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Probing acid replacements of thiophene PTP1B inhibitors

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Abstract—The following account describes our systematic effort to replace one of the carboxylate groups of our diacid thiophene PTP1B inhibitors. Active hits were validated using enzymatic assays before pursuing efforts to improve the potency. Only when the C2 carboxylic acid was replaced with another ionizable functional group was reversible and competitive inhibition retained. Use of a tetrazole ring or 1,2,5-thiadiazolidine-3-one-1,1-dioxide as a carboxylate mimetic led to the discovery of two unique starting series that showed improved permeability (PAMPA) and potency of the order of 300 nM. The SAR from these efforts underscores some of the major challenges in developing small molecule inhibitors for PTP1B.

Protein tyrosine phosphatase 1B (PTP1B) plays a critical role in the signal transduction of both insulin and leptin pathways.[1–4] As a therapeutic target, PTP1B has received considerable attention from the drug industry as a potential treatment for diabetes mellitus.[5] Two-independent studies demonstrated that PTP1B deficient mice show greater insulin sensitivity, prolonged insulin receptor autophosphorylation, and maintained lower glucose and insulin levels.[6,7] More recently, anti-sense oligonucleotides (ASOs) have been shown to effectively block PTP1B activity in vivo to control glucose levels and promote insulin sensitivity in ob/ob mice.[8] ASOs were also found to prolong the lives of Zucker rats with diabetes further validating PTP1B as a potential therapeutic target.[9]

Designing phosphate mimetics with desirable drug-like properties has been a significant challenge. Most of the reported competitive, reversible PTP1B inhibitors have polar, charged phosphate mimetics such as *O*-carboxymethyl salicylic acids,[10] 2-(oxalylamino)-benzoic acids,[11] diaryloxamic acids,[12] difluoro-β-ketophosphonates,[13] fluoro *O*-malonyltyrosines,[14] cinnamic acids,[15] oxa-acetic acids,[16] difluoromethylphosphonates,[17–19] and sulfotyrosines.[20] While potency has been achieved for many of these phosphate bioisosteres, the cell permeability has been compromised significantly in most cases. Several groups have reported the acid replacement and acid mimetics approaches in an effort to improve the PK of their lead series. Replacing the carboxylate group of *O*-carboxymethyl salicylic acid with a tetrazole[21] led to improvements in membrane permeability. Burke and coworkers investigated the use of monocarboxy-phosphotyrosine mimetics leading to a series with poor to moderate potency.[22] Abbott has reported a (2-hydroxyphenoxy) acetic acid based phosphotyrosyl mimetic linked with a previously optimized ligand which resulted in a Caco-2 cell permeable albeit less potent PTP1B inhibitor.[23] An extension of this work involved the design of an isoxazole carboxylic acid with a single negative charge. While this monoacid showed only moderate potency (double digit micromolar), cell based activity was detected as changes in the phosphorylation levels in COS 7 cells.[24] These examples illustrate the challenges in developing a potent, drug-like PTP1B inhibitor.

Our initial efforts combined high-throughput screening (HTS) and structure based drug design to discover the pyridylthiophene and benzothiophene series of PTP1B inhibitors.[25] Further medicinal chemistry effort on these scaffolds culminated in the discovery of a thiophene

Keyword: Protein tyrosine phosphatase 1B (PTP1B).
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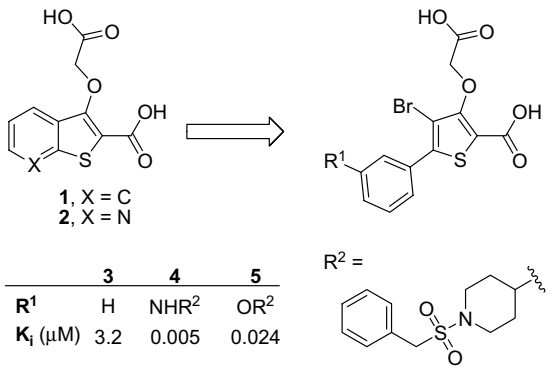
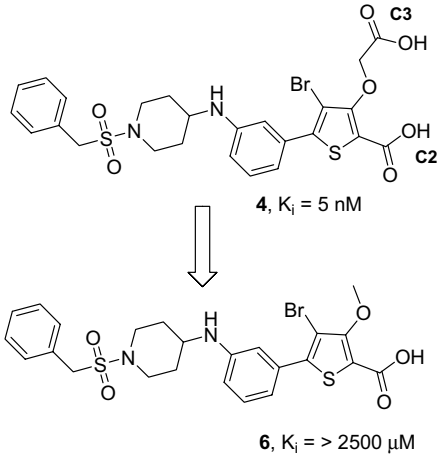


Scheme 1. Pyridylthiophene, benzothiophene, and thiophene series.



Scheme 2. Potency loss from cleaving C3 carboxylate group.

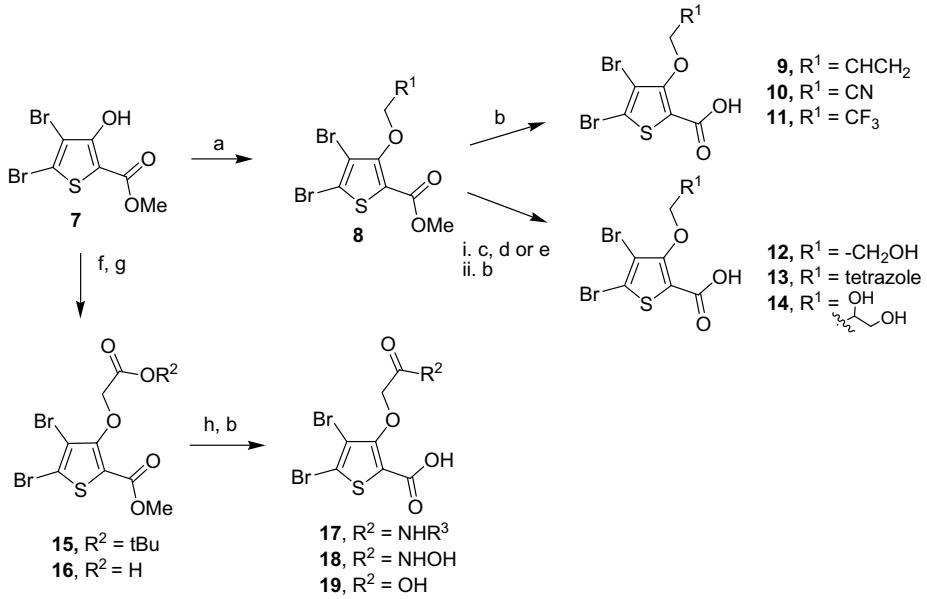
series as potent PTP1B inhibitors.[26] While our goal of achieving high potency had been met, we anticipated compromised permeability associated with the polar head group and therefore embarked on a study to replace one of the acid groups with an appropriate acid mimetic Scheme 1.

Several key binding interactions between the diacid (**3**) and PTP1B are evident from the co-crystal structure.[26] The two acidic side chains, C2 and C3, extend into the phosphate oxygen binding region of the catalytic site; the C3 carboxylate oxygen and Arg221 form a critical electrostatic interaction which is further strengthened by several putative hydrogen bonds between the oxygen atom of the carboxylate and the peptide backbone while the C2 acid contacts Lys120 through a water mediated electrostatic interaction.

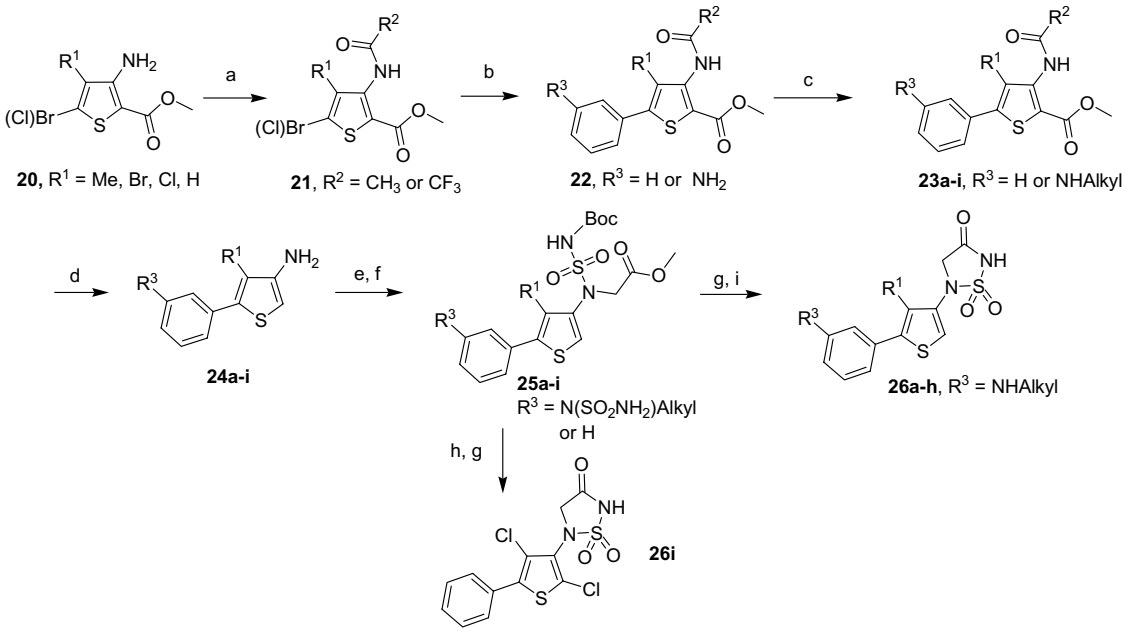
The benzylsulfonamide side chain, appended to C5, improved the potency of our PTP1B inhibitors by roughly 650-fold. We hoped that this improved affinity would compensate for the removal of an acid group. However, in a preliminary experiment, removing the C3 carboxylate group (**4**–**6**, Scheme 2) led to a complete loss in activity. This finding exemplified the significance of the interaction between the C3 carboxylate group of our scaffold and the catalytic site of PTP1B.

We began our synthetic efforts by exploring a mimetic for the C3 carboxylate group. In the second phase, we focused on probing acid replacement groups for the C2 carboxylate group.

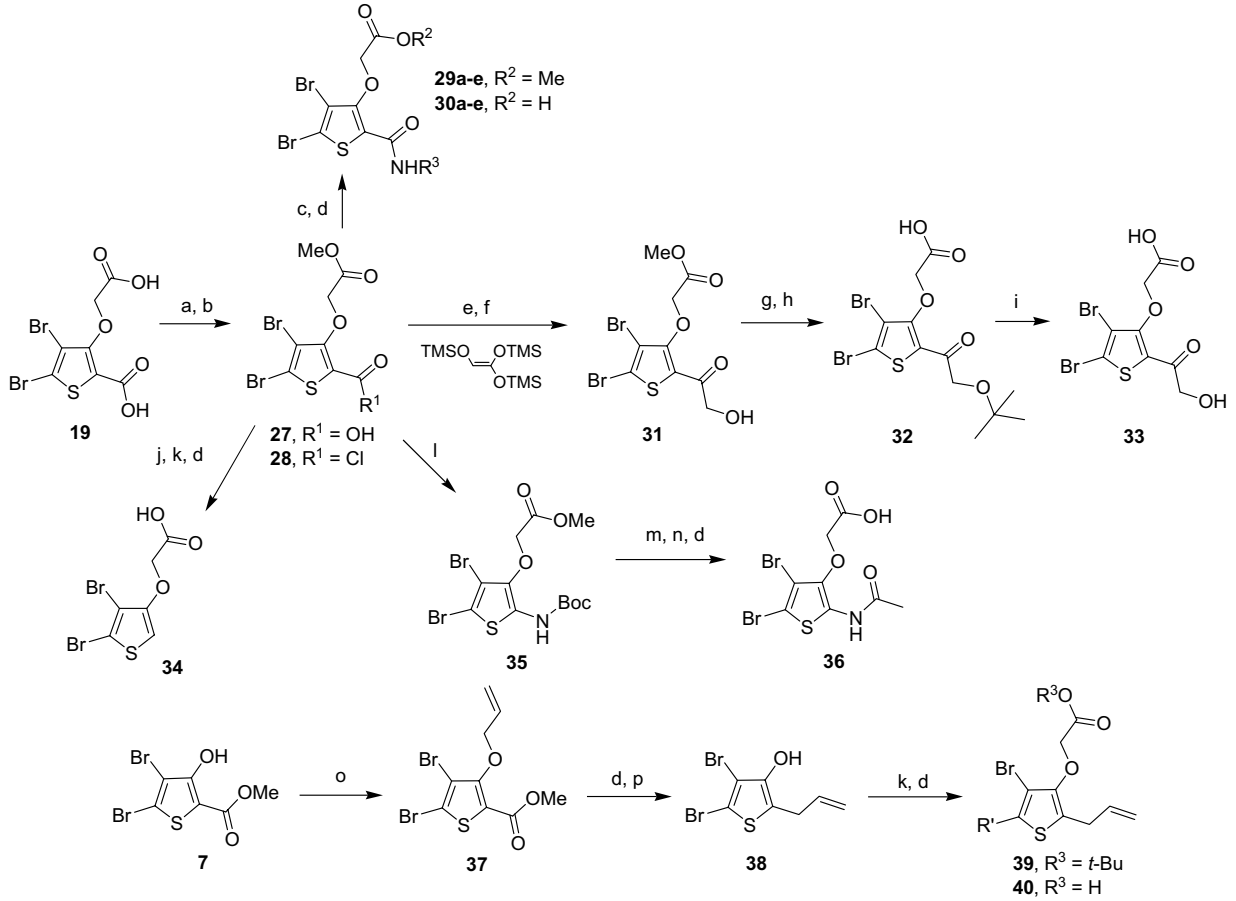
The C3 analogs were prepared from alkylation of the hydroxyl group of methyl 4,5-dibromo-3-hydroxythiophene-2-carboxylate **7** (Scheme 3). The strategy of incorporating 1,2,5-thiadiazolidine-3-one-1,1-dioxide



Scheme 3. Reagents and condition: (a) RCH_2Br, K_2CO_3, DMF, 85–95%; (b) LiOH, THF–H_2O; HCl, 98%; (c) DIBAL, THF, 30%; (d) NaN_3, heat, 45%; (e) OsO_4, NMO, THF–H_2O, 15%; (f) *tert*-butylbromoacetate, K_2CO_3, DMF, 96%; (g) TFA, CH_2Cl_2, 98%; (h) RNH_2, DMF, BOP, $(i\text{-}Pr)_2NEt$, 90–99%.



Scheme 4. General scheme for the synthesis of 1,2,5-thiadiazolidine-3-one-1,1-dioxide derivatives. Reagents and conditions: (a) Ac_2O or TFAA, K_2CO_3, DMF, 99%; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, KF, THF, 67–92%; (c) ketone, $NaCNBH_3$, HOAc, MeOH, 36–98%; (d) i—NaOH/EtOH; ii—HCl, heat, 66–91%; (e) methyl bromoacetate, K_2CO_3, DMF, 72–98%; (f) chlorosulfonyl isocyanate, *t*-BuOH, DIPEA, DCM, 78–89%; (g) i—TFA, DCM; ii—NaH, THF, 37–75% (two steps); (h) SO_2Cl_2, $CHCl_3$, reflux, 76%; (i) THF–MeOH, 2 N NaOH, 60 °C, 74%.



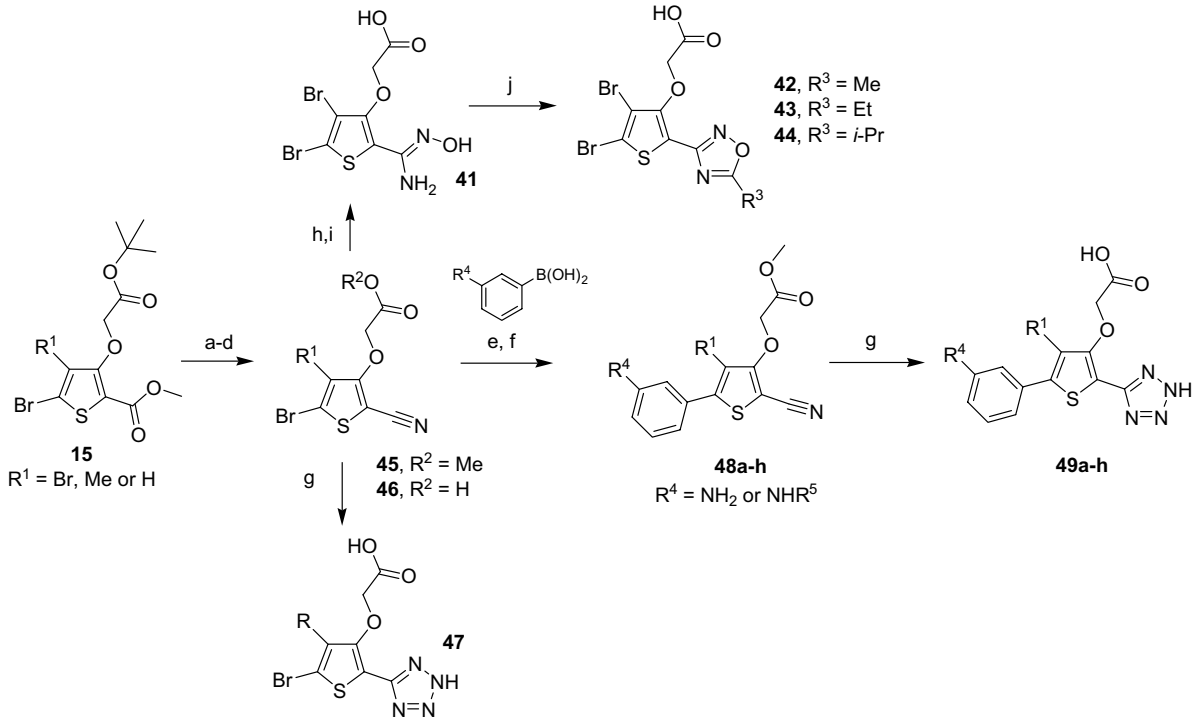
Scheme 5. Reagents and condition: (a) HCl, MeOH, 98%; (b) $SOCl_2$, 99%; (c) amine, THF–H_2O, 64%; (d) LiOH, THF–H_2O; HCl, 78%; (e) $SnCl_2$, CH_2Cl_2;[29] (f) HCl, dioxane, 71% (two steps); (g) isobutylene, H_2SO_4, CH_2Cl_2, 87%; (h) LiOH, THF–H_2O, 64%; (i) TFA, CH_2Cl_2, 38%; (j) DMSO, NaOH, heat; 60%; (k) *tert*-butylbromoacetate, K_2CO_3, DMF, 96%; (l) DPPF, *t*-BuOH, 60%; (m) Ac_2O, Et_3N, DCM, 60%; (n) TFA, CH_2Cl_2, 95%; (o) allylbromide, K_2CO_3, DMF, 89%; (p) heat, xylenes, 94%.[30]

heterocycle into our scaffold was inspired by previously reported work (Scheme 4).[27] The acetate protecting group was introduced in the first step. The tailpiece was introduced through a cross coupling step with 3-aminophenyl boronic acid followed by a reductive amination with a ketone (**22**–**23**). Under basic conditions, the methyl ester was hydrolyzed, the resulting acid was lost as carbon dioxide, and the acetate group was cleaved to give amino thiophene **24**. Interestingly, the de-carboxylation step could not be performed on substrate **20**, presumably due to the donating effect of the 3-amino group. Amine **24** was alkylated with methyl-bromoacetate and then treated with chlorosulfonyl isocyanate in the presence of *tert*-butanol to afford **25a**–**i**. Subsequent treatment of **25a**–**i** with TFA to cleave the Boc group followed by treatment with NaH to induce cyclization of the ring provided the desired analogs **26a**–**i**.

The preparation of the C2 analogs is shown in Schemes 5 and 6. The analogs in Scheme 5 were synthesized from either the de-carboxylated intermediate **34** or from the C3 methyl ester **27**, an intermediate prepared by treatment of the diacid **11** with dilute sulfuric acid in methanol. Acidic esterification of the C3 acid **19** enabled selective activation of the C2 acid in the preparation of these C2 analogs. Scheme 6 shows the preparation of heterocycles at C2.

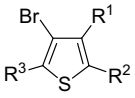
A variety of C3 and C2 analogs were tested as potential inhibitors of the PTP1B enzyme (Tables 1 and 2). The C3 position, corresponding to the phosphate-binding region of the enzyme active site, proved most sensitive, as most of the C3 analogs had no activity (>2500 μM). Efforts to modify the C2 position led, in many instances, to complete losses in activity with the exception of three analogs: allylthiophene **40**, morpholine amide **30c**, and tetrazole **47** (165, 210, and 430 μM, respectively).[28] Replacement of both acids with a thiazolidine heterocycle, **26a**, revealed a more promising result with K_i = 18 μM. With the active C2 and C3 analogs in hand, we directed our next effort toward validating these inhibitors.

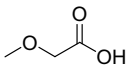
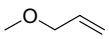
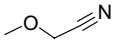
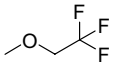
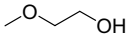
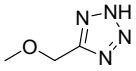
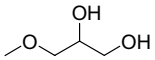
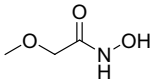
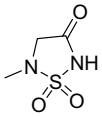
The active compounds were tested for enzyme reversibility (Rev) and enzyme concentration dependence ([E]). In the first validation assay, PTP1B and the inhibitor were incubated, diluted 10-fold, and then the enzymatic activity was assessed. Typically, inhibition due to an irreversible process displayed partial or reduced recovery of enzymatic activity. In the second assay, the IC_{50} was measured at two separate concentrations of PTP1B, 10 and 100 nM. As expected, well-behaved inhibitors showed virtually no change in activity at the two enzyme concentrations, while inhibitors that operate through aggregation, non-specific binding or through an impurity,[32] show enzyme concentration dependence. Use of these assays provided a means of validating the hits and eliminating undesired inhibitors. Analogs **47** and **26a** showed reversible inhibition as well as no enzyme concentration dependence. The morpholine analog **30c** and allyl thiophene **40** were irreversible and displayed enzyme concentration dependence. Hydroxy ketone **33** initially looked promising, however, derivatives made



Scheme 6. Reagents and conditions: (a) TFA–CH_2Cl_2; (b) NH_3, MeOH; (c) H_2SO_4, MeOH, 80% (three steps); (d) cyanuric chloride, DMF, 78%; (e) $Pd(PPh_3)_4$, KF, DME–H_2O, microwave heating; (f) $NaBH(OAc)_3$, AcOH, aldehyde, 45–65% (two steps); (g) $ZnBr_2$, NaN_3, *i*-PrOH–H_2O, reflux, 80%;[31] (h) LiOH, THF–H_2O, HCl; (i) NH_2OH, EtOH, K_2CO_3, 80 °C, 95% (two steps); (j) RCOCl, heat, 20–40%.

Table 1. C3 acid-mimetic analogs[37]



Compound	R^1	R^2	R^3	IC_{50} (μM)
19		$-CO_2H$	Br	29[a]
9		$-CO_2H$	Br	>2500
10		$-CO_2H$	Br	>2500
11		$-CO_2H$	Br	>2500
12		$-CO_2H$	Br	>2500
13		$-CO_2H$	Br	>2500
14		$-CO_2H$	Br	>2500
18		$-CO_2H$	Br	>2500
26a		H	Ph	29[a]

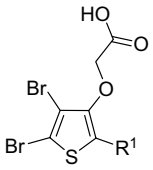
[a] K_i values for validated hits: **19** = 18 μM, **26a** = 18 μM.

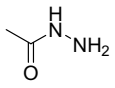
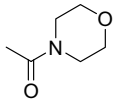
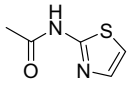
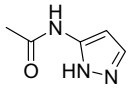
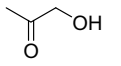
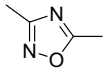
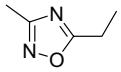
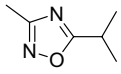
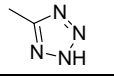
from this core were also irreversible and enzyme concentration dependent.

With compounds **47** and **26a** validated, we set out to improve their potencies using some of the side chains discovered in a previous effort.[25,33] The results are shown in Table 3. Substitution on the thiadiazolidine scaffold resulted in modest improvements in potency where the most active analog had a K_i = 1.7 μM (**26f**). Substitution on the tetrazole scaffold had a greater impact on the potency where meta-substituted cyclic compounds such as **49d** and **49e** showed 15- and 160-fold improvements, respectively. The benzylsulfonyl amide **49g** was the most potent inhibitor with a K_i = 300 nM.

Both tetrazole **49g** and thiadiazolidine **26c** have been crystallized with PTP1B (Figs. 1 and 2). The WPD loop is in the closed conformation similar to the mode shared by many other PTP1B inhibitors reported in the literature.[10] The key interactions highlighted by the co-crystal structure of the tetrazole acid with PTP1B are maintained: the thiophene core is anchored to the A site via electrostatic interactions between the C3 acid and the Arg residue and the tetrazole ring interacts with the Lys120. The key interactions of **26c** indicate that the sulfonyl oxygen atoms interact with Arg221 and Lys 120.

Table 2. C2 acid-mimetic analogs[37]



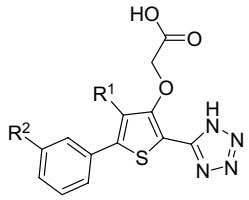
Compound	R^1	IC_{50} (μM)
15[c]		>2500
30a		>2500
30b		>2500
30c		210[a]
30d		>2500
30e		>2500
33		330[b]
34	H	>2500
36		>2500
40		165[a]
42		>2500
43		>2500
44		>2500
46		>2500
47		430[b]

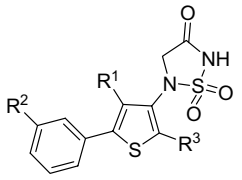
[a] Compounds were found to have one or more of the following: enzyme concentration dependence, irreversible inhibition, dynamic light scattering.

[b] K_i values for validated hits: **33** = 210 μM, **47** = 270 μM.

[c] Side product from DIBAL reduction (Scheme 3, step c).

Table 3. SAR of C2 tetrazole and C3 thiazolidine





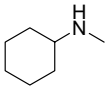
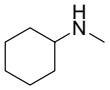
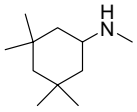
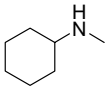
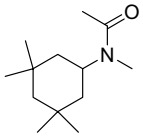
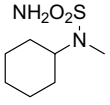
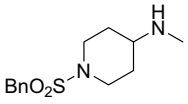
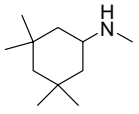
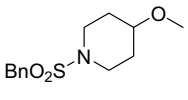
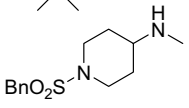
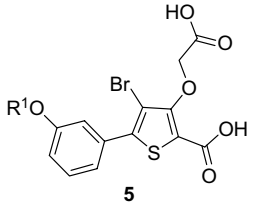
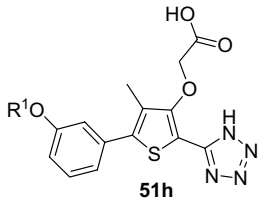
Compound	R^1	R^2	K_i (μM)	Compound	R^1	R^2	R^3	K_i (μM)
49a	Br	H	20	**26a**	Br	H	H	18
49b	Me	H	170	**26b**	Me	H	H	41
49c	H	H	120	**26c**	Cl	H	H	16
49d	Br		18	**26d**	Me		H	12
49e	Br		1.6	**26e**	Cl		H	14
49f	Br		4.6	**26f**	Cl		H	1.7
49g	Br		0.30	**26g**	Me		H	15
49h	Me		1.3	**26h**	Me		H	4.3
				26i	Cl	H	Cl	16

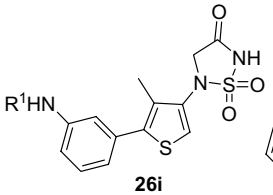
Table 4. PAMPA values for selected tetrazoles and TDDs; PAMPA = Pe × 10–6 s/cm; R^1 = cyclic benzylsulfonamide shown in Table 3



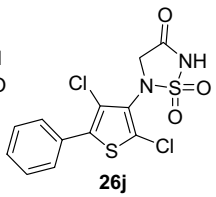
5



51h



26i



26j

PAMPA (Pe × 10–6 cm/s)	0.00	0.22	0.19	3.54

Table 4 shows the PAMPA[34,35] permeability data for some of the best compounds selected from each series. A direct comparison of these compounds has some limitations, as other structural changes are present. Note that **5** and **49h** have oxygen atoms connecting the piperidine sulfonamide group to the phenyl ring groups and the C4 position varies from methyl, to chloro to bromo. Despite these differences, some interesting observations between the series can be made. None of the diacids had PAMPA values above 0.0, whereas a number of tetrazoles showed moderate permeability and the thiadiazolidines, in general, showed improvements over the tetrazoles. Thus, an overall permeability of the series based on PAMPA data gives the following trend: thiadiazolidine > tetrazole > diacid.

The SAR in this study underscores the challenge in designing ligands for phophatase targets. The polar recognition elements required for the ligand to bind with high affinity for the active site often have poor permeability and consequently limited bioavailability. As shown in the SAR tables of the C2 and C3 analogs, replacement of either acid with a neutral functional group or even groups designed to replace the electro-

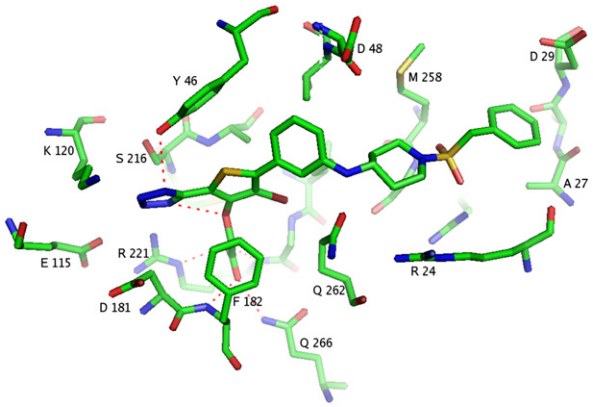


Figure 1. Tetrazole **49g** in the PTP1B active site (PDB code: 2NT7[36]).

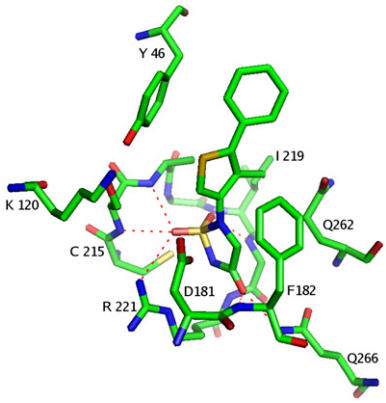


Figure 2. X-ray co-crystal structure of sulfonyl urea **26c** with PTP1B (PDB code: 2NTA[36]).

static interactions of the acid functional group led to dramatic losses in potency (K_i > 2500 μM). Several compounds including the morpholine amide **30c** and allyl thiophene **40** initially looked promising, however, detailed enzymology studies of each analog revealed distinct characteristics consistent with non-classical inhibition. Ultimately, potency was maintained when the C2 or C3 groups in our scaffold were replaced with an ionizable group, the tetrazole ring or the thiadiazolidine ring. Both templates were shown to give improvements in permeability based on PAMPA. Further experiments with these two series will be reported in due course.

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