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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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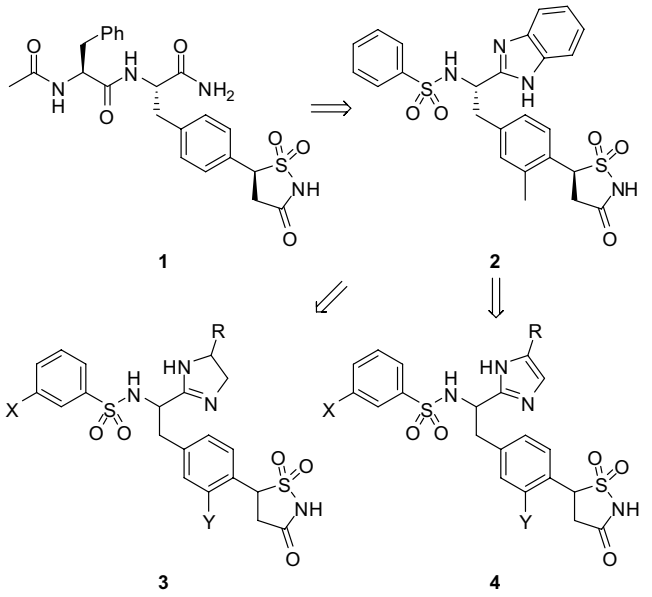
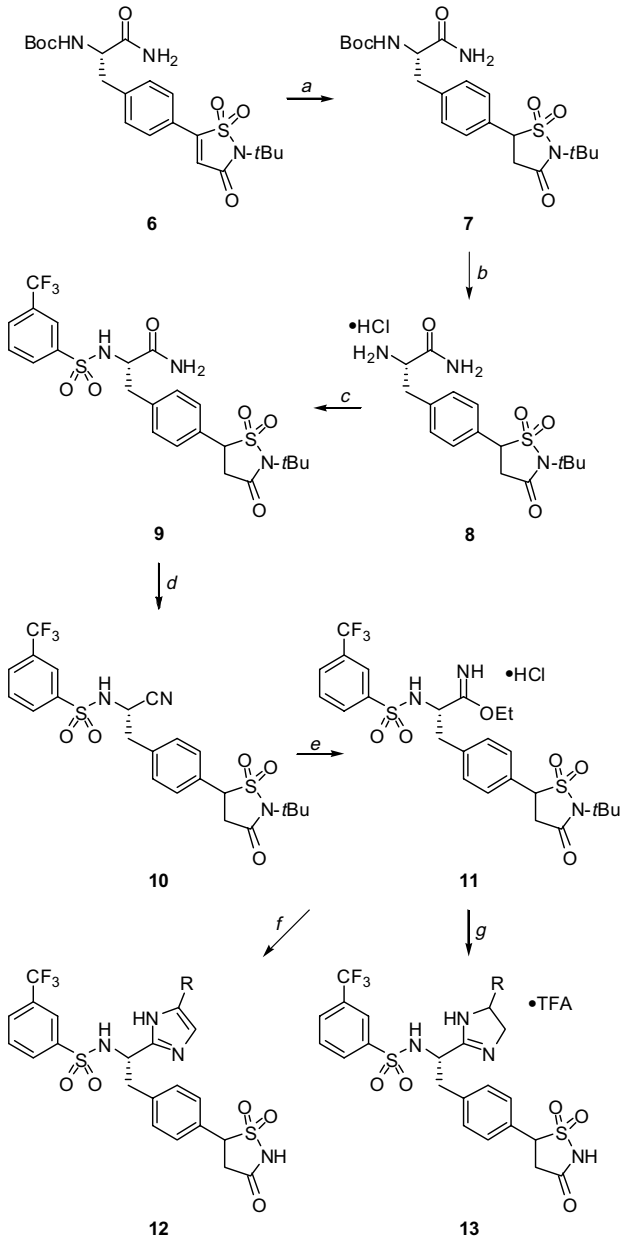


Figure 1. Progression of IZD containing PTP1B inhibitors.

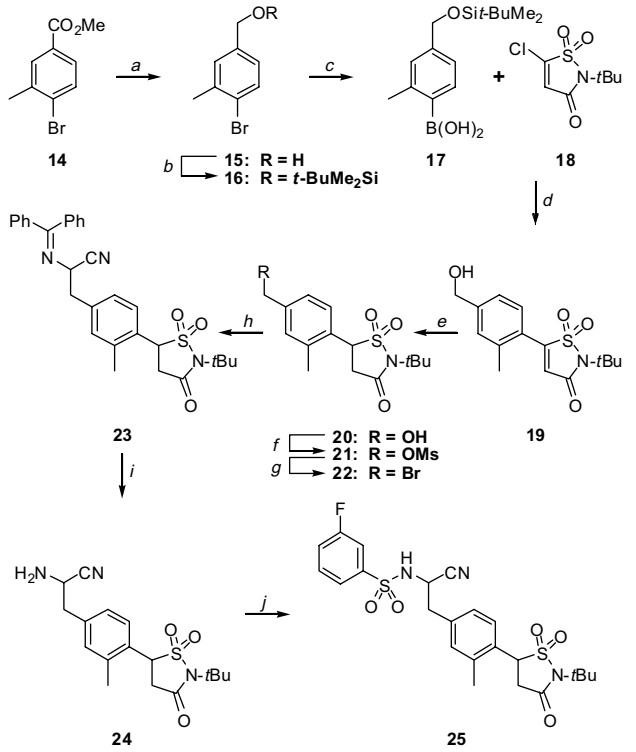
position of the benzimidazole ring had previously produced a loss of activity or limited SAR.[16–18] Isosteric replacements for the benzimidazole were modeled and the imidazoline (**3**) and imidazole (**4**) produced good candidates. Both heterocycles could maintain the critical hydrogen bonding interactions 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



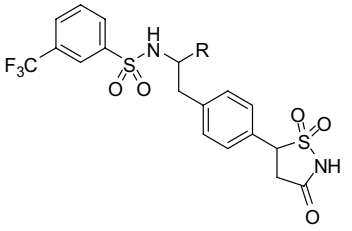
Scheme 2. Synthesis of key intermediate **25**. Reagents and conditions: (a) LAH, Et_2O, 0 °C → 25 °C, 30 min, 90%; (b) *t*-$BuMe_2SiCl$, imidazole, DMF, 0 °C → 25 °C, 1 h (94%); (c) i—*n*-BuLi, THF, −78 °C, 30 min; ii—$(i\text{-}PrO)_3B$, −78 °C → 25 °C, 99%; (d) i—$PdCl_2$ (dppf)·CH_2Cl_2, K_2CO_3, 80 °C, 24 h; ii—TBAF, THF, 0 °C → 25 °C, 1 h, 39% (two steps); (e) Li(*s*-Bu)$_3$BH, THF, −78 °C, 15 min, 81%; (f) MsCl, Et_3N, CH_2Cl_2, −10 °C, 15 min, 96%; (g) NaBr, DMA, 30 min, 98%; (h) i—$Ph_2C{=}NCH_2CN$, *t*-BuOK, −78 °C, 30 min; ii—**22**, THF, −78 °C → 25 °C, 30 min, 95%; (i) 1 N HCl, THF, 1.5 h, 88%; (j) ((3-F)-Ph)SO_2Cl, pyridine, 1 h, 99%.

22 via mesylate **21**. The imine protected amino-cyano group was introduced by alkylation of bromide **22** with *N*-(diphenylmethylene)-aminoacetonitrile[23] to give **23**. The benzophenone imine of **23** was removed (**23** → **24**), and sulfonylation provided sulfonamide nitrile **25**. Sulfonamide nitrile **25** provided access to all functionalized imidazoles and imidazolines with the methyl group adjacent to the (*R*/*S*)-IZD as mixtures of diastereoisomers.

The unsubstituted imidazole **5C** and imidazoline **5D** containing inhibitors were 21- and 7-fold more potent than the primary amide **5A**, respectively, but were less potent than the benzimidazole containing inhibitor **5B** (Table 1). The potency of the imidazole and imidazoline series was optimized with inhibitors that were able to access the B site.

A small library of substituted imidazoline inhibitors was prepared and tested for activity in PTP1B (Table 2). The compounds were also tested for selectivity against T-cell PTP (TCPTP), which is highly structurally related to PTP1B. TCPTP is important for normal T-cell activation and therefore having selectivity for PTP1B is desirable.[13] Initially, the 3-trifluoromethyl substituted sulfonamide was used as it was previously determined

Table 1. Comparison of the primary amide with heterocyclic replacements



5

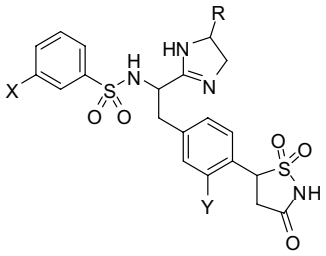
Compounds[a]	R	PTP1B[b] IC_{50} (nM)	TCPTP[b] IC_{50} (nM)
5A	$CONH_2$	5030	5000
5B		67	43
5C		240	270
5D		700	500

[a] Compounds tested as mixture of diastereoisomers.
[b] pNPP enzyme assay.

to be an effective replacement for the *N*-terminal peptide portion of the inhibitor.[16] In later work the 3-fluoro substituted sulfonamide was used and found to produce inhibitors of similar potency. Substitution of the imidazoline with (*R*)-methyl (**3A**) enhanced potency, while (*S*)-methyl (**3B**) decreased activity compared with the unsubstituted imidazoline **5D**. Dimethyl substitution (**3C**) also decreased activity. The difference in activity between the (*R*)- and (*S*)-isomers became greater with phenyl and benzyl substituents (approximately 9-fold). The (*R*)-benzyl analog **3F** was approximately 5-fold more potent compared with the unsubstituted imidazoline **5D**. This indicated additional binding interactions were being made between the enzyme and the (*R*)-substituted imidazoline. To enhance potency further only the (*R*)-substituted imidazolines were prepared.

The (*R*)-(*o*)-fluorobenzyl analog (**3I**) was 3-fold more potent than the corresponding analog without the fluorine substituent (**3H**). An X-ray crystal structure of **3I** bound to the enzyme was obtained to explore the potency enhancement (Fig. 2). Similar to previously prepared IZD inhibitors,[14–17] the isomer that was observed to be bound to the enzyme was the (*S*)-IZD isomer and the center adjacent to the sulfonamide had the (*S*)-configuration.[24] The structure shows the aryl sulfonamide π-stacks on top of the imidazoline. One of the sulfonamide oxygens forms a hydrogen bond to the backbone amide of Arg47 through a bridging water molecule and the imidazoline NH forms a hydrogen bond to Asp48 of the enzyme. The benzyl substituent binds in the B site in a similar position as the aryl group of the phosphotyrosine substrate.[25] B site interactions

Table 2. Imidazoline PTP1B inhibitors



3

Compounds[a]	X	R	Y	PTP1B[b] IC_{50} (nM)	TCPTP[b] IC_{50} (nM)
3A	CF_3	(*R*)-Me	H	540	420
3B	CF_3	(*S*)-Me	H	810	670
3C	CF_3	Di-Me	H	930	700
3D	CF_3	(*R*)-Ph	H	660	430
3E	CF_3	(*S*)-Ph	H	2900	2070
3F	CF_3	(*R*)-CH_2Ph	H	150	120
3G	CF_3	(*S*)-CH_2Ph	H	1300	1100
3H	F	(*R*)-CH_2Ph	H	210	140
3I	F	(*R*)-CH_2(2-F-Ph)	H	64	38
3J	F	(*R*)-$(CH_2)_2$Ph	H	130	68
3K	F	(*R*)-CH_2O(3-SO_2Me-Ph)	Me	800	470
3L	F	(*R*)-$(CH_2)_2O$(3-SO_2Me-Ph)	Me	23	25
3M	F	(*R*)-$(CH_2)_3O$(3-SO_2Me-Ph)	Me	160	84
3N	F	(*R*)-$(CH_2)_4O$(2-CO_2Me,3-OH-Ph)	Me	110	65
3O	F	(*R*)-$(CH_2)_4O$(2-CO_2H,3-OH-Ph)	Me	22	46

[a] Compounds tested as mixture of diastereoisomers.
[b] pNPP enzyme assay.

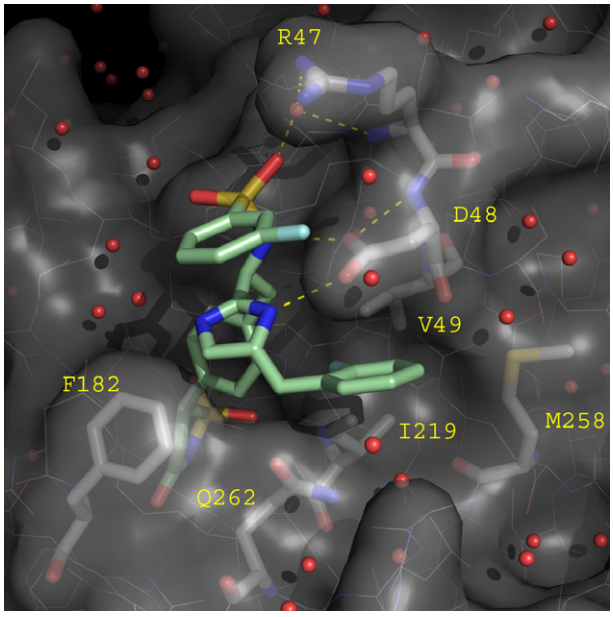


Figure 2. X-ray crystal structure of **3I** bound to PTP1B. PDB deposition number 2VEW.

produced the approximately 5-fold increase in potency compared with the unsubstituted imidazoline **5D**. The 3-fold increase in potency due to the fluorine substituent (**3I** vs **3H**) was also apparent from the X-ray structure which shows the fluorine substituent in close proximity with Val49, Ile219, and Gln262 of the enzyme in a hydrophobic pocket of the B site.

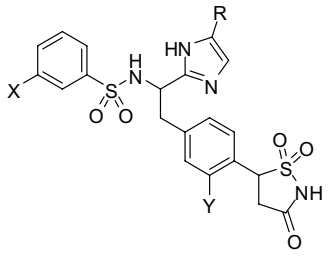
An X-ray crystal structure of the phenethyl substituted imidazoline (**3J**)[24,26] bound to PTP1B also shows the aromatic ring binding in the B site just above Ile219 and Met258. The slight loss in potency compared with **3I** (2-fold) is explained by a loss of the interactions between the fluorine substituent and the enzyme that are present in compound **3I**.

To reach further into the B site, the chain length to the aryl substituent was increased. Polar functionalities on the aryl group were placed at the end of the chain in an attempt to interact with the polar residues in the B site. Sulfonates and salicylates were used to obtain additional binding interactions with the B site. The (*o*)-methyl substituent on the aromatic ring adjacent to the IZD substituent, that previously was found to enhance potency through D site interactions, was also incorporated.

In the sulfonate analogs the addition of one methylene in the chain greatly enhanced potency (approximately 35-fold, **3L** vs **3K**). Extending the chain further resulted in a loss of activity. The salicylate analogs were also potent inhibitors. The salicylic acid analog (**3O**) was 5-fold more potent than the methyl salicylate analog **3N**, and was approximately 2-fold more active against PTP1B versus TCPTP. It was also 32-fold more active than the unsubstituted imidazoline **5D** and the most active in the series.

Next a small library of substituted imidazole inhibitors was prepared. As with the imidazoline series, the 3-trifluoromethyl and 3-fluoro substituted sulfonamides

Table 3. Imidazole PTP1B inhibitors



4

Compounds[a]	X	R	Y	PTP1B[b] IC_{50} (nM)	TCPTP[b] IC_{50} (nM)
4A	CF_3	Ph	H	100	61
4B	CF_3	CH_2Ph	H	300	230
4C	CF_3	CH_2CH_2Ph	H	170	170
4D	CF_3	$CH_2CH_2CH_2Ph$	H	52	51
4E	CF_3	$CH_2CH_2CH_2CH_2Ph$	H	200	160
4F	F	Ph	H	160	90
4G	F	CH_2Ph	H	250	270
4H	F	CH_2CH_2Ph	H	180	100
4I	F	$CH_2CH_2CH_2Ph$	H	43	24
4J	F	$CH_2CH_2CH_2CH_2Ph$	H	260	110
4K	F	$(CH_2)_3O$(2-CO_2Me,3-OH-Ph)	Me	350	170
4L	F	$(CH_2)_3O$(2-CO_2H,3-OH-Ph)	Me	120	170
4M	F	$(CH_2)_4O$(2-CO_2Me,3-OH-Ph)	Me	160	170
4N	F	$(CH_2)_4O$(2-CO_2H,3-OH-Ph)	Me	32	46

[a] Compounds tested as mixture of diastereoisomers.
[b] pNPP enzyme assay.

produced inhibitors of similar potency (Table 3). Substitution of the imidazole ring with phenyl (**4A**) increased potency approximately 2-fold compared with the unsubstituted imidazole (**5C**). X-ray crystal structures of the phenyl and benzyl analogs (**4A** and **4B**) with PTP1B showed that the phenyl group of both analogs interacted with Phe182 of the enzyme, but indicated longer chain lengths would be necessary to reach the B site.[24,26]

As the chain length was increased, the activity of the analogs remained similar until the chain length between the imidazole and phenyl substituent reached three methylenes. At that point the optimum chain length of the phenyl analogs was reached (**4D** and **4I**). Compound **4I** was approximately 5-fold more active than the unsubstituted imidazole **5C**. The addition of one methylene in the chain (**4E** and **4J**) reduced potency compared with the optimum 3-carbon chain length. The potency decreased to that of the unsubstituted imidazole **5C**.

An X-ray crystal structure of compound **4I**[24] bound to PTP1B (Fig. 3) showed the phenyl group was binding in the B site directly above Ile219, Met258, and Gln262. The sulfonamide oxygens and imidazole nitrogens formed hydrogen bonds with the enzyme in a similar manner as imidazoline analog **3I**.

The (*o*)-methyl substituent on the aromatic ring adjacent to the IZD substituent was again incorporated to obtain D site interactions and to maximize potency. We also incorporated the salicylate substituent that produced the highest activity in the imidazoline series. With the

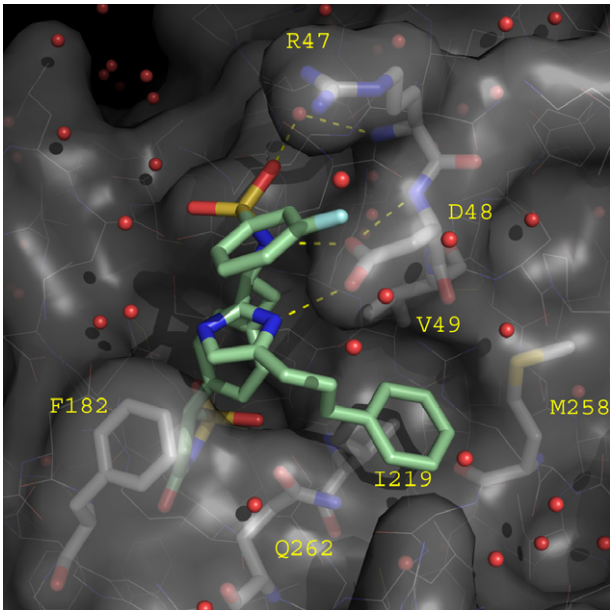


Figure 3. X-ray crystal structure of **4I** bound to PTP1B. PDB deposition number 2VEY.

methyl salicylate analogs, the addition of one methylene in the chain enhanced potency 2-fold (**4K** vs **4M**). The same pattern was observed with the salicylic acid analogs (**4L** vs **4N**). As with the imidazoline series, salicylic acid analog **4N** was 5-fold more potent than the methyl salicylate analog **4M**, and was the most active in the imidazole series. Compound **4N** was now approximately 7-fold more active than the unsubstituted imidazole **5C**.

Polar B site substituents (sulfonates and salicylates) produced the most potent inhibitors with both the imidazoline (**3L** and **3O**) and the imidazole (**4N**) scaffolds. Previously the salicylate substituent of our peptidic IZD analog was shown to bind in the B site.[18] The salicylate formed hydrogen bonds with Arg24 and Arg254 of the enzyme's B site. Presumably the sulfonate and salicylate containing inhibitors reported here are interacting with B site Arg residues in a similar manner. Salicylate containing inhibitors have previously been reported to produce 20-fold selectivity for PTP1B over TCPTP.[27] We observed only minimal specificity (2-fold) with salicylate analog **3O** in the imidazoline series. The same specificity was not observed in the imidazole series or other imidazoline analogs.

The imidazoline and imidazole were discovered as viable replacements for the benzimidazole. While initially the affinity of the unsubstituted imidazoline (**5D**) and imidazole (**5C**) decreased compared to the benzimidazole (**5D**), functionalization to interact with the B site produced two highly potent PTP1B inhibitors **3O** and **4N**. B site interactions increased the affinity 32-fold (**3O** vs **5D**) in the imidazoline series and 7-fold (**4N** vs **5C**) in the imidazole series. X-ray crystal structures of the imidazolines and imidazoles bound to PTP1B showed the phenyl substituent on the end of the methylene chain optimally interacting with the hydrophobic residues of the B site when the chain length was sufficiently long enough to extend deep into the B site.

Acknowledgments

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Supplementary data

X-ray crystal structures of **3J**, **4A**, and **4B** complexed with PTP1B can be found, in the online version, at doi:10.1016/j.bmcl.2007.11.012.

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