Articles

Potent Benzimidazole Sulfonamide Protein Tyrosine Phosphatase 1B Inhibitors Containing the Heterocyclic (*S*)-Isothiazolidinone Phosphotyrosine Mimetic

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Potent nonpeptidic benzimidazole sulfonamide inhibitors of protein tyrosine phosphatase 1B (PTP1B) were derived from the optimization of a tripeptide containing the novel (*S*)-isothiazolidinone ((*S*)-IZD) phosphotyrosine (pTyr) mimetic. An X-ray cocrystal structure of inhibitor **46**/PTP1B at 1.8 Å resolution demonstrated that the benzimidazole sulfonamides form a bidentate H bond to Asp48 as designed, although the aryl group of the sulfonamide unexpectedly interacts intramolecularly in a pi-stacking manner with the benzimidazole. The ortho substitution to the (*S*)-IZD on the aryl ring afforded low nanomolar enzyme inhibitors of PTP1B that also displayed low caco-2 permeability and cellular activity in an insulin receptor (IR) phosphorylation assay and an Akt phosphorylation assay. The design, synthesis, and SAR of this novel series of benzimidazole sulfonamide containing (*S*)-IZD inhibitors of PTP1B are presented herein.

Introduction

Protein tyrosine phosphatase 1B (PTP1B[a]), the prototypical protein tyrosine phosphatase (PTP) from a family of ∼112 intracellular PTPs, has been strongly implicated by in vitro and in vivo experiments as a negative regulator of both insulin and leptin signal transduction pathways.[1] The observation that PTP1B knockout mice exhibit increased insulin sensitivity and are highly resistant to weight gain upon high fat feeding strongly suggests that PTP1B is a viable drug target for the treatment of diabetes and obesity.[2,3] Thus, a potent cell permeable inhibitor of PTP1B has been sought by nearly all pharmaceutical companies to test this hypothesis.[4]

Medicinal chemistry efforts to date have focused on the identification of inhibitors that contain strong binding, nonhydrolysable tyrosine phosphonate (pTyr) mimetics to affect potent binding to PTP1B. A variety of pTyr mimetics have been discovered and incorporated into potent small molecule inhibitors of PTP1B. Unfortunately, they lack cell permeability and oral bioavailability because of the strong negative charge carried by the pTyr mimetics as well as their high molecular weight and/or peptidic nature.

We recently disclosed the structure-based design of novel isothiazolidinone (IZD) pTyr mimetics and their incorporation into the peptidic inhibitors of PTP1B.[5] A thorough evaluation of the structure activity relationships of various pTyr heterocyclic mimetics and the peptidic portion of these inhibitors is described elsewhere.[6] In summary, we determined that the (*S*)-IZD heterocycle is the most potent pTyr mimetic known to date, being ∼10-fold more potent than the difluoromethylphosphonate (DFMP) when incorporated into dipeptide inhibitors and 5-fold more potent than the analogous thiadiazolidinone (TDZ) heterocyclic pTyr mimetic. However, despite the significant improvement in the enzyme potency of these peptidic (*S*)-IZD inhibitors, they also lacked cellular activity because of poor permeability.

We rationalized that the diffusely monoanionic (*S*)-IZD pTyr mimetic was not solely responsible for the lack of permeability and that the reduction in the peptidic nature of the inhibitors might cause a net improvment in permeability. The *C*-terminal primary amide was replaced with a benzimidazole with a 20-fold improvement in potency. The *N*-terminal truncation of the peptide followed by parallel synthesis and purification of N-acylated libraries identified the sulfonamide as a potent replacement for the two terminal peptides. The introduction of ortho substituents on the aromatic ring to the (*S*)-IZD provided relatively low molecular weight (MW ∼450−650) PTP1B inhibitors with low nanomolar enzyme potency. The *ortho*-methyl benzimidazole sulfonamide derivative **79a** has exceptional enzyme potency and was shown to be cell active in an IR phosphorylation assay as well as in an Akt phosphorylation assay. Details of the synthesis and SAR are presented herein.

Chemistry. The synthesis of peptides and benzimidazole sulfonamide derivatives incorporating the (*S*)-IZD pTyr mimetic followed our route previously reported to derive peptide derivative **1** starting with commercially available phenylalanine boronic acid derivative **3** (Scheme 1).[5] Acid **3** was coupled with chloroisothiazolinone **4** in a Suzuki[7] cross-coupling to generate oxidized core **5** in moderate yield. The reduction−deprotection of **5** using palladium on carbon under 50 psi of hydrogen gas gave **6** in high yield. The coupling of acid **6** with benzenedi-

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[a] Abbreviations: PTP1B, protein tyrosine phosphatase 1B; IR, insulin receptor; pTyr, phosphotyrosine; (*S*)-IZD, (*S*)-isothiazolidinone; TZD, thiadiazolidinone; DFMP, difluoromethylphosphonate.

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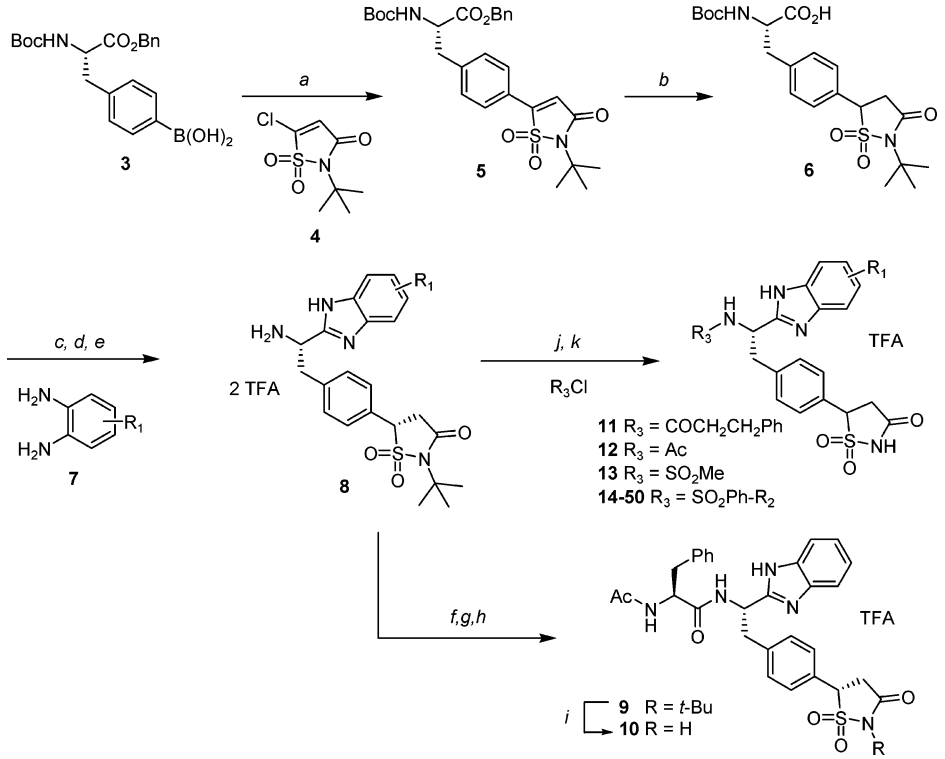
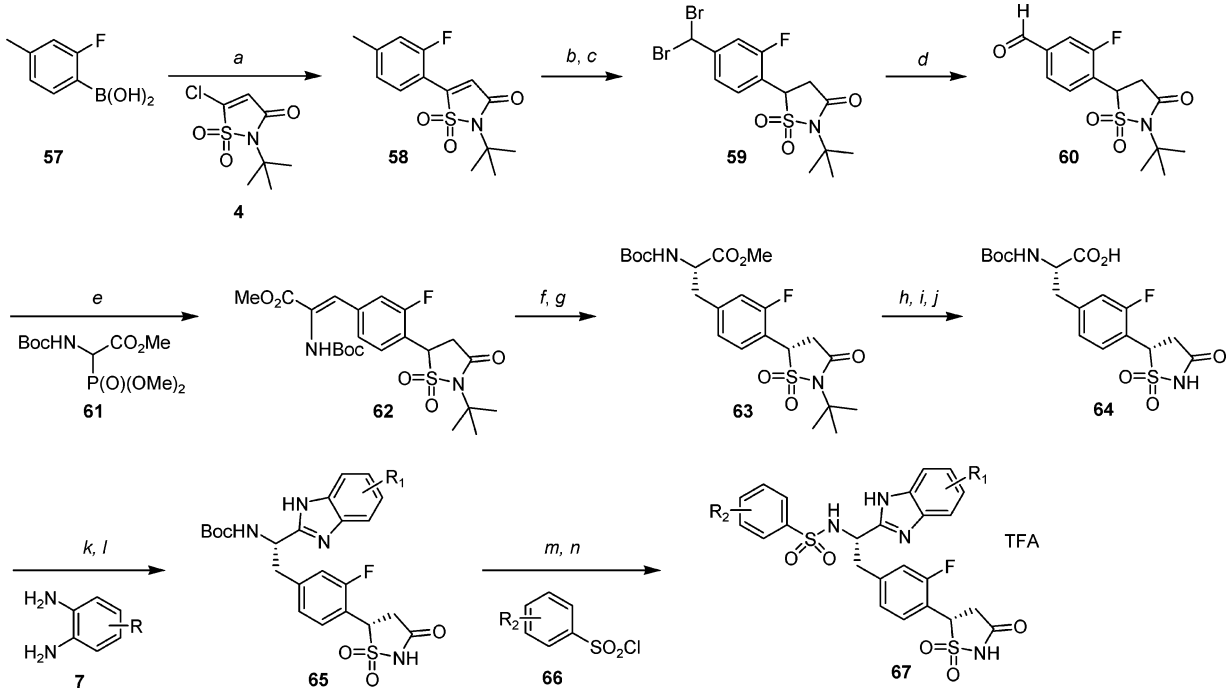
Scheme 1. Synthesis of Benzimidazole-Containing (*S*)-IZD Analogues[a]



[a] (a) 16 mol % Pd(dppf)Cl_2, 3 equiv Et_3N, DCM, 90 °C, 16 h, 68%; (b) 10 wt % Pd/C, EtOH, 93%; (c) **7**, HATU, DIEA, rt, 16 h, 48%; For compds **9**, **10**, **12**, **14**, and **16**, chiral separation of (*R/S*)-IZD diastereomers was performed; (d) AcOH, 40 °C, 2 h; (e) TFA, 30 min, rt, (83% for 2 steps); (f) Boc-Phe, HATU, DIEA, rt, 2 h; (g) TFA, 30 min, rt, (h) Ac_2O, DIEA, DCM, 2 h, rt (80% for 2 steps); (i) MsOH, ACN, rt, 60% (j) R_3Cl, Et_3N, DCM, rt, 5 h; (k) TFA, μW, 1 min (20−80% for 2 steps).

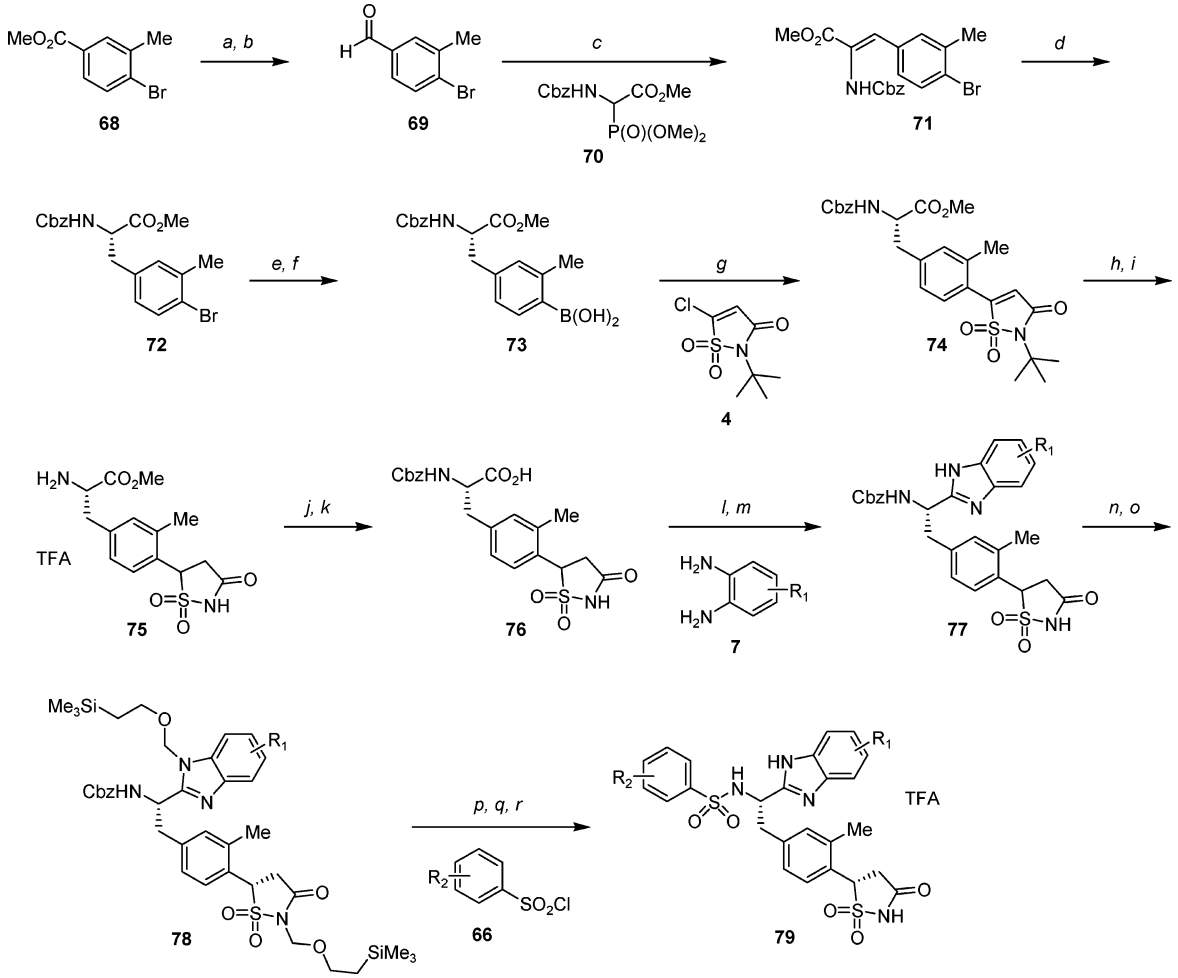
Scheme 2. Synthesis of *ortho*-Fluoro Substituted (*S*)-IZD-Containing Analogues[a]



[a] (a) 10 mol % Pd(dppf)Cl_2, **4**, 3 equiv Et_3N, toluene, 90 °C, 16 h, 61%; (b) 10% Pd/C, EtOH, rt, 16 h, 82%; (c) NBS, benzoyl peroxide, CCl_4, 80 °C, 4 h, 67%; (d) $AgNO_3$, EtOH, H_2O, reflux, 1 h, 85%; (e) DBU, **61**, CH_2Cl_2, 74%; (f) 0.5 mol % *R,R*-(−)-1,2-bis(*o*-methoxyphenyl)(phenyl)phosphinoethan(1,5-cyclooctadiene rhodium; (I), EtOH, 50 psi H_2, 12 h, 93%, 97% ee, 1:1 dr; (g) Chiralcel AD column, 47%, 97% ee, single diastereomer; (h) TFA, 130 °C, μW, 6 min, 74%; (i) Boc_2O, Et_3N, CH_2Cl_2, 97%; (j) LiOH, H_2O, MeOH, 99%; (k) BOPCl, **7**, *i*Pr_2NEt, DMF, rt, 1 h; (l) AcOH, 40 °C, 1.5 h; (m) TFA/CH_2Cl_2 = 1:5; (n) Et_3N, **66**, CH_2Cl_2.

amine **7** followed by cyclization under acidic conditions at room temperature for 24 h afforded the desired benzimidazole. Careful control of the reaction temperature was critical because ring closure at higher temperatures proceeded more rapidly but

Scheme 3. Synthesis of *ortho*-Methyl Substituted Derivatives[a]



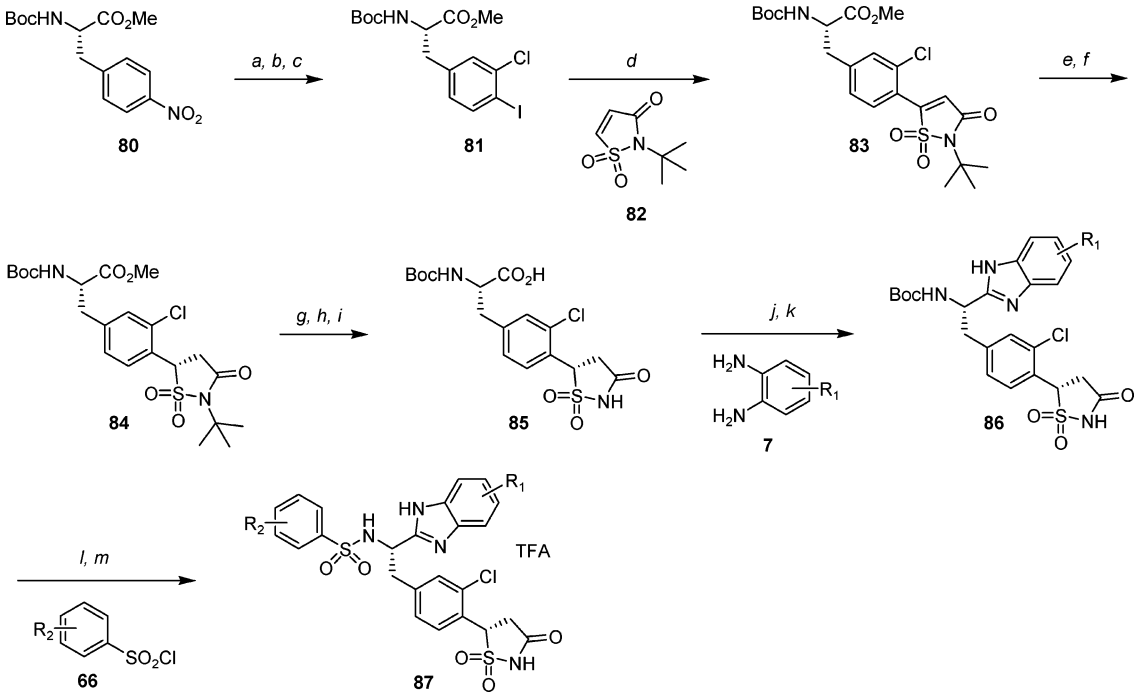
[a] (a) $LiBH_4$, THF, rt, 2 days, 82%; (b) DMSO, oxalyl chloride, CH_2Cl_2, −78 °C, 96%; (c) DBU, **70**, CH_2Cl_2, 85%; (d) 0.5 mol % *R*,*R*-(−)-1,2-bis(*o*-methoxyphenyl)(phenyl)phosphinoethan(1,5-cyclooctadiene rhodium (I), EtOH, 50 psi H_2, 12 h, 83%, 98% ee; (e) $Pd(OAc)_2$, Et_3N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 91% (f) $NaIO_4$, NH_4OAc, THF, H_2O, rt, 18 h, 80%; (g) 15 mol % $Pd(dppf)Cl_2$, **4**, 3 equiv Et_3N, toluene, 80 °C, 24 h, 62%; (h) L-selectride, THF, −78 °C, 88%; (i) TFA, 130 °C, μW, 6 min, 74%; (j) BnOC(O)Cl, Et_3N, CH_2Cl_2; (k) LiOH, H_2O, MeOH; (l) BOPCl, *i*Pr_2NEt, **7**, DMF, rt, 1 h, 82%; (m) AcOH, 40 °C, 1.5 h; (n) 2.2 equiv SEMCl, *i*Pr_2NEt, CH_2Cl_2; (o) Chiralcel AD column, 98% ee, single diastereomer; (p) 10 wt % Pd/C, MeOH, H_2; (q) Et_3N, **66**, CH_2Cl_2; (r) TFA, 130 °C, μW, 6 min;

returned mixtures of diastereomers at the alpha center of the amino acid. At this point in the synthesis, the (*R*/*S*)-IZD diastereomers were easily separated by chiral HPLC to afford two discrete isomers, (*S*)-IZD and diastereomer **8** is shown in Scheme 1. Both diastereomers were further elaborated to the final compounds, providing an active and inactive pair. The active isomer was assigned to the (*S*)-IZD on the basis that all X-ray cocrystal structures solved to date have the (*S*)-IZD isomer bound, such as **46**/PTP1B. All other analogues were derived from diastereomer **8**. The removal of the Boc group from **8** with TFA furnished the free amine, which could be acylated with a variety of reagents under mild conditions to give amides, ureas, sulfonamides, and carbamates such as **10**−**56**.

The synthesis of each desired analogue ortho substituted on the aryl ring to the (*S*)-IZD necessitated the optimization of a unique sequence of chemical reactions. The *ortho*-fluoro and *ortho*-methyl derivatives were synthesized via a similar Suzuki cross-coupling reaction of chloroisothiazolinone **4** and a properly substituted arylboronic acid. The construction of the *ortho*-bromo and *ortho*-chloro derivatives relied on a chemoselective and regioselective Heck coupling of an ortho substituted arylidodide with isothiazolidinone **82**. The separation of (*R*/*S*)-IZD isomers was also necessary in these routes, and the (*S*)-IZD isomer was again assigned by synthesis of the two (*R*/*S*)-IZD diastereomers and the determination of the active compound. The details of each sequence of reactions are described below.

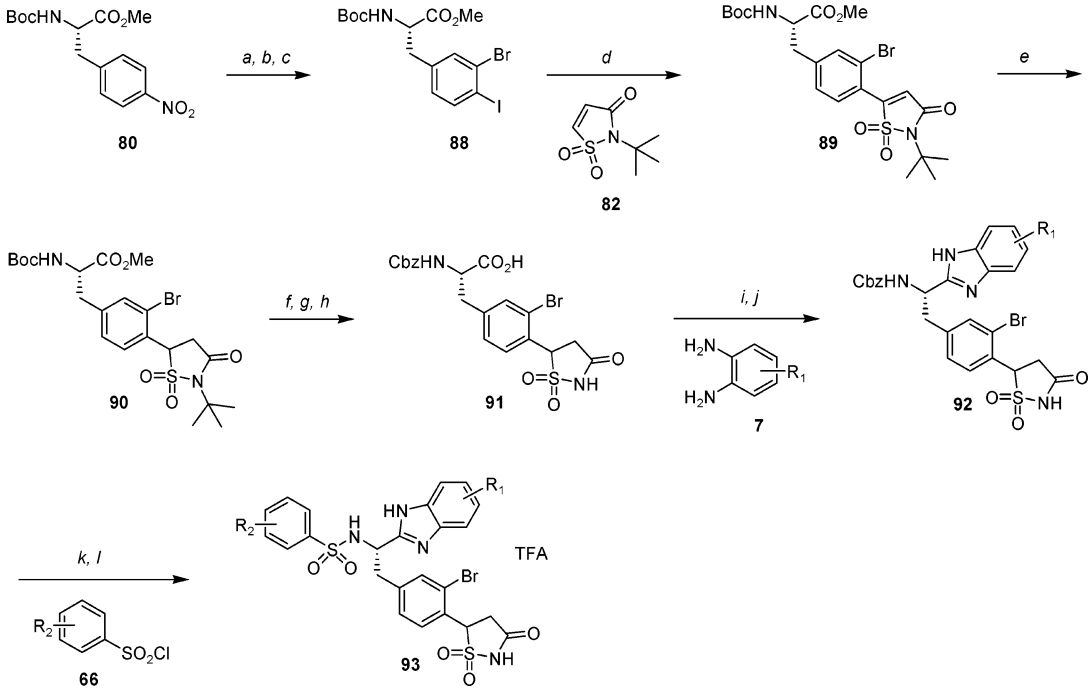
The *ortho*-fluoro derivatives were synthesized via a similar Suzuki cross-coupling approach, though accessing the key amino acid-containing (*S*)-IZD intermediate **64** was more challenging. Starting with commercially available fluoroboronic acid **57** and chloro-isothiazolinone heterocycle **4**, palladium catalyzed cross-coupling employing dppf as the ligand gave a 61% yield of core **58** (Scheme 2). The reduction of heterocyclic olefin followed by the formation of the dibromo acetal equivalent **59** proceeded in 51% yield for two steps. Aldehyde **60** was unmasked using silver nitrite in refluxing aqueous ethanol in 85% yield. A Horner−Wadsworth−Emmons type olefination with phosphonate **61** afforded unsaturated amino acid **62**. The reduction of **62** utilizing *R*,*R*-(−)-1,2-bis(o-methoxyphenyl)-(phenyl)phosphinoethan(1,5-cyclooctadiene) rhodium[8] proceeded with >97% ee to give a 1:1 mixture of diastereomers at the heterocycle, which were separated on a Chiral AD HPLC column. Single isomer **63** was then globally deprotected by microwave irradiation in TFA to afford the free amine. Classical thermal conditions gave significantly lower yields in this deprotection sequence for most derivatives. Reprotection of the amine as the Boc carbamate and saponification of the ester generated the key amino acid containing (*S*)-IZD intermediate

Scheme 4. Synthesis of *ortho*-Chloro Substituted (*S*)-IZD-Containing Analogues[a]



[a] (a) Zn^0, NH_4Cl, MeOH, H_2O; (b) NCS, DMF; (c) $NaNO_2$, 1 N aq HCl, KI, 51%) (3 steps); (d) $Pd(OAc)_2$, Bu_4NCl, **81**, Et_3N, DMF, 100 °C, 64%; (e) $LiBH_4$, MeOH, 0 °C, 72%; (f) Chiralcel AD column, 48%, 97% ee, single diastereomer; (g) TFA, 130 °C, μW, 0.25 h, 88%; (h) Boc_2O, Et_3N, CH_2Cl_2; (i) LiOH, H_2O, MeOH, 81% (2 steps); (j) BOPCl, **7**, *i*Pr_2NEt, DMF, rt, 1 h (k) AcOH, 40 °C, 1.5 h, 72% (2 steps); (l) TFA/CH_2Cl_2 = 1:5; (m) Et_3N, **66**, CH_2Cl_2, 76% (2 steps).

Scheme 5. Synthesis of *ortho*-Bromo Substituted (*S*)-IZD-Containing Analogues[a]



[a] (a) Zn^0, NH_4Cl, MeOH, H_2O; (b) NBS, DMF; (c) $NaNO_2$, 1 *N* aq. HCl, KI 64% (3 steps); (d) $Pd(OAc)_2$, Bu_4NCl, **82**, Et_3N, DMF, 100 °C, 52%; (e) $LiBH_4$, MeOH, 0 °C, 82%; (f) TFA, 130 °C, μW, 0.25 h, 99%; (g) CbzCl, Et_3N, CH_2Cl_2; (h) LiOH, H_2O, MeOH, 81% (2 steps); (i) BOPCl, *i*Pr_2NEt, DMF, rt, 1 h (j) AcOH, 40 °C, 1.5 h, 72% (2 steps); (k)TMSI, CH_3CN; (l) Et_3N, **66**, CH_2Cl_2, 68% (2 steps).

64. Peptide coupling with diamine **7** followed by in situ cyclization in acetic acid afforded benzimidazole **65**. The *N*-terminal amine of the benzimidazole derivatives were deprotected with TFA and reacted with various arylsulfonyl chlorides **66** to furnish benzimidazole sulfonamide derivatives **67** (**a**−**e**).

Synthesis of the *ortho*-methyl scaffold also employed a Suzuki cross-coupling to attach the IZD to the scaffold (Scheme 3). However, it was again necessary to reconstruct the overall synthetic route compared to those of the unsubstituted and *ortho*-fluoro syntheses. Commercial bromide **68** was converted in 80% yield over two steps to aldehyde **69** via a reduction−oxidation sequence. Olefination of the aldehyde with phosphonate ester **70** afforded unsaturated amino acid **71** in 85% yield. The reduction of **71** utilizing *R*,*R*-(−)-1,2-bis(o-methoxyphenyl)-

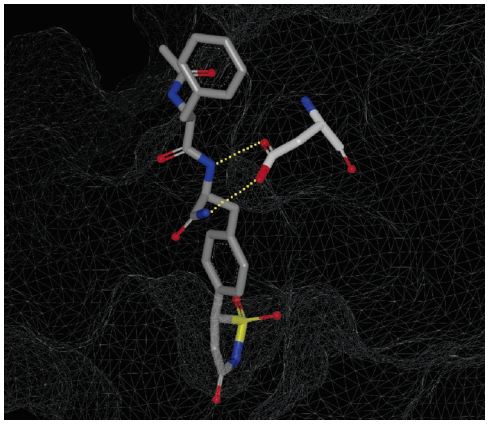


Figure 1. X-ray crystal structure of compound **1** bound to PTP1B. The molecular surface of the protein is shown with the (*S*)-IZD heterocycle binding in the phosphotyrosine binding pocket. The bidentate hydrogen bond of the inhibitor's peptide-like backbone with Asp48, also shown, is indicated with dotted lines.

(phenyl)phosphinoethan(1,5-cyclooctadiene) rhodium proceeded with >97% ee to give **72**. Bromide **72** was converted to boronic acid **73** via coupling to the borate ester followed by oxidative cleavage. Boronic acid **73** was cross-coupled with chloro-isothiazolinone heterocycle **4** employing the same conditions utilized for the *ortho*-fluoro derivative to give IZD scaffold **74**. The reduction of the heterocycle with sodium borohydride and subsequent global deprotection furnished amine salt **75** in 66% yield. Reprotection of the amine as the Cbz carbamate followed by saponification afforded acid **76** in quantitative yield. The coupling of acid **76** with diamine **7** and then in situ cyclization with acetic acid provide the desired benzimidazoles **77**. At this point, the 1:1 diastereomeric mixture at the heterocycle of **77** was separated utilizing a Chiralcel AD HPLC column. The single diastereomer was then bis-SEM protected to supply intermediate **78**. The removal of the Cbz group using hydrogenation followed by coupling with arylsulfonyl chlorides **66** and subsequent deprotection with TFA afforded final products **79**.

The synthesis of the ortho halogenated (*S*)-IZD derivatives (chloro and bromo) could not be affected by a Suzuki cross-coupling because of chemoselectivity issues. A novel synthetic strategy was devised to couple the IZD to *ortho*-halo iodophenyl derivatives **81** and **88** through chemoselective and regioselective Heck reactions (Schemes 4 and 5). The synthesis of *ortho*-chloro derivative **87** is outlined below. The synthesis of *ortho*-bromo derivative **93** was performed as shown in Scheme 5 with only a slight modification in the protecting group strategy.

Key chloro-iodo-derivative **81** was readily obtained from commercial nitro-phenylalanine **80**. The nitro group of **80** was reduced to an amino group using zinc and ammonium chloride in methanol, followed by ortho chlorination to give an intermediate 2-chloroaniline. The aniline was diazatized using sodium nitrite under acidic conditions and the resulting intermediate trapped with potassium iodide to afford **81** in 51% yield over three steps. This intermediate was used in the key Heck[9] reaction with heterocycle **82**. The halogenated core **81** was coupled with **82** in 64% yield with classical ligandless conditions utilizing palladium acetate, tetra-*n*-butylammonium chloride, and triethylamine in DMF.[10] The reduction of **83** using lithium borohydride followed by the separation of the diastereomers utilizing chiral HPLC afforded single enantiomer **84**. Global deprotection using trifluoroacetic acid in the microwave at 130 °C, followed by Boc reprotection of the amine with di-*tert*-butyl dicarbonate and then saponification of the ester supplied

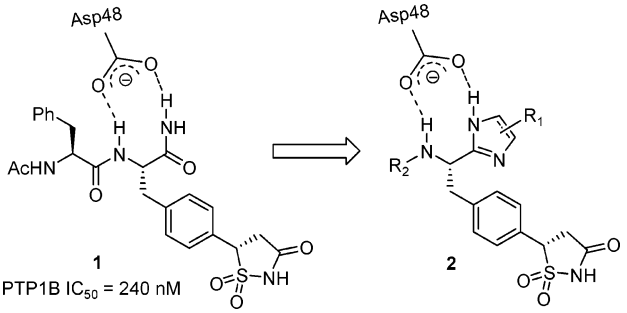
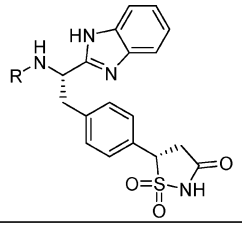
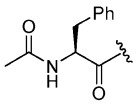
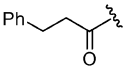
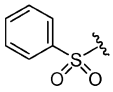


Figure 2. Peptidomimetic approach to optimizing peptide-(*S*)-IZD inhibitors.

Table 1. SAR of the *N*-terminal Truncation of Peptide Benzimidazoles



Cmpd	R	PTP1B pNPP IC_{50} (nM)[a]
10		35
11[b]		600
12		940
13[b]		590
14		32

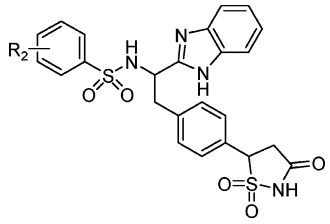
[a] The pNPP assay. [b] The mixture of (*R*/*S*)-IZD diastereomers.

acid **85** in 71% yield over three steps. The coupling of benzenediamine **7** to scaffold **85** and cyclization under acidic conditions gave benzimidazole **86** in 72% yield. The removal of the carbamate with TFA followed by sulfonylation afforded the desired *ortho*-chloro benzimidazole sulfonamide **87** in 76% yield.

Results and Discussion

In our effort to improve the cell permeability and the overall pharmacokinetic properties of our peptidic (*S*)-IZD-containing inhibitors of PTP1B, we endeavored to eliminate the peptidic nature of lead compound **1**. We initially focused on replacing the *C*-terminal amides with less polar, more hydrophobic groups. An inspection of the X-ray structures of several inhibitors, including **1**, revealed a conserved bidentate hydrogen bond between the *C*-terminal amide NH and the adjacent amide NH with Asp48 of PTP1B (Figure 1). Previous analogs from our lab had also shown that *N*-terminal tertiary amides were completely inactive against PTP1B, corroborating that this is an important interaction. Several heterocycles **2** were thus

Table 2. SAR of Arylsulfonamide Substituents



	R_2					PTP1B pNPP
compd[b]	**2-**	**3-**	**4-**	**5-**	**6-**	IC_{50} (nM)[a]
14						100 (32)[c]
15	F					120
16		F				66 (43)[c]
17			F			80
18	Cl					160
19		Cl				60
20			Cl			110
21	Br					170
22		Br				77
23			Br			110
24	Me					300
25		Me				85
26			Me			80
27	CF_3					130
28		CF_3				67
29			CF_3			51
30	CN					45
31			CN			63
32		OMe				48
33			OMe			94
34			Ph			80
35	Cl	Cl				240
36	Cl		Cl			280
37	Cl			Cl		160
38	Cl				Cl	460
39		Cl	Cl			79
40		Cl		Cl		51
41	F		F			110
42	F			F		140
43	F				F	160
44		F	F			110
45		F		F		72

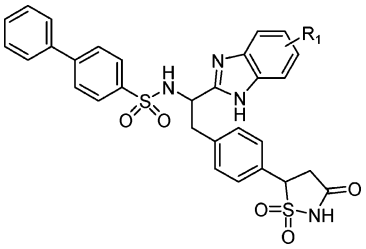
[a] A pNPP assay. [b] The compounds were synthesized in parallel as a mixture of 4 diastereomers (two major: (*R/S*)-IZD and two minor: alpha-center of amino acid) and purified by preparative LCMS. [c] The pNPP data for the separated single diastereomer.

targeted, which could maintain the bidentate hydrogen bonding interaction with Asp48 (Figure 2). The benzimidazole moiety proved to be a very effective replacement for the amide. Benzimidazole peptide **10** was ~10-fold more potent than the primary amide **1** with an $IC_{50} = 35$ nM (Table 1). The mode of inhibition experiments unequivocally demonstrated that **10** was a competitive and reversible inhibitor of PTP1B.

The truncation of the *N*-terminus of peptide inhibitor **10** demonstrated that the peptide portion of the inhibitor significantly contributed to the binding of this molecule to PTP1B (Table 1). The elimination of the terminal acetamide in compound **11** gave a surprising >20-fold loss in activity. It is clear that the hydrogen bond between the amide carbonyl and Arg54 provides a significant amount of the binding energy observed with these peptidic ligands. Truncating further to the simple acylbenzimidazole derivative **12** resulted in an additional 2-fold loss in activity, suggesting that the hydrophobic phenyl substituent of the peptide plays only a minor role in binding to PTP1B. The desolvation of the hydrophobic side chain in this solvent exposed region is likely a contributing factor.

A diverse compound library of different acyl groups (amides, ureas, carbamates, sulfonamides) was synthesized using scaffold **8**, as a mixture of diastereomers, in an effort to identify replacements for the *N*-terminal peptide portion of the inhibitor. Gratifyingly, arylsulfonamides were rapidly identified as potent PTP1B inhibitors. The new benzimidazole sulfonamide lead **14** is nonpeptidic and lower in molecular weight than parent **10** yet has comparable potency ($IC_{50} = 32$ nM). The aryl functionality was important for potency since the simple methylsulfonamide **13** was 5-fold less active. A focused compound library of substituted arylsulfonamides was synthesized in parallel and purified by automated LCMS[11,12] to optimize this functionality. A partial, yet representative set of compounds is shown Table 2. The SAR from this study revealed that a variety of meta or para substituted derivatives were more potent than the ortho substituted compounds, although they are only 2−3-fold better than the unsubstituted parent **14**.

Table 3. SAR of Benzimidazole Substituents



compd[b]	R_1	PTP1B pNPP IC_{50} (nM)[a]
34	H	80
47	4-Me	190
48	5-Me	140
49	5-F	120
50	5-CN	53
51	5-Cl	140
52	5-CO_2Me	150
53	5-CF_3	160
54	5-OMe	130
55	4-OH	240
56[c]	4-*tert*-butyl	460

[a] The pNPP assay. [b] The compounds were synthesized in parallel as a mixture of 4 diastereomers (two major: (*R/S*)-IZD and two minor: alpha-center of amino acid) and purified by preparative LCMS. [c] The compound was submitted as a mixture of 2 diastereomers ((*R/S*)-IZD).

A small library of substituted benzimidazoles was synthesized and showed that a wide variety of functional groups could also be appended to the benzimidazole (Table 3). All 3-substituted derivatives were approximately equipotent against PTP1B, whereas the large *tert*-butyl substituent **56** at the 2-position was less active. Modeling predicted that the benzimidazole would bind in a solvent exposed region on the surface of PTP1B, which we have termed the E-site. The expected orientation of the benzimidazole effectively explains the lack of SAR in the 5-position because these groups would project into the solvent and would not interact with the protein. The loss of activity with large substituents **56** at the 4-position could also be rationalized on the basis of a steric clash with Asp48 or Phe182.

The relatively flat SAR for the sulfonamide was more difficult to rationalize on the basis of our design and modeling, which predicted that the arylsulfonamide NH and benzimidazole NH bidentate H-bond interaction with Asp48 would necessitate that the aryl group of the sulfonamide bind in an extended conformation against the protein in the so-called C-site. An X-ray cocrystal structure of benzimidazole sulfonamide **46**/PTP1B solved to 1.8 Å resolution confirmed the presence of the bidentate H-bonding pattern and the position of the

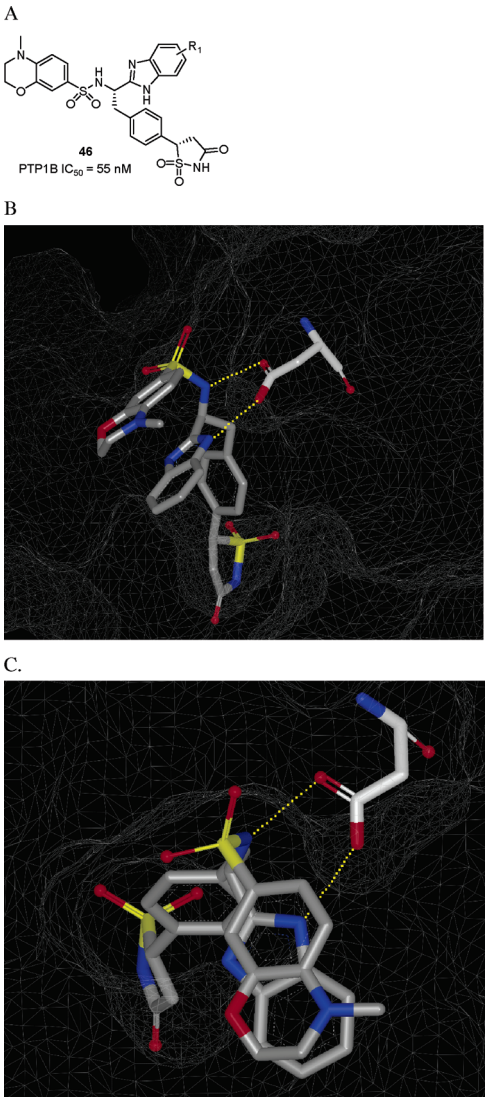


Figure 3. The X-ray cocrystal structure of compound **46**/PTP1B at 1.8 Å resolution. (A) Structure of compound **46**; (B) bidentate hydrogen bond with Asp48 shown between the benzimidazole and sulfonamide NHs; (C) top view showing the intramolecular pi-stacking of the ligands' arylsulfonamide and benzimidazole groups.

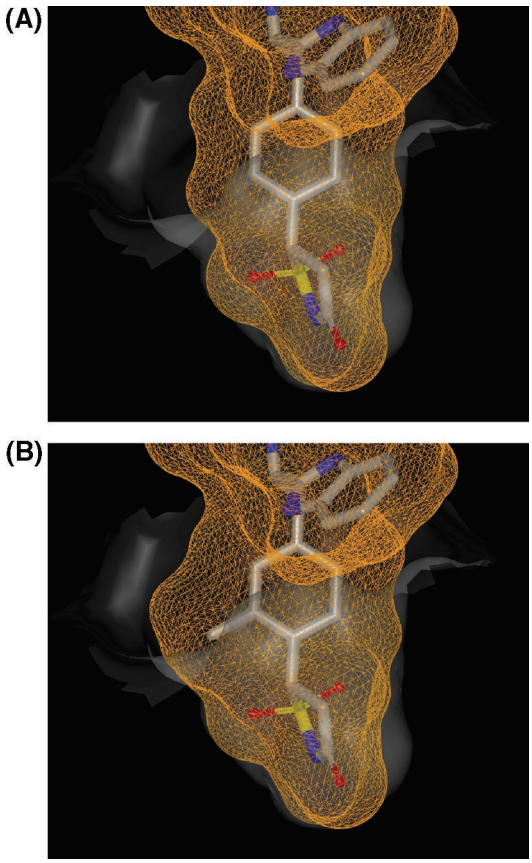
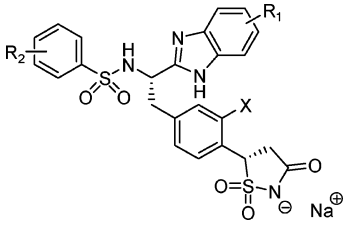


Figure 4. Modeling of *ortho*-methyl (*S*)-IZD. (A) Molecular surface of **46** (orange mesh) shown with the molecular surface of the phosphotyrosine binding site of PTP1B (transparent gray), illustrating the complementarity of the ligand in the enzyme active site. (B) Molecular surface of a model of *ortho*-methyl derivative **79a** with the unchanged enzyme surface showing that *ortho*-methyl occupies the entire available volume of the D-site, a small preformed pocket adjacent to the catalytic site of PTP1B.

benzimidazole in the E-site, but revealed an unexpected conformation for the arylsulfonamide (Figure 3). One observes a 180° rotation of the sulfonamide apparently driven by the intramolecular pi-stacking of the aryl ring of the sulfonamide and benzimidazole while maintaining the H bond to Asp48. The X-ray structure indicates that the aryl of the sulfonamide does not bind with the protein in any site but extends into the solvent with only intramolecular interactions. The failure to significantly improve the binding of these ligands by substitution on the arylsulfonamide is consistent with the observed binding mode in the solid state because the aryl ring does not interact with the protein, although the observed high affinity of these benzimidazole sulfonamide derivatives attests to the strength of this intramolecular interaction. This unique conformation of the ligand has been observed in all X-ray cocrystal structures of benzimidazole sulfonamide inhibitors solved to date. A detailed analysis of these cocrystal structures will be reported elsewhere.

Further optimization of the benzimidazolesulfonamide lead focused on substitutions ortho to the (*S*)-IZD heterocyclic pTyr mimetic on the aryl ring. Substituting ortho to pTyr mimetics has been shown to be an effective strategy for significantly improving the binding (5−20-fold) of nearly all PTP1B inhibitor chemotypes by binding into the relatively small D-site imbedded deep into the protein adjacent to the catalytic site. Thus, a series of ortho substituents to the (*S*)-IZD, including halo and alkyl groups, was targeted. The synthesis of each different ortho substituted scaffold required the development of a unique synthesis of 14−18 linear steps. The significant synthetic effort was rewarded with the identification of the most potent enzyme inhibitors of this series, and the first compounds to show cellular activites. The *ortho*-F derivatives **67** were the most potent, giving 2−4-fold increases in enzyme potency compared to that of the unsubstituted parent, whereas the *ortho*-chloro **87** and *ortho*-methyl **79** congeners were approximately equipotent (Table 4). The sterically larger *ortho*-Br derivative **93** was much less active. Although it is known that the D-site accommodates halogens and small hydrophobic substituents, it was surprising that the *ortho*-bromo derivative was not active because *ortho*-bromo difluoromethylphosphonate (DFMP) derivatives have been reported to increase potency as much as 20-fold over the unsubstituted DFMP derivatives.[13] One possible explanation is that the steric bulk of the bromide adjacent to the (*S*)-IZD causes the optimal binding conformation of the heterocycle to be of much higher energy, thus resulting in a net loss in binding affinity. For the *ortho*-chloro and *ortho*-methyl derivatives, we propose that this negative interaction with the heterocycle is less severe for these smaller substituents and that they are nearly optimal for filling the available space in the D-site (Figure 4).

Table 4. SAR of *ortho*-Substituted (*S*)-IZD Benzimidazole Sulfonamides



compd	X	R_2	R_1	PTP1B pNPP IC_{50} (nM)[a]	IR phos assay fold shift at 80 μM[b]	caco-2 Pm ($\times 10^{-6}$ cm/s)
14	H	H	H	32	1.0 ± 0.3[c]	0.4
67a	F	H	H	18	1.6 ± 0.6	0.2
67b	F	3-F	H	15	1.1	<0.1
67c	F	3-CF_3	5-Cl	10	2.3	0.3
87	Cl	H	H	50	1.0	<0.1
93	Br	H	H	340[c]	0.7[c]	<0.1[c]
79a	Me	H	H	35	2.8 ± 0.8	0.4
79b[d]	Me	H	H	>10000	1.0	n.t.
79c	Me	3-CF_3, 4-Br	H	16	2.0	<0.1
79d	Me	2-CN	H	18	1.4	<0.1
79e	Me	3-Cl	H	76	1.9	0.2

[a] The pNPP assay. [b] The IRp assay results are given as averages of triplicates taken on the same day. The standard deviations are calculated for compounds **14** and **67a** on the basis of triplicate assays performed on three different days. SD for **79a** was calculated on the basis of 10 different day triplicate runs. [c] The assay result is from a mixture of (*R/S*)-IZD isomers. [d] **79d** is a single diastereomer with (*R*)-IZD heterocycle configuration.

The activity of the *ortho*-fluoro derivative is likely optimal because of its ability to partially fill the D-site while maintaining the optimal conformation of the (*S*)-IZD heteocycle in the catalytic site. The increased activity of the *ortho*-fluoro derivatives compared to that of the *ortho*-chloro and *ortho*-methyl derivatives can also be attributed to their intrinsic ability to hydrogen bond to Lys120 in the D-site. The *ortho*-fluoro derivatives may also pull the density from the pi-cloud of the phenyl ring and, thus, increase the ring-stacking interaction with the Phe182 that caps the ligand in the catalytic site.

Cellular Activity. Cellular activities for our most potent PTP1B inhibitors were assessed using an insulin receptor (IR) phosphorylation assay. We took advantage of the observation that the heterologous overexpression of an IR leads to constitutive autophosphorylation of the receptor in the absence of the ligand[14,15] presumably because of overwhelming endogenous negative regulation by PTP1B. Indeed this was the case. As shown in Figure 5A, the overexpression of IR leads to detectable, constitutive autophosphorylation (lane 1) that is reduced upon the coexpression of PTP1B (lane 2). This assay format proved more robust than the potentiation of ligand stimulated IR phosphorylation, which is a transient phenomenon that is difficult to control during tests of large numbers of compounds in a miniaturized format. As validation of this assay, a specific shRNA that reduces PTP1B protein levels by approximately 50% reverses the suppression of IR phosphorylation levels by PTP1B (compare lanes 1 vs 4 and 2 vs 3). Therefore, in this cellular assay, there is direct and dynamic regulation of IR phosphorylation by PTP1B. Treatment of cells with the nonselective tyrosine phosphatase inhibitor bpV also reverses the effect of PTP1B on pIR levels.

The *ortho*-methyl (*S*)-IZD compound **79a** significantly increased the levels of IR phosphorylation in a dose-dependent manner (up to 4-fold at 400 μM) (Figure 5B). As a control, inactive (*R*)-IZD diastereomer **79b** was tested and found not to affect pIR levels up to 80 μM, providing further confirmation that the observed cellular activity of inhibitor **79a** was mediated through intracellular inhibition of PTP1B. To determine whether the inhibition of PTP1B impacted signaling downstream of IR, a phospho-Akt (Ser473) ELISA was performed using human hepatoma HepG2 cells. The treatment with 80 μM of compound **79a** stimulated Akt phosphorylation by 55% and 217% in the absence or presence of 2 nM insulin compared with that of either DMSO control, demonstrating that inhibition of PTP1B in these cells potentiated insulin signaling.

A comparison of analogous benzimidazole sulfonamides with different ortho substituents showed that *ortho*-fluoro derivatives **67** also exhibited modest cellular activity, whereas unsubstituted **14**, *ortho*-chloro **87**, and *ortho*-bromo **93** derivatives were all inactive. The observed small increases in caco-2 permeability and correlated cellular activities for *ortho*-methyl **79** and *ortho*-fluoro **67** derivatives suggests that hydrophobic shielding of the (*S*)-IZD by the *ortho*-methyl group in particular may play a role in increasing the cell permeability of these (*S*)-IZD-containing PTP1B inhibitors.

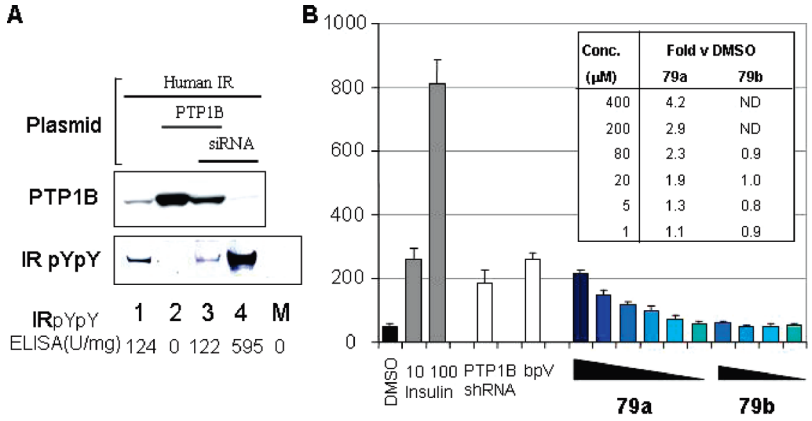


Figure 5. *ortho*-Methyl (*S*)-IZD derivative **79a** enhances cellular insulin receptor phosphorylation. (A) Insulin receptor (IR) phosphorylation assay. The transfection of HEK293 cells with plasmids encoding hIR leads to the autophosphorylation of the receptor on tyrosines 1162 and 1163 (IRpYpY), which can be quantitated by a specific ELISA. Cotransfection of PTP1B increases the PTP1B protein with concomitant down modulation of IRpYpY levels. shRNA against PTP1B suppresses PTP1B protein accumulation and restores IRpYpY levels. (B) Cells treated with compound **79a**, the enzyme active (*S*)-IZD isomer, demonstrate a dose-dependent increase in IRpYpY levels, whereas the enzyme inactive compound **79b** fails to modulate IR phosphorylation. Additional controls include the incubation of cells with 10 μM bpV(pic) or PTP1B shRNA to block PTP1B activity or the protein and two doses of insulin 10 and 100 nM. The inset shows the relative stimulation compared with the DMSO control for compounds **79a** and its (*R*)-IZD diastereomer **79b**.

Conclusion

The structure-based design and synthesis of nonpeptidic ligands of PTP1B led to the identification of potent, cell permeable benzimidazole sulfonamide inhibitors. The X-ray cocrystal structure of benzimidazole sulfonamide **46** revealed an unusual bound conformation that effectively explains the lack of SAR for substitution on either the sulfonamide or benzimidazole aryl rings. An ortho substitution to the (*S*)-IZD heterocyclic pTyr mimetic resulted in the discovery of potent *ortho*-fluoro and *ortho*-methyl enzyme inhibitors, such as **79a**, with cellular activity in an IR phosphorylation assay. These results provide further evidence that nonpeptidic compounds incorporating the (*S*)-IZD heterocyclic pTyr mimetic can be potent, cell permeable inhibitors of phosphatases, such as PTP1B. Further optimization of these nonpeptidic ligands to improve their cell permeability and, thus, cellular activity will be necessary to provide PTP1B inhibitors suitable for in vivo proof of principle animal studies in diabetes and obesity.

Experimental Section

Chemistry. All reactions were run under an atmosphere of dry nitrogen. All solvents were used without further purification as acquired from commercial sources. NMR spectra were obtained using a Varian Mercury-300, a Mercury-400, or an Inova-500 spectrometer. The chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as the internal standard. All final products important to SAR and discussed in the text were characterized by ^{1}H NMR, ^{13}C NMR, HRMS, LCMS, and two HPLC methods.

Purifications by flash chromatography were performed on RediSep columns using an Isco CombiFlash SG100c. Preparative LCMS purifications were performed on a Waters FractionLynx system using mass directed fractionation and compound-specific method optimization (*J. Comb. Chem.* **2004**, *6*, 874−883). The LC method utilized a Waters SunFire column (19 × 100 mm, 5 μM particle size), with a water/0.1% TFA and acetonitrile/0.1% TFA gradient at a flow rate of 30 mL/min over a total run time of 5 min.

Benzyl *N*-(*tert*-butoxycarbonyl)-4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)-L-phenylalaninate (5). (4-(2*S*)-3-(benzyloxy)-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropylphenyl)-boronic acid (**3**) (250 mg, 0.63 mmol), 2-*tert*-butyl-5-chloro-1,1-dioxo-1,2-dihydro-1λ^6-isothiazol-3-one (**4**) (330 mg, 1.5 mmol), potassium carbonate (433 mg, 3.13 mmol), and 1,4-dioxane (2 mL) were combined and degassed with nitrogen gas for 10 min before [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (80 mg, 0.10 mmol) was added, and degassing continued for another 10 min. The orange suspension was heated to 80 °C overnight. The mixture was filtered through a plug of silica with 25% ethyl acetate/hexanes, and concentration of the filtrates gave the crude material, which was purified on silica gel to give **5** (230 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65(d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.30 (m, 4H), 7.00 (s, 1H), 5.12 (dd, J = 23.6, 12.0 Hz, 2H), 4.43 (dd, J = 9.2, 6.8 Hz, 1H), 3.20 (dd, J = 14.0, 6.4 Hz, 1H), 3.00 (dd, J = 13.6, 9.2 Hz, 1H), 1.70 (s, 9H), 1.40 (s, 9H). LCMS found for $C_{28}H_{35}N_2O_7S$ $(M + Na)^+$: m/z = 565.0.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]propanoic acid (6). Benzyl *N*-(*tert*-butoxycarbonyl)-4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)-L-phenylalaninate (**5**) (230 mg, 0.42 mmol) and 10% palladium on carbon (115 mg) in ethanol (3 mL) were shaken overnight on a Parr hydrogenation apparatus. LCMS indicated a fully reduced heterocycle, but only half of the benzyl ester was cleaved. The mixture was resubmitted to the same conditions overnight after filtration to remove the catalyst. LCMS indicated complete reaction. Filtration and concentration gave **6** (180 mg, 93%). NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 5.22 (t, J = 9.6 Hz, 1H), 4.35 (m, 1H), 3.40 (m, 1H), 3.15 (dd, J = 17.2, 8.4 Hz, 1H), 3.03 (dd, J = 13.6, 4.4 Hz, 1H), 2.81 (m, 1H), 1.55 (s, 9H), 1.25 (s, 9H). LCMS found for $C_{21}H_{31}N_2O_7S$ $(M + Na)^+$: m/z = 477.0.

(5*S*)-5-4-[(2*S*)-2-Amino-2-(1*H*-benzimidazol-2-yl)ethyl]phenyl-2-*tert*-butylisothiazolidin-3-one 1,1-dioxide Bis(trifluoroacetate) (8). (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]propanoic acid (**6**) (160 mg, 0.35 mmol), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (160 mg, 0.42 mmol), DMF (1.1 mL), and *N*,*N*-diisopropylethylamine (0.30 mL, 1.8 mmol) were premixed for 5 min and then added to 1,2-benzenediamine (**7**) (57 mg, 0.53 mmol) and stirred at room temperature overnight. The preformed ester was yellow in color and, upon addition to the diamine, continued to darken over several minutes. Purification by preparative LCMS and lyophillization gave the diastereomeric mixture (95 mg, 48%). The mixture (60 mg) was treated with Si-dipiperidine (Silicycle, 1 mmol/g) in MeOH (3 mL) for 1 h and filtered. Separation on Chiralcel OD using 60% EtOH/hex and injecting in MeOH gave *tert*-butyl ((1*S*)-2-[(2-aminophenyl)amino]-1-4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]benzyl-2-oxoethyl)carbamate (12 mg, 20%) (Peak2). ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.55 (s, 1H), 7.40 (dd, J = 18.4, 8.0 Hz, 4H), 7.20 (d, J = 7.6 Hz, 1H), 7.00 (m, 2H), 6.90 (d, J = 7.6 Hz, 1H), 6.75 (m, 1H), 5.23 (t, J = 9.6 Hz, 1H), 42.5 (m, 1H), 3.40 (dd, J = 17.6, 10.0 Hz, 1H), 3.18 (dd, J = 17.6, 8.4 Hz, 1H), 3.08 (dd, J = 13.6, 4.8 Hz, 1H), 2.88 (m, 1H), 1.48 (s, 9H), 1.30 (s, 9H). LCMS found for $C_{27}H_{37}N_4O_6S$ $(M + H)^+$: m/z = 545.2. *tert*-Butyl ((1*S*)-2-[(2-aminophenyl)amino]-1-4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]benzyl-2-oxoethyl)carbamate (12 mg, 0.022 mmol) was dissolved in acetic acid (2 mL) and stirred at 40 °C for 2 h. LCMS indicated complete cyclization. Evaporation and Boc removal with TFA at room temperature for 30 min before re-evaporation gave the desired single diastereomer amine **8** as the bis TFA salt (12 mg, 83%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.70 (s, 3H), 7.60 (dd, J = 6.0, 3.2 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.20 (m, 4H), 5.22 (dd, J = 11.4, 8.8 Hz, 1H), 4.83 (m, 1H), 3.42 (dd, J = 14.0, 8.4 Hz, 1H), 3.35 (dd, J = 16.8, 10.0 Hz, 2H), 3.08 (dd, J = 17.2, 8.4 Hz, 1H), 1.52 (s, 9H). LCMS found for $C_{26}H_{29}F_6N_4O_7S$ $(M + H)^+$: m/z = 427.2.

(2*S*)-2-(Acetylamino)-*N*-((1*S*)-1-(1*H*-benzimidazol-2-yl)-2-4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)-3-phenylpropanamide Trifluoroacetate (9). (5*S*)-5-4-[(2*S*)-2-amino-2-(1*H*-benzimidazol-2-yl)ethyl]phenyl-2-*tert*-butylisothiazolidin-3-one 1,1-dioxide bis(trifluoroacetate) (**8**) (10.0 mg, 0.015 mmol) was stirred in DMSO (0.5 mL), and *N*,*N*-diisopropylethylamine (7 μL, 0.04 mmol) was added. In a separate vial, *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (6.1 mg, 0.023 mmol), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (8.7 mg, 0.023 mmol) and *N*,*N*-diisopropylethylamine (13 μL, 0.075 mol) were stirred in NMP (0.5 mL) for 5 min before adding to the above prepared amine solution. The mixture was stirred at room temperature overnight. The mixture was diluted with methanol and purified by preparative LCMS to give (12 mg, 100%) the BocPhe intermediate. LCMS found for $C_{36}H_{43}N_5O_6S$ $(M + H)^+$: m/z = 674.3. This intermediate, *tert*-butyl (1*S*)-2-[((1*S*)-1-(1*H*-benzimidazol-2-yl)-2-4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)amino]-1-benzyl-2-oxoethylcarbamate, (12 mg, 0.018 mmol) was stirred in TFA (1 mL) for 30 min. This amine was stirred in acetonitrile (2 mL) and treated with Si-dipiperidine (Silicycle, 1 mmol/g, 100 mg) for 30 min. Filtration and evaporation gave the free base, which was stirred in dioxane (1 mL) and treated with acetic anhydride (5 μL, 0.05 mmol) for 1 h. Purification by preparative LCMS gave the desired amide (10 mg, 80%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.75 (m, 2H), 7.61 (m, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.06 (m, 2H), 7.04 (m, 3H), 5.48 (dd, J = 8.0, 8.0 Hz, 1H), 5.05 (dd, J = 9.2, 9.2 Hz, 1H), 4.55 (dd, J = 7.2, 7.2 Hz, 1H), 3.47 (m, 2H), 3.19 (m, 2H), 2.96 (dd, J = 7.2, 6.4 Hz, 1H), 2.78 (dd, J = 9.2, 9.2 Hz, 1H), 1.89 (s, 3H), 1.60 (s, 9H). LCMS found for $C_{33}H_{37}N_5O_5S$ $(M + H)^+$: m/z = 616.2.

(2*S*)-2-(Acetylamino)-*N*-((1*S*)-1-(1*H*-benzimidazol-2-yl)-2-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)-3-phenylpropanamide Trifluoroacetate (10). (2*S*)-2-(acetylamino)-*N*-((1*S*)-1-(1*H*-benzimidazol-2-yl)-2-4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)-3-phenylpropanamide trifluoroacetate (**9**) (10 mg, 0.01 mmol) was stirred in acetonitrile (1 mL), and methanesulfonic acid (150 μL) was added. The clear solution was evaporated under a nitrogen stream for 30 min to remove most of the acetonitrile. The solution was diluted with acetonitrile and purified by preparative LCMS to give the desired product as a colorless glass, (6 mg, 60%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.74 (m, 2H), 7.61 (m, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.07 (m, 2H), 7.02 (m, 2H), 7.02 (m, 1H), 5.48 (dd, J = 7.5, 7.5 Hz, 1H), 5.12 (dd, J = 8.6, 8.6 Hz, 1H), 4.56 (dd, J = 7.5, 7.5 Hz, 1H), 3.46 (m, 2H), 3.31 (m, 2H), 2.98 (dd, J = 13.8, 6.9 Hz, 1H), 2.89 (dd, J = 13.7, 8.6 Hz, 1H), 1.89 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6(+TFA)): δ 174.2, 173.8, 170.2, 154.1, 138.3, 138.1, 132.3, 131.0, 130.9, 130.2, 130.2, 129.4, 128.0, 128.0, 115.3, 66.4, 56.3, 50.0, 39.1, 38.4, 38.2, 22.6. HRMS calcd for $C_{29}H_{29}N_5O_5S$ $(M + H)^+$: 560.1889; found, 560.1963.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)acetamide Trifluoroacetate (12).** (5*S*)-5-4-[(2*S*)-2-amino-2-(1*H*-benzimidazol-2-yl)ethyl]phenyl-2-*tert*-butylisothiazolidin-3-one 1,1-dioxide bis(trifluoroacetate) (30 mg, 0.046 mmol) was stirred in *N*,*N*-dimethylformamide (0.5 mL), pyridine (0.5 mL), and acetic anhydride (0.5 mL) for 2 h at room temperature. The reaction was quenched with methanol and purified by preparative LCMS to give the *tert*-butyl intermediate. TFA cleavage of *tert*-butyl in a microwave at 130 °C for 3 min followed by evaporation and preparative LCMS gave the desired product (16 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (d, J = 8.1 Hz, 1H), 7.54 (m, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.20 (m, 2H), 5.31 (dt, J = 7.9, 6.1 Hz, 1H), 5.15 (t, J = 9.0 Hz, 1H), 3.42 (dd, J = 14.1,5.6 Hz, 1H), 3.32 (dd, J = 17.1, 9.8 Hz, 1H), 3.17 (dd, J = 17.0, 8.4 Hz, 1H), 3.14 (dd, J = 14.3, 9.2 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.2, 169.1, 154.5, 138.8, 137.1, 129.3, 128.9, 127.6, 122.1, 114.1, 64.1, 48.5, 38.3, 37.4, 22.3. HRMS calcd for $C_{20}H_{20}N_4O_4S$ $(M + H)^+$: 413.1285; found, 413.1285.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)benzenesulfonamide Trifluoroacetate (14).** (5*S*)-5-4-[(2*S*)-2-amino-2-(1*H*-benzimidazol-2-yl)-ethyl]phenyl-2-*tert*-butylisothiazolidin-3-one 1,1-dioxide bis(trifluoroacetate) (30 mg, 0.04 mmol) was stirred in methylene chloride (3.0 mL), and benzenesulfonyl chloride (16.2 mg, 0.0917 mmol) was added. The resulting solution was stirred for 5 h before evaporation and purification by preparative LCMS to yield the desired product as the trifluoroacetate salt (12 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6 (+TFA)): δ 9.02 (d, J = 5.8 Hz, 1H), 7.74 (m, 2H), 7.52 (d, J = 7.7 Hz, 2H), 7.49 (m, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.23 (dd, J = 9.4, 8.6 Hz, 1H), 4.89 (m, 1H), 3.37 (dd, J = 17.3, 9.9 Hz, 1H), 3.30 (dd, J = 13.9, 6.0 Hz, 1H), 3.23 (dd, J = 17.1, 7.9 Hz, 1H), 3.18 (dd, J = 13.8, 8.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6(+TFA)): δ 168.5, 152.7, 136.5, 138.8, 132.5, 131.5, 129.3, 129.2, 128.9, 127.7, 126.2, 125.5, 114.4, 64.1, 51.7, 38.3, 37.1. HRMS calcd for $C_{24}H_{22}N_4O_5S_2$ $(M + H)^+$: 511.1112; found, 511.1122.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenylethyl)-3-fluorobenzenesulfonamide Trifluoroacetate (16).** (5*S*)-5-4-[(2*S*)-2-amino-2-(1*H*-benzimidazol-2-yl)ethyl]phenyl-2-*tert*-butylisothiazolidin-3-one 1,1-dioxide bis(trifluoroacetate) (45 mg, 0.069 mmol) was stirred in methylene chloride (3.0 mL) with *N*,*N*-diisopropylethylamine (48 μL, 0.27 mmol). 3-Fluorobenzenesulfonyl chloride (27 mg, 0.14 mmol) was added, and the resulting solution was stirred for 5 h before evaporation and purification by preparative LCMS to yield the desired product (14 mg, 32%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.70 (m, 2H), 7.57 (m, 2H), 7.42 (dt, J = 7.9, 1.4 Hz, 1H), 7.37 (dd, J = 8.2, 5.2 Hz, 1H), 7.34 (dt, J = 8.2, 1.9 Hz, 1H), 7.27 (d, 8.1 Hz, 2H), 7.22 (td, J = 7.8, 2.7 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 5.06 (t, J = 8.6 Hz, 1H), 5.01 (dd, J = 8.7, 6.7 Hz, 1H), 3.29 (m, 2H), 3.28 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 170.9, 163.7 (J = 257.3 Hz), 154.3, 142.6, 137.5, 132.7, 132.7, 130.9, 130.8, 130.2, 127.9, 124.0, 121.3, 115.3, 115.1, 66.3, 53.9, 40.1, 39.0. HRMS calcd for $C_{24}H_{21}FN_4O_5S_2$ $(M + H)^+$: 529.1017; found, 529.1014.

2-*tert*-Butyl-5-(2-fluoro-4-methylphenyl)isothiazol-3(2*H*)-one 1,1-dioxide (58). (2-Fluoro-4-methylphenyl)boronic acid (**57**) (19.5 g, 0.127 mol), 2-*tert*-butyl-5-chloro-1,1-dioxo-1,2-dihydro-1λ^6-isothiazol-3-one (**4**) (30.5 g, 0.136 mol), and [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complexed with dichloromethane (1:1) (10.4 g, 12.7 mmol) were dissolved in toluene (500 mL) and treated with triethylamine (53 mL, 0.38 mol). The reaction was degassed and placed under an atmosphere of nitrogen. The reaction was then heated to 90 °C for 18 h. The reaction was diluted with ethyl acetate (500 mL) and washed with 1 N aqueous hydrochloric acid (500 mL). The ethyl acetate was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was filtered through Celite and then silica gel. The crude material was then purified by silica gel chromatography (5−10% ethyl acetate/hexanes) to afford the product as a white solid (24.5 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (t, J = 7.8 Hz, 1H), 7.11−7.03 (m, 2H), 6.86 (d, J = 1.8 Hz, 1H), 2.42 (s, 3H), 1.73 (s, 9H).

2-*tert*-Butyl-5-[4-(dibromomethyl)-2-fluorophenyl]isothiazolidin-3-one 1,1-dioxide (59). 2-*tert*-Butyl-5-(2-fluoro-4-methylphenyl)isothiazol-3(2*H*)-one 1,1-dioxide (**58**) (4.5 g) in ethanol (120 mL) was treated with palladium (900 mg, 8.5 mmol) (10% palladium on carbon) and placed on a Par hydrogenator under a 50 psi atmosphere of hydrogen for 24 h. The reaction solution was filtered though Celite. After concentration, the crude material was purified by silica gel chromatography (3−10% ethyl acetate/hexanes) to afford the product as a white solid (3.6 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.21−7.17 (m, 1H), 7.02−6.96 (m, 2H), 5.04 (dd, J = 9.0, 7.0 Hz, 1H), 3.26 (dd, J = 17.2, 9.0 Hz, 1H), 3.08 (dd, J = 17.2, 7.0 Hz, 1H), 2.37 (s, 3H), 1.66 (s, 9H). 2-*tert*-Butyl-5-(2-fluoro-4-methylphenyl)isothiazolidin-3-one 1,1-dioxide (6.2 g, 21 mmol), *N*-bromosuccinimide (11.0 g, 62 mmol), and benzoyl peroxide (1.2 g, 5.2 mmol) in carbon tetrachloride (100 mL) were heated at reflux for 3.5 h. The solution was filtered to remove the solid, washed with satd. aqueous sodium bicarbonate solution (200 mL), dried over sodium sulfate, and concentrated. Purification by silica gel chromatography (10−30% ethyl acetate/hexanes) afforded the product as a white solid (5.8 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.33 (m, 3H), 6.59 (s, 1H), 5.07 (dd, J = 8.8, 7.2 Hz, 1H), 3.31 (dd, J = 17.2, 8.8 Hz, 1H), 3.12 (dd, J = 17.1, 7.2 Hz, 1H), 1.65 (s, 9H). LCMS found for $C_{14}H_{17}Br_2FNNaO_3S$ $(M + Na)^+$: m/z = 480.

4-(2-*tert*-Butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-fluorobenzaldehyde (60). 2-*tert*-Butyl-5-[4-(dibromomethyl)-2-fluorophenyl]isothiazolidin-3-one 1,1-dioxide (**59**) (4.2 g, 9.2 mmol) and silver nitrate (3.12 g, 18.4 mmol) in ethanol (200 mL) and water (50 mL) were heated at reflux for 0.5 h. The solution was cooled to room temperature, filtered to remove the precipitate, and concentrated to remove most of the ethanol. The residue was diluted with ethyl acetate (200 mL). The organic layer was washed with water (200 mL) and then dried over sodium sulfate. Concentration in vacuo followed by purification by silica gel chromatography (30% ethyl acetate/hexanes) afforded the product as a white solid (2.4 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (d, J = 2.0 Hz, 1H), 7.78−7.75 (m, 1H), 7.70−7.65 (m, 1H), 7.56−7.52 (m, 1H), 5.13 (dd, J = 8.9, 6.6 Hz, 1H), 3.35 (dd, J = 17.2, 8.9 Hz, 1H), 3.15 (dd, J = 17.2, 6.6 Hz, 1H), 1.66 (s, 9H). LCMS found for $C_{14}H_{17}FNNaO_4S$ $(M + Na)^+$: m/z = 336.

Methyl (2*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-fluorophenyl]acrylate (62). Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (**61**) (3.53 g, 11.9 mmol) in methylene chloride (180 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (1.92 mL, 12.9 mmol). After five minutes, 4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-fluorobenzaldehyde (**60**) (3.1 g, 9.9 mmol) was

added and the solution stirred at room temperature for 1 h. The solution was diluted with methylene chloride (50 mL), washed with 1 N aqueous hydrochloric acid solution (250 mL), and the organic phase dried over sodium sulfate. Purification by silica gel chromatography (5−25% ethyl acetate/hexanes) afforded the product as a white foam (3.7 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.29 (m, 3H), 7.17 (s, 1H), 5.04 (dd, J = 9.0, 7.1 Hz, 1H), 3.87 (s, 3H), 3.29 (dd, J = 17.2, 9.0 Hz, 1H), 3.17 (dd, J = 17.2, 7.0 Hz, 1H), 1.65 (s, 9H), 1.39 (s, 9H). LCMS found for $C_{22}H_{30}FN_2NaO_7S$ $(M + Na)^+$: m/z = 507.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-fluorophenyl}-propanoate (63). Methyl (2*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-fluorophenyl]acrylate (**62**) (1.24 g, 2.56 mmol) in ethanol (100 mL) was degassed, and (*R*,*R*)-(−)-1,2-bis[(o-methoxyphenyl)(phenyl)phosphino]ethane(1,5-cyclooctadiene) rhodium (I) tetrafluroborate (58 mg, 0.077 mmol) was added under nitrogen. The solution was placed under a hydrogen atmosphere (50 psi) and shaken for 16 h. The solution was concentrated in vacuo and purified by silica gel chromatography (10−40% ethyl acetate/hexanes) to afford the product as a white foam (1.14 g, 92%). The crude residue was purified by normal phase chiral HPLC (ChiralCel OD-H [20 × 250 mm, 5 μm], 30% EtOH/70% hexanes, 15 mL/min, 30 °C) to yield isomer 1 (peak 1) (531 mg, active isomer) and isomer 2 (peak 2) (493 mg, inactive isomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.27 (m, 1H), 7.03−6.95 (m, 2H), 5.06−5.02 (m, 2H), 4.61−4.57 (brs, 1H), 3.73 (s, 3H), 3.31−3.27 (m, 1H), 3.15−3.06 (m, 3H), 1.66 (s, 9H), 1.42 (s, 9H). LCMS found for $C_{22}H_{32}FN_2NaO_7S$ $(M + Na)^+$: m/z = 509.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-fluorophenyl}propanoic Acid (64). Methyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-{4-[(5*S*)-2-*tert*-butyl-1,1-dioxido-3-oxo-isothiazolidin-5-yl]-3-fluorophenyl}propanoate (**63**) (1.10 g, 2.26 mmol) in trifluoroacetic acid (10 mL) was heated for 2 min at 130 °C in the microwave. The solution was concentrated in vacuo and purified by preparative LCMS to afford the product as a white solid (614 mg, 61%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.53 (m, 1H), 7.18−7.14 (m, 2H), 5.33−5.30 (m, 1H), 4.39 (m, 1H), 3.82 (s, 3H), 3.43−3.12 (m, 4H). LCMS found for $C_{13}H_{16}FN_2O_5S$ $(M + H)^+$: m/z = 331. Methyl (2*S*)-2-amino-3-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-fluorophenyl}-propanoate trifluoroacetate (558 mg, 1.26 mmol) in methylene chloride (50 mL) was treated with di-*tert*-butyl dicarbonate (548 mg, 2.51 mmol) and triethylamine (0.88 mL, 6.3 mmol). The solution was stirred at room temperature for 2 h. The solution was concentrated in vacuo, diluted with methanol (8 mL), and then treated with 2 M lithium hydroxide in water (1.5 mL). After 2 h, the solution was acidified using a 1 N aqueous hydrochloric acid solution (2 mL), and the solution was directly purified by preparative LCMS to afford the product as a white solid (507 mg, 97%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.47−7.42 (m, 1H), 7.18−7.11 (m, 2H), 5.39−5.35 (m, 1H), 4.39−4.35 (m, 1H), 3.35−3.28 (m, 2H), 3.25−3.20 (m, 1H), 2.97−2.91 (m, 1H), 1.35 (s, 9H). LCMS found for $C_{17}H_{22}FN_2NaO_7S$ $(M + Na)^+$: m/z = 439.

***tert*-Butyl (1*S*)-1-(1*H*-benzimidazol-2-yl)-2-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-fluorophenyl}ethylcarbamate Trifluoroacetate (65).** (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-fluorophenyl}propanoic acid (**64**) (402 mg, 0.965 mmol) in DMF (30 mL) was treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (512 mg, 1.16 mmol). After 5 min at room temperature, *N*,*N*-diisopropylethylamine (0.50 mL, 2.9 mmol) and 1,2-benzenediamine (**7**) (156 mg, 1.45 mmol) were added and the solution stirred for 2 h. The solution was concentrated in vacuo and the residue dissolved in acetic acid (5 mL) and heated at 40 °C for 2 h. The acetic acid was removed in vacuo, and the residue was purified by preparative LCMS to afford the product as a white solid (373 mg, 64%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.75−7.71 (m, 2H), 7.59−7.56 (m, 2H), 7.47−7.43 (m, 1H), 7.15−7.09 (m, 2H), 5.43−5.39 (m, 2H), 3.44−3.21 (m, 4H), 1.42 (s, 9H). LCMS found for $C_{23}H_{26}FN_4O_5S$ $(M + H)^+$: m/z = 489.

***N*-{(1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-fluorophenyl]ethyl}benzenesulfonamide Trifluoroacetate (67a).** *tert*-Butyl {(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-[4-(1,1-dioxido-3-oxoisthiazolidin-5-yl)-3-fluorophenyl]-ethyl}carbamate trifluoroacetate (12.4 mg, 2.06 μmol) in methylene chloride (1 mL) was treated with trifluoroacetic acid (0.5 mL). The solution stirred at room temperature for 1 h and was then concentrated in vacuo. The residue was dissolved in methanol (1 mL) and treated with triethylamine (20 μL, 14.4 μmol) and benzensulfonyl chloride (10.5 μL, 8.2 μmol). The solution was stirred 4 h at room temperature and then purified by preparative HPLC to afford the product as a white solid (7.5 mg, 57%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.07 (d, J = 5.9 Hz, 1H), 7.78 (m, 2H), 7.53 (m, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.35 (m, 1H), 7.33 (m, 2H), 7.04 (d, J = 11.3 Hz, 1H), 6.99 (dd, J = 8.1, 1.6 Hz, 1H), 5.38 (t, J = 8.5 Hz, 1H), 4.96 (m, 1H), 3.36 (dd, J = 8.5, 2.1 Hz, 2H), 3.31 (dd, J = 13.6, 4.4 Hz, 1H), 3.16 (dd, J = 13.9, 9.9 Hz, 1H). ^{13}C NMR (125 MHz, d_6-DMSO, 30 °C): δ 168.7, 160.2, 152.7, 139.2, 138.6, 132.6, 131.0, 130.2, 128.9, 126.1, 125.8, 125.4, 116.3, 115.7, 114.3, 57.9, 51.4, 37.5, 36.3. HRMS calcd for $C_{24}H_{22}FN_4O_5S_2$ $(M + H)^+$: 529.1025; found, 529.0981.

***N*-(1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-fluorophenyl}ethyl-3-fluorobenzenesulfonamide Trifluoroacetate (67b).** 5-4-[(2*S*)-2-Amino-2-(1*H*-benzimidazol-2-yl)ethyl]-2-fluorophenylisothiazolidin-3-one 1,1-dioxide bis(trifluoroacetate) (12 mg, 0.019 mmol) in methylene chloride (2 mL) was treated with triethylamine (16 μL, 0.12 mmol) and 3-fluorobenzenesulfonyl chloride (10 μL, 0.078 mmol). After 3 h at room temperature, the solution was purified by preparative LCMS to afford the product as a white solid (9.2 mg, 72%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.20 (d, J = 6.3 Hz, 1H), 7.78 (dd, J = 6.9, 3.4 Hz, 2H), 7.53 (dd, J = 6.1, 2.1 Hz, 2H), 7.38 (m, 1H), 7.37 (m, 1H), 7.34 (m, 1H), 7.33 (m, 1H), 7.30 (m, 1H), 7.10 (d, J = 11.2 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 5.40 (t, J = 7.8 Hz, 1H), 5.04 (m, 1H), 3.38 (m, 2H), 3.36 (m, 1H), 3.16 (dd, J = 13.6, 9.5 Hz, 1H). ^{13}C NMR (125 MHz, d_6-DMSO, 30 °C): δ 168.6, 161.2, 160.1, 150.2, 140.9, 139.4, 131.5, 131.3, 130.1, 125.6, 125.5, 122.3, 119.7, 116.5, 115.7, 114.4, 113.4, 57.9, 51.8, 37.8, 36.3. HRMS calcd for $C_{24}H_{21}F_2N_4O_5S_2$ $(M + H)^+$: 547.0931; found, 547.0941.

5-{4-[(2*S*)-2-(5-Chloro-1*H*-benzimidazol-2-yl)-2({[3-(trifluoromethyl)phenyl]sulfonyl}amino)ethyl]-2-fluorophenyl}-3-oxoisothiazolidin-2-ide 1,1-dioxide Trifluoroacetate (67c). *tert*-Butyl {(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-[4-(1,1-dioxido-3-oxoisthiazolidin-5-yl)-3-fluorophenyl]-ethyl}carbamate trifluoroacetate (236 mg, 0.370 mmol) in methylene chloride (15 mL) was treated with trifluoroacetic acid (5 mL). The solution was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was dissolved in methanol (8 mL) and treated with triethylamine (0.51 mL, 3.70 mmol) and *m*-trifluoromethyl benzenesulfonyl chloride (0.36 mL, 2.2 mmol). The solution was stirred 4 h at room temperature and then purified by preparative HPLC to afford the product as a white solid (131 mg, 54%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.53 (dd, J = 8.8, 2.0 Hz, 1H), 7.52 (dd, J = 7.5, 7.5 Hz, 1H), 7.31 (dd, J = 7.8, 7.8 Hz, 1H), 6.96 (dd, J = 11.0, 1.5 Hz, 1H), 5.28 (dd, J = 8.1, 8.1 Hz, 1H), 5.13 (dd, J = 7.6, 5.7 Hz, 1H), 3.35 (m, 1H), 3.33 (m, 1H), 3.27 (m, 1H), 3.26 (m, 1H). ^{13}C NMR (125 MHz, d_6-DMSO, 30 °C): δ 170.5, 162.5, 155.1, 142.1, 140.5 134.0, 133.0, 132.0, 131.9, 131.7, 131.4, 131.4, 130.7, 128.3, 126.8, 124.7, 124.6, 118.0, 117.6, 116.7, 115.3, 59.9, 53.3, 39.5, 38.0. HRMS calcd for $C_{24}H_{22}FN_4O_5S_2$ $(M + H)^+$: 631.0508; found, 631.0633.

4-Bromo-3-methylbenzaldehyde (69). A solution of methyl 4-bromo-3-methylbenzoate (**68**) (50.0 g, 218 mmol), lithium tetrahydroborate (5.70 g, 262 mmol), and tetrahydrofuran (500 mL) was stirred at 25 °C for 2 days. The reaction was cooled to 0 °C,

quenched with saturated NH_4Cl solution, and diluted with ethyl acetate. The aqueous layers were extracted with ethyl acetate three times, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the desired product (36.0 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 1.3 Hz, 1H), 7.02 (m, 1H), 4.59 (s, 2H), 2.39 (s, 3H). LCMS found for $C_8H_{10}BrO$ (M + H-H_2O)$^+$: m/z = 183, 185. To a solution of dimethyl sulfoxide (21.2 mL, 0.298 mol) in methylene chloride (150 mL) was added oxalyl chloride (5.0 mL, 0.060 mol) at −78 °C under an atmosphere of nitrogen. The resulting mixture was stirred at the same temperature for 20 min. A solution of (4-bromo-3-methylphenyl)methanol (6.0 g, 30 mmol) in methylene chloride (50 mL) was cannulated into the reaction flask. After stirring for 1.0 h, triethylamine (21 mL, 0.15 mol) was added. The reaction mixture was stirred at −78 °C for 1 h and warmed to room temperature for 1 h. The reaction was quenched with 1 N HCl solution, and the aqueous phase was separated and extracted once with methylene chloride. The combined organic solutions were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the desired product (5.7 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.73 (m, 1H), 7.71 (s, 1H), 7.55 (m, 1H), 2.49 (s, 3H).

Methyl (2*Z*)-2-[(benzyloxy)carbonyl]amino-3-(4-bromo-3-methylphenyl)acrylate (71). To a solution of *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester (**70**) (10.0 g, 30.2 mmol) in methylene chloride (200 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (4.96 mL, 33.2 mmol) at room temperature under an atmosphere of nitrogen. After stirring for 10 min, a solution of 4-bromo-3-methylbenzaldehyde (6.01 g, 30.2 mmol) in methylene chloride (50 mL) was cannulated into the reaction solution. The resulting solution was stirred at room temperature for 1.5 h. The reaction was diluted with ethyl acetate and quenched with 1.0 N HCl solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic solutions were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the desired product (10.4 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.5 Hz, 1H), 7.3 (m, 7H), 7.17 (m, 1H), 5.11 (s, 2H), 3.82 (s, 3H), 2.33 (s, 3H). LCMS found for $C_{19}H_{18}BrNO_4Na$ (M + Na)$^+$: m/z = 426.

Methyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-(4-bromo-3-methylphenyl)propanoate (72). A solution of methyl-2-[(benzyloxy)carbonyl]amino-3-(4-bromo-3-methylphenyl)acrylate (**71**) (10.4 g, 25.7 mmol) in ethanol (200 mL) was degassed with nitrogen. (*R*,*R*)-(−)-1,2-Bis[(*o*-methoxyphenyl)(phenyl)phosphino]ethane(1,5-cyclooctadiene) rhodium (I) tetrafluroborate (194 mg, 257 μmol) was added under nitrogen. The reaction was placed under a hydrogen atmosphere (50 psi) and shaken for 24 h. The solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography to yield the desired product (8.7 g, 83%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.40 (d, J = 8.2 Hz, 1H), 7.33−7.25 (m, 5H), 7.13 (s, 1H), 6.91 (dd, J = 8.2, 1.9 Hz, 1H), 5.00 (m, 2 H), 4.42 (dd, J = 9.6, 5.3 Hz, 1H), 3.70 (s, 3H), 3.09 (dd, J = 13.9, 5.3 Hz, 1H), 2.84 (dd, J = 13.9, 9.8 Hz, 1H), 2.32 (s, 3H). LCMS found for $C_{19}H_{20}BrNO_4Na$ (M + Na)$^+$: m/z = 428.

[4-((2*S*)-2-[(Benzyloxy)carbonyl]amino-3-methoxy-3-oxopropyl)-2-methylphenyl]boronic Acid (73). To a mixture of methyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-(4-bromo-3-methylphenyl)-propanoate (**72**) (1.23 g, 3.03 mmol), 1,4-dioxane (8 mL), triethylamine (1.7 mL, 12 mmol), palladium acetate (17 mg, 0.076 mmol), and *O*-(dicyclohexylphosphino)biphenyl (106 mg, 0.303 mmol) was added dropwise 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.10 mL, 7.57 mmol). The greenish reaction mixture was stirred at 80 °C for 30 min. The reaction was quenched with saturated NH_4Cl solution. The aqueous solution was extracted twice with ethyl acetate. The organic solutions were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the desired product (1.25 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 1H), 7.37−7.25 (m, 5H), 6.90 (m, 2H), 5.22 (d, J = 8.4 Hz, 1H), 5.10 (m, 2H), 4.64 (m, 1H), 3.70 (s, 3H), 3.06 (m, 2H), 2.48 (s, 3H), 1.33 (s, 12H). LCMS found for $C_{25}H_{33}BNO_6$ (M + H)$^+$: m/z = 454. A solution of methyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanoate (6.90 g, 15.2 mmol), sodium periodate (16.3 g, 76.1 mmol), THF (150 mL), ammonium acetate (4.69 g, 60.9 mmol), and water (150 mL) was stirred at 25 °C for 24 h. The reaction was diluted with ethyl acetate and 1 N HCl solution. The aqueous solution was extracted once with ethyl acetate. The combine organic solutions were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude residue was crystallized in ethyl acetate to yield the desired product (5.65 g, 80%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.3 (m, 5H), 7.16 (d, J = 7.5 Hz, 1H), 7.0 (m, 2H), 5.02 (m, 2H), 4.42 (dd, J = 9.4, 5.3 Hz, 1H), 3.68 (s, 3H), 3.10 (dd, J = 13.8, 5.3 Hz, 1H), 2.88 (dd, J = 13.6, 9.4 Hz, 1H), 2.28 (s, 3H). LCMS found for $C_{19}H_{23}BNO_6$ (M + H)$^+$: m/z = 372.

Methyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)-3-methylphenyl]-propanoate (74). A solution of 2-*tert*-butyl-5-chloro-1,1-dioxo-1,2-dihydro-1λ^6-isothiazol-3-one (**4**) (1.86 g, 8.30 mmol), [4-((2*S*)-2-[(benzyloxy)carbonyl]amino-3-methoxy-3-oxopropyl)-2-methylphenyl]boronic acid (**73**) (2.80 g, 7.54 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (924 mg, 1.13 mmol), potassium carbonate (5.21 g, 37.7 mmol), and 1,4-dioxane (38 mL) was degassed with nitrogen and stirred at 80 °C for 24 h. The reaction was diluted with water and extracted three times with ethyl acetate, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the desired product (2.4 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 1H), 7.35 (m, 5H), 7.03 (m, 2H), 6.46 (s, 1H), 5.27 (d, J = 8.0 Hz, 1H), 5.11 (m, 2H), 4.67 (m, 1H), 3.74 (s, 3H), 3.14 (dd, J = 11.9, 5.9 Hz, 1H), 3.07 (dd, J = 11.9, 6.1 Hz, 1H), 2.36 (s, 3 H), 1.73 (s, 9 H). LCMS found for $C_{26}H_{31}N_2O_7S$ (M + H)$^+$: m/z = 515.

Methyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]propanoate (75). To a solution of methyl (2*S*)-2-[(benzyloxy)carbonyl]-amino-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)-3-methylphenyl]propanoate (**74**) (570 mg, 1.11 mmol) in THF (11 mL) was added 1 M l-selectride in THF (2.1 mL) at −78 °C. After stirring for 10 min, the reaction was quenched with acetic acid (1.0 mL) and diluted with water. The aqueous phase was separated and extracted three times with ethyl acetate. The combined organic solutions were dried with sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography to yield the desired product (501 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.31 (m, 5H), 7.20 (dd, J = 8.0, 3.1 Hz, 2H), 7.00 (m, 2H), 5.21 (d, J = 8.6 Hz, 1H), 5.10 (m, 2H), 5.04 (t, J = 8.3 Hz, 1H), 4.65 (m, 1H), 3.72 (s, 3H), 3.23 (dd, J = 17.0, 8.4 Hz, 1H), 3.1 (m, 3H), 2.43 (s, 3H), 1.65 (s, 9H). LCMS found for $C_{26}H_{33}N_2O_7S$ (M + H)$^+$: m/z = 517.

(2*S*)-2-[(Benzyloxy)carbonyl]amino-3-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]propanoic Acid (76). A solution of methyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]propanoate (**75**) (450 mg, 0.871 mmol) in trifluoroacetic acid (3 mL) was heated in a microwave reactor at 130 °C for 5 min, and the solvent was removed in vacuo. The residue was purified with preparative LCMS to give the desired product (210 mg, 74%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (dd, J = 7.6, 6.0 Hz, 1H), 7.23−7.17 (m, 2H), 5.47 (t, J = 8.1 Hz, 1H), 4.34 (m, 1H), 3.81 (s, 3H), 3.37−3.30 (m, 2H), 3.25 (d, J = 5.9 Hz, 1H), 3.13 (dd, J = 14.4, 7.8 Hz, 1H), 2.49 (s, 3H). LCMS found for $C_{14}H_{20}N_2O_5S$ (M + H)$^+$: m/z = 327. Methyl (2*S*)-2-amino-3-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]propanoate trifluoroacetate (286 mg, 0.649 mmol) in methanol (7 mL) was treated with triethylamine (362 μL, 2.60 mmol) and cooled to 0 °C. Benzyl

chloroformate (116 μL, 0.812 mmol) was added and the solution stirred for 2 h. Lithium hydroxide (4.0 M) in water (0.81 mL) was added and the solution stirred for additional 1 h. The reaction soluiton was acidified with 1 N HCl and extracted with ethyl acetate. The crude product was used in the next step without purification. LCMS found for $C_{21}H_{23}N_2O_7S$ $(M + H)^+$: $m/z = 447$.

Benzyl (1*S*)-1-(1*H*-benzimidazol-2-yl)-2-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]ethylcarbamate (77). A solution of (2*S*)-2-[(benzyloxy)carbonyl]amino-3-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]propanoic acid (**76**) (200 mg, 0.448 mmol) in DMF (2 mL) was treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.218 g, 0.493 mmol). After stirring for 10 min at 0 °C, a solution of 1,2-benzenediamine (**7**) (72.7 mg, 0.672 mmol) and *N*,*N*-diisopropylethylamine (0.39 mL, 2.24 mmol) in DMF (1 mL) was cannulated into the reaction flask. The solution was stirred at 25 °C for 2 h. The solution was diluted with ethyl acetate and washed with satd. aqueous sodium bicarbonate solution and 1.0 N hydrochloric acid solution. The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by preparative LCMS to yield the desired product (196 mg, 82%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.47 (d, $J = 8.0$ Hz, 0.5H), 7.39−7.22 (m, 9H), 7.12 (d, $J = 7.8$ Hz, 0.5H), 7.07 (s, 1H), 6.82 (d, $J = 7.6$ Hz, 0.5H), 6.71 (d, $J = 7.4$ Hz, 0.5H), 5.50 (t, $J = 8.2$ Hz, 1H), 5.10 (s, 2H), 4.47 (m, 1H), 3.3 (m, 2H), 3.07 (m, 2H), 2.48 (s, 1.5H), 2.38 (s, 1.5H). LCMS found for $C_{27}H_{29}N_4O_6S$ $(M + H)^+$: $m/z = 537$. A solution of benzyl (1*S*)-2-[(2-aminophenyl)amino]-1-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylbenzyl]-2-oxoethylcarbamate trifluoroacetate (1.20 g, 1.84 mmol) and acetic acid (40 mL) was stirred at 40 °C for 2 h. The solvent was removed in vacuo. The crude product was used in the next step without purification. LCMS found for $C_{27}H_{27}N_4O_5S$ $(M + H)^+$: $m/z = 519$.

Benzyl [(1*S*)-2-[4-((5*S*)-1,1-dioxido-3-oxo-2-{[2-(trimethylsilyl)-ethoxy]methyl}isothiazolidin-5-yl)-3-methylphenyl]-1-(1-{[2-(trimethylsilyl)propoxy]methyl}-1*H*-benzimidazol-2-yl)ethyl]carbamate (78). A solution of benzyl (1*S*)-1-(1*H*-benzimidazol-2-yl)-2-[4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)-3-methylphenyl]-ethylcarbamate acetate (**77**) (956 mg, 1.65 mmol), 2-trimethylsilyl)-ethoxy methyl chloride (0.73 mL, 4.1 mmol), *N*,*N*-diisopropyl-ethylamine (1.73 mL, 9.91 mmol), and methylene chloride (30 mL) was stirred at 25 °C for 3 h. The reaction was diluted with 1 N HCl solution and extracted three times with ethyl acetate, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by normal phase chiral HPLC (ChiralCel OD-H (20 × 250 mm, 5 μm), 30% EtOH/70% hexanes, 15 mL/min, 30 °C) to yield **78** (390 mg, 30%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (m, 1H), 7.64 (m, 1H), 7.42−7.30 (m, 9H), 7.16 (s, 1H), 5.64 (d, $J = 11.5$ Hz, 1H), 5.52−5.45 (m, 3H), 5.17−5.00 (m, 4H), 3.76 (t, $J = 8.2$ Hz, 2H), 3.58−3.37 (m, 6H), 2.42 (s, 3H), 1.02 (t, $J = 8.0$ Hz, 2H), 0.96−0.86 (m, 2H), 0.11 (s, 9H), 0.00 (s, 9H). LCMS found for $C_{39}H_{55}N_4O_7SSi_2$ $(M + H)^+$: $m/z = 779$.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-methylphenyl}ethyl)benzenesulfonamide (79a).** A solution of benzyl [(1*S*)-2-[4-((5*S*)-1,1-dioxido-3-oxo-2-{[2-(trimethylsilyl)ethoxy]methyl}isothiazolidin-5-yl)-3-methylphenyl]-1-(1-{[2-(trimethylsilyl)propoxy]methyl}-1*H*-benzimidazol-2-yl)ethyl]carbamate (**78**) (50.0 mg, 64.2 μmol), methanol (3.5 mL), and 10% palladium on carbon (15 mg, 14 μmol) was degassed and placed under a hydrogen balloon at 25 °C for 1.5 h. The reaction was diluted with methanol, filtered through Celite, and concentrated in vacuo. The crude product (28.0 mg, 34.7 μmol), methylene chloride (1.7 mL), *N*,*N*-diisopropylethylamine (30 μL, 0.17 mmol), and benzenesulfonyl chloride (**66**) (8.9 μL, 70 μmol) were stirred at 25 °C for 5 h. The reaction was concentrated and treated with trifluoroacetic acid (1.3 mL). The reaction was heated at 130 °C for 2 min in the microwave. The reaction was concentrated and purified by preparative LCMS to yield desired product **79a** (6.5 mg, 29%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.69 (m, 2H), 7.63 (d, $J = 7.6$ Hz, 2H), 7.53 (m, 2H), 7.50 (tt, $J = 7.4$, 1.2 Hz, 1H), 7.39 (t, $J = 7.7$ Hz, 2H), 7.27 (d, $J = 8.1$ Hz, 1H), 7.00 (d, $J = 7.7$ Hz, 1H), 6.82 (s, 1H), 5.38 (t, $J = 8.4$ Hz, 1H), 4.91 (t, $J = 7.9$ Hz, 1H), 3.27 (m, 2H), 3.22 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 170.9, 155.0, 140.9, 140.6, 137.5, 134.2, 132.8, 132.5, 130.3, 129.4, 129.2, 128.4, 128.0, 127.4, 115.4, 62.9, 53.9, 40.5, 40.0, 19.9; HRMS calculated for $C_{25}H_{25}N_4O_5S_2$ $(M + H)^+$: $m/z = 525.1245$.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{4-[(5*R*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-methylphenyl}ethyl)benzenesulfonamide (79b).** The title compound was prepared using a procedure similar to that used to prepare **79a** using a single enantiomer with (*R*)-IZD of **78**. ^{1}H NMR (500 MHz, CD_3OD): δ 7.68 (m, 2H), 7.64 (dt, $J = 7.2$, 1.4 Hz, 2H), 7.53 (m, 2H), 7.50 (tt, $J = 7.5$, 1.2 Hz, 1H), 7.37 (tt, $J = 7.5$, 1.2 Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 1H), 6.93 (d, $J = 1.4$ Hz, 1H), 6.86 (dd, $J = 8.0$, 1.6 Hz, 1H), 5.32 (t, $J = 8.1$ Hz, 1H), 4.90 (dd, $J = 8.4$, 7.2 Hz, 1H), 3.26 (dd, $J = 11.6$, 8.1, 2H), 3.21 (t, $J = 7.2$ Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 172.3, 154.7, 140.6, 140.4, 137.2, 134.5, 133.3, 132.6, 130.4, 129.7, 129.3, 128.3, 128.1, 127.6, 115.4, 62.6, 54.1, 40.4, 39.5, 20.2; HRMS calculated for $C_{25}H_{24}N_4O_5S_2Na$ $(M + Na)^+$: 547.1075; found, 547.1075.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-methylphenyl}ethyl)-4-bromo-3-(trifluoromethyl)benzenesulfonamide (79c).** Compound **79c** was prepared using a procedure similar to that used to prepare compound **79a**. ^{1}H NMR (500 MHz, CD_3OD, 30 °C): δ 7.97 (d, $J = 2.3$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.70 (m, 2H), 7.60 (dd, $J = 8.5$, 2.3 Hz, 1H), 7.57 (m, 2H), 7.29 (d, $J = 8.1$ Hz, 1H), 7.08 (dd, $J = 8.0$, 1.3 Hz, 1H), 6.93 (d, $J = 1.3$ Hz, 1H), 5.38 (t, $J = 8.1$ Hz, 1H), 5.05 (dd, $J = 8.6$, 7.4 Hz, 1H), 3.33 (m, 2H), 3.28 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD, 30 °C): δ 170.9, 153.9, 141.1, 140.6, 137.7, 132.8, 132.7, 132.5, 131.8, 129.4, 129.1, 128.5, 128.0, 127.4, 123.7, 120.3, 115.3, 115.2, 62.6, 53.8, 40.0, 38.9, 20.2; HRMS calculated for $C_{26}H_{23}BrF_3N_4O_5S_2$ $(M + H)^+$: 671.0245; found, 671.0218.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-methylphenyl}ethyl)-2-cyanobenzenesulfonamide (79d).** Compound **79d** was prepared using a procedure similar to that used to prepare compound **79a**. ^{1}H NMR (500 MHz, CD_3OD, 30 °C): δ 7.90 (d, $J = 7.9$ Hz, 1H), 7.80 (m, 2H), 7.69 (d, $J = 7.4$ Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 1H), 7.62 (d, $J = 7.4$ Hz, 1H), 7.61 (m, 2H), 7.25 (d, $J = 7.9$ Hz, 1H), 7.08 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.01 (d, $J = 1.1$ Hz, 1H), 5.39 (t, $J = 8.5$ Hz, 1H), 5.18 (dd, $J = 10.2$, 4.5 Hz, 1H), 3.34 (dd, $J = 14.3$, 4.8 Hz, 1H), 3.31 (m, 2H), 3.21 (dd, $J = 14.4$, 10.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD, 30 °C): δ 171.1, 154.7, 142.9, 140.9, 137.6, 137.5, 134.9, 134.7, 133.2, 133.0, 131.2, 130.1, 129.2, 129.0, 128.5, 117.3, 115.8, 111.4, 62.7, 54.3, 40.2, 39.4, 20.8; HRMS calculated for $C_{26}H_{24}N_5O_5S_2$ $(M + H)^+$: 550.1219; found, 550.1194.

***N*-((1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-methylphenyl}ethyl)-3-chlorobenzenesulfonamide (79e).** Compound **79e** was prepared in a manner similar to that used for compound **79a**. ^{1}H NMR (500 MHz, d_6-DMSO +10 μL TFA, 30 °C): δ 9.26 (d, $J = 6.1$ Hz, 1H), 7.80 (m, 2H), 7.56 (m, 2H), 7.53 (s, 1H), 7.46 (d, $J = 8.1$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.32 (t, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.03 (s, 1H), 7.02 (d, $J = 8.1$ Hz, 1H), 5.49 (t, $J = 8.6$ Hz, 1H), 5.03 (dd, $J = 9.2$, 4.5 Hz, 1H), 3.39 (dd, $J = 17.1$, 9.2 Hz, 1H), 3.28 (dd, $J = 14.1$, 4.7 Hz, 1H), 3.22 (dd, $J = 17.3$, 8.6 Hz, 1H), 3.12 (dd, $J = 13.9$, 9.6 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO +10 μL of TFA, 30 °C): δ 168.7, 152.6, 140.5, 138.3, 136.0, 133.7, 132.5, 131.3, 130.8, 130.6, 128.1, 126.8, 126.4, 126.2, 126.0, 124.7, 114.3, 60.6, 51.6, 37.7, 37.3, 19.4; HRMS calculated for $C_{25}H_{24}ClN_4O_5S_2$ $(M + H)^+$: 559.0881; found, 559.0881.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(3-chloro-4-iodophenyl)propanoate (81). Methyl (2*S*)-3-(4-aminophenyl)-2-[(*tert*-butoxycarbonyl)amino]propanoate (**80**) (1.0 g, 3.22 mmol) and *N*-chlorosuccinimide (474 mg, 3.55 mmol) were dissolved in DMF (20 mL) and allowed to stir under an atmosphere of nitrogen for 24 h. The reaction was quenched with water and diluted with

ethyl acetate (100 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by silica gel column (5−20% ethyl acetate/hexanes) to afford the product as a clear oil (645 mg, 61%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.05 (s, 1H), 6.90−6.87 (m, 1H), 6.76−6.74 (m, 1H), 4.27−4.23 (m, 1H), 3.68 (s, 3H), 2.97−2.92 (m, 1H), 2.78−2.72 (m, 1H), 1.39 (s, 9H); LCMS found for $C_{10}H_{14}ClN_2O_2$ $(M + H)^+$: m/z = 229. Methyl (2*S*)-3-(4-amino-3-chlorophenyl)-2-[(*tert*-butoxycarbonyl)amino]propanoate (3.00 g, 9.12 mmol) in aqueous hydrochloric acid solution (1.0 N, 100 mL) at 0 °C was treated with a solution of sodium nitrite (692 mg, 10.0 mmol) in water (10 mL). The solution was stirred at 0 °C for 30 min. A solution of potassium iodide (1.89 g, 11.4 mmol) in water (10 mL) was added and the solution stirred 30 min at room temperature and then 10 min at 35 °C. The solution was diluted with ethyl acetate (200 mL) and quenched with an aqueous sodium thiosulfate solution (1.0 N, 500 mL), and the organic phase was separated. The organic layer was washed with aqueous hydrochloric acid solution (1.0 N, 100 mL), brine (100 mL), dried over sodium sulfate, and concentrated in vacuo. Purification by silica gel chromatography (10−40% ethyl acetate/hexanes) afforded the product as a yellow solid (2.1 g, 53%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (d, J = 8.0 Hz, 1H), 7.37 (s, 1H), 6.90 (d, J = 8.2 Hz, 1H), 4.36−4.33 (m, 1H), 3.70 (s, 3H), 3.12−3.07 (m, 1H), 2.86−2.80 (m, 1H), 1.37 (s, 9H). LCMS found for $C_{10}H_{12}ClINO_2$ $(M + H)^+$: m/z = 340.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)-3-chlorophenyl]-propanoate (83). 2-*tert*-Butylisothiazol-3(2*H*)-one 1,1-dioxide (**82**) (284 mg, 1.50 mmol), palladium acetate (48 mg, 0.21 mmol), and tetra-*N*-butylammonium chloride (238 mg, 0.858 mmol) were combined. To this mixture was added methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(3-chloro-4-iodophenyl)propanoate (377 mg, 0.858 mmol) in DMF (4 mL). The reaction was treated with triethylamine (0.60 mL, 4.3 mmol). The reaction was degassed and then allowed to stir under an atmosphere of nitrogen at 65 °C for 2 h. The reaction was quenched with water (50 mL), diluted with ethyl acetate (100 mL), and washed with an aqueous hydrochloric acid solution (1.0 N, 100 mL). The organic solution was dried over sodium sulfate, filtered. and concentrated in vacuo. The crude material was purified by silica gel chromatography (5−25% ethyl acetate/hexanes) to afford the product as a white solid (480 mg, 64%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 4.44−4.40 (m, 1H), 3.73 (s, 3H), 3.25−3.20 (m, 1H), 2.95 (dd, J = 10.0, 13.7 Hz, 1H), 1.70 (s, 9H), 1.37 (s, 9H). LCMS found for $C_{17}H_{22}ClN_2O_5S$ $(M + H)^+$: m/z = 401.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-{4-[(5*S*)-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl]-3-chlorophenyl}propanoate (84). Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)-3-chlorophenyl]propanoate (**83**) (300 mg, 0.598 mmol) in THF (6 mL) was cooled to 0 °C and treated with a lithium tetrahydroborate solution in THF (2.0 M, 0.33 mL). The reaction was allowed to stir for 0.5 h at room temperature. After the addition of acetic acid (0.5 mL), the solution was diluted with ethyl acetate (100 mL), washed with water (100 mL), separated, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (5−30% ethyl acetate/hexanes) to afford the product as a white solid (162 mg, 54%). The two diastereomers were separated by normal phase chiral HPLC (ChiralCel OD-H (20 × 250 mm, 5 μm), 30% EtOH/70% hexanes, 15 mL/min, 30 °C) to yield **84** (103 mg, 48%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.45−7.42 (m, 2H), 7.31−7.27 (m, 1H), 5.59 (t, J = 8.0 Hz, 1H), 4.39−4.36 (m, 1H), 3.70 (s, 3H), 3.38−3.33 (m, 1H), 3.25−3.14 (m, 2H), 2.95−2.92 (m, 1H), 1.67 (s, 9H), 1.37 (s, 9H). LCMS found for $C_{17}H_{24}ClN_2O_5S$ $(M + H)^+$: m/z = 403.

(2*S*)-2-(*tert*-Butoxycarbonyl)amino-3-{3-chloro-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}propanoic Acid (85). Methyl (2*S*)-2-amino-3-{3-chloro-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}-propanoate trifluoroacetate (**84**) (350 mg, 0.70 mmol) was dissolved in trifluoroacetic acid (3 mL) and heated in the microwave at 130 °C for 5 min. The reaction was concentrated in vacuo and then dissolved in methylene chloride (5 mL). The solution was treated with triethylamine (364 μL, 2.61 mmol) and di-*tert*-butyl-dicarbonate (228 mg, 0.152 mmol). The reaction was stirred at room temperature for 2 h and then treated with an aqueous lithium hydroxide solution (4.0 M, 0.52 mL) and allowed to stir for 2 h. The reaction was quenched with aqueous hydrochloric acid solution (1.0 N, 5 mL) and purified by reverse phase HPLC to afford the product as a white solid (184 mg, 81%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.44−7.41 (m, 1H), 7.18−7.13 (m, 1H), 5.37 (brs, 1H), 4.36−4.33 (m, 1H), 3.38−3.32 (m, 3H), 2.98−2.95 (m, 1H), 1.37 (s, 9H). LCMS found for $C_{17}H_{21}ClN_2O_7S$ $(M + H)^+$: m/z = 433.

***tert*-Butyl (1*S*)-1-(1*H*-benzimidazol-2-yl)-2-{3-chloro-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}ethylcarbamate Trifluoroacetate (86).** *tert*-Butyl (1*S*)-2-[(2-aminophenyl)amino]-1-{3-chloro-4-[(5*S*)-1,1-dioxido-3-oxo-isothiazolidin-5-yl]benzyl}-2-oxoethylcarbamate (**85**) (75 mg, 0.17 mmol) in DMF (2 mL) was treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (91.8 mg, 0.207 mmol). After 5 min at room temperature, *N*,*N*-diisopropylethylamine (0.090 mL, 0.519 mmol) and 1,2-benzendiamine 7 (28 mg, 0.26 mmol) were added and the solution stirred for 1 h at room temperature. The solution was concentrated and then heated in acetic acid (5 mL) at 40 °C for 1 h. The solution was concentrated in vacuo. Purification by preparative LCMS afforded the product as a white solid (77 mg, 72%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.76−7.72 (m, 2H), 7.59−7.55 (m, 2H), 7.43−7.40 (m, 1H), 7.17−7.12 (m, 2H), 5.44−5.40 (m, 2H), 3.40−3.23 (m, 3H), 3.13−3.11 (m, 1H), 1.37 (s, 9H). LCMS found for $C_{24}H_{26}ClN_4O_5S$ $(M + H)^+$: m/z = 506.

***N*-(1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-{3-chloro-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}ethylbenzenesulfonamide Trifluoroacetate (87).** (2*S*)-*N*-(2-Aminophenyl)-3-{3-chloro-4-[(5*S*)-1,1-dioxido-3-oxoisothiazolidin-5-yl]phenyl}-2-[(phenylsulfonyl)-amino]propanamide trifluoroacetate (**86**) (22.9 mg, 0.037 mmol) was treated with trifluoroacetic acid (1 mL) in methylene chloride (5 mL). After 1 h at room temperature, the solution was concentrated in vacuo, and the residue was dissolved in methanol (2.0 mL). Triethylamine (0.050 mL, 0.36 mmol) and benzenesulfonyl chloride (**66**) (0.028 mL, 0.022 mmol) were added. After 3 h at room temperature, the solution was concentrated. Purification by preparative LCMS afforded the product as a white solid (18.5 mg, 76%). ^{1}H NMR (400 MHz, d_6-DMSO, 30 °C): δ 9.02 (d, J = 6.2 Hz, 1H), 7.76 (m, 2H), 7.50 (m, 2H), 7.49 (m, 2H), 7.43 (m, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H), 7.31 (m, 2H), 7.16 (dd, J = 8.1, 1.3 Hz, 1H), 5.56 (t, J = 8.2 Hz, 1H), 4.91 (m, 1H), 3.42 (dd, J = 17.2, 8.5 Hz, 1H), 3.36 (dd, J = 17.0, 7.9 Hz, 1H), 3.29 (dd, J = 13.9, 3.8 Hz, 1H), 3.11 (dd, J = 13.6, 10.0 Hz, 1H) ^{13}C NMR (125 MHz, d_6-DMSO, 30 °C): δ 168.9, 152.9, 138.8, 138.7, 134.3, 132.5, 132.0, 130.3, 129.8, 128.8, 128.2, 126.5, 125.8, 125.4, 114.5, 60.7, 51.7, 37.4. HRMS calcd for $C_{24}H_{22}ClN_4O_5S_2$ $(M + H)^+$: 545.0721; found, 545.0729.

Methyl (2*S*)-3-(3-bromo-4-iodophenyl)-2-[(*tert*-butoxycarbonyl)amino-]propanoate (88). Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)-amino]-3-(4-nitrophenyl)propanoate (**80**) (44.0 g, 136 mmol) in methanol (750 mL) and water (75 mL) was treated with ammonium chloride (10.9 g, 203 mmol) and then zinc (71 g, 1.1 mol). The solution was stirred at reflux for 1 h. The solution was filtered through Celite, the residue was concentrated under vacuum to remove the methanol, and the water solution was extracted with ethyl acetate (500 mL) and dried over sodium sulfate. The product was a yellow foam (38.2 g, 96%). ^{1}H NMR (400 MHz, CD_3OD): δ 6.91 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.3 Hz, 2H), 4.28−4.22 (m, 1H), 3.66 (s, 3H), 2.98−2.90 (m, 1H), 2.86−2.78 (m, 1H), 1.39 (s, 9H). LCMS found for $C_{15}H_{22}N_2O_4Na$ $(M + Na)^+$: m/z = 317.

Methyl (2*S*)-3-(4-aminophenyl)-2-[(*tert*-butoxycarbonyl)amino]-propanoate (17.2 g, 58.4 mmol) in DMF (400 mL) was treated with *N*-bromosuccinimide (11.4 g, 64.3 mmol). The solution was stirred at room temperature overnight. The solution was diluted with ethyl

acetate (500 mL), washed with water (500 mL), a satd. aqueous sodium bicarbonate solution (500 mL), and an aqueous hydrochloric acid solution (1.0 N, 500 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Silica gel chromatography (10−50% ethyl acetate/hexanes) afforded the product as a viscous, slightly yellow gel (20.1 g, 92%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.21 (d, J = 1.7 Hz, 1H), 6.92 (dd, J = 8.2, 1.8 Hz), 6.75 (d, J = 8.2 Hz, 1H), 4.27−4.23 (m, 1H), 3.68 (s, 3H), 2.97−2.92 (m, 1H), 2.77−2.72 (m, 1H), 1.39 (s, 9H). LCMS found for $C_{15}H_{21}BrN_2O_4Na$ $(M + Na)^+$: m/z = 396.

Methyl (2*S*)-3-(4-amino-3-bromophenyl)-2-[(*tert*-butoxycarbonyl)amino]-propanoate (19.8 g, 53.0 mmol) suspended in 1 N aqueous hydrochloric acid (500 mL) was treated dropwise at 0 °C with sodium nitrite (3.66 g, 53.0 mmol) in water (75 mL). After 15 min at 0 °C, potassium iodide (8.81 g, 53.1 mmol) in water (75 mL) was added, and the solution was heated at 40 °C for 15 min. The solution was quenched with a satd. aqueous sodium thiosulfate solution (100 mL) and extracted with ethyl acetate (500 mL). The organic phase was washed with a 0.1 N hydrochloric acid solution (500 mL) and a satd. aqueous sodium bicarbonate solution (500 mL) and dried over sodium sulfate. Purification by silica gel chromatography (10−40% ethyl acetate/hexanes) afforded the product as slightly yellow solid (18.7 g, 73%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 6.92 (dd, J = 8.0, 1.9 Hz), 4.36−4.29 (m, 1H), 3.71 (s, 3H), 3.10−3.04 (m, 1H), 2.85−2.79 (m, 1H), 1.37 (s, 9H). LCMS found for $C_{15}H_{19}BrINO_4Na$ $(M + Na)^+$: m/z = 506.

Methyl (2*S*)-3-[3-bromo-4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)phenyl]-2-[(*tert*-butoxycarbonyl)amino]-propanoate (89). Methyl (2*S*)-3-(3-bromo-4-iodophenyl)-2-[(*tert*-butoxycarbonyl)amino]-propanoate (2.35 g, 4.85 mmol), 2-*tert*-butylisothiazol-3(2*H*)-one 1,1-dioxide (**82**) (1.61 g, 8.49 mmol), palladium acetate (218 mg, 0.971 mmol), tetra-*N*-butylammonium chloride (1.35 g, 4.85 mmol), and then triethylamine (2.03 mL, 14.6 mmol) were dissolved in DMF (40 mL). The solution was degassed and then stirred with heating at 70 °C under nitrogen for 120 min. LCMS indicated an absence of starting material. The solution was diluted with ethyl acetate (150 mL) and washed with water (150 mL) and a 1.0 N aqueous hydrochloric acid solution (150 mL). The organic phase was filtered through Celite with ethyl acetate washing. The organic solution was dried over sodium sulfate, concentrated in vacuo, and then purified by silica gel chromatography (10−25% ethyl acetate/hexanes) to afford the product as a yellow solid (1.38 g, 52%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.80 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.23 (d, J = 8.2 Hz, 1H), 6.89 (s, 1H), 5.08−5.05 (m, 1H), 4.62−4.59 (m, 1H), 3.76 (s, 3H), 3.23−3.20 (m, 1H), 3.06−3.02 (m, 1H), 1.79 (s, 9H), 1.43 (s, 9H). LCMS found for $C_{22}H_{29}BrN_2O_7SNa$ $(M + Na)^+$: m/z = 567.

Methyl (2*S*)-3-[3-bromo-4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]-2-[(*tert*-butoxycarbonyl)amino]-propanoate (90). Methyl (2*S*)-3-[3-bromo-4-(2-*tert*-butyl-1,1-dioxido-3-oxo-2,3-dihydroisothiazol-5-yl)phenyl]-2-[(*tert*-butoxycarbonyl)-amino]propanoate (**89**) (834 mg, 1.53 mmol) in THF (20 mL,) was chilled to 0 °C and treated dropwise with 2 M lithium tetrahydroborate in tetrahydrofuran (0.80 mL). The solution was stirred at 0 °C for 30 min. After 10 drops of acetic acid was added, the solution was diluted with ethyl acetate (150 mL), washed with water (150 mL), and dried over sodium sulfate. Silica gel chromatography (10−40% ethyl acetate/hexanes) afforded the product as a slightly yellow foam (682 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.45 (m, 1H), 7.32−7.29 (m, 1H), 7.24−7.18 (m, 1H), 5.46−5.42 (m, 1H), 5.05−5.00 (m, 1H), 4.60−4.54 (m, 1H), 3.35−3.30 (m, 1H), 3.20−3.16 (m, 1H), 3.08−3.00 (m, 2H), 1.68 (s, 9H), 1.43 (s, 9H). LCMS found for $C_{22}H_{31}BrN_2O_7S$ $(M + Na)^+$: m/z = 569.

(2*S*)-2-[(Benzyloxy)carbonyl]amino-3-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]propanoic Acid (91). Methyl (2*S*)-3-[3-bromo-4-(2-*tert*-butyl-1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]-2-[(*tert*-butoxycarbonyl)amino]propanoate (**90**) (458 mg, 0.654 mmol) was dissolved in trifluoroacetic acid (10 mL) and heated at 130 °C in the microwave for 2 min. The solution was concentrated in vacuo to give a white foam (420 mg, 99%). The product was used in subsequent steps without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (dd, J = 14.2, 1.6 Hz, 1H), 7.56−7.51 (m, 1H), 7.40−7.36 (m, 1H), 5.65 (t, J = 7.4 Hz, 1H), 4.39 (t, J = 6.8 Hz, 1H), 3.82 (s, 3H), 3.47−3.42 (m, 1H), 3.36−3.25 (m, 2H), 2.18−3.11 (m, 1H). LCMS found for $C_{13}H_{16}BrN_2O_5S$ $(M + Na)^+$: m/z = 391.

Methyl (2*S*)-2-amino-3-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]-propanoate trifluoroacetate (83.8 mg, 0.166 mmol) in methanol (2 mL) was treated with triethylamine (92 μL, 0.66 mmol) and chilled to 0 °C. Benzyl chloroformate (20.8 μL, 0.146 mmol) was added and the solution stirred 2 h at 0 °C. An aqueous lithium hydroxide solution (4.0 M, 0.21 mL) was added and the solution stirred 2 h. Purification by preparative LCMS afford the product as a white solid (69 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (brs, 1H), 7.46−7.43 (m, 1H), 7.31−0.7.26 (m, 6H), 5.65 (t, J = 8.2 Hz, 1H), 5.03 (s, 2H), 4.45−4.41 (m, 1H), 3.45 (dd, J = 17.5, 8.5 Hz, 1H), 3.36−3.19 (m, 2H), (2.94 dd, J = 14.2, 9.7 Hz, 1H). LCMS found for $C_{20}H_{20}BrN_2O_7S$ $(M + H)^+$: m/z = 511.

Benzyl (1*S*)-1-(1*H*-benzimidazol-2-yl)-2-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]ethylcarbamate Trifluoroacetate (92). (2*S*)-2-[(Benzyloxy)-carbonyl]amino-3-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]propanoic acid (**91**) (65.3 mg, 0.128 mmol) in DMF (4 mL) was treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (67.8 mg, 0.153 mmol). After 5 min, 1,2-benzenediamine 7 (20.7 mg, 0.192 mmol) and *N*,*N*-diisopropylethylamine (111 μL, 0.638 mmol) were added and the solution stirred at room temperature for 2 h. Purification by preparative LCMS afforded the product as a white solid (58 mg, 76%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.72 (s, 1H), 7.56−7.23 (m, 10H), 6.91−6.85 (m, 1H), 5.67 (t, J = 7.7 Hz, 1H), 5.09 (s, 2H), 4.50−4.47 (m, 1H), 3.46 (dd, J = 16.5, 8.8 Hz, 1H), 3.34−3.24 (m, 1H), 3.26−3.08 (m, 2H). LCMS found for $C_{26}H_{26}BrN_4O_6S$ $(M + H)^+$: m/z = 601.

Benzyl (1*S*)-2-[(2-aminophenyl)amino]-1-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)benzyl]-2-oxoethylcarbamate (28.2 mg, 0.0469 mmol) was dissolved in acetic acid (2.76 mL) and stirred at 60 °C for 1 h. The solution was concentrated and purified by preparative LCMS to afford the product as a white solid (26.1 mg, 95%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.79−7.56 (m, 5H), 7.42−7.12 (m, 7H), 5.61−5.57 (m, 1H), 5.35−5.31 (m, 1H), 5.03 (s, 2H), 3.47−3.28 (m, 3H), 3.22−3.14 (m, 1H). LCMS found for $C_{26}H_{24}BrN_4O_5S$ $(M + H)^+$: m/z = 583.

***N*-{(1*S*)-1-(1*H*-Benzimidazol-2-yl)-2-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]ethyl}benzenesulfonamide (93).** Benzyl (1*S*)-1-(1*H*-benzimidazol-2-yl)-2-[3-bromo-4-(1,1-dioxido-3-oxoisothiazolidin-5-yl)phenyl]ethylcarbamate (**92**) (15.8 mg, 2.71 mmol) in acetonitrile (0.5 mL) was treated with iodotrimethylsilane (11.6 μL, 8.12 mmol) at 25 °C and stirred for 30 min. The solution was quenched with a 1 N aqueous HCl solution (0.5 mL), diluted with acetonitrile (1 mL), and directly purified by preparative LCMS to afford the product as a clear solid (15.1 mg, 99%). To a solution of 5-4-[(2*S*)-2-amino-2-(1*H*-benzimidazol-2-yl)ethyl]-2-bromophenylisothiazolidin-3-one 1,1-dioxide trifluoroacetate (11.3 mg, 20.0 mmol) and triethylamine (8.4 mL, 60 mmol) in methanol (0.9 mL) was added a solution of benzenesulfonyl chloride (**66**) (3.0 μL, 24 mmol) and methanol (0.1 mL), and the resulting mixture was stirred at 25 °C for 2h. The reaction solution was diluted with water and methanol and purified by preparative LCMS to yield the desired product (8.1 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.77−7.74 (m, 2H), 7.64−7.52 (m, 5H), 7.45−7.25 (m, 5H), 5.56−5.52 (m, 1H), 4.98−5.90 (m, 1H), 3.46−3.40 (m, 2H), 3.26−3.15 (m, 2H); HRMS calcd for $C_{21}H_{24}BrN_4O_5S_2$ $(M + Na)^+$: 611.0034; found, 611.0016.

PTP1B Expression and Biochemical Assays. Human PTP1B, SHP1, SHP2, and TC-PTP were expressed in *E. coli*, essentially as described in the literature (*J. Biol. Chem.* **2000**, *275*, 10300−10307; *J. Struct. Biol.* **1997** *120*, 201−203; *Cell* **1998** *92*, 441−450; and *J. Biol. Chem.* **2002** *277*, 19982−19990). PTP enzymatic assays were performed as described in the literature (*J. Am. Chem.*

Soc. **2003**, *125*, 4087−4096). The pNPP assay was performed as described in the literature with the following modifications. The reactions were carried out in clear bottom 384-well plates containing 80 μL per well. Dilutions of compounds were made in DMSO, and PTP1B in the assay buffer (25 mM bis-tris-propane at pH 7.0, 1 mM EDTA, 0.1 mg/mL of BSA) was added (final [DMSO] of 2%). To 60 μL of this mixture, 20 μL of 4-nitrophenyl phosphate (pNPP) was added per well, for a final pNPP concentration of 1 mM and a final PTP1B concentration of 5 nM. The rate of formation of the phenolate ion was monitored at 410 nm on a Spectramax 384 plate reader. The slopes of initial reaction rates (15 min reactions) were plotted and fitted to the sigmoidal dose−response equation to obtain IC_{50} values of the compounds (GraphPad Software Prism 3.0). For the mode of inhibition analysis, final pNPP concentrations in the reactions varied between 0.46 and 30 mM. The initial reaction rates of these reactions were fitted to the Michaelis−Mention equation by nonlinear regression analysis (Graphpad Prism). A competitive K_i value was determined by linear regression of a plot of *K*m vs [inhibitor] such that $K_i = -(x\text{-intercept})$.

Insulin Receptor (IR) and Akt Phosphorylation Cellular Assays. HEK293-MSR cells were transfected with plasmids encoding full length human PTP1B and the insulin receptor using Fugene 6. In some experiments, a plasmid encoding a short hairpin RNA (shRNA) against PTP1B (CGGATTAAACTACATCAAGAcgaaTCTTGATGTAGTTTAATCC, corresponding to nucleotides 165 to184) was cotransfected as a control. The cells were dispensed into 96-well plates and allowed to attach for 24 h. Compounds were diluted from DMSO stocks (0.4% final v/v) into DMEM without the serum, and the cells were treated for 16 h. The nonselective tyrosine phosphatase inhibitor bpV (pic) and insulin were added for 30 min prior to harvesting. The cells were lysed in a buffer (25 mM Tris-HCl at pH 7.4, 150 mM NaCl, 1% Triton X-100, 0.5% Deoxycholate; 1 mM EDTA supplemented with a protease inhibitor cocktail) on ice, the cell extracts were clarified by centrifugation, and the supernatants were used for the detection of phospho-IR using an ELISA (Biosource), which specifically detects the activated IR on the critical regulatory phospho-tyrosine residues (Y1162 and Y1163) in the beta subunit (Ellis et al., 1986). Data were normalized to total protein content as determined by the bicinchoninic acid assay. In preliminary experiments, the data was normalized to total IR using an anti-IR ELISA (Biosource) and total protein content with good correlation between the two methods. For the measurement of Akt phosphorylation, HepG2 cells were seeded into collagen-coated 96-well plates. Compound treatment and cell lysis were performed exactly as described above, and detection was achieved using a phospho-Akt ELISA (Ser473, Biosource) and normalized to total protein content. For immunoblotting experiments, cell lysates were separated by SDS−PAGE, transferred to nitrocellulose filters, and probed with antibodies to PTP1B (Oncogene Research Products, Ab-1) or phospho-Insulin Receptor (pY1162pY1163, Biosource) and appropriate horseradish peroxidase conjugated secondary antibodies and developed with enhanced chemiluminescence reagents.

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Supporting Information Available: HPLC purity analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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