plk3, Chk1, Chk2, BCR-ABL, Fyn, Src and Ras) [9], among which Plk3 was considered as a negative regulator responsible for the inhibition of cell cycle progression and tumor cell development at multiple stages of mitosis. Based on the structure of PBIP1 which was isolated as a PBD-interacting protein crucial for centromeric localization of Plk1, a minimal peptide (PLHSpT, **1**) was identified as an inhibitor with high affinity toward the Plk1 PBD and high selectivity against Plk2 PBD and Plk3 PBD [10].

After the identification of minimal peptide (**1**) with high affinity toward the Plk1 PBD, several phosphate peptides and peptidomimetics were reported (Fig. 1, **2–4**) [11–19]. Then a series of (2*S*,3*R*)-2-amino-3-methyl-4-phosphonobutanoic acid (Pmab) incorporated

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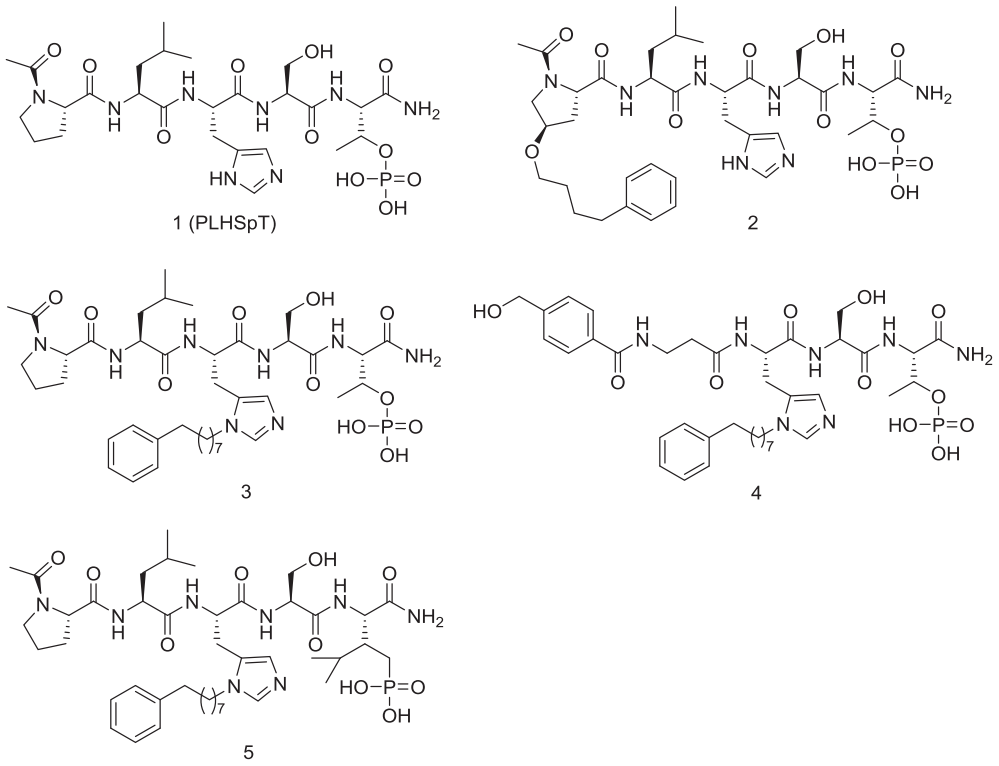

Fig. 1. Examples of the reported phosphate peptides and peptidomimetics as Plk1 PBD inhibitors.

peptidomimetic was reported (Fig. 1, **5**) to produce a phosphatase-stable peptidomimetic with complete retention of inhibitory potency [20]. To date, most of the modification made to peptides and peptidomimetics acting as Plk1 PBD inhibitors focusing on the 1–3 *N*-terminal residues of PLHSpT. Very few modification has been made to the C-terminal SpT part which was considered essential for high-affinity binding [10]. In this study, we make the modification on the C-terminal SpT residue based on the highly potent Plk1 tripeptide (Fig. 1, **4**) reported [17] and provide new non-peptide skeleton for further modification toward the discovery and development of highly potent and selective Plk1 PBD inhibitors.

2. Results and discussion

2.1. Design, synthesis and evaluation

According to the binding mode of **4** with Plk1 PBD (PDB ID: 4WHH), the *N*-terminal fragment of peptidomimetic **4** and $C_6H_5(CH_2)_8$-group on the imidazole ring were directed toward the Tyr-rich hydrophobic channel, whereas the negatively charged pThr phosphoryl group mediated strong electrostatic interactions with the H538 and K540 residues [17]. The residues of Ser and Thr in **4** acted as a linker and limited the direction of the phosphate acid substitution. In our research, the imidazole ring of the His in **4** was substituted by a triazole ring for easier synthesis ([1]blue in Fig. 2). The linker formed by Ser and Thr was substituted by a rigid linker (red in Fig. 2) which may also limit the direction of the terminal phosphate acid. It was reported that Pmab incorporated peptidomimetic could produce a phosphatase-stable analogue of phosphothreonine (pThr) [20]. Thus 3-phosphonopropanoic acid was attached to the aromatic ring as compound **5**. Then compound **6**, **7** and **8** were designed as shown in Fig. 2.

The key intermediate **22** was synthesized using the method as shown in Scheme 1 and Scheme 2. Compound **6** was synthesized according to the route shown in Scheme 3 and Scheme 4. The intermediate of **7** and **8** was prepared according to the method as shown in Scheme 5. And the target compound **7** and **8** were readily obtained using the route in Scheme 8.

The binding affinity of **6**, **7** and **8** to Plk1 PBD was evaluated using our optimized fluorescein polarization (FP) binding assay [21]. As shown in Table 1, none of the three compound (**6**, **7** and **8**) showed binding affinity to Plk1 PBD. The binding of the pT residue is essential for high-affinity binding, a slight change may cause complete loss of binding. Further modification was focused on how to adjust the direction of the 3-phosphonopropanoic acid side chain. Triazole group was introduced to mimic the aromatic ring (red in Fig. 2) linked with 3-phosphonopropanoic acid.

Appropriate azide was reacted with alkyne in the presence of copper sulfate and sodium ascorbate (VcNa) to give the protected triazolyl contained intermediate (Scheme 6). The alternative 1,5-regioisomer was achieved using the ruthenium catalyst $Cp^*RuCl(PPh_3)_2$ (Scheme 7) [22,23]. Then compound **9** and **10** were synthesized using the similar method as **7** and **8** as shown in Scheme 8.

The binding affinity of **9** and **10** to Plk1 PBD was evaluated using FP assay. As shown in Table 1, the 1,5-regioisomer **9** showed no binding affinity to Plk1 PBD, while the 1,4-regioisomer **10** showed moderate Plk1 PBD binding affinity (IC_{50} = 3.37 μM). Thus the 1,4-regioisomer **10** was selected for further exploration. Compounds with different length of the linker between the triazolyl and the phosphonic acid was made to find the optimal length. Compound **11** and **12** was synthesized using the same method as **10**. The binding affinity of **11** and **12** was evaluated using FP assay. As shown in Table 1, **11** showed similar Plk1 PBD binding affinity (IC_{50} = 5.45 μM) as **10**, while the binding affinity of **12** was slightly decreased (IC_{50} = 11.12 μM), suggesting that the 1,4-regioisomer triazolyl attached with ethyl or propyl could be an optimal length of linker for the phosphonic acid. The binding affinity of **10**, **11** and **12** with Plk2 PBD and Plk3 PBD was also evaluated using FP assay. As shown in Table 1, none of the tested compounds showed binding affinity to Plk2 PBD and Plk3 PBD. The new identified non-peptide

[1] For interpretation of color in Fig. 2, the reader is referred to the web version of this article.

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