ACS Medicinal Chemistry Letters

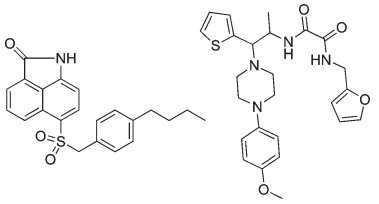
pubs.acs.org/acsmedchemlett

Identification and Characterization of Novel Inhibitors of mPTPB, an Essential Virulent Phosphatase from *Mycobacterium tuberculosis*

Lan Chen,[†,‡] Bo Zhou,[†] Sheng Zhang,[†] Li Wu,[†,‡] Yuehong Wang,[§] Scott G. Franzblau,[§] and Zhong-Yin Zhang*[,†]

[†]Department of Biochemistry and Molecular Biology, and [‡]Chemical Genomics Core Facility, Indiana University School of Medicine, 635 barnhill Drive, Indianapolis, Indiana 46202, and [§]Institute of Tuberculosis Research, University of Illinois at Chicago, Illinois 60612

ABSTRACT *Mycobacterium* protein tyrosine phosphatase B (mPTPB) is an essential virulence factor required for *Mycobacterium tuberculosis* (*Mtb*) survival in host macrophages. Consequently, mPTPB represents an exciting new target with a completely novel mechanism of action. We screened a library of 7500 compounds against mPTPB and identified several 2-oxo-1,2-dihydrobenzo[*cd*]indole-6-sulfonamide and piperazinyl-thiophenyl-ethyl-oxalamide derivatives as two distinct classes of mPTPB inhibitors. We showed that both classes of inhibitors are capable of blocking the mPTPB-mediated ERK1/2 inactivation. We further demonstrated that both classes of mPTPB inhibitors are effective in inhibiting the growth of *Mtb* in macrophages. Thus, improvement of the lead compounds may produce a novel class of anti-TB agents.



KEYWORDS *Mycobacterium tuberculosis*, mPTPB inhibitors, anti-TB agents, high throughput screening, protein tyrosine phosphatase

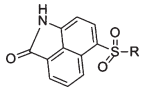
Mycobacterium tuberculosis (*Mtb*) is the causative agent of tuberculosis (TB), a leading killer worldwide that currently infects one-third of the human population.[1] Standard TB treatment takes a lengthy period of 6−9 months and uses a combination of different antibiotics that target several metabolic processes, RNA and cell wall synthesis, and energy metabolism in mycobacteria, resulting in bactericidal action.[2] The limited effectiveness and lengthy treatment lead to poor patient compliance, which often selects multidrug-resistant (MDR) and extensively resistant (XDR) TB. The emergence of MDR TB and of the virtually untreatable XDR TB has heightened the need for new targets and innovative strategies to tackle TB infections. One such strategy is to target pathogen virulence factors to compromise infection and persistence.[3] The success of *Mtb* is due in part to its ability to survive and replicate within host macrophages. *Mycobacterium* protein tyrosine phosphatase B (mPTPB) is an essential virulence factor possessed by all mycobacterial species that cause TB in humans or animals and is secreted into the cytosol of infected macrophages to target components of host signaling pathways, thus enabling bacterial survival.[4,5] Moreover, deletion of the gene encoding mPTPB attenuated growth and virulence of *Mtb* in interferon-γ (IFN-γ)-stimulated macrophages and in guinea pigs.[6] Accordingly, specific inhibitors of mPTPB may augment intrinsic host signaling pathways to eradicate TB infection.

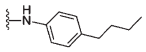
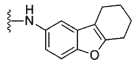
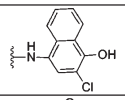
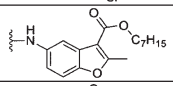
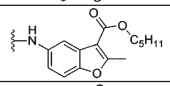
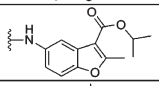
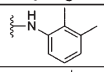
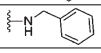
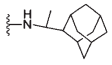
Because mPTPB inhibitors have no structural or mechanistic overlap with current drugs used for TB treatment and function within host macrophage cytosol, they have great potential to target the intracellular pool and compliment/synergize with existing therapeutic approaches. Furthermore, the lack of human orthologues of mPTPB also makes this enzyme an attractive new target for TB drug development because of minimal side effects on the host. Perhaps the greatest advantage of this target is that, due to its secretion into macrophages, it is not necessary to deliver drugs across the poorly permeable waxy mycobacterial cell wall, which has stymied many attempts to translate target inhibition to activity against the intact pathogen. Consequently, specific mPTPB inhibitors may have therapeutic value with a unique mode of action and speed up treatment of MDR and XDR TB by enabling macrophages to target the intracellular reservoirs of the bacteria that remain after exposure with current drugs. Not surprisingly, there is increasing interest in targeting mPTPB for therapeutic development.[5,7−12] However, the common architecture of the PTP active site (i.e., pTyr-binding pocket) poses a significant challenge for the acquisition of selective PTP inhibitors. Moreover, the highly positively charged pTyr-binding pocket impedes the development of inhibitors possessing favorable pharmacological properties. Thus, although several compounds

Received Date: May 12, 2010
Accepted Date: June 30, 2010
Published on Web Date: July 07, 2010

DOI: 10.1021/ml1001135 | *ACS Med. Chem. Lett.* **2010**, *1*, 355–359

Table 1. mPTPB Inhibitory Activity of the 2-Oxo-1,2-dihydrobenzo[*cd*]indole-6-Sulfonamide Analogues[a]



R Group	Compound number, and ChemDiv ID	IC_{50} (μM)
	**1**, 4236-0754	1.2± 0.1 (-pre) 1.4± 0.03 (+pre) K_i=1.1± 0.03 (non-comp)
	**2**, 5591-1074	10.3± 0.7 (-pre) 10.8± 0.7 (+pre)
	**3**, 5591-3591	15.5± 1.0 (-pre) 12.8± 1.4 (+pre)
	**4**, 5591-0431	19.5± 1.7 (-pre) 22.8± 2.5 (+pre)
	**5**, 4456-0518	21.1± 3.4 (-pre) 20.8± 4.4 (+pre)
	**6**, 3461-2082	No inhibition at 20 μM
	**7**, 5591-3082	No inhibition at 20 μM
	**8**, 3461-2296	No inhibition at 20 μM
	**9**, 4553-1947	No inhibition at 20 μM
	**10**, 3461-2192	No inhibition at 20 μM
	**11**, 3594-1274	No inhibition at 20 μM
	**12**, 3594-1275	No inhibition at 20 μM
	**13**, 3594-0887	No inhibition at 20 μM
	**14**, 3461-2191	No inhibition at 20 μM
	**15**, 4456-2552	No inhibition at 20 μM

[a] +pre, mPTPB preincubated with compound at 25 °C for 30 min; −pre, no preincubation of mPTPB and compound; and non-comp, noncompetitive inhibition mode.

have been reported to exhibit inhibitory activity against mPTPB, continued efforts are required to develop compounds with robust biochemical selectivity and in vivo activity.

To search for novel mPTPB inhibitors, we screened a structurally diverse, pharmacophore-rich, druglike small molecule library of 7500 compounds from ChemDiv against mPTPB at a final concentration of 10 μM in 384-well plates using *p*-nitrophenyl phosphate (*p*NPP) as a substrate. From the initial screen, 147 compounds showed greater than 50% inhibition at 10 μM concentration. We then carried out counter screens of the same 147 compounds against a panel of PTPs including PTP1B, TC-PTP, SHP2, FAP1, Lyp, YopH, VHR, VHX, low molecular weight PTP, and mPTPA under the same conditions. For each PTP screened, the *p*NPP concentration used was set to its K_m value, and the enzyme concentration was varied based on its catalytic activity. Compounds also possessing inhibitory activity againt one or more PTPs from the panel were removed from the original 147 mPTPB hits list, resulting in the identification of 48 compounds that displayed selectivity toward mPTPB. To further confirm the activity of the 48 selective mPTPB hits, the compounds were rescreened against mPTPB using the same activity-based assay. Out of the 48 compounds, 40 compounds displayed reproducible activity. The structures of the selective hits were analyzed, and two distinct structural groups stood out as the most promising mPTPB inhibitors: 2-oxo-1,2-dihydrobenzo-[*cd*]indole-6-sulfonamide and piperazinyl-thiophenyl-ethyl-oxalamide derivatives. Importantly, compounds from these two structural groups have never been previously reported as PTP inhibitors. Thus, we decided to pursue them further.

A total of 15 compounds belonging to the 2-oxo-1,2-dihydrobenzo[*cd*]indole-6-sulfonamide structural class were cherry-picked from the original plates for structure−activity relationship (SAR) study (Table 1). For each compound, the

DOI: 10.1021/ml1001135 | *ACS Med. Chem. Lett.* **2010**, *1*, 355–359

ACS Medicinal Chemistry Letters
pubs.acs.org/acsmedchemlett

Scheme 1. Synthesis of Compound **1**

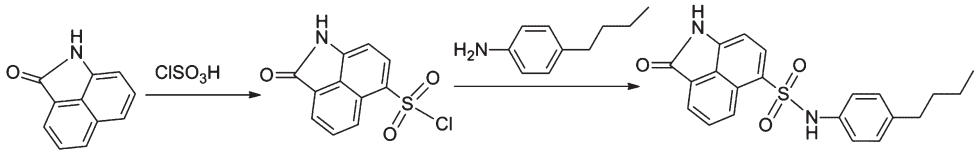


Table 2. IC_{50} Values (in μM) of **1**, **16**, and **17** for mPTPB and a Panel of Other PTPs[a]

compound	mPTPB	mPTPA	PTP1B	other PTPs
1	1.3 ± 0.1	> 50	59.4 ± 5.9	> 50
16	5.6 ± 0.2	> 50	14.4 ± 0.6	> 50
17	11.5 ± 0.6	> 50	> 50	> 50

[a] All measurements were made using *p*NPP as a substrate at pH 7.0, 25 °C, and I = 0.15 M. Other PTPs included SHP2, Lyp, FAP1, MEG2, LAR, PTPα, VHR, VHX, MKP3, PRL1, PRL3, Cdc14A, and the low molecular weight PTP.

IC_{50} value was determined under two different conditions: (1) The compound was premixed with *p*NPP, and the reaction was initialized by addition of mPTPB; and (2) the compound was premixed with mPTPB for 30 min, and the reaction was initialized by addition of *p*NPP. Reversible inhibitors are expected to exhibit similar IC_{50} values under these two conditions, while irreversible or tight-binding inhibitors will exhibit significantly reduced IC_{50} values when they are preincubated with the enzyme. As shown in Table 1, five out of the 15 compounds have IC_{50} values of ~20 μM or less. All five compounds are reversible mPTPB inhibitors as they displayed similar IC_{50} values with or without enzyme preincubation.

From Table 1, it appears that aromatic substitution at the sulfonamide position is essential for mPTPB inhibition. Interestingly, among compounds with an aromatic substitution, those with a linear hydrocarbon chain attached to the aromatic ring, such as compounds **1**, **4**, and **5**, have much higher potency against mPTPB than those (**6**−**8**) without one. In contrast, compounds with aliphatic substitutions at the sulfonamide position, such as **9**−**15**, are inactive. Of all the analogues tested, compound **1** emerged as the most potent inhibitor of mPTPB, which was selected for further characterization. Because compound **1** was no longer available for resupply from ChemDiv, we synthesized it in large quantities (Scheme 1). The benz[*cd*]indol-2(1*H*)-one was first sulfonated with chlorosulfuric acid. The resulting sulfonyl chloride was then reacted with 4-butylaniline to give the desired product. Compound **1** was then purified by high-performance liquid chromatography for use in subsequent biochemical and cellular assays.

Having established compound **1** as an inhibitor of mPTPB, we then investigated whether the inhibition was selective toward this phosphatase. Hence, the capacity of the compound to inhibit mPTPA as well as a panel of human PTPs was assessed. As shown in Table 2, compound **1** is highly selective for mPTPB, exhibiting a 51-fold preference over PTP1B and greater than 30-fold preference for mPTPB over mPTPA, SHP2, Lyp, FAP1, MEG2, LAR, PTPα, VHR, VHX, PRL1, PRL3, Cdc14A, and the low molecular weight PTP. Further kinetic analysis revealed that the mode of mPTPB inhibition by compound **1** is noncompetitive with a K_i of 1.1 ± 0.03 μM (Figure 1A).

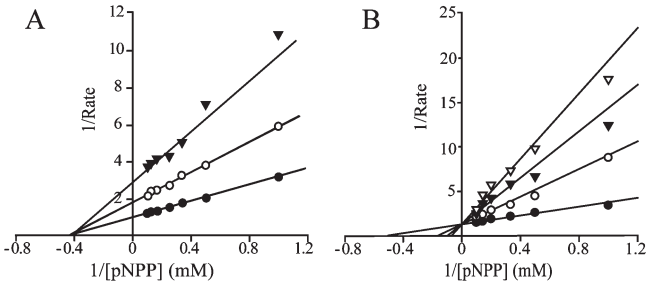


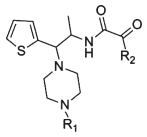
Figure 1. Lineweaver−Burk plots for compounds **1**- and **16**-mediated mPTPB inhibition. (A) Compound **1** concentrations were 0 (●), 1.0 (○), and 2.0 (▼) μM, respectively. (B) Compound **16** concentrations were 0 (●), 10 (○), 20 (▼), and 30 (▽) μM, respectively.

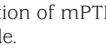
A total of 13 analogues that differ in substitutions of the piperazinyl-thiophenyl-ethyl-oxalamide core were used for SAR study (Table 3). Among this group of compounds, only analogues with aromatic substitutions at both the piperazine and the oxalamide moiety (e.g., **16**−**20**) have measurable inhibitory activity at 10 μM. In contrast, substitutions at either R1 or R2 with an aliphatic group yield analogues with a significant loss in activity. Again, compounds **16**−**20** are likely reversible inhibitors of mPTPB because of the similar the IC_{50} values obtained with or without enzyme preincubation (Table 3). Among all analogues in this group, **16** and **17** were found to be most potent against mPTPB. Unlike compound **1**, however, compounds **16** and **17** inhibited mPTPB competitively with K_i values of 3.2 ± 0.3 and 4.0 ± 0.5 μM, respectively (Figure 1B). In addition, compounds **16** and **17** are more than several fold selective for mPTPB versus all PTPs examined (Table 2). Together, the results show that compounds **1**, **16**, and **17** are among the most potent and specific mPTPB inhibitors reported to date. More importantly, compounds **1**, **16**, and **17** display excellent cellular activity as shown below.

Our ultimate goal is to develop potent and specific mPTPB inhibitors as novel anti-TB agents. Given the excellent potency and selectivity of **1**, **16**, and **17** toward mPTPB, we proceeded to evaluate their cellular efficacy in Raw264.7 macrophages engineered to express mPTPB. We had previously shown that mPTPB promotes mycobacterial survival in macrophages by downregulating the extracellular signal-regulated protein kinase (ERK1/2)-mediated production of interleukin-6 (IL-6), which is important for upregulating microbicidal activity in macrophages.[5] Thus, we predicted that inhibition of mPTPB activity should reverse the effect of the bacterial phosphatase on ERK1/2 activity in response to INF-γ stimulation. Similar to previous observations, Raw264.7 cells expressing mPTPB displayed 2.5−3-fold decreased ERK1/2 activity when compared to the vector control (Figure 2). No

DOI: 10.1021/ml1001135 | *ACS Med. Chem. Lett.* **2010**, *1*, 355–359

Table 3. mPTPB Inhibitory Activity of the Piperazinyl-Thiophenyl-Ethyl-Oxalamide Analogues[a]



R_1 Group	R_2 Group	Compound number, and ChemDiv ID	IC_{50} (μM)
		**16**, C609-0383	4.8± 0.1 (-pre) 6.3± 0.4 (+pre) K_i=3.2± 0.3 (comp)
		**17**, C609-0327	9.1± 0.5 (-pre) 14.0± 0.8 (+pre) K_i=4.0± 0.5 (comp)
		**18**, C609-0333	12.1± 0.5 (-pre) 17.5± 0.6 (+pre)
		**19**, C609-0336	11.4± 0.5 (-pre) 15.8± 0.8 (+pre)
		**20**, C609-0177	30.4± 3.4 (-pre) 25.1± 4.6 (+pre)
		**21**, C609-0368	No inhibition at 20 μM
		**22**, C609-0364	No inhibition at 20 μM
		**23**, C609-0060	No inhibition at 20 μM
		**24**, C609-0117	No inhibition at 20 μM
		**25**, C609-0316	No inhibition at 20 μM
		**26**, C609-0168	No inhibition at 20 μM
		**27**, C609-0079	No inhibition at 20 μM
		**28**, C609-0133	No inhibition at 20 μM

[a] +pre, mPTPB preincubated with compound at 25 °C for 30 min; −pre, no preincubation of mPTPB and compound; and comp, competitive inhibition mode.

change in ERK1/2 phosphorylation was observed when the catalytically inactive mPTPB/C106S was introduced to the macrophage, indicating that mPTPB's phosphatase activity is required for the decrease in ERK1/2 activity. Consistent with compound **1** being an mPTPB inhibitor, treatment of mPTPB expressing Raw264.7 macrophages with 5−10 μM **1** restored the INF-γ-induced ERK1/2 activation (Figure 2A). Similarly, compounds **16** and **17** also reversed the mPTPB-induced ERK1/2 inactivation in a dose-dependent manner (Figure 2B). To ensure that the cellular activity displayed by compounds **1**, **16**, and **17** was not due to nonspecific effects, we also evaluated compounds **15** and **22**, which are inactive analogues of compounds **1** and **16**, respectively (Tables 1 and 3). As shown in Figure 2, compounds **15** and **22** were unable to block the mPTPB-induced ERK1/2 inactivation. This observation plus the fact that three structurally unrelated classes of mPTPB inhibitors (compounds **1**, **16**, and **17** and I-A09, a benzofuran salicylic acid derivative[5]) exert similar biochemical changes inside the cell strongly suggest that the ability of these compounds to block the mPTPB-mediated cellular processes is unlikely due to off-target effects. Remarkably, compounds **1**, **16**, and **17** inhibited mPTPB in intact cells with similar potency as those observed toward the isolated enzyme, whereas most previous PTP

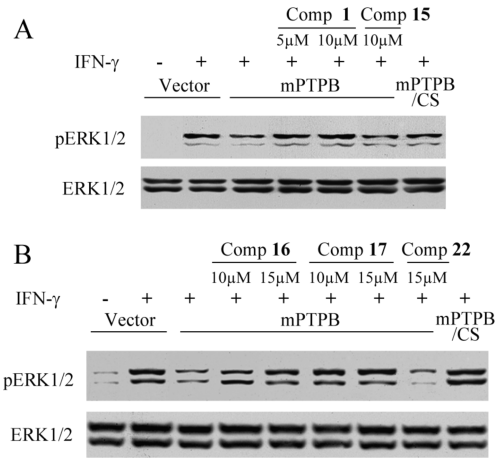


Figure 2. mPTPB inhibitors block mPTPB-mediated ERK1/2 inactivation. Cells overexpressing mPTPB have decreased ERK1/2 activity that can be reversed by treatment with compound **1** (A) and compounds **16** and **17** (B).

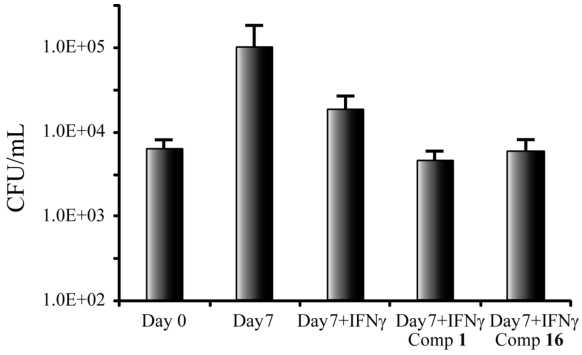


Figure 3. Compounds **1** and **16** reduce bacterial load in infected macrophages. Mouse macrophages were exposed to infectious *Mtb*, and the infection was allowed to establish until the bacterial load approached 10000 CFU/mL. Parallel cultures were treated with IFN-γ alone or with mPTPB inhibitors **1** or **16** at a 10 μM concentration. After a further 7 days, the cultures were washed and lysed, and the bacterial load was determined by standard methods.

inhibitors have shown 100−10000-fold loss of potency between biochemical and cellular assays. Together, the data demonstrate that **1**, **16**, and **17** are cell permeable and can effectively restore a major host pathway targeted by mPTPB.

As we observed excellent cellular activity of compounds **1**, **16**, and **17** in Raw264.7 cells, we next investigated whether they could inhibit the growth of *Mtb* in macrophages. Cultures of a mouse macrophage J774A.1 cell line infected with actively growing *Mtb* Erdman were treated with a 10 μM concentration of either compound **1** or **16** starting on day 0, and the cultures were allowed to incubate for a further 7 days before assessment of the remaining bacterial load in the cells.[13] The bacterial population in the macrophages increased nearly 16-fold by day 7 (Figure 3). Consistent with the genetic observation that deletion of mPTPB impairs the ability of *Mtb* to survive in activated macrophages,[6] compound **1** or **16** was able to further potentiate the effect of INF-γ, leading to nearly complete blockage of bacterial growth. To exclude the possibility that the observed decrease in bacterial load was due to compound cytotoxicity, we found

DOI: 10.1021/ml1001135 | *ACS Med. Chem. Lett.* **2010**, *1*, 355–359

that macrophage viability was unaffected by the presence of **1** or **16** at concentrations up to 100 μM. We also found the minimum inhibitory concentrations for **1** and **16** on extracellular *Mtb* H37Rv and *Mtb* Erdman to be >100 μM, indicating a lack of bactericidal activity of these compounds. Thus, compounds **1** and **16** inhibit intracellular TB growth in the macrophage, presumably by impairing mPTPB's ability to overcome host defense mechanisms.

In summary, we have identified and characterized two distinct structural classes of novel mPTPB inhibitors: 2-oxo-1,2-dihydrobenzo[*cd*]indole-6-sulfonamide and piperazinyl-thiophenyl-ethyl-oxalamide derivatives. Both classes are reversible inhibitors, but the 2-oxo-1,2-dihydrobenzo[*cd*]indole-6-sulfonamide analogues (as exemplified by compound **1**) inhibit mPTPB in a noncompetitive manner, while the piperazinyl-thiophenyl-ethyl-oxalamide analogues (as exemplified by compounds **16** and **17**) inhibit mPTPB competitively. The availability of a number of analogues of both structural classes made possible a preliminary SAR study. Importantly, both classes of compounds are capable of reversing the altered cellular immune response induced by the bacterial phosphatase and phenocopying the effect of mPTPB deletion, attenuating TB growth in host cells.

Finally, the fact that compounds **1**, **16**, and **17** are highly efficacious in cell-based assays has significant implication in drug discovery efforts targeting the PTPs, which provide an exciting array of infectious, diabetes/obesity, autoimmunity, and oncology targets.[14] Obtaining PTP inhibitors with optimal potency and pharmacological properties has been difficult, due primarily to the highly conserved and positively charged nature of the active site pocket shared by all PTP family members. Consequently, almost all existing PTP inhibitors contain negatively charged nonhydrolyzable pTyr mimetics and suffer poor membrane permeability and cellular efficacy.[15] It is noteworthy that compounds **1** and **16** have no formal charges, indicating that it is possible to target the PTPs with neutral compounds having more acceptable physicochemical properties. Improvement of compounds **1** and **16** as well as their structurally related analogues in their selectivity toward mPTPB over its human counterparts and their potency in vivo thus may lead to the development of a novel class of anti-TB agents that could be used either alone or in combination with other existing drugs to treat TB and shorten treatment regimens.

SUPPORTING INFORMATION AVAILABLE

Details on mPTPB expression and purification, high-throughput screening, kinetic characterization of mPTPB inhibitors, synthesis of compound **1**, chemical data and purity information for compounds **1**, **16**, and **17**, immunoblotting, macrophage assay, MIC, and cytotoxicity measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author: *To whom correspondence should be addressed. E-mail: zyzhang@iupui.edu.

ACKNOWLEDGMENT This work was supported by National Institutes of Health Grants CA69202 and CA126937. The high-throughput screening was performed at the Indiana University Chemical Genomics Core Facility.

REFERENCES

(1) Butler, D. New fronts in an old war. *Nature* **2000,** *406*, 670–672.
(2) Zhang, Y. The magic bullets and Tuberculosis drug targets. *Annu. Rev. Pharmacol. Toxicol.* **2005,** *45*, 529–564.
(3) Clatworthy, A. E.; Pierson, E.; Hung, D. T. Targeting virulence: A new paradigm for antimicrobial therapy. *Nat. Chem. Biol.* **2007,** *3*, 541–548.
(4) Koul, A.; Herget, T.; Klebl, B.; Ullrich, A. Interplay between mycobacteria and host signalling pathways. *Nat. Rev. Microbiol.* **2004,** *2*, 189–202.
(5) Zhou, B.; He, Y.; Zhang, X.; Xu, J.; Luo, Y.; Wang, Y.; Franzblau, S. G.; Yang, Z.; Chan, R. J.; Liu, Y.; Zheng, J.; Zhang, Z.-Y. Targeting mycobacterium protein tyrosine phosphatase B for anti-tuberculosis agents. *Proc. Natl. Acad. Sci. U.S.A.* **2010,** *107*, 4573–4578.
(6) Singh, R.; Rao, V.; Shakila, H.; Gupta, R.; Khera, A.; Dhar, N.; Singh, A.; Koul, A.; Singh, Y.; Naseema, M.; Narayanan, P. R.; Paramasivan, C. N.; Ramanathan, V. D.; Tyagi, A. K. Disruption of mptpB impairs the ability of *Mycobacterium tuberculosis* to survive in guinea pigs. *Mol. Microbiol.* **2003,** *50*, 751–762.
(7) Müller, D.; Krick, A.; Kehraus, S.; Mehner, C.; Hart, M.; Küpper, F. C.; Saxena, K.; Prinz, H.; Schwalbe, H.; Janning, P.; Waldmann, H.; König, G. M. Brunsvicamides A-C: Sponge-related cyanobacterial peptides with *Mycobacterium tuberculosis* protein tyrosine phosphatase inhibitory activity. *J. Med. Chem.* **2006,** *49*, 4871–4878.
(8) Nören-Müller, A.; Reis-Corrêa, I., Jr.; Prinz, H.; Rosenbaum, C.; Saxena, K.; Schwalbe, H. J.; Vestweber, D.; Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. Discovery of protein phosphatase inhibitor classes by biology-oriented synthesis. *Proc. Natl. Acad. Sci. U.S.A.* **2006,** *103*, 10606–10611.
(9) Grundner, C.; Perrin, D.; Hooft van Huijsduijnen, R.; Swinnen, D; Gonzalez, J.; Gee, C. L.; Wells, T. N.; Alber, T. Structural basis for selective inhibition of *Mycobacterium tuberculosis* protein tyrosine phosphatase PtpB. *Structure* **2007,** *15*, 499–509.
(10) Soellner, M. B.; Rawls, K. A.; Grundner, C.; Alber, T.; Ellman, J. A. Fragment-based substrate activity screening method for the identification of potent inhibitors of the *Mycobacterium tuberculosis* phosphatase PtpB. *J. Am. Chem. Soc.* **2007,** *129*, 9613–9615.
(11) Beresford, N. J.; Mulhearn, D.; Szczepankiewicz, B.; Liu, G.; Johnson, M. E.; Fordham-Skelton, A.; Abad-Zapatero, C.; Cavet, J. S.; Tabernero, L. Inhibition of MptpB phosphatase from *Mycobacterium tuberculosis* impairs mycobacterial survival in macrophages. *J. Antimicrob. Chemother.* **2009,** *63*, 928–936.
(12) Tan, L. P.; Wu, H.; Yang, P. Y.; Kalesh, K. A.; Zhang, X.; Hu, M.; Srinivasan, R.; Yao, S. Q. High-throughput discovery of *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MptpB) inhibitors using click chemistry. *Org. Lett.* **2009,** *11*, 5102–5105.
(13) Falzari, K.; Zhu, Z.; Pan, D.; Liu, H.; Hongmanee, P.; Franzblau, S. G. In vitro and in vivo activities of macrolide derivatives against *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.* **2005,** *49*, 1447–1454.
(14) Zhang, Z.-Y. Protein tyrosine phosphatases: Prospects for therapeutics. *Curr. Opin. Chem. Biol.* **2001,** *5*, 416–423.
(15) Zhang, S.; Zhang, Z.-Y. PTP1B as a drug target: Recent development in PTP1B inhibitor discovery. *Drug Discovery Today* **2007,** *12*, 373–381.

DOI: 10.1021/ml1001135 | *ACS Med. Chem. Lett.* **2010,** *1*, 355–359