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Discovery and structure–activity relationships of novel sulfonamides as potent PTP1B inhibitors

Christopher P. Holmes,* Xianfeng Li, Yijun Pan, Caiding Xu, Ashok Bhandari, Claire M. Moody, Joy A. Miguel, Steven W. Ferla, M. Nuria De Francisco, Brian T. Frederick, Siqun Zhou, Natalie Macher, Larry Jang, Jennifer D. Irvine and J. Russell Grove

Affymax, Inc., 4001 Miranda Avenue, Palo Alto, CA 94304, USA

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Abstract—A series of novel sulfonamides containing a single difluoromethylene-phosphonate group were discovered to be potent inhibitors of protein tyrosine phosphatase 1B. Structure–activity relationships around the scaffold were investigated, leading to the identification of compounds with IC_{50} or K_i values in the low nanomolar range. These sulfonamide-based inhibitors exhibit 100 and 30 times higher inhibitory activity than the corresponding tertiary amines and carboxamides, respectively.

Protein tyrosine phosphatase 1B (PTP1B), an intracellular non-receptor PTPase, plays an essential role in the regulation of insulin signaling pathway by dephosphorylating the activated insulin receptor.[1] Recent knock-out studies have demonstrated that PTP1B-deficient mice display enhanced insulin sensitivity and resistance to diet-induced obesity.[2,3] Furthermore, diabetic mice treated with a specific PTP1B antisense oligonucleotide exhibit normalization of blood glucose level and improvement in insulin sensitivity.[4] Therefore, there has been tremendous interest in the development of PTP1B inhibitors that would provide novel therapeutic agents in treating Type II diabetes and obesity.[5]

An effective strategy for designing PTP1B inhibitors has focused on the incorporation of non-hydrolyzable phosphotyrosine (pTyr) mimetics in appropriate peptide substrates or small molecule scaffolds. Among these, α,α-difluoromethylenephosphonic acids (DFMP) are especially effective in obtaining potent small molecule inhibitors of PTP1B. Burke et al.[6] first reported that simple aromatics containing one DFMP group are weak, competitive inhibitors of PTP1B. Subsequently, both the Taylor and Zhang groups extended this approach by identifying a series of compounds bearing two DFMP groups as potent PTP1B inhibitors.[7,8] These bis-phosphonates exhibit much higher potency by binding to both the catalytic site and the second phosphate binding site of the enzyme resulting from its complementarity with the tandem $pTyr_{1162}$ and $pTyr_{1163}$ groups of the natural substrate.[9] However, introduction of an additional phosphonate group in the molecule is likely to have a negative impact on cell permeability and oral bioavailability, which will be key attributes of any successful drug against this class of enzymes.

Numerous small molecules have been described over the last few years with activity against PTP1B. These include triaryl compounds from Merck Frosst,[10] oxalylarylaminobenzoic acids from Abbott,[11] numerous compounds from Pharmacia,[12] hundreds of compounds from Wyeth–Ayerst,[13] 2-oxalylaminobenzoic acids from Novo Nordisk,[14] α-ketoacids from Seto,[15] aminothiazoles from Wipf,[16] and formylchromanes from Cho.[17] We have recently reported the discovery of a series of α,α-difluoro-β-ketophosphonates as low micromolar PTP1B inhibitors.[18] For example, sulfonamide **1** was shown to inhibit PTP1B with an IC_{50} of 12 μM. During the course of our studies, we found that replacement of α,α-difluoro-β-ketophosphonate with a DFMP moiety gave a slightly more active compound **2** with an IC_{50}

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* Corresponding author. Tel.: +1 650 812 8737; fax: +1 650 424 0832; e-mail: chris_holmes@affymax.com

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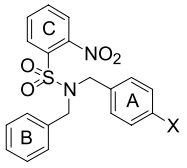
of 7 μM. Both **1** and **2** contain a sulfonamide scaffold, which represents a good starting point for further optimization. Sulfonamides are known to function as good hydrogen bond acceptors in many biological systems, and more importantly, they are common features of many known drugs. Given the easy synthesis and availability of large number of building blocks, our approach was to make analogs in a parallel fashion to maximize interactions with PTP1B. In this paper, we report our optimization of **2** by introducing substitutions in all three aryl rings as well as altering the sulfonamide backbone (Fig. 1).

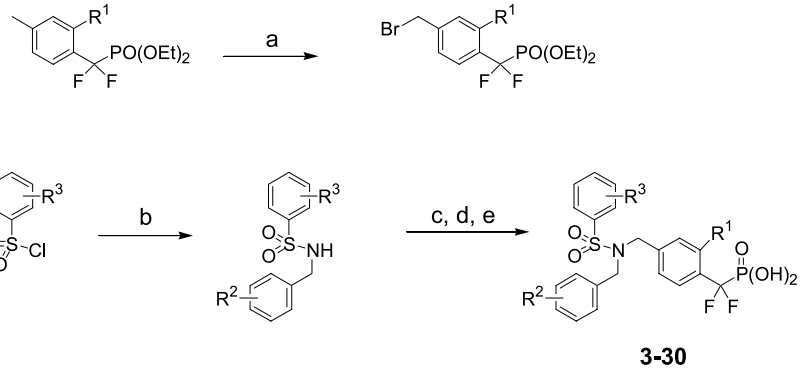


1, X = $COCF_2PO(OH)_2$, IC_{50} = 12 μM
2, X = $CF_2PO(OH)_2$, IC_{50} = 7 μM

Figure 1.

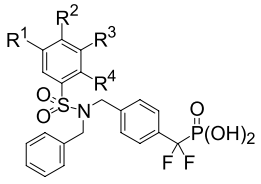
The general method for the synthesis of sulfonamides **3**–**30** is shown in Scheme 1. Bromination of 4-methyl difluoromethylenephosphonate diethylesters (R^1=H, OMe, Br) with NBS in carbon tetrachloride in the presence of benzoyl peroxide gave the benzylbromide intermediates. Mono-substituted sulfonamides were prepared by reacting benzenesulfonyl chlorides with primary amines. For those benzenesulfonylchlorides that are not commercially available, they were prepared by reaction of the substituted benzenes with chlorosulfonic acid according to the literature.[19] Alkylation of the mono-substituted sulfonamides with 4-bromomethyl phosphonates gave the di-substituted sulfonamides, which were subsequently converted to products **3**–**30** by treatment with TFA and TMSBr to hydrolyze the *t*-butyl esters and the phosphonate diethylesters. The desired phosphonic acids were isolated by preparative HPLC and their molecular composition was confirmed by ESI-MS.

The inhibitory activity against PTP1B was evaluated by our previous described method using *O*-methyl fluorescein monophosphate (OMFP) as a substrate.[18] IC_{50} values are shown in Tables 1 and 2. For representative



Scheme 1. Reagents and conditions: (a) NBS/Bz_2O_2, *hv*, CCl_4; (b) $R^2ArCH_2NH_2$, Et_3N, CH_2Cl_2; (c) $BrCH_2R^1C_6H_3CF_2PO(OEt)_2$, K_2CO_3, CH_3CN, 70 °C; (d) when R^3 contains CO_2tBu, 50% CF_3CO_2H in CH_2Cl_2; (e) TMSBr, CH_2Cl_2, then H_2O.

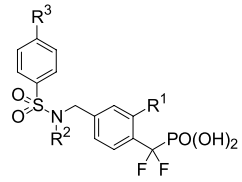
Table 1. Effects of acidic groups in C-ring on inhibition of PTP1B

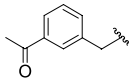
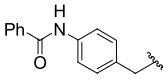
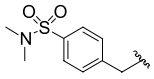
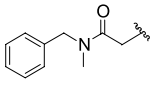
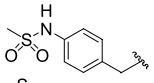
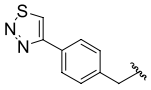
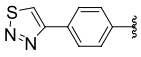
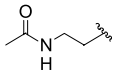
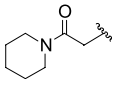
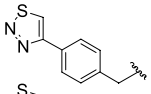
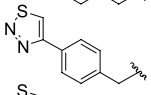
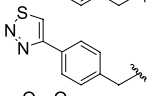
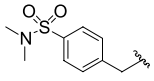
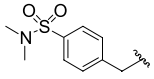
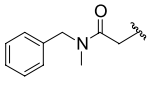


Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)[a]	K_i (μM)
3	H	H	H	H	4.2	
4	H	OCH_2COOH	H	H	0.6	1.1
5	F	OCH_2COOH	H	H	3.0	
6	Cl	OCH_2COOH	H	H	3.0	
7	Br	OCH_2COOH	H	H	4.0	
8	F	OCH_2COOH	F	H	1.0	
9	CF_3	OCH_2COOH	H	H	4.0	
10	OCF_3	OCH_2COOH	H	H	5.0	
11	CH_3	OCH_2COOH	H	H	4.0	
12	CH_3	OCH_2COOH	CH_3	H	1.9	
13	H	OH	COOH	H	2.9	
14	H	F	OCH_2COOH	F	1.6	

[a] PTP1B assays were conducted as previously reported in Ref. 18. Values are means of duplicate experiments.

Table 2. Effects of substitutions of R^1–R^3 on inhibition of PTP1B



Compound	R^1	R^2	R^3	IC_{50} (μM)[a]	K_i (μM)
15	H		OCH_2COOH	0.77	
16	H		OCH_2COOH	0.63	
17	H		OCH_2COOH	1.1	
18	H		OCH_2COOH	0.6	0.59
19	H		OCH_2COOH	1.0	
20	H		OCH_2COOH	0.18	
21	H		OCH_2COOH	0.074	0.056
22	H		OCH_2COOH	0.22	
23	H		OCH_2COOH	9.0	
24	H		OCH_2COOH	6.8	
25	H		H	0.21	0.098
26	Br		OCH_2COOH	0.035	0.053
27	OCH_3		OCH_2COOH	0.060	
28	Br		OCH_2COOH	0.028	0.013
29	OCH_3		OCH_2COOH	1.1	
30	Br		OCH_2COOH	0.031	0.014

[a] PTP1B assays were conducted as previously reported in Ref. 18. Values are means of duplicate experiments.

compounds, inhibition kinetics was also determined and K_i values are given in Tables 1 and 2.

The sulfonamide scaffold, with three readily available groups, allows one to readily explore structure–activity relationships in three directions. Our initial efforts focused on converting either the B or C aryl rings to a phenoxyacetic acid to explore if binding with the non-catalytic binding site of PTP1B could be enhanced.[9,20] Early work indicated that incorporation of the acidic group in the B-ring does not improve inhibitor potency (data not shown), whereas incorporation of an acid in

the C-ring, however, led to more active compounds. As shown in Table 1, **4** containing an acid in the *para* position of the C-ring showed a sevenfold improvement in potency compared to **3**. This compound inhibited PTP1B with an IC_{50} of 0.6 μM and is a competitive inhibitor with a K_i of 1.1 μM. Subsequently, several substituents were introduced into the C-ring of **3** to further probe interactions with the enzyme. All these attempts (**5**–**14**), however, resulted in slightly decreased activity. It is interesting that both **8** and **14** exhibit the same affinity to the enzyme with the acidic side chain in either the *para* or *meta* position, suggesting that the binding pocket for the phenoxyacetic acid group of the C-ring is not overly limited.

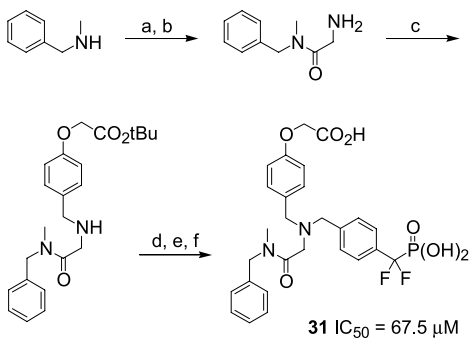
After the identification of **4**, a large number of new analogs were synthesized to explore substitutions in the B-ring on PTP1B activity. Representative examples (**15**–**30**) from this set of compounds are shown in Table 2.

Replacement of the benzyl ring of **4** by aliphatic chains lacking an aromatic group resulted in dramatic decreases in activity (**23** and **24**), suggesting that an aromatic ring is required for tight binding. Extending the distance between the sulfonamide and the B-ring aromatic group by inserting an amide group (**18**) did not alter the potency, suggesting that the enzyme binding pocket is fairly large; in agreement with this, both *para* or *meta* substituents on the B-ring aromatic group were well tolerated (**15**–**17**). The most effective substitution was a *para* thiadiazole group in the phenyl ring, the introduction of which resulted in a 10-fold improvement in potency. Thus, **21** is a potent PTP1B inhibitor with an IC_{50} of 0.074 μM and a K_i of 0.056 μM. Removing the benzylic carbon atom to make anilinosulfonamide **22** resulted in a threefold loss in activity. Of particular note is compound **25** displaying a K_i of 0.098 μM (IC_{50} 0.21 μM), despite having lost the acidic side chain considered to be important for activity.

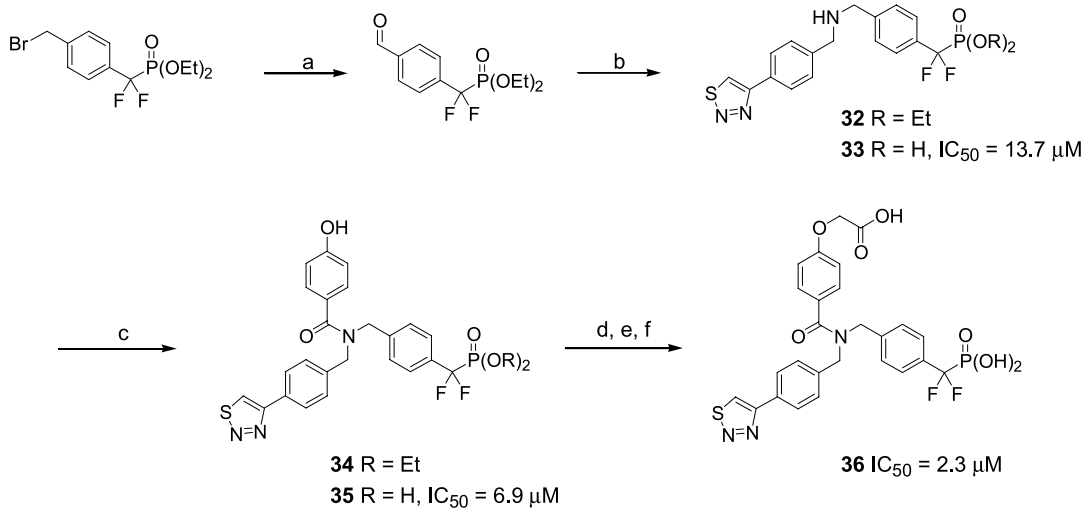
As the DFMP moiety in these compounds presumably provides the critical interactions with the enzyme, we investigated substitutions on the aryl ring bearing the DFMP group. Introduction of a methoxy group next to the DFMP group showed no beneficial effect on inhibitory activity (compounds **27** and **29**). Introduction of a bromine atom into **21** afforded **26** with twofold better binding, but identical inhibitory activity (i.e., K_i values are the same). When a bromine atom was introduced in less active compounds such as **17** or **18**, a significant increase in potency was observed. Thus, both **28** and **30** showed roughly a 40-fold improvement over **17** and **18**, and were the most potent PTP1B inhibitors in this series with K_i values of 0.013 and 0.014 μM, respectively. These results are consistent with recent results where introduction of an *ortho* bromo substituent in a deoxybenzoin-based PTP1B inhibitor resulted in 20-fold increase in potency,[10a] or where a bulky tetrazole could be accommodated *ortho* to the phosphate mimetic.[12c]

To further understand the structural requirements for these inhibitors, we next investigated isosteric replacements of the sulfonamide linking the three aryl rings. Scheme 2 shows the synthesis of **31**, which is the tertiary amine analog of **18**. Reaction of benzylmethylamine with Boc-Gly-OH followed by deprotection of the Boc group gave *N*-methyl-*N*-benzyl glycine amide. Subsequent reductive amination with OHC–C_6H_4–OCH_2- CO_2tBu afforded the corresponding secondary amine. Alkylation of the secondary amine with 4-bromomethyl diethyl-phenylphosphonate and treatment with TFA and TMSBr gave tertiary amine **31**. Compound **31**, however, proved to be a poor inhibitor with an IC_{50} of 67.5 μM. Hence, the replacement of SO_2 with CH_2 resulted in 100-fold decrease in potency, indicating that the sulfonamide does more than simply serving as a linker for the three aryl groups. The poor activity of the tertiary amine **31** is in contrast to the results observed by workers at Novo Nordisk in their 2-oxalylaminobenzoic acid series,[14b] where distal amino groups enhanced activity against PTP1B.

Shown in Scheme 3 is the synthesis of **36**, which is the carboxamide analog of sulfonamide **21**. The key step is the preparation of 4-formyl DFMP by a Sommelet reaction. Reductive amination of this aldehyde with 4-(1,2,3-thiadiazol-4-yl)benzylamine gave secondary amine **32**. The coupling of **32** with 4-hydroxybenzoic acid gave carboxyamide **34**. Subsequent alkylation of **34** with *t*-butyl bromoacetate followed by TFA and TMSBr treatment afforded **36**. Both **32** and **34** were deprotected to afford **33** and **35** for biological evaluation. The SAR is again very strong in this series, with **35** containing a 4-hydroxybenzoic acid group showing twofold better activity than **33**, and conversion of the phenol to a phenoxyacetic acid group to form **36** further improving activity by another threefold. Compound **36** inhibited PTP1B with an IC_{50} of 2.3 μM, which is 30-fold less potent than **21**, yet is still 30-fold better than **31**. Discounting the absence of the beneficial thiadiazole ring in **31** (enhancing activity up to eightfold in **18** → **21**), it is tempting to postulate that the superior H-bond accepting properties of the sulfonamide over the carboxamide and tertiary amines of **36** and **31**, respectively, accounts for the better activity of **21**. In addition, the sulfonamide framework may display a subtly different three-dimensional orientation than the carboxamide or tertiary



Scheme 2. Reagents and conditions: (a) Boc-$NHCH_2CO_2H$, EDC, CH_2Cl_2; (b) 50% TFA in CH_2Cl_2; (c) OHC-C_6H_4-OCH_2CO_2tBu, MeOH, then $Na(OAc)_3BH$; (d) $BrCH_2C_6H_4CF_2PO(OEt)_2$, K_2CO_3, CH_3CN, 70 °C; (e) 50% CF_3CO_2H in CH_2Cl_2; (f) TMSBr, CH_2Cl_2, then H_2O.



Scheme 3. Reagents and conditions: (a) $C_6H_{12}N_4$, $CHCl_3$, reflux, then 50% AcOH/H_2O; (b) thiadiazolyl-C_6H_4-CH_2NH_2, MeOH, then $Na(OAc)_3BH$; (c) HO_2C-C_6H_4-OH, EDCI, CH_2Cl_2; (d) $BrCH_2CO_2tBu$, K_2CO_3, CH_3CN; (e) 50% CF_3CO_2H in CH_2Cl_2; (f) TMSBr, CH_2Cl_2, then H_2O.

amines which provides significant interactions with the enzyme active site. Previously, sulfonamides have been used to mimic a water of hydration in the active site of PTP1B[21] or as potential PTyr mimetics[22] in the synthesis of PTP1B inhibitors. Finally, it is worth noting that the series of compounds described here is very selective against a number of other PTPs including LAR, VHR, CD45, cdc25, and SHP-2, except the closely related TC-PTP.

In summary, we have identified potent sulfonamide-based PTP1B inhibitors containing a single DFMP group and established the SAR of this class of compounds. Sulfonamide-based inhibitors are 100- and 30-times more potent than the corresponding tertiary amines and carboxamides, respectively. The presence of a thiadiazole ring and a DFMP group is sufficient to afford potent inhibitors of PTP1B, and even more potent inhibitors result from inclusion of an additional oxyacetic group into the molecules.

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