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Research paper

Discovery of novel high potent and cellular active ADC type PTP1B inhibitors with selectivity over TC-PTP via modification interacting with C site

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ABSTRACT

PTP1B serving as a key negative regulator of insulin signaling is a novel target for type 2 diabetes and obesity. Modification at ring B of N-{4-[(3-Phenyl-ureido)-methyl]-phenyl}-methane-sulfonamide template to interact with residues Arg47 and Lys41 in the C site of PTP1B by molecular docking aided design resulted in the discovery of a series of novel high potent and selective inhibitors of PTP1B. The structure activity relationship interacting with the C site of PTP1B was well illustrated. Compounds **8** and **18** were shown to be the high potent and most promising PTP1B inhibitors with cellular activity and great selectivity over the highly homologous TCPTP and other PTPs.

1. Introduction

Protein tyrosine phosphatase 1B (PTP1B) is a novel target for type 2 diabetes and obesity [1]. PTP1B-deficient mice have remarkably low adiposity and are protected from diet-induced obesity [2]. Studies in cell lines, animal models and clinical trials on the role of PTP1B have clearly shown that it serves as a key negative regulator of insulin signaling and is involved in the insulin resistance associated with Type 2 diabetes [3,4]. However, the catalytic site of PTP1B is highly conserved, positively charged, shallow and not deep enough to form a nice pocket, hence PTP1B enzyme drug design is different compare to a typical enzyme-based drug design. It is difficult for the discovery of potent cell permeable and orally bioavailable PTP1B inhibitors [5]. Achieving PTP1B selectivity over closely associated PTPs, especially T-cell protein tyrosine phosphatase (TC-PTP) is another major challenge [6]. TC-PTP has a critical role in the development of the immune system and has been identified as a negative regulator of inflammation [7]. The TC-PTP KO mice die at 3–5 weeks of age because of impaired B cell and T cell functions [6]. TC-PTP is the most homologous phosphatase to PTP1B with 74% sequence identity in the catalytic domain and identical active sites. Thus discovery PTP1B inhibitors with selectivity over TCPTP are really important and difficult. Nevertheless, this well validated therapeutic target PTP1B for diabetes and obesity has continued to inspire medicinal chemists to pursue novel inhibitors with selectivity and oral availability.

Up to now, only two small-molecule PTP1B inhibitors, Ertiprotafib [8] and Trodusquemine [9] (Fig. 1), have reached clinical trials. Several classes of PTP1B inhibitors have been described in the literature, and the most frequently reported structural features of PTP1B inhibitors include the isosteric difluoromethylene phosphonate (DFMP) containing inhibitors [10,11], dicarboxylic acid containing inhibitors [12–14], monoacid containing inhibitors [15–17], 1,2,5-thiadiazolidin-3-one-1,1-dioxide (TDZ) based inhibitors [18,19], isothiazolidin-3-one-1,1-dioxide (IZD) based inhibitors [20–24], and arylsulfamic acid containing inhibitors [25], as exemplified by compounds **1**–**6** shown in Fig. 1.

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In our pursuit to discover novel potent and selective PTP1B inhibitors, a series of N-{4-[(3-Phenyl-ureido)-methyl]-phenyl}-methane-sulfonamide analogues were identified as PTP1B inhibitors through fragment-docking-oriented de novel design. Compound **7** (Fig. 1) was shown to possess potent PTP1B enzyme inhibition activity ($IC_{50} = 203$ nM) and high selectivity against TC-PTP (no activity) [26]. Following this promising lead, structure activity relationship (SAR) studies were initiated with the aim to further improve the potency on PTP1B and remaining selectivity against TC-PTP. Herein we will describe in detail the discovery of these novel high potent and selective ADC type PTP1B inhibitors based on N-{4-[(3-Phenyl-ureido)-methyl]-phenyl}-methane-sulfonamide template (compound **7**, Fig. 1) through modification at ring B.

2. Inhibitors design

Docking simulations of compound **7** and all other designed inhibitors within the ADC site of PTP1B (PDB entry 2CNE) have been performed using geom docking program (sybyl X 2.0) with the default setting. The key features of the binding mode of compound **7** are summarized as follows (shown in Fig. 2): First, the two sulfonyloxygens of ring A in compound **7** bond with the residues ILe219, Gly220, and Arg221 in the A site of PTP1B through hydrogen bonding interactions. Second, the 2-ethoxy group pointed to and interacted with the D site [26] (lined with polar and charged residues Tyr46, Glu115, Lys120, Asp181, and Ser216) and the 5-ethoxy group interacted the hydrophobic residues (Val49, Phe52, Ile219 and Met258). Third, the 1,3-double-NHs of the urea group in compound **7** strongly interacted with the carboxylate group of residue ASP48.

The interactions between PTP1B and its ligand (PDB entry 2CNE) in the C site included the multiple hydrogen bonding interactions with the residues Arg47 and Lys41 [27]. We envisioned that introducing suitable hydrogen bond acceptors to the B ring of compound **7** to form hydrogen bonding interactions with the residues Arg47 and Lys41 maybe greatly improve the PTP1B inhibition activities. Docking simulation results suggested that introducing -COOMe group as hydrogen bond acceptors at the meta-position with suitable group -OR at para-position of ureido group on ring B in compound **7** gave compound **8** and analogues forming strong new hydrogen bonding interactions with the residue Arg47, as shown in Fig. 2, based on the binding mode of compound **7**. Compounds **8-10** containing —COOMe group (shown in Fig. 3) were designed for exploring the optimal interactions with residue Arg47.

Then -COOMe group was substituted with -CONHR group for improving the structural stability of the designed compounds and also for detecting the structure activity relationship. To form interaction with the distant residue Lys41, -CONHR group was further converted to substituted -CONHPh groups for exploring the positions and varieties of the substituents on the new phenyl group. Docking results demonstrated compound **18** with 3,4-di-MeO-Ph-groups replaced the small -CONHR group on meta-position of the ring B in compound **8** formed effective hydrogen bonding interactions with residues Arg47 and Lys41 (shown in Fig. 2) based on the binding mode of compound **8**. Thus compounds **11-18** (shown in Fig. 3) were designed to detect the detailed SAR in the C site of PTP1B.

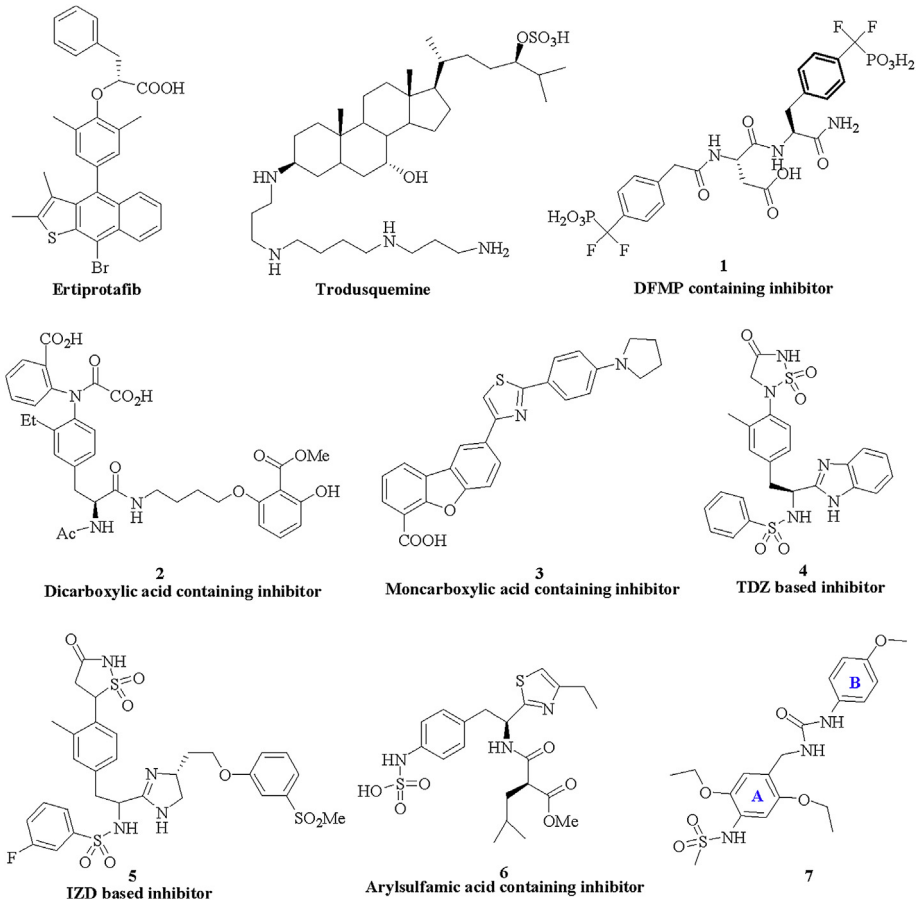

Fig. 1. Representative examples of PTP1B inhibitors previously reported.