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Design, synthesis and in vitro activity of phidianidine B derivatives as novel PTP1B inhibitors with specific selectivity

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ABSTRACT

A series of phidianidine B derivatives were synthesized by introducing various heterocyclic rings. Their inhibitory effects on PTP1B and other PTPs (TCPTP, SHP1, SHP2 and LAR) were evaluated. A majority of them displayed significant inhibitory potency and specific selectivity over PTP1B. The SAR and molecular docking analysis were also described.

Protein tyrosine phosphatases (PTPs), a large family of signaling enzymes, act as paramount regulatory components in numerous cell functions, such as growth, mitogenesis, motility, cell–cell interaction, metabolism, gene transcription, and immune responses.[1] Protein tyrosine phosphatases 1B (PTP1B), a member of PTPs family, is a key negative regulator in both insulin and leptin signaling pathways, thereby modulates both glucose and lipid metabolism.[2] The independent studies from Elchebly and Klaman, respectively, revealed that PTP1B knock-out mice processed lower insulin and glucose levels with increased sensitivity to insulin, and resistance to high-fat induced weight gain without any adverse effects,[3] which enable PTP1B to become a potential target for the treatment of type II diabetes and obesity. Great efforts have been made for the development of PTP1B inhibitors as potential therapeutics for type II diabetes. However, low selectivity over the other PTPs and poor cell permeability are still two major challenges in the discovery of efficient PTP1B inhibitors.[4]

Marine natural products are valuable resources and provide abundant lead compounds to the development of new clinical drugs.[5] Our group has long been dedicated on the chemical and biological investigation of marine natural products. For instance, phidianidines A and B (Fig. 1), two indole alkaloids bearing an uncommon 1,2,4-oxadiazole ring connected to the indole system, were isolated from the marine opisthobranch mollusk *Phidiana militaris* in 2011.[6] The subsequent vitro assays showed that phidianidines A and B exhibited significant cytotoxicity against tumor and nontumor mammalian cell lines after their total syntheses by Lindersley and co-workers in 2012.[7] Our further studies indicated that some of phidianidine-based derivatives exhibited potential in vitro neuroprotective effects against amyloid-β_{25-35}(Aβ_{25-35})-, hydrogenperoxide (H_2O_2)-, and oxygen-glucose deprivation (OGD)-induced neurotoxicity in SH-SY5Y cells.[8]

The bioactivities of phidianidines toward diverse pharmacological targets could be attributed to their unique structures. The indole fragment is a common but important pharmacophore widely presented in numerous bioactive natural products or drugs.[9] The oxadiazole ring has been incorporated in drug discovery programs as an essential element of pharmacophore in contribution of ligand binding.[10] The guanidine moiety, however, was proved to be not required for certain biological activity according to Lindersley's research.[7b] Based on the above observations and in the courses of our continuous searching for novel effective PTP1B inhibitors,[8] the function-oriented synthesis (FOS) of

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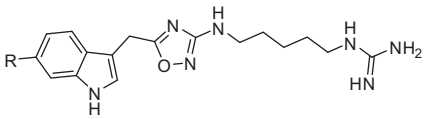


Figure 1. Structure of phidianidine A and B.

phidianidine B derivatives aiming to simplify the structure and synthetic routes while retain the activities were conducted.

In this Letter, we prepared a series of phidanidine-based compounds (**6a**–**6c**, **7a**–**7x**) by introducing heterocyclic rings to replace the guanidyl chain. Their PTP1B inhibitory activity was evaluated and the structure–activity relationship (SAR) was investigated. Selected compounds were subjected to specific selectivity studies towards PTP1B over other PTPs (TCPTP, SHP1, SHP2 and LAR). A subsequent docking study of compound **7o** into the active site of PTP1B was performed to rationalize the results.

The preparation of phidianidine B derivatives was carried out following the synthetic route shown in Scheme 1. Synthesis was started from the commercially available bromo aromatic aldehyde **1** (**1a**–**1c**, represented thiophenyl, phenyl, and pyridyl, respectively). The reaction of **1** with hydroxylamine hydrochloride in the presence of NaOAc gave oximes **2a**–**2c**. Dehydration of **2** with dichloro(*p*-cymene)ruthenium(II) dimer in CH_3CN afforded nitriles **3**.[11] The treatment of **3** with hydroxylamine hydrochloride and Et_3N in MeOH provided *N*-hydroxy-amidines **4a**–**4c**. Esterification of **4** with 3-indoleacetic acid in the presence of HATU and DIEA in CH_2Cl_2 gave rise to compounds **5a**–**5c**. Intramolecular cyclization of **5** in the presence of NaOAc in 30% EtOH gave bromo oxadiazole analogs **6a**–**6c**.[12] The target compounds **7a**–**7x** was obtained by the coupling of **6a**–**6c** with various substituted phenylboronic acids or pinacol esters catalyzed by bis(triphenylphosphine)palladium(II) dichloride in the presence of K_2CO_3 in mixture solvent of 1,4-dioxane and H_2O.

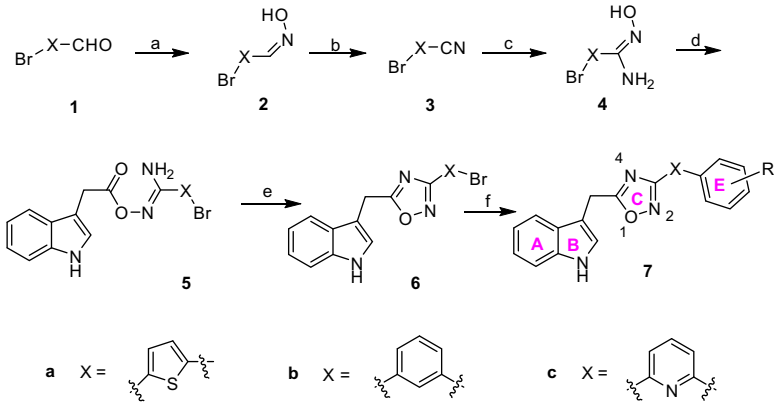
The inhibitory activities of the synthesized heterocyclic ring-substituted phidianidine B derivatives **6a**–**6c**, **7a**–**7x** against PTP1B were measured using *p*-nitrophenyl phosphate (pNPP) as a substrate. Oleanolic acid, a known PTP1B inhibitor (IC_{50} = 3.02 ± 0.22 μM), was used as the positive control. The results are summarized in Table 1.

The bioassay results indicated that most of the target compounds displayed PTP1B inhibitory activity with IC_{50} values in the range of 8.80–31.49 μM. Among them, compounds **7f**, **7o**, **7v** and **7x** showed the most potent inhibitory effects with IC_{50} values of 8.96, 8.80, 9.66 and 9.66 μM, respectively, which is comparable with the positive control oleanolic acid (IC_{50} = 3.02 μM). The primary SAR has been studied regarding to the different functional groups on the side chain. Firstly, the aforementioned results suggested that the PTP1B inhibitory activity was not significantly affected by the aromatic rings (thiophene, benzene or pyridine) on the X position of **6** or **7**. A comparison of the activities across the position and physicochemical properties of the substituents on the phenyl ring E indicated that strong nucleophiles such as hydroxyl or amino was not critical for the activity against PTP1B, since **7a**, **7j**, **7k**, and **7s** showed no or very low inhibition. The introduction of carbonyl in ring E resulted in the disappear of the activity. The activity of **7b**, **7c**, **7l**, **7m**, **7t** and **7u** indicated that the substitution at 2 or 3-position lead to the decrease or disappear of activity. The substitution at 4-position in the ring E played an important role in the activity, the introduction of *n*-butyl group is beneficial for the improvement of PTP1B inhibitory activity, as revealed from those of **7h**, **7q**, and **7x**.

The selectivity bioassay was also evaluated by the investigation of bioactivities against other PTPs. All the derivatives showed no activities against TCPTP, leukocyte antigen-related phosphatase (LAR), Src homology phosphatase (SHP)-1 and SHP-2, suggesting the highly specific selectivity of these molecules towards PTP1B.

In order to understand the inhibitory activity against PTP1B, the most bioactive compound **7o** has been selected to perform the molecular docking analysis. The X-ray crystal structure of PTP1B with a resolution of 2.40 Å (Protein Data Bank, 1NL9) was used for the docking studies. Figure 2 displayed the binding mode of compound **7o** with PTP1B. From this figure, it can be observed that the N–H in the ring B forms a hydrogen bond (–NH···O=C–, 1.88 Å) with the carboxyl of Glu115, 4-site of the nitrogen atom in ring C accepted another H-bond (–N···HN–, 2.84 Å) with the key residue Ala217. Rings A and B form two π–σ bonds with Lys120. Moreover, rings C and D form π–σ bonds with Ala217, Ile219 and Val49, respectively. Sulfur bond is observed between ring A and sulfur atom of Cys215. According to this molecular docking model, the studied phidianidine B analog **7o** was suggested to bind into the catalytic site of PTP1B for the activity.

In summary, inspired by a function-oriented synthesis (FOS) point of view, a series of phidianidine B derivatives with simplified structures and synthetic routes were synthesized and identified as novel PTP1B inhibitors. Compound **7o** exhibited the best inhibitory activity with an IC_{50} value of 8.80 μM. The preliminary SAR study provides a functional direction for the design of novel class of PTP1B inhibitors. The selective inhibitory investigation of the active compounds against other PTPs showed no inhibitory activities against TCPTP, LAR, SHP-1 or SHP-2, indicating their specific selectivity against PTP1B. The mechanisms involved in



Scheme 1. Reagent and conditions: (a) $NH_2OH{\cdot}HCl$, AcONa, rt, 15 h; (b) $[Ru_2(p\text{-}Pr^iC_6H_4Me)_2(\mu\text{-}Cl)Cl]_2$, CH_3CN, 80 °C, 3 h; (c) $NH_2OH{\cdot}HCl$, Et_3N, MeOH, rt, 15 h; (d) 3-indoleacetic acid, HATU, DIEA in CH_2Cl_2, rt, 2 h; (e) AcONa in 30% EtOH, reflux, 12 h; (f) phenylboronic acid, $Pd(PPh_3)_2Cl_2$, K_2CO_3, 1,4-dioxane, H_2O, rt.