Letters

Selective Protein Tyrosine Phosphatase 1B Inhibitors: Targeting the Second Phosphotyrosine Binding Site with Non-Carboxylic Acid-Containing Ligands

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Abstract: Protein tyrosine phosphatase (PTPase) 1B (PTP1B) has been implicated as a key negative regulator of both insulin and leptin signaling cascades. We identified several salicylic acid-based ligands for the second phosphotyrosine binding site of PTP1B using a NMR-based screening. Structure-based linking with a catalytic site-directed oxalylarylaminobenzoic acid-based pharmacophore led to the identification of a novel series of potent PTP1B inhibitors exhibiting 6-fold selectivity over the highly homologous T-cell PTPase (TCPTP) and high selectivity over other phosphatases.

Protein tyrosine phosphatase (PTPase) 1B (PTP1B) has been implicated as a major negative regulator of the insulin and leptin signaling pathway.[1] The most compelling data came from two independent studies on the targeted disruption of PTP1B gene in mice.[2,3] These PTP1B knock out mice exhibit phenotypes of increased insulin sensitivity, improved glucose tolerance, resistance to diet-induced obesity, enhanced response toward leptin-mediated weight loss, and suppression of feeding.[2−5] These observations provide a high level of validation for PTP1B as a therapeutic target for the treatment of both type II diabetes and obesity.

T-cell PTPase (TCPTP), a phosphatase implicated in regulating T-cell activation,[6] has the highest homology to PTP1B, with 74% sequence identity to PTP1B in the catalytic domain and 100% sequence identity in the catalytic site. Selective inhibition of PTP1B over TCPTP is therefore highly desirable and represents one of the most challenging aspects for drug discovery. Indeed, only two groups have addressed the TCPTP selectivity in a structure-based fashion, despite the large number of PTP1B inhibitors reported in the recent years.[7]

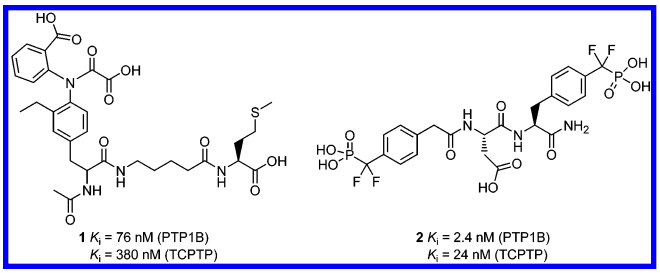

Figure 1. Known PTP1B inhibitors with selectivity over TCPTP.

Zhang and co-workers first identified a second phosphotyrosine (pTyr) binding site (site 2) in the vicinity of PTP1B catalytic site. They also pioneered the notion of achieving selectivity among PTP1B, TCPTP, and other phosphatases by targeting the less homologous site 2.[8] We recently reported a series of oxamic acid-based PTP1B inhibitors which for the first time validated such strategy. A highly potent, oxamic acid-based PTP1B inhibitor occupying both the catalytic site and site 2 was discovered using a linked-fragment approach.[9] More recently, the discovery of a highly potent PTP1B inhibitor **1** (Figure 1, K_i = 76 nM) with 5-fold TCPTP selectivity identified the region of site 2 important for imparting TCPTP selectivity.[10]

Zhang and co-workers demonstrated another approach for achieving TCPTP selectivity with the discovery of a difluorophosphonic acid-based, highly potent PTP1B inhibitor **2** (Figure 1, K_i = 2.4 nM) with 10-fold TCPTP selectivity.[11] X-ray crystallography of PTP1B complexed with a derivative of **2** revealed that targeting the area defined by residues Lys41, Arg47, and Asp48 can also be exploited to enhance potency and selectivity of PTP1B inhibitors.[12]

Site 2 ligands discovered so far for achieving TCPTP selectivity are all carboxylic acids.[9,10] Given that most of the catalytic site-directed PTP1B inhibitors are highly charged molecules, non-carboxylic acid-containing ligands targeting site 2 are highly desirable for improving the overall druglike properties. Herein, we report the discovery of first nonacid-containing, salicylate-based ligands for site 2 of PTP1B, and a structure-based linking approach for identifying potent PTP1B inhibitors with selectivity over TCPTP.

To identify site 2 ligands for PTP1B, NMR-based screening was developed using a selectively ^{13}C-labeled PTP1B (residues 1−288).[13] The unique signal of Met258 in site 2 provided an unambiguous marker for interaction with any potential site 2 ligands. Approximately 10 000 compounds in the SAR-by-NMR library (MW < 200 Da) were screened.[14] From this screening, a variety of small organic acids were identified as potential site 2 ligands. Figure 2 shows two salicyclic acid (**3**, **4**) derivatives and a quinaldic acid (**5**) derivative with dissociation constants (K_ds) in the submillimolar to low millimolar range. The salicylic acid-based ligands be-

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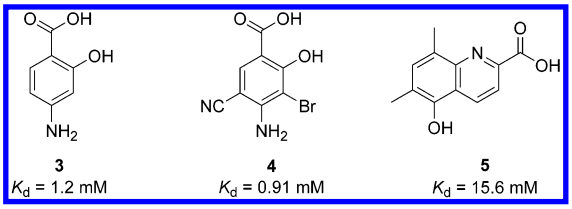


Figure 2. PTP1B site 2 ligands identified using NMR screening with ^{13}C-labeled protein and their respective dissociation constants.

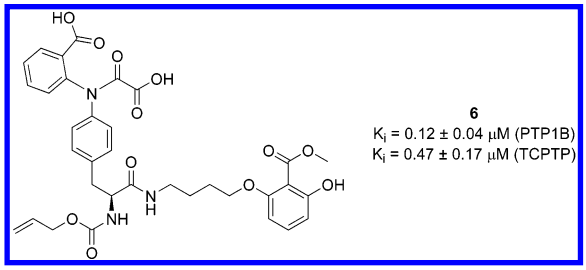


Figure 3. First PTP1B inhibitor with salicylate-based site 2 ligand for achieving selectivity over TCPTP.

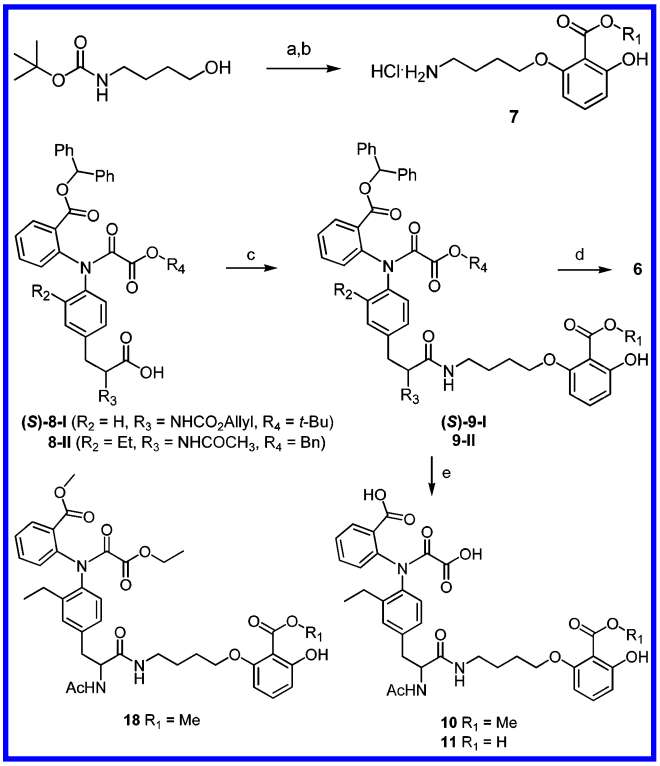
came the focus of linking efforts because of their binding affinity and structural diversity.

The weak affinity of salicylic acids **3** and **4** prevented direct determination of their binding modes using X-ray crystallography. The X-ray structure of PTP1B complexed with **1** provided critical guidance for incorporating the new site 2 ligands.[10] The methionine amide could be replaced by an ether linkage to provide the same hydrogen bond between **1** and Gln262. To preserve the free hydroxyl group of site 2 ligands, a C_2 symmetrical methyl 2,6-dihydroxybenzoate was coupled to our catalytic site inhibitor. To our delight, the resulting inhibitor **6** (Figure 3) exhibited good inhibitory potency and phosphatase selectivity. The kinetic analysis of **6** using *p*NPP as substrate in a colorimetric assay confirmed compound **6** as a competitive and potent PTP1B inhibitor (K_i = 120 nM) with 4-fold selectivity over TCPTP (K_i = 470 nM). Much greater specificity (>300-fold) over less homologous phosphatases was also observed (Table 2).

Inhibitor **6** and related analogue **10** were synthesized as shown in Scheme 1. Briefly, a Mitsunobu and deprotection sequence from *tert*-butyl 4-hydroxybutylcarbamate and methyl 2,6-dihydroxybenzoate yielded salicylate ether **7**. The readily available acid cores ***S*-8-I** and **8-II** (see Supporting Information) were coupled with **7** to give amides ***S*-9-I** and **9-II**. Removal of the acid-labile protecting groups yielded **6** and **10**. Surprisingly, due to steric hindrance and deprotonation of the phenolic hydroxy group, the methyl ester of **6** could not be hydrolyzed under basic conditions. Instead, decarboxylation took place after prolonged heating. The salicylic acid analogue **11** was secured through hydrogenation of a benzyl ester intermediate. Other related analogues (**12**−**17**) were prepared in the same fashion using readily available resorcinol derivatives for Mitsunobu ether formation (see Supporting Information).

Diffraction of the PTP1B crystals (residues 1−322) soaked with **6** (resolution of 2.2 Å) revealed the usual binding mode associated with this series of pTyr mimetics in the active site (Figure 4).[15] However, the X-ray structure of the complex did not offer clear clues for the origin of TCPTP selectivity in site 2. As shown in Figure

Scheme 1.[a] Preparation of Oxalylaminobenzoic Acid-Based PTP1B Inhibitors with Salicylate-Based Site 2 Ligands



[a] Reagents and conditions: (a) DEAD, Ph_3P, 2,6-dihydroxybenzoates, THF, rt; (b) 4 N HCl/dioxane, rt; (c) TBTU, 7, Et_3N, DMF, rt; (d) TFA, anisole, CH_2Cl_2, rt; (e) H_2, 10% Pd/C, MeOH.

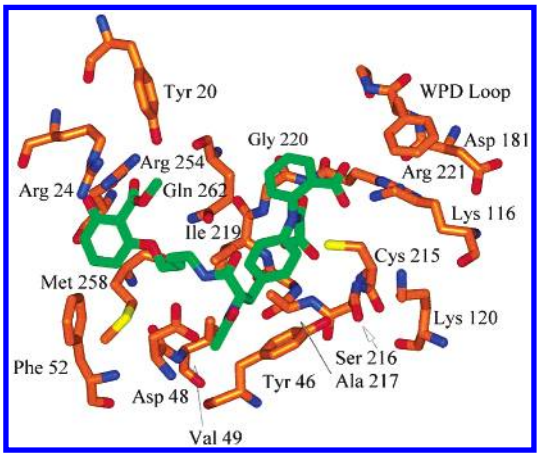
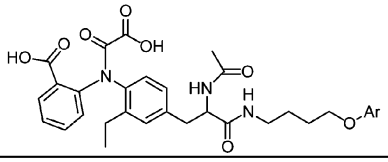
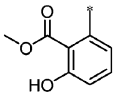
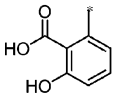
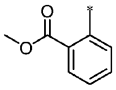
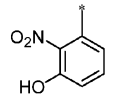
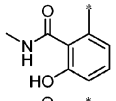
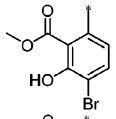
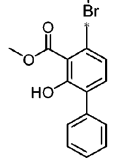
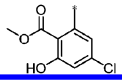


Figure 4. X-ray crystal structure of PTP1B (resolution 2.2 Å) in complex with **6**. Carbon is in orange for PTP1B and green for compound **6**, oxygen is in red, nitrogen is in blue, sulfur is in yellow.

4, diamide linker of **6** makes critical hydrogen bond contacts with Asp48 to position the salicylate in site 2. The ether oxygen of **6** forms a hydrogen bond with Gln262 (3.05 Å) to hold the salicylate in place. Forced by the two ortho-substituents, the salicylate carboxylate group adapts an out of plane conformation and is in hydrogen bond contact with Tyr20 (2.84 Å) and Arg254 (3.07 Å). The hydroxyl group of **6** hydrogen bonds with Arg24 (2.92 Å) and Arg254 (2.84 Å). Because of the diminished electron-withdrawing effect of the carboxylate group, the hydroxyl group of the salicylate is expected to remain as un-ionized under physiological pH (~7.4). The aromatic portion of the salicylate lies

Table 1. SAR of the Salicylate-Based Site 2 Ligands for PTP1B Inhibitors



Compd	Ar	PTP1B $K_i \pm$ SEM (μM)	TCPTP $K_i \pm$ SEM (μM)
10[a]		0.018 ± 0.004	0.065 ± 0.015
11[a]		0.042 ± 0.019	0.073 ± 0.007
12[a]		1.6 ± 0.86	0.86 ± 0.23
13[a]		0.13 ± 0.05	0.12 ± 0.02
14[a]		0.37 ± 0.12	0.83 ± 0.32
15[a]		0.39 ± 015	2.6 ± 2.8
16[a]		0.56 ± 0.23	0.84 ± 0.07
17[a]		0.040 ± 0.012	0.23 ± 0.02

[a] 1:1 mixture of enantiomers.

on top of the hydrophobic side chain of Met258, providing complimentary van der Waals interaction.

Despite the high homology in the catalytic domain, PTP1B and TCPTP clearly fulfill different biological functions, as demonstrated by the knock out mice.[2−3,6] Fine structural differences not readily identifiable by primary sequence analyses may account for the observed differences in inhibitor recognition by PTP1B and TCPTP. The recently published TCPTP crystal structure[16] has identified two areas that could confer different substrate recognition capacities between PTP1B and TCPTP. In particular, the area defined by Cys32/*His34*, Lys39/*Glu41*, and Phe52/*Tyr54* (TCPTP residues in italics) in site 2 is in very close proximity to the salicylate-binding region. Thus, the subtle differences between PTP1B and TCPTP in site 2 could partly explain the different inhibitor recognition for **6**.

Encouraged by the superior in vitro profiles of **6**, we then sought to expand the structure−activity relationship (SAR) of the salicylate-based site 2 ligands. Since the 3-ethylphenylalanine derivatives as PTP1B inhibitors were generally 5−10 times more potent than the unsubstituted ones,[17] we prepared all the new analogues with this new template as shown in Table 1. The SAR of the salicylate was first explored. Compared to **6**, the catalytic site ethyl-substituted analogue **10** is 6-fold more potent (K_i = 18 nM) with 4-fold selectivity over TCPTP (K_i = 65 nM). Compounds **11** and **12** exemplified the importance of the methyl ester and the hydroxyl group of the salicylate. Salicylic acid **11** showed both reduced PTP1B potency and TCPTP selectivity. The carbonyl of the methyl salicylate hydrogen bonds with PTP1B, while the methoxy part points to the solvent space (Figure 4). The entropy gain from the fixed position of the carbonyl group might explain the potency and selectivity difference between ester **10** and acid **11**. Removal of the hydroxyl group (**12**) led to an almost 100-fold decrease of inhibitory potency with deterioration of TCPTP selectivity as well. Replacing the methyl ester with a nitro group (**13**) resulted in a 10-fold loss of potency and complete loss of selectivity over TCPTP. Replacement of the methyl ester with a methyl amide (**14**) resulted in a 20-fold loss of binding potency and a 2-fold decrease in TCPTP selectivity.

Table 2. Phosphatase Selectivity Profile of PTP1B Inhibitors **6** and **17**

	K_i (μM)					
	PTP1 B	LAR	SHP-2	CD45	cdc25 C	calcineurin
6	0.12	33	96	>200	178	>200
17	0.040	>3.0[a]	>3.0[a]	>3.0[a]	>3.0[a]	>3.0[a]

[a] Highest concentration tested.

The X-ray structure of **6** indicated that Phe52 in site 2 was readily accessible to the salicylate. Since this residue is not conserved between PTP1B and TCPTP, interaction with Phe52 had the potential to impart greater selectivity to this series of PTP1B inhibitors. We attempted to extend off the 5-position of the salicylate with either a bromine (**15**) or a phenyl group (**16**) to interact with Phe52. However, such substitutions were not well tolerated, with over 10-fold decrease of inhibitory potency for both analogues, compared to **10**. There seem to be real differences in TCPTP selectivity for these two analogues. Bromine substitution (**15**) gave 6-fold selectivity over TCPTP, while the phenyl analogue **16** showed no TCPTP selectivity. Interestingly, compared to **10**, a 4-chloro substituent (**17**) maintained the inhibitory potency (K_i = 40 nM) and gave almost 6-fold selectivity over TCPTP. The additional hydrophobic interaction between the chlorine of **17** and Met258 of PTP1B could partially explain the slightly improved selectivity profiles.

Compound **17** was profiled more extensively against other phosphatases in our selectivity panel. As shown in Table 2, **17** showed greater than 75-fold selectivity[18] over other PTPases, including leukocyte antigen-related tyrosine phosphatase (LAR), SH2-domain-containing phosphotyrosine phosphatase-2 (SHP-2), and CD45, respectively (Table 2). Additionally, **17** also exhibited excellent selectivity profiles (>75-fold)[18] over a dual specificity phosphatase cdc25C, and a protein serine/threonine phosphatase calcineurin.

Even with the non-carboxylic acid-containing site 2 ligand, compound **10** is still a highly charged molecule with limited ability to cross a cell membrane, as indicated by low permeability across Caco-2 cell monolayers ($P_{app} < 1 \times 10^{-6}$ cm/s).[19] Therefore, when **10** was tested for augmentation of insulin-stimulated protein kinase B (PKB) phosphorylation (Ser473) in FAO cells,[20]

no augmenting effect was observed, possibly as the result of low permeability of **10** via passive diffusion. To circumvent this problem, a prodrug approach using the diester of **10** was explored. The ester prodrug **18** (Scheme 1) exhibited significantly increased penetration of Caco-2 cell monolayers ($P_{app} > 1 \times 10^{-6}$ cm/s). More importantly, **18** showed augmentation of submaximal insulin (0.025 nM)-stimulated PKB phosphorylation in a dose dependent manner at concentrations of 100 μM (65% increase) and 300 μM (150% increase), respectively, when compared to the level of PKB phosphorylation in vehicle treated cells (see Supporting Information). The conversion of ester **18** to the parent compound **10** was confirmed by LC-MS when **18** was incubated with lysate of FAO cells (see Supporting Information). Similar prodrug strategies for improving cellular permeability of PTP1B inhibitors have been reported by Bleasdale et al.[21] and Andersen et al.,[22] respectively.

In summary, a novel series of salicylate-based ligands for the second phosphotyrosine binding site of PTP1B was discovered through NMR-based fragment screening and structure-based assembly strategy. Linking with the oxalylarylaminobenzoic acid-based catalytic site pharmacophore resulted in a series of highly potent PTP1B inhibitors with selectivity over TCPTP. The unique binding mode of this series of PTP1B inhibitors was determined by X-ray crystallography. The identification of the salicylate-based site 2 ligands offers opportunities for linking with other novel, less charged, active site-directed pTyr mimetics to yield highly potent, selective, and cell permeable PTP1B inhibitors.

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Supporting Information Available: Experimental details and analytical and spectral characterization data of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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