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Short communication

Design, synthesis, and evaluation of 2-substituted ethenesulfonic acid ester derivatives as protein tyrosine phosphatase 1B inhibitors

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ABSTRACT

Thirty-two 2-substituted ethenesulfonic acid ester derivatives were designed, synthesized, and evaluated for their inhibitory activities against protein tyrosine phosphatase 1B (PTP1B) and selectivity over T-Cell protein tyrosine phosphatase (TCPTP). Preliminary structure–activity relationship studies demonstrated that the substitution at the aromatic center and the length of linker between the hydrophobic tail and aromatic center markedly affected the inhibitory activity against PTP1B and the selectivity over TCPTP. Specifically, compounds **43** and **36** revealed excellent inhibitory activity to PTP1B with IC_{50} = 1.3 μM and 1.5 μM, respectively, and marked 10- and 20-fold selectivity over TCPTP. Cytotoxicity data showed low cytotoxicity for COS-7 cell with IC_{50} values >100 μM for most synthesized chemicals.

1. Introduction

Protein tyrosine phosphatases (PTPs) comprise an extensive family of homologous enzymes that regulate various events in cellular signal transduction and metabolism [1,2]. Protein tyrosine phosphatase 1B (PTP1B), the first purified and characterized PTPs, plays an essential role in the regulation of insulin signaling pathway by dephosphorylating the activated insulin receptor [3,4]. Recent studies on the PTP1B-knockout mice have shown enhancing insulin sensitivity, as well as lower plasma glucose and insulin levels [5]. Since then, there has been tremendous attention and development of potential PTP1B inhibitors that could potentially act as therapeutic agents in treating Type II diabetes and obesity [6]. However, due to the fact that T-Cell protein tyrosine phosphatase (TCPTP) shares a structurally very similar active site with PTP1B and ~80% homologous in the catalytic domain, poor selectivity and pharmacokinetic properties of inhibitors have became a common problem; therefore, imminent development of potent and PTP1B-specific inhibitor remains necessary [7,8].

PTP1B is a 50 kDa monomeric enzyme containing 435 amino acids. The N-terminal domain (amino acids 1–298) includes two aryl phosphate binding sites: a high-affinity catalytic site (containing the nucleophile cysteine residue, Cys215) and a low-affinity non-catalytic site (demarcated by Arg24 and Arg254 residues) [8]. The efficient inhibition of PTP1B is accomplished by occupying its high-affinity catalytic active site and forming a thiol covalent bond with the catalytic Cys215 residue, similar to the thiol-phosphate linkage formed during normal enzymatic catalysis [9]. Recently, 3, 4-dihydroxy stilbene carbonyl compound **I** [10], difluoromethylenesulfonic acid **II** [11] and 1, 2, 3, 4-tetrahydro-isoquinolinyl sulfamic acid **III** [12] were reported as inhibitors (Fig. 1.) that target PTP1B active site. Current trend of the research is to exploit inhibitors not only bind to the high-affinity catalytic site, but also establish hydrophobic interaction with the secondary low-affinity non-catalytic site of the enzyme. The collective interactions with both sites are proposed to increase the inhibitory activity for PTP1B and enhance the selectivity over TCPTP [13–15]. For example, compound **IV** was found to interact with the PTP1B catalytic site through establishment of a covalent bond with Cys215 and hydrophobic interactions of the aromatic rings with the nonpolar residues of PTP1B [16]. Further structural analysis of **IV** suggested that an effective inhibitor of PTP1B may require a combination of four moieties: a hydrophilic head, an aromatic center, a linker and a hydrophobic tail as displayed in Fig. 1.

In searching for novel PTP1B inhibitors, we prepared a series of compounds with functional module arrangement similar to that of compound **IV** to increase the inhibitory activity for PTP1B and

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enhance the selectivity over TCPTP. Herein, we report the design, synthesis, and evaluation of 2-substituted ethenesulfonic acid ester derivatives (Fig. 2) as a new class of PTP1B inhibitors. We proposed that the ethenesulfonic acid ester group of our designed compounds may form a thiol covalent bond with the catalytic Cys215 residue within the active site whereas their hydrophobic tail substituents at the aromatic center may offer hydrophobic interactions with the nonpolar residues of PTP1B.

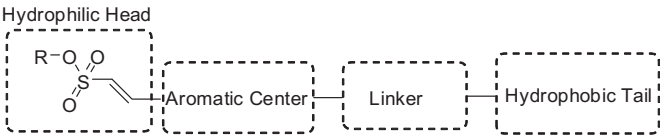

Fig. 2. Schematic design of 2-substituted ethenesulfonic acid ester derivatives as novel PTP1B inhibitors.

2. Synthetic chemistry

The synthetic routes for the five series of novel 2-substituted ethenesulfonic acid ester derivatives are outlined in Schemes 1–5. Most of the intermediates were prepared according to the procedures previously reported [17–24]. In general, compounds **9a**–**h** were prepared in five steps starting from commercially available methyl 4-bromo-3-oxopentanoate **1** and respective substituted benzamides **2** (Scheme 1). Reduction of intermediate methyl 2-(5-methyl-2-phenyloxazol-4-yl) acetate **3** in the presence of $LiAlH_4$ afforded 2-(5-methyl-2-phenyloxazol-4-yl) ethanol **4**, then protection of its hydroxyl group with MsCl gave 2-(5-methyl-2-phenyloxazol-4-yl) ethyl methanesulfonate **5**, further introduction of (5-substituted-2-phenyloxazol-4-yl)ethyloxy to the phenyl with intermediate compound **6** by electrophilic substitution yielded 4-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)benzaldehyde **7**. Finally, compounds **9a**–**h** were yielded by Wittig–Horner reaction with **7** and intermediate **8**.

Compound **11a** was synthesized in two steps starting from intermediate **4** (Scheme 2). Specifically, 2-(5-methyl-2-phenyloxazol-4-yl) ethanol **4** was oxidized with Dess–Martin agent to afford **10**, which was further reacted with **8** under Wittig–Horner conditions to give **11a**.

Compound **16a** was afforded according to the procedure in Scheme 3. The key intermediate **14** was prepared from 2, 4-dihydroxybenzaldehyde **12**. Specifically, treating **12** with (chloromethyl)benzene in the presence of KI and $NaHCO_3$ gave 4-(benzyloxy)-2-hydroxybenzaldehyde **13**, which was reacted with $BrCH_2COOEt$ via intermolecular cyclization to afford ethyl 6-(benzyloxy) benzofuran-2-carboxylate **14**. Compound **14** was followed by detaching benzyl group, reduction, condensation and oxidation to give intermediate **15**. The final step was conducted similar as that of **9a**–**h** to yield compound **16a**.

Compounds **21a**–**21b** were given with the method as shown in Scheme 4. Treating **17** with diethyl oxalate gave ethyl 2, 4-dioxo-4-phenylbutanoate **18**, which was reacted with $NH_2OH{\cdot}HCl$ to afford ethyl 5-phenylisoxazole-3-carboxylate **19**. 4-((5-Phenylisoxazol-3-yl) methoxy)benzaldehyde **20** was obtained via reduction and condensation of **19**, and the target compounds were obtained by Wittig–Horner reaction.

Compounds **26a**–**26c** were synthesized as shown in Scheme 5. Treatment of acetophenone **22** with thiourea and I_2 afforded 4-phenylthiazol-2-amine **23**. 4-(3-(4-phenyl thiazol-2-ylamino) propoxy)benzaldehyde **25** was given by electrophilic substitution with **23** and **24** in the presence of K_2CO_3, and the target compounds were prepared with the similar method as that in Scheme 1.

All synthesized compounds were characterized by the NMR and MS analyses.

3. Results and discussion

3.1. Inhibition of PTP1B

In order to find the suitable hydrophilic head, aromatic center, linker and hydrophobic tail, we initially designed five series of 2-substituted ethenesulfonic acid ester derivatives, screened their inhibitory activity against PTP1B and selectivity over TCPTP, respectively, and hope to find a structure template for further optimization. The data were shown in Table 1.

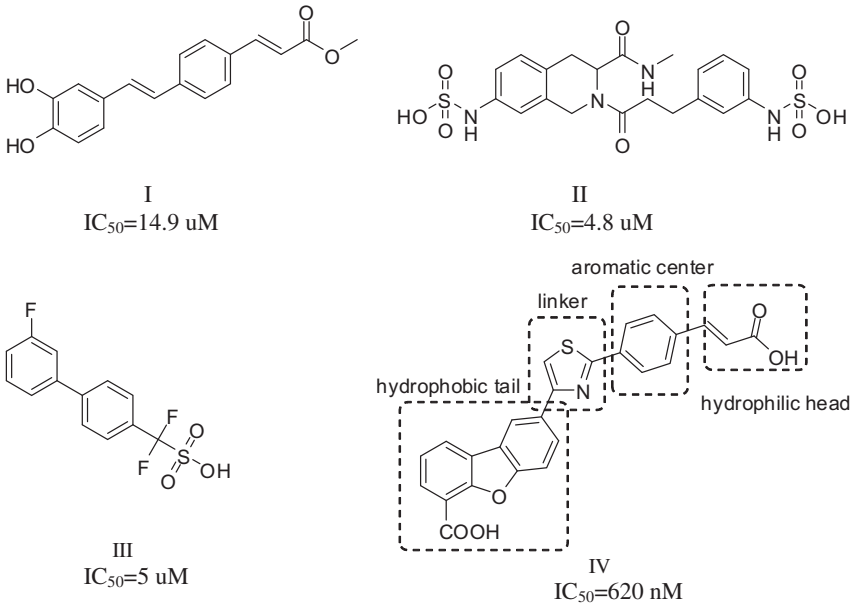

Fig. 1. Representative known PTP1B inhibitors.