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Isothiazolidinone inhibitors of PTP1B containing imidazoles and imidazolines

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Abstract—The structure-based design and synthesis of isothiazolidinone (IZD) inhibitors of PTP1B containing imidazoles and imidazolines and their modification to interact with the B site of PTP1B are described here. The X-ray crystal structures of **3I** and **4I** complexed with PTP1B were solved and revealed the inhibitors are interacting extensively with the B site of the enzyme.

The inhibition of protein tyrosine phosphatase 1B (PTP1B) has attracted much attention in recent years due to its potential of treating diabetes and obesity.[1–3] PTP1B decreases insulin signaling by dephosphorylating tyrosine residues present in the insulin receptor (IR).[4] Inhibition of PTP1B should therefore increase insulin sensitivity and responsiveness. The data to support this were reported by two independent laboratories that showed PTP1B knock-out mice had lower insulin and glucose levels along with increased sensitivity to insulin and resistance to high-fat induced weight gain all without any adverse effects.[5,6]

The research into discovering small molecule inhibitors of PTP1B has been focused on finding mimics of phosphotyrosine (pTyr).[7–13] The common theme with these inhibitors is the highly charged and polar functionalities, such as phosphonates and carboxylates that are used to occupy the active site of PTP1B. In view of the existing inhibitors that were already reported in the literature, we sought a new pTyr mimetic that would not only be a potent inhibitor of PTP1B, but that would also avoid or minimize the polarity found in the existing inhibitors. Toward that end, we embarked on a program to discover a novel inhibitor of PTP1B using computer-assisted structure-based designs. Our efforts led to the identification of the isothiazolidinone (IZD) heterocycle as a very effective mimic of pTyr.[14] We have disclosed the SAR of heterocycles similar to IZD along with the development of alternatives to the original peptide scaffold which included the use of benzimidazoles and sulfonamides to replace amides.[15–17]

In an effort to further increase binding affinity and selectivity, ligands that interact with the adjacent binding sites of PTP1B were examined. We had previously determined that the IZD heterocycle resides deep within the catalytic or A site of the enzyme as designed.[14,15] The two additional sites, C and E, are solvent-exposed, shallow, and contain few enzymatic residues for productive binding interactions.[18,19] Introduction of substituents into the D site, a very small pocket that interacts with small substituents attached to the phenyl ring adjacent to the IZD, provided only a small increase in potency.[18] We report herein inhibitors that explore the B site—a second, non-catalytic phosphate binding site that is relatively close to the catalytic site and contains several hydrophobic and hydrophilic residues for potential binding interactions (Val49, Phe52, Ile219, Met258, Arg24, and Arg254).[18,19] We reasoned that the appropriate functionalization of our analogs to reach the B site should produce more potent inhibitors (Fig. 1). Functionalization of the benzimidazole moiety of inhibitor **2** was unattractive since derivatization at the 4 or 5

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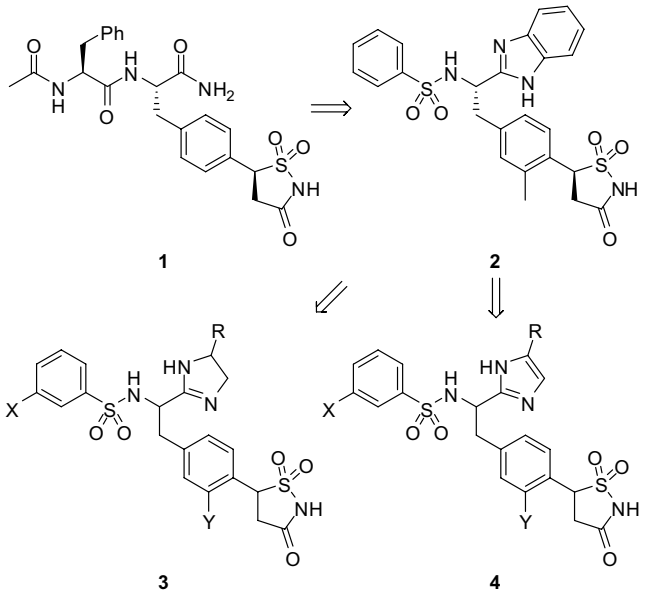
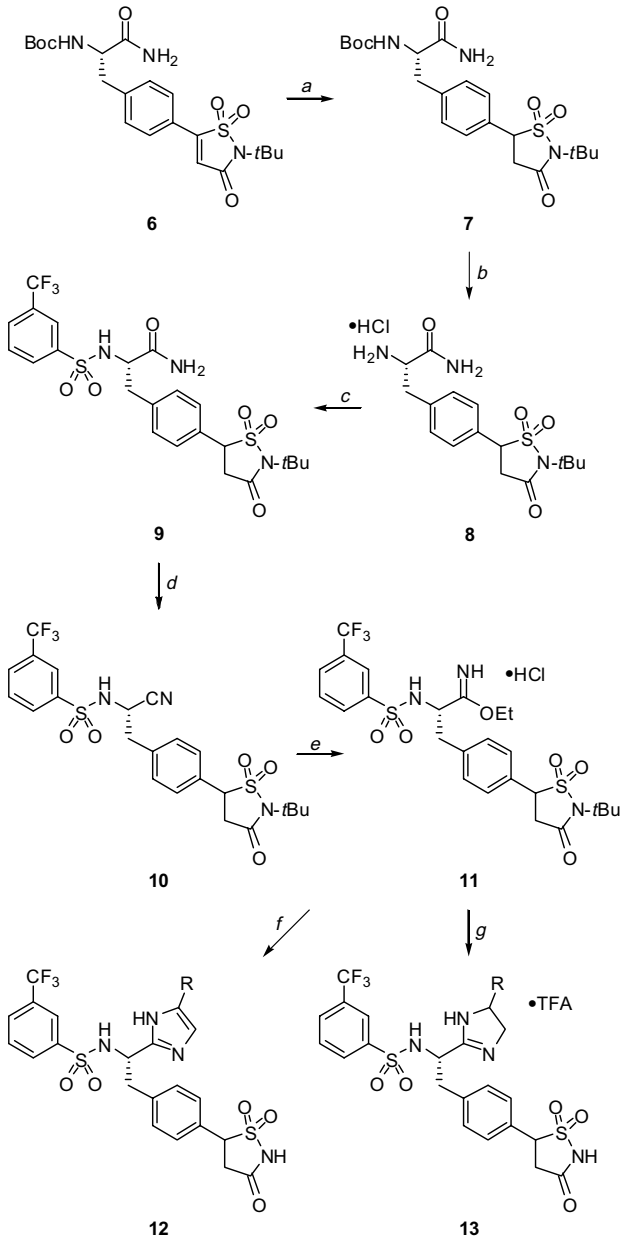


Figure 1. Progression of IZD containing PTP1B inhibitors.

position of the benzimidazole ring had previously produced a loss of activity or limited SAR.[16–18] Isosteric replacements for the benzimidazole were modeled and the imidazoline (**3**) and imidazole (**4**) produced good candidates. Both heterocycles could maintain the critical hydrogen bonding interactions with Asp48 of PTP1B through the nitrogen atoms which were found to be necessary for high affinity binding in our earlier work.[14–16] In this paper, we describe our design and synthesis of imidazoles and imidazolines as novel PTP1B inhibitors that bind extensively in the B site.

The functionalized imidazoles could be easily prepared from sulfonamide imidates and substituted aminomethyl ketones. Alternatively, the functionalized imidazolines could also be prepared from the same imidate intermediate with substituted diamines and chiral diamines that allow the introduction of stereochemistry at the stereogenic center. The synthesis of functionalized imidazoles and imidazolines began with the unsaturated IZD substituted primary amide **6** reported in our previous work (Scheme 1).[15] Reduction of the unsaturated IZD afforded the (*R*/*S*)-IZD primary amide **7**. Removal of the Boc group (**7** → **8**), followed by reaction with (3-CF_3Ph)SO_2Cl, provided the sulfonamide **9**. The primary amide was dehydrated with trichloroacetyl chloride to sulfonamide nitrile **10** which was converted to the imidate hydrochloride **11**. The imidazoles were prepared from the condensation of **11** and appropriately substituted 2-amino-methyl ketones.[20] The *tert*-butyl group was removed from the IZD in TFA upon microwave irradiation. The two-step process afforded the sulfonamide imidazoles **12** in 7–43% yields. The functionalized imidazolines were also prepared from imidate hydrochloride **11** and substituted diamines. The chiral diamines were derived from amino acids.[21,22] Deprotection of the *t*-butyl group provided the sulfonamide imidazolines **13** in 38–86% yields. Sulfonamide imidazolines and imidazoles were prepared as mixtures of diastereoisomers.



Scheme 1. Synthesis of imidazole and imidazoline analogs. Reagents and conditions: (a) $LiBH_4$, THF, 0 °C → 25 °C, 2 h, 76%; (b) 4 M HCl in dioxane, CH_2Cl_2, 1.5 h, 98%; (c) ((3-CF_3)-Ph)SO_2Cl, *i*-Pr_2NEt, CH_2Cl_2, 75%; (d) CCl_3COCl, *i*-Pr_2NEt, CH_2Cl_2, −10 °C → 0 °C, 5 h, 50%; (e) HCl (gas), CH_2Cl_2/EtOH (2:1), 1 h, quantitative; (f) i—aminoketone, KOAc, MeOH, Δ, 16 h; ii—TFA, 130 °C (microwave), 1 min, 7–43%; (g) i—diamine, EtOH, 0 °C → 25 °C, 1 h; ii—TFA, 150 °C (microwave), 30 s, 38–86%.

The synthesis of analogs with a methyl group adjacent to the IZD substituent began with commercially available methyl 4-bromo-3-methylbenzoate **14** (Scheme 2). Reduction of **14** followed by silylation provided the protected benzylic alcohol **16**. Lithium halogen exchange of bromide **16** and quenching with triisopropyl borate afforded boronic acid **17**. Suzuki coupling of **17** with the chloro-IZD **18** using $PdCl_2$(dppf)·CH_2Cl_2 catalyst[15] and removal of the TBDMS group provided unsaturated IZD-alcohol **19** in modest yield. Reduction of **19** gave the (*R*/*S*)-IZD **20** which was converted to the bromide