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Synthesis and Structure−Activity Relationships of Aza- and Diazabiphenyl Analogues of the Antitubercular Drug (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (PA-824)

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New heterocyclic analogues of the potent biphenyl class derived from antitubercular drug PA-824 were prepared, aiming to improve aqueous solubility but maintain high metabolic stability and efficacy. The strategy involved replacement of one or both phenyl groups by pyridine, pyridazine, pyrazine, or pyrimidine, in order to reduce lipophilicity. For *para*-linked biaryls, hydrophilicities (ClogP) correlated with measured solubilities, but highly soluble bipyridine analogues displayed weak antitubercular activities. A terminal pyridine or proximal heterocycle allowed retention of potency and provided solubility improvements, particularly at low pH, with examples from the latter classes displaying the better *in vivo* efficacies, high metabolic stabilities, and excellent pharmacokinetics. Five such compounds were >100-fold better than the parent drug in a mouse model of acute *Mycobacterium tuberculosis* infection, and two orally bioavailable pyridine analogues (3−4-fold more soluble than the parent at low pH) were superior to antitubercular drug OPC-67683 in a chronic infection model.

Introduction

The contagious airborne disease tuberculosis (TB)[a] has reemerged as a serious health threat, fueled by the spread of multidrug-resistant (MDR) strains and synergy with the HIV pandemic, prompting the World Health Organization in 1993 to declare it a global emergency. Despite recent control efforts based largely around DOTS (directly observed therapy short course; using four drugs over 6−9 months), 9 million new TB cases are reported annually (0.5 million MDR-TB), and many die (mortality estimated at 1.8 million in 2008, including 0.5 million HIV-positive individuals).[1,2] Furthermore, achievement of the Stop TB Partnership target of halving 1990 rates of prevalence and mortality by 2015 has recently been described as "appearing impossible in African countries" and therefore "unlikely globally", based on current trends.[2] This is largely a result of poverty, inadequate access to proper therapy, and HIV coinfection (one-third of HIV sufferers also have TB, but treatment can be complicated by drug−drug interactions and higher toxicities; poor treatment adherence then leads to disease progression and drug resistance).[1,3] More effective, low-cost drugs are urgently required to shorten treatment times and better meet the increasing challenges of MDR-TB.[1,3,4]

The (6*S*)-2-nitroimidazo[2,1-*b*][1,3]oxazines, exemplified by PA-824 (**1**),[5] and the related 6-nitroimidazo[2,1-*b*][1,3]oxazoles, exemplified by OPC-67683 (**2**),[6] are highly efficacious against both replicating and nonreplicating persistent forms of *Mycobacterium tuberculosis* (*M. tb*, the causative agent of TB). The latter activity reportedly arises from an unusual route of reductive metabolism of the nitroimidazole ring,[7] leading to the release of nitric oxide as an active species.[8] Compounds **1** and **2** and the even more lipophilic diarylquinoline TMC-207 (**3**)[9] (Chart 1) are currently in phase II clinical trials for the treatment of both drug-susceptible and drug-resistant TB.[3,4]

In a previous SAR study[10] of biphenyl analogues of **1**, we showed that within this class there were positive correlations between aerobic MIC potency and both overall compound lipophilicity and the electron-withdrawing capability of substituents on the terminal ring, with several analogues (e.g., **4**−**6**) showing markedly superior activity to **1**, both *in vitro* and *in vivo*. For example, **5** and **6** gave efficacy enhancements over **1** of >205-fold and 419-fold in lung colony forming unit (CFU) reduction, respectively, following oral dosing in a mouse model of acute TB infection. The effectiveness of these highly lipophilic agents (cf. **2**, **3**) may in part be related to their ability to penetrate the exceptionally lipophilic cell wall of *M. tb*.[11] Despite such encouraging results, we noted that the very poor aqueous solubilities of the biphenyl analogues

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[a] Abbreviations: TB, tuberculosis; MDR, multidrug-resistant; DOTS, directly observed therapy short course; *M. tb*, *Mycobacterium tuberculosis*; SAR, structure−activity relationship; MIC, minimum inhibitory concentration; CFU, colony forming unit; NBS, *N*-bromosuccinimide; DMF, *N*,*N*-dimethylformamide; SD, standard deviation; AUC, area under the curve; HREIMS, high-resolution electron impact mass spectrometry; HRFABMS, high-resolution fast atom bombardment mass spectrometry; HRESIMS, high-resolution electrospray ionization mass spectrometry; APCI MS, atmospheric pressure chemical ionization mass spectrometry; THF, tetrahydrofuran; AIBN, azobisisobutyronitrile; DME, dimethoxyethane; DMSO, dimethyl sulfoxide; PBS, phosphate-buffered saline; PAR, peak area ratio; IS, internal standard; TFAA, trifluoroacetic anhydride; NMM, *N*-methylmorpholine.

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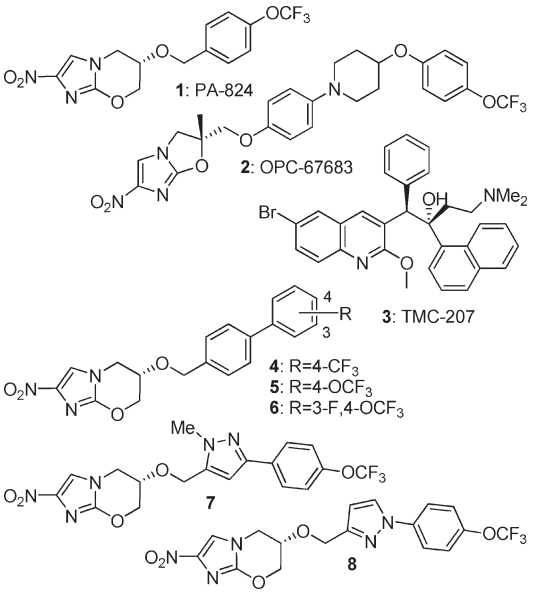
Chart 1. Structures of Antitubercular Agents

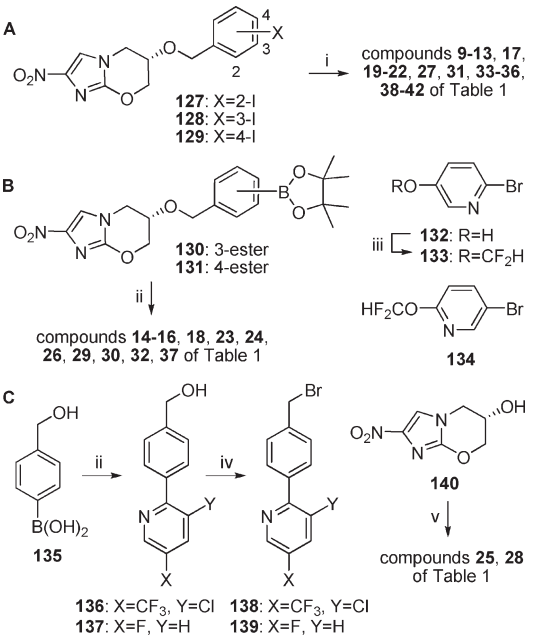


(e.g., $\ll$0.5 μg/mL for **5**, $\gg$20-fold less than **1**[12]) would likely limit their oral bioavailabilities at higher doses, reducing their potential utility as TB drugs. Indeed, absorption issues were noted during clinical trials of the similarly lipophilic **2** and necessitated changes to its formulation.[13] Furthermore, high plasma binding (expected to be much greater for **5** and **6** than the 94% found for **1**[14]), while providing the opportunity for a longer half-life possibly suitable for intermittent administration, may also be associated with lower than expected activity in the clinical setting.[15] Although dry powder aerosols show some promise for the alternative local drug delivery of **1** (guinea pig model),[16] such alternative routes of administration seem unlikely to overcome all of these challenges. However, attempts to improve the aqueous solubility of the biphenyl class simply with appended hydrophilic groups led to a dramatic loss of potency (particularly *in vivo*).[10]

In an alternative solubilization strategy, we recently explored the replacement of the proximal phenyl ring in the biaryl side chain (closest to the ether linkage) with a variety of more hydrophilic five-membered ring heterocycles.[12] Several of the resulting arylheterocyclic derivatives showed encouraging solubility improvements over biphenyl analogues, and four nitrogen heterocyclic subseries were found to provide higher *in vitro* potencies than predicted (based on their lipophilicities). Two pyrazole-based examples (**7**, **8**), displaying improved solubilities over **5** (**8** was twice as soluble as **1**), were also found to be significantly superior to **1** in the mouse model above (efficacy enhancements over **1** of 12-fold and 41-fold for **7** and **8**, respectively). However, pyrazole analogue **8** exhibited a less ideal microsomal stability profile,[12] a deficiency that we hypothesized might be circumvented by using six-membered ring heterocycles instead. We also expected that these new heterocycles could provide analogues with higher efficacy by providing a more linear geometry for the biaryl side chain, which, based on our earlier findings,[10] appeared particularly favorable for binding to proposed[17] hydrophobic regions in the nitroreductase.

Herein, we now describe the results of a systematic study of aza- and diazabiphenyl analogues of **1**, which represent alternative, less lipophilic, weakly basic (chargeable) derivatives of the biphenyl class, seeking more stable second generation

Scheme 1[a]



[a] Reagents and conditions: (i) $ArB(OH)_2$ (or pinacol ester), toluene, EtOH, 2 M K_2CO_3, $Pd(dppf)Cl_2$ under N_2, reflux, 10 min−3 h; (ii) substituted halopyridine, toluene, EtOH, 2 M K_2CO_3 (or Na_2CO_3), $Pd(dppf)Cl_2$ under N_2, reflux, 0.5−3 h; (iii) $NaOCOCClF_2$, K_2CO_3, DMF, 80 °C, 20 h; (iv) NBS, PPh_3, CH_2Cl_2, 20 °C, 3−4 h; (v) **138** or **139**, NaH, DMF, 0−20 °C, 2.2−2.5 h.

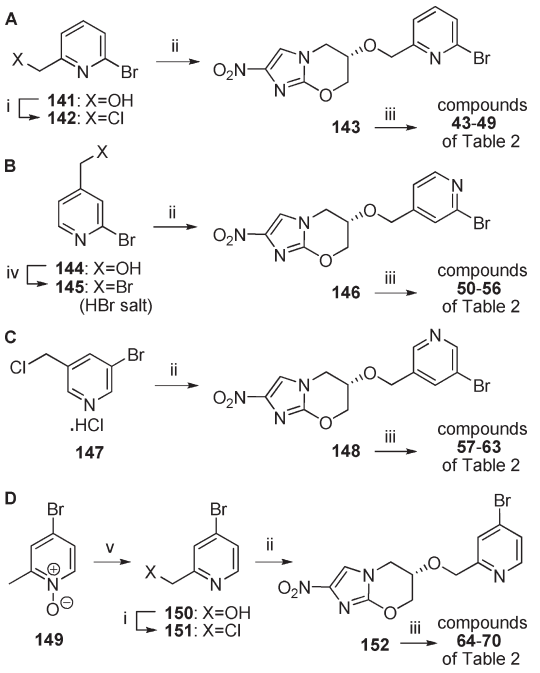
candidates having better aqueous solubilities, acceptable pharmacokinetics, high oral bioavailabilities, and robust efficacies in mouse models of advanced disease.

Chemistry

Compounds **9**−**42**, having a substituted pyridine as the terminal ring of the biaryl side chain, were generally prepared from either the known[10] iodobenzyl ethers **127**−**129** or the known[10] pinacol boronate esters **130** and **131** via Suzuki couplings with the corresponding substituted pyridinylboronic acids or halopyridines, respectively (Scheme 1A,B). Due to the difficulty in obtaining the isomeric halo(trifluoromethoxy)-pyridines,[18] the corresponding difluoromethoxypyridine analogues (**16**, **29**, **37**) were targeted instead. The OCF_2H substituent has similar electronic properties to OCF_3 (σ_m and σ_p 0.31 and 0.18, compared with 0.38 and 0.35, respectively),[19] and the required known[20,21] bromopyridine derivatives **133** and **134** were readily accessed from 6-bromo-3-pyridinol (**132**) and 5-bromo-2(1*H*)-pyridinone, respectively, via difluoromethylations with sodium chlorodifluoroacetate.[22] An alternative synthetic route to the final compounds, involving initial assembly of the biaryl side chain prior to coupling with the known[23] chiral oxazine alcohol **140** (exemplified for **25** and **28**), was preferred for the larger scale synthesis of some analogues obtained from boronate ester **131**, due to better overall yields from **140** and greater ease of purification (Scheme 1C). Thus 4-(hydroxymethyl)phenylboronic acid (**135**) readily underwent Suzuki couplings with halopyridines to provide the required biaryl alcohols (**136**, **137**), which were then brominated with NBS/PPh_3[24] and coupled to alcohol **140**.

Biaryl analogues containing a pyridine ring proximal to the ether linkage (**43**−**103**) were predominantly synthesized via Suzuki couplings on isomeric bromopicolyl ether derivatives

Scheme 2[a]

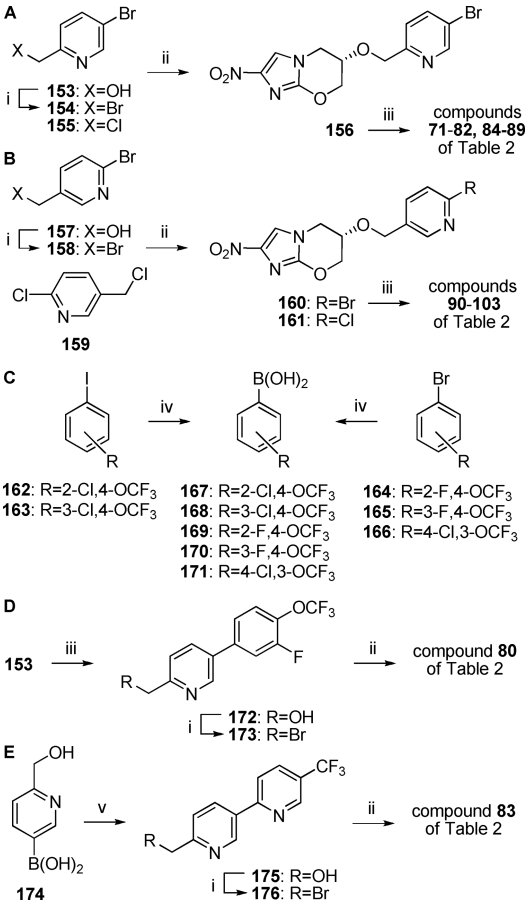


[a] Reagents and conditions: (i) $SOCl_2$, $CHCl_3$, 0−20 °C, 20 h, or reflux, 1 h; (ii) **140**, NaH, DMF, −5 to 20 °C, 1−16 h; (iii) $ArB(OH)_2$ (or pinacol ester), toluene, EtOH, 2 M K_2CO_3, $Pd(dppf)Cl_2$ under N_2, reflux, 10 min −6 h; (iv) $SOBr_2$, CH_2Cl_2, 0−20 °C, 15 h; (v) TFAA, 20 °C, 30 min, then reflux, 30 min, then aqueous $NaHCO_3$, 20 °C, 16 h.

(**143**, **146**, **148**, **152**, **156**, **160**), obtained by base-catalyzed alkylation of alcohol **140** with various picolyl halides (Schemes 2 and 3). For the *meta*-linked biaryls (Scheme 2), 2-bromo-6-(chloromethyl)pyridine[25] (**142**), 3-bromo-5-(chloromethyl)-pyridine hydrochloride[26] (**147**), and 4-bromo-2-(chloromethyl)-pyridine (**151**) were prepared from precursor alcohols by chlorination with thionyl chloride [in the case of **147**, prior conversion of (5-bromo-3-pyridinyl)methanol into its hydrochloride salt was necessary to avoid undesirable side reactions[26]]. (4-Bromo-2-pyridinyl)methanol[27] (**150**) was more conveniently obtained from 4-bromo-2-methylpyridine 1-oxide[28] (**149**) by a one-pot reaction with trifluoroacetic anhydride[29] (rather than Ac_2O[27]), followed by a mild *in situ* base-catalyzed hydrolysis of the resulting trifluoroacetate ester, with the product being sufficiently pure to use directly in the following chlorination step (to give **151**). However, yields for the alkylation of alcohol **140** using these picolyl chlorides were only moderate (30−54%), and attempts to acquire pure **146** by this methodology were largely unsuccessful. Therefore, (2-bromo-4-pyridinyl)methanol (**144**) was instead reacted with thionyl bromide to provide the picolyl bromide **145**[30] (isolated as a crystalline HBr salt), from which the desired ether **146** was obtained cleanly and in good yield (65%, Scheme 2B), although Suzuki couplings on this substrate were somewhat capricious.

In contrast to the above results for *meta*-linked biaryls, *para*-halopicolyl ethers **156**, **160**, and **161** were synthesized in high yield (>80%) from both picolyl chlorides and bromides (Scheme 3A,B and Supporting Information). 5-Bromo-2-(bromomethyl)pyridine[31] (**154**) and 2-bromo-5-(bromomethyl)-pyridine[31,32] (**158**), usually prepared by free radical bromination of the corresponding bromopicolines, were readily obtained in much better yield and purity from the precursor alcohols (**153**, **157**), by bromination with NBS/PPh_3 (0.1−5 g scale), or by mesylation and displacement with lithium bromide. 5-Bromo-

Scheme 3[a]

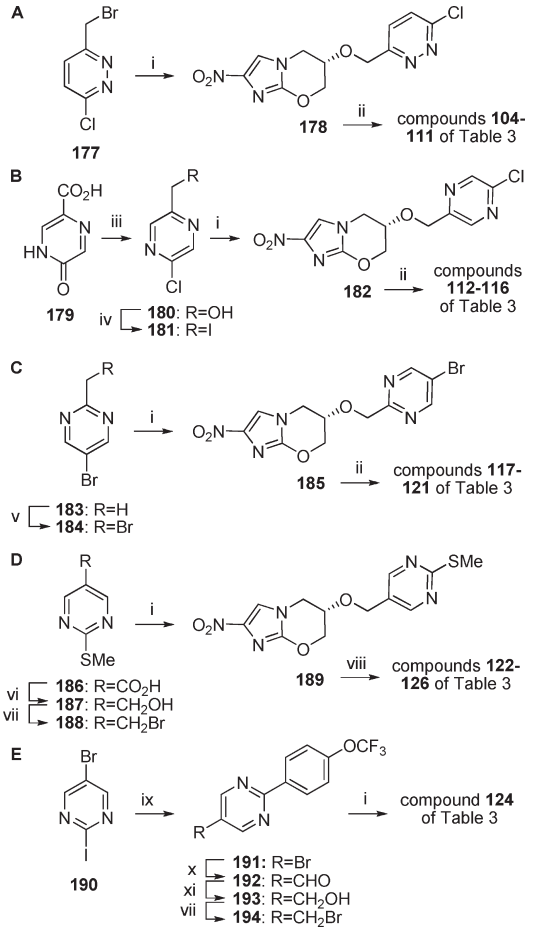


[a] Reagents and conditions: (i) NBS, PPh_3, CH_2Cl_2, 20 °C, 3−3.5 h; or MsCl, Et_3N, THF, 0 °C, 1 h, then LiBr, Me_2CO, reflux, 1 h; (ii) **140**, NaH, DMF, 0−20 °C, 2−3 h; (iii) $ArB(OH)_2$ (or pinacol ester), toluene, EtOH, 2 M K_2CO_3 (or Na_2CO_3), $Pd(dppf)Cl_2$ under N_2, reflux, 20 min −21 h; (iv) *n*BuLi, $B(OiPr)_3$, toluene, THF, −78 °C, 4 h, then −78 to −20 °C, 2 h, then 2 N HCl, −20 to 20 °C, 40 min; (v) 2-Cl-5-CF_3pyridine, toluene, EtOH, 2 M Na_2CO_3, $Pd(dppf)Cl_2$ under N_2, 88 °C, 4 h.

2-(chloromethyl)pyridine[29] (**155**) was also acquired from **153**, following treatment with thionyl chloride. However, whereas the bromopicolyl ether derivatives were generally excellent substrates for Suzuki coupling, a similar reaction employing chloropicolyl ether **161** (derived from commercial chloromethylpyridine **159**) was much slower and proved challenging to complete. Rare halo(trifluoromethoxy)phenylboronic acids **167**−**171**[33−37] required for the synthesis of compounds **77**−**81** and **96**−**100** were readily obtained in high yield from (commercial or known[10]) substituted iodo- or bromobenzenes (**162**−**166**) via a lithium−halogen exchange and "in situ quench" protocol (Scheme 3C).[38] Following drying, some of these arylboronic acids were found by NMR to contain varying amounts of the corresponding arylboroxines[39] (cyclic anhydride form), as expected, but reacted without complication in Suzuki coupling reactions to give the desired products cleanly (except in the case of the 2-Cl analogue **96**, where ∼10% dechlorination of the product was unexpectedly observed, necessitating repeated chromatographic purification cycles).

As noted above, construction of the side chain first, prior to coupling with alcohol **140** (exemplified here for **80**, Scheme 3D), was alternatively preferred for the larger scale synthesis of some analogues due to greater ease of final purification. Importantly, this approach also enabled synthesis of bipyridine **83**

Scheme 4[a]



[a] Reagents and conditions: (i) **140**, NaH, DMF, −78 to 0 °C, 0.5−1 h (−42 °C, 2 h for **178**); (ii) $ArB(OH)_2$, toluene, EtOH, 2 M K_2CO_3, $Pd(dppf)Cl_2$ under N_2, reflux, 0.5 h; (iii) $SOCl_2$, catalytic DMF, reflux, 1 h, then $NaBH_4$, dioxane, H_2O,10−20 °C, 1 h; (iv) MsCl, Et_3N, THF, 0 °C, 0.5 h, then NaI, Me_2CO, reflux, 1 h; (v) NBS, AIBN, CCl_4, 60 °C, 3 h; (vi) *i*BuOCOCl, NMM, DME, 0 °C, 20 min, then $NaBH_4$, H_2O, 0 °C, 10 min; (vii) MsCl, Et_3N, CH_2Cl_2 or THF, 0 °C, 0.5−1 h, then LiBr, Me_2CO, reflux, 1 h; (viii) $ArB(OH)_2$, CuTC, P(2-furyl)$_3$, $Pd_2(dba)_3 \cdot CHCl_3$ under N_2, THF, 50 °C, 18 h; (ix) 4-$OCF_3PhB(OH)_2$, toluene, Na_2CO_3, H_2O, $Pd(PPh_3)_4$ under N_2, reflux, 17.5 h; (x) *n*BuLi, THF, −95 °C, 30 s, then DMF, −90 °C, 20 min; (xi) $NaBH_4$, MeOH, 0 °C, 1 h.

(Scheme 3E), which was challenging to prepare from **156** due to facile protodeboronation of the highly electron deficient trifluoromethyl-substituted 2-pyridyl boronate ester (a recently reported copper(I)-facilitated Suzuki coupling reaction[40] provides an alternative solution to this problem). Thus, 6-(hydroxymethyl)-3-pyridinylboronic acid (**174**) underwent a successful Suzuki coupling with 2-chloro-5-(trifluoromethyl)pyridine to give bipyridine alcohol **175** in low yield, which was elaborated to **83** via bromination (NBS/PPh_3) and alkylation reactions, as above.

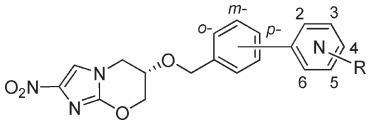
Further biaryl analogues containing a pyridazine, pyrazine, or pyrimidine ring proximal to the ether linkage (**104**−**126**) were predominantly generated via Suzuki couplings on chloro- or bromoheterocyclic methyl ether derivatives of alcohol **140** (**178**, **182**, and **185**, Scheme 4A−C). Chloropyridazine **178** and bromopyrimidine **185** were prepared from known bromomethyl precursors, **177**[41] and **184**,[42] obtained via free radical bromination of methyl-substituted haloheterocycles. In contrast, the synthesis of chloropyrazine **182** was achieved via unstable iodide **181** (obtained by mesylation of alcohol **180** and iodide displacement) after an attempted bromination (PBr_3) of **180** resulted in partial replacement of the ring chlorine (leading to potential side reactions in the alkylation step). Alcohol **180**[43] was itself derived[44] from the commercial acid **179** via reduction of the acid chloride. The 2-aryl-5-pyrimidinylmethyl analogues (**122**−**126**) were initially accessed from a 2-methylthiopyrimidine precursor, rather than a halopyrimidine derivative, in order to avoid competing pyrimidinyl ether formation during base-catalyzed coupling of the halomethylpyrimidine with alcohol **140**. 2-(Methylthio)pyrimidine-5-carboxylic acid[45] (**186**) (obtained from its methyl ester[46]), was first reduced (with $NaBH_4$, via the *in situ*-formed mixed anhydride) to alcohol **187**,[47] which was successively brominated (via mesylation and bromide displacement) and reacted with **140** as usual (Scheme 4D). Leibeskind−Srogl cross-coupling[48] of the resulting 2-(methylthio)pyrimidine **189** with arylboronic acids then furnished the required biaryl derivatives in moderate yield (∼40%) on a small (50 mg) scale. However, since purification of the final products from this reaction was not straightforward, an alternative route was developed for the larger scale synthesis of **124**, in which the biaryl side chain was assembled first (Scheme 4E). Thus, a selective Suzuki coupling on 2-iodo-5-bromopyrimidine (**190**) gave the known[49] 2-aryl derivative **191**, from which pyrimidinecarboxaldehyde **192** was obtained in good yield (74%) following a sufficiently low-temperature[50] (−95 °C) metal−halogen exchange and rapid DMF quench. Elaboration to bromide **194**, via the mesylate of derived alcohol **193**, followed by coupling to alcohol **140**, then completed an improved (0.5 g) synthesis of **124**.

Results and Discussion

Tables 1−3 provide physicochemical and biological data for 118 new analogues of **1**, in which one or both of the phenyl groups of the previously described[10] biphenyl class was replaced by pyridine, pyridazine, pyrazine, or pyrimidine. Compound lipophilicities were estimated by CLogP values, calculated using ACD LogP/LogD prediction software (version 8.0; Advanced Chemistry Development Inc., Toronto, Canada). The comparative effects of these heterocyclic replacements on ClogP values were evaluated for representative compound subsets by calculating mean differences in ClogP values between compounds in each subset and biphenyl analogues bearing the same substituents (Table 4). Broadly, these showed that replacement of one of the phenyl groups by pyridine lowered ClogP values by ∼1.3 units, whereas replacement by a diaza heterocycle had a more variable effect, with lipophilicity differences ranging from −1.41 (3′,5′-pyrimidine) to −2.84 (pyridazine). Additional replacement of the second phenyl group by pyridine further reduced ClogP values (by ∼0.6−1.1 units) providing particularly hydrophilic analogues.

Solubilities in water at pH = 7 were measured for all of the solid compounds with sufficient stock available (111 of the 118 analogues). In general, the compounds that displayed the highest solubilities included monopyridine analogues lacking substituents adjacent to the pyridine nitrogen (e.g., **9**, **17**, **31**, **35**, **59**), bipyridine analogues (e.g., **56**, **70**, **82**−**89**, **101**−**103**), and (to a lesser extent) the pyridylpyrazine and pyridylpyrimidine analogues (**116**, **121**), consistent with their greater hydrophilic character. The *ortho*- and *meta*-linked biaryls also displayed higher solubilities than the *para*-linked biaryls overall. Although calculated log *P* values are only a broad indicator of aqueous solubility, which is also influenced by factors such as crystallinity and H-bond networks, eq 1 shows

Table 1. Physicochemical Properties and MIC Values for Heterobiaryl Analogues of **1** Having a Terminal Pyridine Ring



				solubility[b] (μg/mL)		MIC (μM)[c]	
compd	link	R	CLogP[a]	pH = 7	pH = 1	MABA	LORA
1			2.70	19		0.50 ± 0.30	2.6 ± 1.4
4			4.48	0.43		0.03 ± 0.01	1.4 ± 0.5
5			4.36	1.2	1.1	0.035 ± 0.015	1.3 ± 0.1
9	*ortho*	3-aza	2.19	116		> 8	> 32
10	*ortho*	3-aza, 4-F	2.19	35		> 8	16 ± 1
11	*ortho*	3-aza, 4-OCH_3	2.69	48		5.2 ± 2.4	8.3 ± 1.5
12	*ortho*	3-aza, 4-OCH_2Ph	4.35	1.2		2.7 ± 1.2	10 ± 2
13	*ortho*	4-aza	2.12			> 8	> 32
14	*meta*	2-aza	2.16			1.4 ± 0.4	11 ± 4
15	*meta*	2-aza, 4-CF_3	3.54	4.0		0.32 ± 0.08	4.3 ± 2.3
16	*meta*	2-aza, 4-OCF_2H	2.59	6.7		0.21 ± 0.02	6.4 ± 2.7
17	*meta*	3-aza	2.19	110		1.4 ± 0.3	9.7 ± 2.6
18	*meta*	3-aza, 4-CF_3	3.57	1.1		0.47 ± 0.03	8.4 ± 0.9
19	*meta*	3-aza, 4-F	2.19	26		0.37 ± 0.12	5.1 ± 1.6
20	*meta*	3-aza, 4-OCH_3	2.69	18		0.40 ± 0	1.7 ± 0.3
21	*meta*	3-aza, 4-OCH_2Ph	4.35	0.15		0.07 ± 0.01	3.0 ± 0.5
22	*meta*	4-aza	2.12			1.4 ± 0.5	> 32
23	*para*	2-aza	2.16	7.3		0.21 ± 0	1.7 ± 0.5
24	*para*	2-aza, 4-CF_3	3.54	0.20	5.1	0.06 ± 0.03	1.0 ± 0.2
25	*para*	2-aza, 4-CF_3, 6-Cl	4.46	3.3	2.0	0.025 ± 0.005	1.0 ± 0.6
26	*para*	2-aza, 4-CN	1.82	1.7		0.08 ± 0.02	2.5 ± 0.8
27	*para*	2-aza, 3-F	2.25	4.3		0.14 ± 0.03	1.1 ± 0.4
28	*para*	2-aza, 4-F	2.09	67	275	0.035 ± 0.005	1.3 ± 0.3
29	*para*	2-aza, 4-OCF_2H	2.59	2.9	23	0.08 ± 0.03	1.5 ± 0.6
30	*para*	2-aza, 4-OCH_3	2.41	2.5		0.13 ± 0.05	1.2 ± 0.5
31	*para*	3-aza	2.19	29		0.51 ± 0.04	5.7 ± 1.0
32	*para*	3-aza, 4-CF_3	3.57	1.0	11	0.03 ± 0	2.1 ± 0.2
33	*para*	3-aza, 4-CN	1.86	3.0		0.20 ± 0.05	2.4 ± 0.9
34	*para*	3-aza, 4-F	2.19	8.0	10	0.095 ± 0.025	2.1 ± 0.2
35	*para*	3-aza, 5-F	2.21	55		0.55 ± 0.25	2.8 ± 0.9
36	*para*	3-aza, 4-NH_2	2.16	13		2.6 ± 0.9	19 ± 7
37	*para*	3-aza, 4-OCF_2H	2.87	3.2		0.045 ± 0.005	0.66 ± 0.30
38	*para*	3-aza, 4-OCH_3	2.69	4.4		0.045 ± 0.015	0.61 ± 0.12
39	*para*	3-aza, 4-OCH_2Ph	4.35	0.03		0.04 ± 0	> 32
40	*para*	4-aza	2.12	22		0.50 ± 0.25	9.2 ± 2.1
41	*para*	4-aza, 2-F	2.62	16		0.56 ± 0.29	3.9 ± 2.1
42	*para*	4-aza, 3-F	2.21	14	15	0.23 ± 0.02	1.4 ± 0.3

[a] CLogP values, calculated using the ACD LogP/LogD prediction software (version 8.0, Advanced Chemistry Development Inc., Toronto, Canada). [b] Solubility in water at 20 °C, determined by HPLC (see Experimental Section, Method A). [c] Minimum inhibitory concentration, determined under aerobic (MABA)[53] or anaerobic (LORA)[52] conditions. Each value is the mean of at least two independent determinations ± SD.

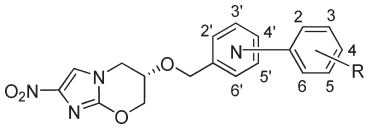
that these do provide a reasonable prediction of solubility within the larger series of *para*-linked biaryls (across a solubility range of ~23000-fold):

$$\log[\text{solubility } (\mu\text{g/mL})] = -0.46\ (\pm 0.07)\ \text{ClogP} + 1.78\ (\pm 0.16)$$
$$n = 73 \quad R = 0.63 \quad F = 46.3 \qquad (1)$$

Aqueous solubilities at pH = 1 were also measured for selected compounds containing functionalities that may exhibit weak base behavior. Encouragingly, most of the pyridine analogues tested displayed markedly increased solubilities at low pH (e.g., >100-fold for **59**, **74**, **92**, **93**, **97**), consistent with their calculated pK_a values (ranging from 2.03 for **24** and **28** to 3.88 for **59** and **92**). The exceptions to this (**25**, **34**, **42**) could be accounted for by their negative calculated pK_a values, as could the results for the pyrazine and pyrimidine analogues (**114**, **119**, **124**; pyridazine **107**, having a calculated pK_a of 1.01, showed a moderate 5-fold enhanced solubility at pH = 1).

The compounds were screened in assays to quantify their antitubercular activity under both aerobic and anaerobic conditions (this permitted the elucidation of SAR for each, as previously described[10,12]). Briefly, the 8 day microplate-based assay using Alamar blue reagent (added on day 7) for determination of growth (MABA)[51] gave an assessment of activity against replicating *M. tb*, while the 11 day high-throughput, luminescence-based low-oxygen-recovery assay (LORA)[52] measured activity against bacteria in a nonreplicating state that models clinical persistence. Minimum inhibitory concentrations (MICs) are defined as the lowest compound concentration effecting >90% growth inhibition, and the values recorded in Tables 1−3 represent the mean of at least two independent determinations (±SD). The compounds were additionally screened for mammalian cytotoxicity in a 72 h

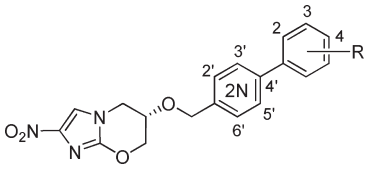
Table 2. Physicochemical Properties and MIC Values for Heterobiaryl Analogues of **1** Having a Proximal Pyridine Ring



compd	link	aza	R	CLogP[a]	solubility[b] (μg/mL) pH = 7	solubility[b] (μg/mL) pH = 1	MIC (μM)[c] MABA	MIC (μM)[c] LORA
43	3′ (*meta*)	2′	4-CF_3	3.14	5.0		0.29 ± 0.03	2.9 ± 1.0
44	3′ (*meta*)	2′	4-CN	1.48	24		0.48 ± 0.24	10 ± 4
45	3′ (*meta*)	2′	4-F	2.10	15		0.30 ± 0.09	2.7 ± 0.8
46	3′ (*meta*)	2′	4-OCF_3	3.01	3.0		0.16 ± 0.10	1.4 ± 0.3
47	3′ (*meta*)	2′	4-OCF_2H	2.16	9.6		0.17 ± 0.01	2.7 ± 0.8
48	3′ (*meta*)	2′	3-F, 4-OCH_3	1.95	10		0.30 ± 0.06	4.3 ± 1.4
49	3′ (*meta*)	2′	3-aza, 4-OCH_3	1.35	14		0.71 ± 0.16	5.2 ± 1.8
50	3′ (*meta*)	4′	4-CF_3	3.14	2.8		0.075 ± 0.015	4.4 ± 0.5
51	3′ (*meta*)	4′	4-CN	1.48	8.0		0.38 ± 0.13	13 ± 1
52	3′ (*meta*)	4′	4-F	2.10	31		0.17 ± 0.06	1.2 ± 0.2
53	3′ (*meta*)	4′	4-OCF_3	3.01	3.9		0.035 ± 0.005	2.4 ± 0.6
54	3′ (*meta*)	4′	4-OCF_2H	2.16	16		0.055 ± 0.005	2.7 ± 0.3
55	3′ (*meta*)	4′	3-F, 4-OCH_3	1.95	7.2		0.34 ± 0.04	6.2 ± 0.5
56	3′ (*meta*)	4′	3-aza, 4-OCH_3	1.35	93		1.3 ± 0.5	12 ± 1
57	3′ (*meta*)	5′	4-CF_3	3.17	2.8		0.15 ± 0.06	3.5 ± 1.0
58	3′ (*meta*)	5′	4-CN	1.51	29		0.69 ± 0.21	18 ± 5
59	3′ (*meta*)	5′	4-F	2.13	45	41000	0.31 ± 0.16	7.7 ± 1.1
60	3′ (*meta*)	5′	4-OCF_3	3.04	9.5		0.17 ± 0.05	2.4 ± 1.3
61	3′ (*meta*)	5′	4-OCF_2H	2.19	9.2		0.53 ± 0.31	5.9 ± 2.9
62	3′ (*meta*)	5′	3-F, 4-OCH_3	1.98	24		0.91 ± 0.01	9.0 ± 1.8
63	3′ (*meta*)	5′	3-aza, 4-OCH_3	1.38	31		2.8 ± 1.3	22 ± 2
64	3′ (*meta*)	6′	4-CF_3	3.10	43		0.88 ± 0.04	24 ± 11
65	3′ (*meta*)	6′	4-CN	1.44	19		2.1 ± 0.3	> 32
66	3′ (*meta*)	6′	4-F	2.06	16		0.46 ± 0.25	28 ± 1
67	3′ (*meta*)	6′	4-OCF_3	2.97			0.76 ± 0.27	18 ± 4
68	3′ (*meta*)	6′	4-OCF_2H	2.12	86		0.67 ± 0.20	26 ± 6
69	3′ (*meta*)	6′	3-F, 4-OCH_3	1.91	25		2.3 ± 0.7	16 ± 0
70	3′ (*meta*)	6′	3-aza, 4-OCH_3	1.31	96		3.8 ± 0.1	31 ± 8
71	4′ (*para*)	2′	4-CF_3	3.17	2.3		0.04 ± 0.01	3.4 ± 0.1
72	4′ (*para*)	2′	4-CN	1.51	45		0.18 ± 0.08	7.5 ± 0.7
73	4′ (*para*)	2′	4-F	2.13	17		0.13 ± 0.02	3.2 ± 1.5
74	4′ (*para*)	2′	4-OCF_3	3.04	2.5	1360	0.065 ± 0.038	3.7 ± 1.2
75	4′ (*para*)	2′	4-OCF_2H	2.19	4.0		0.02 ± 0	4.0 ± 0.9
76	4′ (*para*)	2′	3-F, 4-OCH_3	1.98	10		0.17 ± 0.05	3.4 ± 0.6
77	4′ (*para*)	2′	2-Cl, 4-OCF_3	3.75	1.4		0.14 ± 0.03	2.6 ± 0.9
78	4′ (*para*)	2′	3-Cl, 4-OCF_3	3.56	0.85		0.04 ± 0.01	2.4 ± 0.9
79	4′ (*para*)	2′	2-F, 4-OCF_3	3.60	1.4		0.06 ± 0.03	1.7 ± 0.8
80	4′ (*para*)	2′	3-F, 4-OCF_3	3.02	30	334	0.05 ± 0.02	1.3 ± 0.6
81	4′ (*para*)	2′	3-OCF_3, 4-Cl	3.51	0.80		0.06 ± 0	2.3 ± 0.7
82	4′ (*para*)	2′	2-aza, 3-F	0.93	41		1.4 ± 0.5	20 ± 1
83	4′ (*para*)	2′	2-aza, 4-CF_3	2.22	5.9	442	0.83 ± 0.09	9.6 ± 3.0
84	4′ (*para*)	2′	3-aza, 4-CF_3	2.25	12		0.24 ± 0	16 ± 10
85	4′ (*para*)	2′	3-aza, 4-F	0.87	43		0.49 ± 0	19 ± 9
86	4′ (*para*)	2′	3-aza, 5-F	0.89	130		2.6 ± 0.8	21 ± 7
87	4′ (*para*)	2′	3-aza, 4-OCH_3	1.38	24		0.36 ± 0.14	9.6 ± 3.4
88	4′ (*para*)	2′	4-aza, 2-F	1.30	700		3.2 ± 0.8	20 ± 4
89	4′ (*para*)	2′	4-aza, 3-F	0.89	42		1.7 ± 0.2	14 ± 4
90	4′ (*para*)	3′	4-CF_3	3.14	1.2		0.053 ± 0.005	0.53 ± 0.17
91	4′ (*para*)	3′	4-CN	1.48	2.9		0.18 ± 0.06	6.0 ± 0.6
92	4′ (*para*)	3′	4-F	2.10	3.8	1000	0.06 ± 0	2.9 ± 0.1
93	4′ (*para*)	3′	4-OCF_3	3.01	2.3	542	0.05 ± 0.01	0.54 ± 0.24
94	4′ (*para*)	3′	4-OCF_2H	2.16	1.6		0.02 ± 0	3.4 ± 0.4
95	4′ (*para*)	3′	3-F, 4-OCH_3	1.95	2.1		0.09 ± 0.04	1.9 ± 0
96	4′ (*para*)	3′	2-Cl, 4-OCF_3	3.72	8.8		0.030 ± 0.014	1.6 ± 0.1
97	4′ (*para*)	3′	3-Cl, 4-OCF_3	3.53	0.18	39	0.017 ± 0.005	1.0 ± 0.1
98	4′ (*para*)	3′	2-F, 4-OCF_3	3.57	2.2		0.047 ± 0.017	1.9 ± 0.4
99	4′ (*para*)	3′	3-F, 4-OCF_3	2.99	3.0	71	0.025 ± 0.005	0.93 ± 0.29
100	4′ (*para*)	3′	3-OCF_3, 4-Cl	3.48	0.22		0.18 ± 0	2.4 ± 1.2
101	4′ (*para*)	3′	3-aza, 4-CF_3	2.22	7.0		0.19 ± 0.02	17 ± 9
102	4′ (*para*)	3′	3-aza, 4-F	0.84	51		0.37 ± 0.12	13 ± 1
103	4′ (*para*)	3′	3-aza, 4-OCH_3	1.35	51		0.24 ± 0.02	7.3 ± 0.5

[a] CLogP values, calculated using the ACD LogP/LogD prediction software (version 8.0, Advanced Chemistry Development Inc., Toronto, Canada). [b] Solubility in water at 20 °C, determined by HPLC (see Experimental Section, Method A). [c] Minimum inhibitory concentration, determined under aerobic (MABA)[53] or anaerobic (LORA)[52] conditions. Each value is the mean of at least two independent determinations ± SD.

Table 3. Physicochemical Properties and MIC Values for Heterobiaryl Analogues of **1** Having a Proximal Pyridazine, Pyrazine, or Pyrimidine Ring



				solubility (μg/mL)[b]		MIC (μM)[c]	
compd	aza	R	CLogP[a]	pH = 7	pH = 1	MABA	LORA
104	2′,3′	4-CF_3	1.64	5.4		0.06 ± 0	2.8 ± 0.3
105	2′,3′	4-CN	−0.01	22		0.36 ± 0.03	13 ± 3
106	2′,3′	4-F	0.60	8.3		0.19 ± 0.02	5.6 ± 1.9
107	2′,3′	4-OCF_3	1.52	6.1	31	0.075 ± 0.025	1.7 ± 0.1
108	2′,3′	4-OCF_2H	0.67	1.3		0.17 ± 0.05	7.5 ± 0.4
109	2′,3′	3-F, 4-OCH_3	0.46	6.8		0.25 ± 0.03	6.6 ± 1.2
110	2′,3′	3-aza, 4-CF_3	0.73	12		0.55 ± 0.22	14 ± 5
111	2′,3′	3-aza, 4-OCH_3	−0.15	34		0.72 ± 0.28	20 ± 8
112	2′,5′	4-CF_3	2.31	0.84		0.08 ± 0.01	0.97 ± 0.53
113	2′,5′	4-F	1.27	8.9		0.085 ± 0.015	2.0 ± 0.8
114	2′,5′	4-OCF_3	2.19	2.6	2.8	0.023 ± 0.005	1.0 ± 0.6
115	2′,5′	4-OCF_2H	1.33	5.0		0.20 ± 0.04	1.3 ± 0.6
116	2′,5′	3-aza, 4-CF_3	1.39	27		0.33 ± 0.10	3.7 ± 0.5
117	2′,6′	4-CF_3	2.75	2.7		0.06 ± 0	3.5 ± 1.4
118	2′,6′	4-F	1.71	50		0.13 ± 0.01	12 ± 1
119	2′,6′	4-OCF_3	2.63	8.1	5.1	0.11 ± 0.01	1.9 ± 0.5
120	2′,6′	4-OCF_2H	1.77	7.8		0.12 ± 0.04	7.4 ± 1.2
121	2′,6′	3-aza, 4-CF_3	1.83	85		0.28 ± 0.07	14 ± 2
122	3′,5′	4-CF_3	2.82			0.025 ± 0.005	9.4 ± 0.9
123	3′,5′	4-F	2.07			0.11 ± 0.02	5.4 ± 0.3
124	3′,5′	4-OCF_3	3.05	2.1	3.0	0.027 ± 0.009	1.8 ± 1.0
125	3′,5′	4-OCF_2H	2.20	1.1		0.13 ± 0.07	4.4 ± 1.7
126	3′,5′	3-aza, 4-CF_3	2.14			0.16 ± 0.07	12 ± 3

[a] CLogP values, calculated using the ACD LogP/LogD prediction software (version 8.0, Advanced Chemistry Development Inc., Toronto, Canada). [b] Solubility in water at 20 °C, determined by HPLC (see Experimental Section, Method A). [c] Minimum inhibitory concentration, determined under aerobic (MABA)[53] or anaerobic (LORA)[52] conditions. Each value is the mean of at least two independent determinations ± SD.

tetrazolium dye assay using VERO cells[53] (CCL-81; American Type Culture Collection); the compounds were all relatively nontoxic in this assay, with IC_{50}s > 128 μM (data not shown).

In Table 1, we first explored the effect of replacing the terminal phenyl ring with a substituted pyridine by comparing *ortho*- (compounds **9**−**13**), *meta*- (compounds **14**−**22**), and *para*- (compounds **23**−**42**) linked analogues. Each series was further subdivided according to the position of the aza atom in the ring. Substituents on this pyridine ring were selected to enable a broad range of lipophilicities to be studied, but a greater emphasis was placed on lipophilic, electron-withdrawing groups that have previously provided particular utility[10,12] (using OCF_2H as a substitute for the favored OCF_3). The *ortho*-linked compounds (**9**−**13**) were generally more soluble than related *meta*- and *para*-linked analogues but had poor activities, consistent with previous results for *ortho*-linked biphenyl analogues.[10] The *meta*-linked compounds (**14**−**22**) were more effective overall, particularly the lipophilic benzyloxy analogue **21** (MABA MIC 0.07 μM). Comparison of **15** (2-aza) with **18** (3-aza) suggests that the position of the aza atom has little effect, but compounds lacking a ring substituent (**14**, **17**, **22**) had weaker activity (>3-fold in MABA). As expected, the larger *para*-linked series (**23**−**42**) provided the best activity, with compounds **24**, **25**, **28**, **32**, **37**, and **38** standing out for their high potencies in both assays. Compound **28** (2-aza, 4-F) was also particularly notable for its good aqueous solubility (67 μg/mL at pH = 7, 3.5-fold better than **1**), which was further improved at low pH (to 275 μg/mL). Within this *para*-linked series, a closer comparison of the 2-aza and 3-aza analogues bearing common 4-substituents (R = CF_3, CN, F, OCF_2H, OCH_3) suggests that again the position of the aza atom is not critical (mean MABA MICs 0.077 and 0.083 μM, mean LORA MICs 1.50 and 1.57 μM, respectively). However, the 4-aza analogues (**40**−**42**), amino compound **36**, and other analogues lacking a substituent adjacent to the pyridine nitrogen (**31**, **35**) were markedly less effective.

Table 4, part A, compares the mean MIC data for the various subseries against the mean MICs for the corresponding substituted biphenyl analogues (where these were available), using previously published data.[10] In most cases where there was more than a single compound in a subset, the pyridyl analogues were 2−8-fold less potent than the corresponding biphenyls in both the MABA and LORA assays (although compounds **23**−**30** displayed slightly higher mean potency in LORA than the biphenyls). We have previously shown, for a large series of *para*-linked biphenyl analogues,[10] that MICs in the MABA assay correlate positively with global compound lipophilicity (eq 2).

$$\log(\mathrm{MIC_{MABA}}) = -0.25\mathrm{CLogP} - 0.52\sum\sigma - 0.014 \quad (2)$$

According to this equation, the 2−5-fold reduced mean MABA potency shown by the three subsets of *para*-linked compounds in Table 1 could be explained (at least in part) by their lower lipophilicities (average ΔCLogP of −0.9 to −1.4 units, leading to predicted potency values 1.4−3-fold higher than observed, Table 4, part A). In summary, replacement of

Table 4. Summary of Calculated Lipophilicity Differences, Mean Aqueous Solubilities, and Mean MICs for Compound Subsets

					mean MABA MIC (μM)				mean LORA MIC (μM)		
compd	link	aza	ΔCLogP[a]	av solubility[b]	aza[c]	deaza[d]	ratio[e]	calcd[f]	aza[c]	deaza[d]	ratio[e]
					(A) Compounds of Table 1						
9−10	*o*	3	−1.29	76	>8	0.92	>8.7		>24	3.0	>8
13	*o*	4	−1.39		>8	0.64	>12		>32	2.5	>13
14−16	*m*	2	−1.07	5.4	0.64	0.092	7.0		7.2	2.6	2.8
17−19	*m*	3	−1.16	46	0.75	0.097	7.7		7.7	2.9	2.7
22	*m*	4	−1.39		1.4	0.095	15		>32	2.1	>15
23−30	*p*	2	−1.06	11	0.095	0.038	2.5	0.070	1.4	2.3	0.61
31−38	*p*	3	−0.90	15	0.51	0.096	5.3	0.16	4.4	2.4	1.8
40−42	*p*	4	−1.37	17	0.43	0.093	4.6	0.20	4.8	2.3	2.1
					(B) Compounds of Table 2						
43−48	*m*	2′	−1.35	11	0.28	0.13	2.2		4.0	3.1	1.3
49	*m*	2′	−1.97	14	0.71	0.40	1.8		5.2	1.7	3.1
50−55	*m*	4′	−1.35	11	0.18	0.13	1.4		5.0	3.1	1.6
56	*m*	4′	−1.97	93	1.3	0.40	3.3		12	1.7	7.1
57−62	*m*	5′	−1.32	20	0.46	0.13	3.5		7.8	3.1	2.5
63	*m*	5′	−1.94	31	2.8	0.40	7.0		22	1.7	13
64−69	*m*	6′	−1.39	38	1.2	0.13	9.2		>24	3.1	>7.7
70	*m*	6′	−2.01	96	3.8	0.40	9.5		31	1.7	18
71−76	*p*	2′	−1.32	13	0.10	0.033	3.0	0.071	4.2	1.2	3.5
77−81	*p*	2′	−1.32	6.9	0.070	0.037	1.9	0.079	2.1	0.74	2.8
82−89	*p*	2′	−2.45	125	1.4	0.21	6.7	0.86	16	1.9	8.4
90−95	*p*	3′	−1.35	2.3	0.076	0.033	2.3	0.072	2.5	1.2	2.1
96−100	*p*	3′	−1.35	2.9	0.060	0.037	1.6	0.080	1.6	0.74	2.2
101−103	*p*	3′	−2.28	36	0.27	0.057	4.7	0.21	12	1.6	7.5
					(C) Compounds of Table 3						
104−109	*p*	2′,3′	−2.84	8.3	0.18	0.033	5.5	0.17	6.2	1.2	5.2
110	*p*	2′,3′	−3.75	12	0.55	0.030	18	0.26	14	2.1	6.7
112−115	*p*	2′,5′	−2.17	4.3	0.097	0.033	2.9	0.12	1.3	1.2	1.1
116	*p*	2′,5′	−3.09	27	0.33	0.030	11	0.18	3.7	2.1	1.8
117−120	*p*	2′,6′	−1.73	17	0.11	0.033	3.3	0.089	6.2	1.2	5.2
121	*p*	2′,6′	−2.65	85	0.28	0.030	9.3	0.14	14	2.1	6.7
122−125	*p*	3′,5′	−1.41	1.6	0.073	0.033	2.2	0.074	5.3	1.2	4.4
126	*p*	3′,5′	−2.34		0.16	0.030	5.3	0.12	12	2.1	5.7

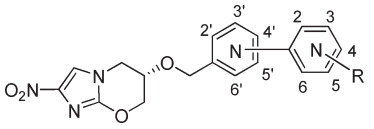
[a] Mean difference in CLogP values between the heterobiaryl subclass and the biphenyl compounds from ref 10 bearing the same substituents. [b] Average solubility (μg/mL) in water at pH = 7. [c] Heterobiaryl compounds of this paper. [d] Comparison data for corresponding substituted biphenyl compounds from ref 10 (most subclasses) or for terminal pyridine ring analogues in Table 1 (for pyridylheterocycles of Tables 2 and 3). [e] Ratio of mean MICs (aza/deaza), as defined above. [f] Predicted mean MABA MICs based on eq 2 (see text), using mean observed MABA MIC data for *para*-linked biphenyl analogues and ΔCLogP values for related heterobiaryl subclasses.

the terminal phenyl ring by pyridine in the most promising (4-substituted) *para*-linked series has provided several promising new analogues which combine improved aqueous solubilities (particularly at low pH) with excellent potencies in both antitubercular assays.

In Table 2, we next explored the effect of replacing the phenyl ring proximal to the ether linkage with a substituted pyridine, including examples of all six positional isomers of the more favorable *meta*- and *para*-linked series. The use of a larger set of common substituents in this work (4-CF_3, 4-CN, 4-F, 4-OCF_3, 4-OCF_2H, 3-F-4-OCH_3, and 3-aza-4-OCH_3) enabled a more definitive assessment of the subtle effects produced by this variation, as well as the separate evaluation of a more hydrophilic bipyridyl side chain (Table 4, part B). Thus, comparing the four largest subsets of *meta*-linked compounds, an aza atom at the 4′-position (compounds **50−55**) gave the highest mean MABA potency (similar to biphenyl analogues), with compound **53** (4-OCF_3) the best overall (MABA MIC 0.035 μM). An aza atom at the 2′-position (compounds **43−48**) was slightly more advantageous for LORA potency across these subsets (comparable to biphenyl analogues) and was preferred among the more weakly active bipyridyl compounds (compound **49**; both assays). The two 6′-aza subsets (compounds **64−69** and bipyridine **70**) were ranked lowest by potency but provided the highest aqueous solubilities of the *meta*-linked series (up to 0.1 mg/mL at pH = 7 for **70**). A similar comparison for the *para*-linked series shows that the less soluble 3′-aza subset (compounds **90−95**) was slightly more potent overall than the 2′-aza subset (compounds **71−76**), particularly in LORA (mean MICs 2.5 and 4.2 μM, respectively). Both 4-OCF_2H analogues (**75**, **94**) had excellent MABA potencies (MICs 0.02 μM), whereas the 4-CF_3 and 4-OCF_3 analogues with a 3′-aza atom (**90**, **93**) had notably high LORA potencies (MICs ~0.5 μM).

For the more potent *para*-linked series, we examined some additional, more lipophilic phenyl ring substituent patterns (2-Cl-4-OCF_3, 3-Cl-4-OCF_3, 2-F-4-OCF_3, 3-F-4-OCF_3, and 3-OCF_3-4-Cl) that had provided improved LORA potencies in the biphenyl series.[10] Both the 2′-aza and 3′-aza subsets with these substituents (compounds **77−81** and **96−100**, respectively) had higher mean potencies than the previous subsets above (having the standard substituents), particularly in the LORA assay (1.6−2-fold). While these were still somewhat less (1.6−2.8-fold) than for related biphenyl analogues, the mean measured MABA potencies were actually similar or slightly better than predicted (Table 4, part B), based on their reduced mean lipophilicities (ΔCLogP of −1.32 to −1.35 units). From

Table 5. Microsomal Stability and Acute *in Vivo* Efficacy Data for Selected Compounds



				TD solubility[a]		microsomes (% remaining at 1 h)		
compd	link	aza	R	pH = 7	pH = 1	H[b]	M[c]	*in vivo* efficacy[d] (ratio vs **1**)
1				11	11	82	94	1.00
5				< 0.1	< 0.1	97	96	> 205
24	*para*	2	4-CF_3	0.42	0.84	93	90	33
25	*para*	2	4-CF_3, 6-Cl			86	80	5.1
28	*para*	2	4-F			83	61	0.65
29	*para*	2	4-OCF_2H			98	80	3.3
32	*para*	3	4-CF_3	0.17	0.38	86	91	15
34	*para*	3	4-F			88	79	0.66
37	*para*	3	4-OCF_2H			95	75	1.9
38	*para*	3	4-OCH_3			40	61	0.26
42	*para*	4	3-F			93	86	0.95
53	*meta*	4′	4-OCF_3			54	31	0.12
59	*meta*	5′	4-F			71	39	0.02
74	*para*	2′	4-OCF_3	0.44	65	97	97	27
80	*para*	2′	3-F, 4-OCF_3	1.5	67	97	86	233
92	*para*	3′	4-F	5.9	> 93	88	80	7.8
93	*para*	3′	4-OCF_3	< 0.1	45	83	87	> 89
97	*para*	3′	3-Cl, 4-OCF_3	0.19	17	87	77	> 933
99	*para*	3′	3-F, 4-OCF_3	0.32	34	100	90	> 840
107	*para*	2′,3′	4-OCF_3	3.0	10	94	92	11
114	*para*	2′,5′	4-OCF_3	0.44	0.44	98	91	167
119	*para*	2′,6′	4-OCF_3			92	87	3.7
124	*para*	3′,5′	4-OCF_3	1.2	1.5	96	87	> 1120

[a] Thermodynamic solubility (μg/mL) in aqueous buffer at pH = 7.4 or pH = 1.0 and 20 °C, determined by HPLC (see Experimental Section, Methods B and C). [b] Pooled human liver microsomes. [c] Pooled CD-1 mouse liver microsomes. [d] Fold reduction in lung CFUs for compound compared with the fold CFU reduction for **1** in a mouse model of acute TB infection (see text).

these subsets, compounds **97** (3-Cl-4-OCF_3) and **99** (3-F-4-OCF_3) in particular stood out for their impressive overall potency profiles, although **97** was significantly less soluble than most at pH = 7.

A larger set of *para*-linked bipyridines, including more favorable CF_3 or F substituents, was also prepared and evaluated (compounds **82**−**89** and **101**−**103**). These compounds were considerably less lipophilic than the corresponding monopyridines of Table 1 (mean CLogP values 1.13 and 0.93 units lower, respectively), which translated into some dramatically improved solubilities (up to 0.7 mg/mL at pH = 7 for **88**). However, unsurprisingly (based on the predicted MABA data), their mean potencies were 5−8-fold less than for the related monopyridine analogues (of Table 1) in both assays (some 4−24-fold less than for related biphenyl analogues), with the particularly weak LORA results suggesting limited utility.

In an alternative exploration of the effect of diaza substitution, and based on previous success with pyrazole-, triazole-, and tetrazole-based analogues,[12] we finally investigated the effect of replacing the phenyl ring proximal to the ether linkage with a substituted pyridazine, pyrazine, or pyrimidine in the most favored *para*-linked series (Table 3). All four possible structural classes were studied, using a minimum of four terminal phenyl ring substituents (4-CF_3, 4-F, 4-OCF_3, 4-OCF_2H; 4-CN and 3-F-4-OCH_3 were also included in the first set for comparison with the pyridine analogues of Table 2). The 3-aza-4-CF_3 substituent pattern, which was the most preferred for the bipyridines above (and had previously proven quite effective in a 5-aryl thiophene series[12]) was employed for the study of related pyridyl heterocyclic compounds.

The pyridazine class (compounds **104**−**109**) was the most hydrophilic of all the monoheterocyclic and bipyridyl derivatives examined here (ΔCLogP value −2.84 units), although the mean solubility value was only moderate (lower than for 2′-aza compounds **71**−**76** but better than for 3′-aza compounds **90**−**95**). Within this class, the more lipophilic examples, **104** (4-CF_3) and **107** (4-OCF_3), showed fairly good potency profiles, despite the overall activity of the set being about 5-fold less than for related biphenyl analogues (and roughly 2-fold less than for 2′-aza or 3′-aza analogues). Of greater interest was the somewhat more lipophilic pyrazine class (compounds **112**−**115**) due to the very high LORA potencies determined (mean MIC 1.3 μM; equivalent to biphenyl analogues) and good overall MABA activity. Compound **114** (4-OCF_3) had the best activity of any diaza compound (MICs 0.023 and 1.0 μM in MABA and LORA, respectively), comparable to some of the best pyridine derivatives, although its aqueous solubility was relatively low (2.6 μg/mL). 2′,6′-Pyrimidine derivatives (compounds **117**−**120**) had the highest mean aqueous solubility of the four classes, despite their slightly higher lipophilicities (ΔCLogP value −1.73 units), but their activity was moderate. Conversely, the 3′,5′-pyrimidine isomers (compounds **122**−**125**), which were of very similar lipophilicities to the pyridine analogues (Table 2), provided the highest mean MABA potency of all (0.073 μM), with the more lipophilic examples, **122** (4-CF_3) and **124** (4-OCF_3), standing out (MABA MICs 0.025 and 0.027 μM, respectively); however, this was the least soluble class. More soluble pyridyl heterocyclic derivatives (**110**, **116**, **121**, and **126**) mirrored these trends but were generally about 2-fold less active in MABA than predicted and gave generally

Table 6. Pharmacokinetic Parameters for Selected Analogues in CD-1 Mice Following a Single Oral Dose of 40 mg/kg

	plasma			lung			
compd	$AUC_{0\text{-inf}}$[a] (μg·h/mL)	C_{max} (μg/mL)	$t_{1/2}$ (h)	$AUC_{0\text{-inf}}$[a] (μg·h/mL)	C_{max} (μg/mL)	$t_{1/2}$ (h)	AUC ratio[b]
5	198	7.4	14	218	9.0	13	1.1
24	20	1.1	8.8	67	34	10	3.4
32	217	14	–[c]	414	373	9.1	1.9
74	418	26	5.4	427	35	8.2	1.0
80	137	7.6	8.4	155	9.1	7.9	1.1
92	61	5.3	2.7	136	11	2.8	2.2
93	296	12	24	81	18	2.2	0.27
97	88	2.9	22	284	10	14	3.2
99	175	7.0	14	251	12	12	1.4
107	52	3.6	2.9	94	7.0	3.4	1.8
114	152	9.6	7.2	>324	23	>8	>2.1
124	43	1.2	23	131	4.0	18	3.0

[a] Area under the curve, extrapolated to infinity. [b] Lung AUC/plasma AUC. [c] Not calculable.

weak LORA results, similar to bipyridine analogues, suggesting little interest in further evaluating these compounds.

A selection of the more interesting compounds was assayed to determine relative metabolic stabilities using human and mouse liver microsome preparations (Table 5; data for **1** and the biphenyl analogue **5** are also provided for comparison). All of the compounds evaluated (except for the 3-aza-4-OCH_3 analogue **38**) were acceptably stable toward human microsomes (>50% remaining after incubation at 37 °C for 1 h), and all except *meta*-linked pyridyl analogues **53** and **59** were similarly stable toward mouse microsomes. The very high stabilities of many of the most potent *para*-linked heterocyclic analogues (>80%, several comparable to **5**) were particularly encouraging, indicating that these heterocycles did not introduce a significant metabolic liability.

The compounds selected above were also evaluated for their antitubercular effects in a mouse model of acute *M. tb* infection using a once daily oral dose of 100 mg/kg for 5 days a week for 3 weeks, following established protocols.[53] In this assay, **1** was used as an internal reference standard, with the activity of new analogues recorded as the ratio of the fold decrease in CFUs recovered from the lungs of compound-treated mice compared to the corresponding fold CFU decrease achieved by treatment with **1**, to allow interexperiment comparisons (Table 5). Examining the series where the terminal phenyl ring had been replaced by pyridine (**24**–**42**), the best compounds were the isomeric trifluoromethyl-substituted analogues **24** and **32** (respectively 33-fold and 15-fold more effective than **1**). Difluoromethoxy analogues **29** and **37** had disappointingly low efficacies, suggesting that OCF_2H was not an effective substitute for the favored OCF_3 group.

Of major interest were the compounds in which the proximal phenyl ring had been replaced by pyridine (**53**–**99**) or diaza heterocycles (**107**–**124**). While the low stability *meta*-linked analogues **53** and **59** were ineffective (as anticipated), all of the other five pyridine analogues containing a 4-OCF_3 phenyl substitutent (with or without an adjacent halo atom) were markedly superior to **1**, with **80** (2′-aza, 3-F-4-OCF_3Ph; 233-fold), **93** (3′-aza, 4-OCF_3Ph; >89-fold), **97** (3′-aza, 3-Cl-4-OCF_3Ph; >933-fold), and **99** (3′-aza, 3-F-4-OCF_3Ph; >840-fold) clearly preeminent (comparable to the best biphenyl analogues). A closer comparison of **93** and **99** with **74** and **80** indicated that 3′-aza compounds were more efficacious than 2′-aza analogues and that 3-F-4-OCF_3 (or 3-Cl-4-OCF_3; see **97**) phenyl substitution may provide higher efficacy in this model than 4-OCF_3 substitution alone. Finally, among the diaza heterocyclic derivatives, the slightly more hydrophilic pyrazine **114** (ClogP 2.19; 167-fold better than **1**) and less hydrophilic 3′,5′-pyrimidine **124** (ClogP 3.05; >1120-fold better than **1**) also displayed outstanding efficacies. Even the highly hydrophilic pyridazine **107** (ClogP 1.52) was 11-fold more effective than **1**, demonstrating that very high compound lipophilicities (e.g., ClogP > 4) were not mandatory to achieve excellent *in vivo* efficacies.

To further assess the merits of these leading candidates for more advanced development, first, accurate (thermodynamic) solubility measurements were performed at pH = 7.4 and pH = 1 (Table 5; data for **1** and the biphenyl analogue **5** are also provided for comparison). While all of the compounds evaluated had inferior aqueous solubilities to **1** at pH = 7.4 (the best was 3′-aza, 4-FPh analogue **92** at 5.9 μg/mL, which was about 2-fold less than **1**), several pyridine derivatives (**74**, **80**, **92**, **93**, and **99**) had significantly (3- to >8-fold) higher solubilities than **1** at low pH, consistent with previous data. Mouse pharmacokinetic data were also obtained for this compound set, following single oral dosing at 40 mg/kg (Table 6; comparative data for **5** are also provided). Most compounds (except perhaps 4-FPh-pyridine **92** and pyridazine **107**) demonstrated excellent plasma half-lives (5–24 h) and generally high exposures in both lung tissue and plasma (AUCs > 100 μg·h/mL, peak plasma levels >7 μg/mL), with some (notably 4-CF_3pyridine **24**, 3-Cl-4-OCF_3Ph-pyridine **97**, pyrazine **114**, and 3′,5′-pyrimidine **124**) exhibiting preferential accumulation in lung tissue. Such high exposure levels (similar to **5**) were indicative of very good oral bioavailability, and this was confirmed by similar pharmacokinetic assessments in the rat (Table 7) for four compounds of particular interest (**74**, **93**, **99**, and **114**). Extended plasma half-lives were again found, and the determined oral bioavailabilities ranged from 45% (for pyrazine **114**) to an impressive 93% (for 3-F-4-OCF_3Ph-pyridine **99**).

Finally, a smaller selection of compounds was evaluated for their antitubercular effects in a mouse model of chronic *M. tb* infection, using a once daily oral dose of either 100 mg/kg for 5 days a week for 3 weeks or 30 mg/kg for 5 days a week for 8 weeks, starting ~50–70 days postinfection (Table 8). This was a much more stringent assay, requiring the killing of bacteria in a well-established, plateau phase of growth. In the initial 3 week assay, both **1** and **2** were employed as internal reference standards for the two experiments, with the objective of identifying lead compounds superior to both clinical trial drugs (**2** was about 10-fold more efficacious than **1** in this assay). Here, pyridine analogues **92** (4-FPh) and **93** (4-OCF_3Ph) respectively showed 20-fold and 15-fold higher efficacies than **1**, and

Table 7. Pharmacokinetic Parameters and Oral Bioavailability for Selected Analogues in Male Sprague-Dawley Rats Following a Single Dose

	intravenous (5 mg/kg)[a]				oral (20 mg/kg)			
compd	C_0[b] (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{last}[c] (μg·h/mL)	C_{max} (μg/mL)	T_{max} (h)	AUC_{last}[c] (μg·h/mL)	F[d] (%)
74	8.7	0.083	>6	35.9	16	6	66.7	46
93	3.9	0.083	>6	12.1	8.1	5	30.1	62
99	0.53[a]	0.083	33	6.97[a]	7.2	6	129.4	93
114	3.9	0.167	24	16.3	7.0	5	29.4	45

[a] The intravenous dose for **99** was 1 mg/kg. [b] Maximum plasma concentration extrapolated to $t = 0$. [c] Area under the curve calculated to the last time point; for **74**, **93**, and **114** this was 6 h but for **99** the last time point was 24 h. [d] Oral bioavailability, determined using dose normalized AUC_{last} values.

Table 8. Chronic *in Vivo* Efficacy Data for Selected Analogues

	3 week study (100 mg/kg)			8 week study (30 mg/kg)	
compd	fold CFU reduction[a]	relative efficacy (ratio vs **1**)	relative efficacy (ratio vs **2**)	fold CFU reduction[a]	relative efficacy (ratio vs **2**)
1	157, 81[b]	1.0	0.07, 0.14[b]		
2	2111, 593[b]	13, 7.3[b]	1.0	571, 1042[b]	1.0
24	271	1.7	0.13		
32	371[b]	4.6[b]	0.63[b]		
74	142	0.9	0.07	828	1.4
92	3156	20	1.5		
93	1219[b]	15[b]	2.1[b]	3478, 6410[b]	6.1, 6.2[b]
99				3846[b]	3.7[b]
114				1333	2.3

[a] Fold reduction in lung CFUs in a mouse model of chronic TB infection (see text). [b] Data from second experiment.

1.5-fold and 2.1-fold higher efficacies than **2**, whereas the trifluoromethyl pyridine analogues **24** and **32** and the 2′-aza isomer of **93** (**74**) had low activity. For the subsequent 8 week study, the test compounds were evaluated against **2** only, also in two separate experiments. Under these conditions, however, compound **74** demonstrated comparable activity to **2**. Pyridine analogue **93** (4-OCF_3Ph) consistently showed the best efficacy, about 6-fold greater than **2**, while close analogue **99** (3-F-4-OCF_3Ph) and pyrazine **114** also showed 3.7-fold and 2.3-fold higher efficacies than **2**, respectively.

Conclusions

This study explored aza and diaza analogues of the biphenyl class of 2-nitroimidazooxazines as a strategy for developing more soluble compounds that retained high antitubercular activity, and efficient synthetic routes to a wide range of these compounds were developed. The study was sparked by previous work describing replacement of one of the phenyl rings by various five-membered heterocycles, which suggested that potency and lipophilicity could be decoupled (to some extent). The new aza analogues were appreciably less lipophilic than the biphenyl class (ΔClogP values ranged from 0.9 to 3.75 units lower), and there was a reasonable correlation between hydrophilicity and measured aqueous solubility for the larger series of *para*-linked biaryls. Bipyridine and pyridyl diazaheterocyclic analogues provided the best solubility improvements (up to 0.7 mg/mL at pH = 7) but displayed weak potencies in antitubercular assays, as predicted by their very high hydrophilicities.

Several compounds in which the terminal phenyl ring was replaced by pyridine retained high *in vitro* potencies against both replicating and nonreplicating *M. tb* and showed improved aqueous solubilities, particularly at low pH (e.g., 0.28 mg/mL for **28**), although only two of these (trifluoromethyl analogues **24** and **32**) were significantly more efficacious than **1** in a mouse model of acute *M. tb* infection. Further analogues, in which the phenyl ring proximal to the ether linkage was replaced by pyridine, pyridazine, pyrazine, or pyrimidine, were generally more effective. Whereas two of the more hydrophilic classes (2′,6′-pyrimidine and pyridazine) displayed better solubilities at pH = 7 but more modest potencies, the two *para*-linked phenylpyridine classes in particular combined improved solubilities (up to 1.4 mg/mL at low pH) with very high activities, both *in vitro* and *in vivo*. For these latter classes, additional lipophilic substitution on the terminal phenyl ring (e.g., 3-F, 3-Cl) generally improved *in vitro* potency and efficacy in the acute *in vivo* model.

Overall, ten compounds were substantially (>10-fold) more efficacious than **1** in the mouse model of acute *M. tb* infection, with five of these showing a >100-fold improvement over **1**. In several cases (**93**, **97**, **99**, **124**), no CFUs could be detected following the plating of undiluted lung homogenates, indicating complete sterilization. Pharmacokinetic assessments of these compounds revealed lengthy half-lives and high exposures in both plasma and lung tissue following oral dosing, consistent with excellent oral bioavailabilities, and this was established for four leading candidates. Two of these, pyridines **93** and **99**, were respectively 4-fold and 3-fold more soluble than **1** at low pH and exhibited superior (3.7−6.2-fold greater) efficacies compared to the clinical trial drug **2** in a more stringent mouse model of chronic *M. tb* infection.

Experimental Section

Combustion analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal IA9100 melting point apparatus and are as read. NMR spectra were measured on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H and are referenced to Me_4Si. Chemical shifts and coupling constants are recorded in units of parts per million and hertz, respectively. High-resolution electron impact (HREIMS) and fast atom bombardment (HRFABMS) mass spectra were determined on a VG-70SE mass spectrometer at nominal 5000 resolution. High-resolution electrospray ionization (HRESIMS) mass spectra were determined on a Bruker micrOTOF-Q II mass spectrometer. Low-resolution atmospheric pressure chemical ionization (APCI) mass spectra were measured for organic solutions on a ThermoFinnigan Surveyor MSQ mass spectrometer, connected to a Gilson autosampler. Thin-layer chromatography was carried out on aluminum-backed silica gel plates (Merck 60 F_{254}), with visualization of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel (Merck 230−400 mesh). Compounds of Tables 1−3 were isolated following trituration in Et_2O, unless otherwise indicated. Tested compounds were ≥95% pure, as determined by combustion analysis, or by HPLC conducted on an Agilent 1100 system, using a reversed-phase C8 column with diode array detection.

Compounds of Table 1. Procedure A. (6*S*)-2-Nitro-6-{[2-(3-pyridinyl)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (9) (Scheme 1A). (6*S*)-6-[(2-Iodobenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[10] (**127**) (0.100 g, 0.249 mmol) and 3-pyridinylboronic acid (0.040 g, 0.325 mmol) were suspended in toluene/EtOH (5 mL/2 mL), and then aqueous K_2CO_3

(2 M, 1 mL) was added. The stirred mixture was purged with N_2, treated with Pd(dppf)Cl_2 (9.5 mg, 0.013 mmol), and heated under reflux in an N_2 atmosphere for 30 min. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The dried ($MgSO_4$) organic extracts were adsorbed onto silica gel and chromatographed, eluting with EtOAc, to give **9** (0.085 g, 97%) as a light brown powder: mp 157−159 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.59 (dd, J = 4.8, 1.6 Hz, 1 H), 8.55 (dd, J = 2.3, 0.8 Hz, 1 H), 7.98 (s, 1 H), 7.75 (ddd, J = 7.9, 2.2, 1.8 Hz, 1 H), 7.51−7.48 (m, 1 H), 7.45−7.40 (m, 3 H), 7.32−7.28 (m, 1 H), 4.57−4.48 (m, 3 H), 4.40 (br d, J = 12.0 Hz, 1 H), 4.20−4.09 (m, 3 H). Anal. ($C_{18}H_{16}N_4O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds of Table 1 from known[10] iodobenzyl ethers **127**, **128**, or **129**.

Procedure B. (6*S*)-2-Nitro-6-{[3-(2-pyridinyl)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (14) (Scheme 1B). A mixture of (6*S*)-2-nitro-6-{[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[10] (**130**) (0.101 g, 0.252 mmol) and 2-bromopyridine (0.055 g, 0.35 mmol) in toluene (5 mL), EtOH (3 mL), and K_2CO_3 (2 M, 1 mL) was purged with N_2. Pd(dppf)Cl_2 (8 mg, 0.011 mmol) was added, and the stirred mixture was refluxed under N_2 for 30 min and then partitioned between EtOAc and water. The organic layer was dried and evaporated, and then column chromatography of the residue on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **14** (74 mg, 83%) as a pale yellow gum: ^{1}H NMR [$(CD_3)_2SO$] δ 8.65 (ddd, J = 4.8, 1.8, 1.0 Hz, 1 H), 8.03−7.96 (m, 3 H), 7.92 (dt, J = 8.0, 1.1 Hz, 1 H), 7.87 (td, J = 8.0, 1.8 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.40−7.33 (m, 2 H), 4.76 (d, J = 12.0 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.69 (dt, J = 11.9, 2.6 Hz, 1 H), 4.49 (br d, J = 11.9 Hz, 1 H), 4.33−4.20 (m, 3 H); HRFABMS calcd for $C_{18}H_{17}N_4O_4$ m/z [M + H]$^+$ 353.1250, found 353.1247. HPLC purity: 100%.

2-Bromo-5-(difluoromethoxy)pyridine (133). A mixture of 6-bromo-3-pyridinol (**132**) (2.40 g, 13.8 mmol), sodium chlorodifluoroacetate (4.20 g, 27.5 mmol), and K_2CO_3 (2.40 g, 17.4 mmol) in anhydrous DMF (20 mL) was stirred at 80 °C for 20 h, then cooled, and partitioned between Et_2O and water. The organic layer was washed with water and brine, dried ($MgSO_4$), and carefully concentrated under reduced pressure to minimize evaporation of the product. Column chromatography of the residue, eluting with 9:1 hexanes:Et_2O, gave **133**[20] (1.98 g, 64%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 2.8 Hz, 1 H), 7.49 (d, J = 8.5 Hz, 1 H), 7.37 (dd, J = 8.5, 2.8 Hz, 1 H), 6.54 (t, J_{H-F} = 72.2 Hz, 1 H). APCI MS m/z 226, 224 [M + H]$^+$.

(6*S*)-6-({3-[5-(Difluoromethoxy)-2-pyridinyl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (16). Reaction of boronate ester **130** and bromide **133** under the Suzuki coupling conditions described in procedure B gave **16** (76%) as a white solid: mp 120−122 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.55 (d, J = 2.8 Hz, 1 H), 8.02−7.94 (m, 4 H), 7.74 (dd, J = 8.7, 2.8 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 1 H), 7.39 (br d, J = 7.6 Hz, 1 H), 7.35 (t, J_{H-F} = 73.4 Hz, 1 H), 4.76 (d, J = 12.0 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.68 (dt, J = 12.0, 2.5 Hz, 1 H), 4.48 (br d, J = 11.9 Hz, 1 H), 4.32−4.21 (m, 3 H). Anal. ($C_{19}H_{16}F_2N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of related compounds of Table 1 from known[10] boronic acid pinacol esters **130** or **131**.

Procedure C. {4-[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]phenyl}-methanol (136) (Scheme 1C). A stirred mixture of 4-(hydroxymethyl)-phenylboronic acid (**135**) (0.850 g, 5.59 mmol) and Pd(dppf)Cl_2 (0.826 g, 1.13 mmol) in toluene (56 mL) and EtOH (28 mL) was degassed for 15 min (vacuum pump), and then N_2 was added. Aqueous Na_2CO_3 (14 mL of 2 M, 28 mmol) was added by syringe, the stirred mixture was again degassed for 15 min, and then N_2 was added. 2,3-Dichloro-5-(trifluoromethyl)pyridine (2.41 g, 11.2 mmol) was added by syringe, and the resulting mixture was stirred at 88 °C for 3 h. The cooled mixture was then diluted with aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (5 × 100 mL). The extracts were evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 0−20% Et_2O/petroleum ether first gave foreruns, and then further elution with 20−50% Et_2O/petroleum ether gave the crude product, which was further chromatographed, eluting with CH_2Cl_2 (foreruns) and then with 33% Et_2O/CH_2Cl_2, to give **136** (1.037 g, 64%) as a cream solid (following pentane trituration): mp 70−71 °C; ^{1}H NMR ($CDCl_3$) δ 8.84 (br d, J = 1.0 Hz, 1 H), 8.04 (br d, J = 1.6 Hz, 1 H), 7.77 (dt, J = 8.3, 1.7 Hz, 2 H), 7.50 (br d, J = 8.3 Hz, 2 H), 4.79 (d, J = 5.9 Hz, 2 H), 1.74 (t, J = 6.0 Hz, 1 H); HRESIMS calcd for $C_{13}H_{10}ClF_3NO$ m/z [M + H]$^+$ 290.0369, 288.0398, found 290.0372, 288.0400.

[4-(5-Fluoro-2-pyridinyl)phenyl]methanol (137). Reaction of boronic acid **135** and 2-bromo-5-fluoropyridine (2.2 equiv) under the Suzuki conditions described in procedure C (with 0.14 equiv of Pd(dppf)Cl_2 catalyst), followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 and 0−25% Et_2O/petroleum ether (foreruns) and then with 25−33% Et_2O/petroleum ether, gave **137** (54%) as a cream solid (following pentane trituration): mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 2.9 Hz, 1 H), 7.94 (dt, J = 8.4, 1.9 Hz, 2 H), 7.72 (ddd, J = 8.8, 4.2, 0.5 Hz, 1 H), 7.50−7.43 (m, 3 H), 4.76 (d, J = 6.0 Hz, 2 H), 1.69 (t, J = 6.0 Hz, 1 H); HRESIMS calcd for $C_{12}H_{11}FNO$ m/z [M + H]$^+$ 204.0819, found 204.0824.

Procedure D. 2-[4-(Bromomethyl)phenyl]-3-chloro-5-(trifluoromethyl)pyridine (138). A solution of alcohol **136** (1.035 g, 3.60 mmol) and PPh_3 (1.089 g, 4.15 mmol) in anhydrous CH_2Cl_2 (40 mL) was carefully treated with recrystallized *N*-bromosuccinimide (0.739 g, 4.15 mmol) (water bath cooling), and the mixture was stirred at room temperature for 4 h. The resulting solution was added to excess petroleum ether at the top of a silica gel column (30 g in petroleum ether), rinsing on with minimal extra CH_2Cl_2. Elution with petroleum ether first gave foreruns, and then further elution with 20% Et_2O/petroleum ether gave **138** (1.219 g, 97%) as a white solid that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.84 (br d, J = 1.0 Hz, 1 H), 8.04 (br d, J = 1.8 Hz, 1 H), 7.76 (dt, J = 8.4, 1.9 Hz, 2 H), 7.52 (dt, J = 8.3, 1.8 Hz, 2 H), 4.55 (s, 2 H); HRESIMS calcd for $C_{13}H_9BrClF_3N$ m/z [M + H]$^+$ 353.9504, 351.9532, 349.9554, found 353.9510, 351.9537, 349.9559.

2-[4-(Bromomethyl)phenyl]-5-fluoropyridine (139). Bromination of alcohol **137** using procedure D (with 1.2 equiv of PPh_3 and NBS) for 3 h, followed by chromatography of the product directly on silica gel, eluting with pentane (foreruns) and then with 20−50% Et_2O/pentane, gave **139** (87%) as a white solid that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 2.9 Hz, 1 H), 7.92 (dt, J = 8.4, 1.9 Hz, 2 H), 7.72 (ddd, J = 8.7, 4.3, 0.4 Hz, 1 H), 7.52−7.43 (m, 3 H), 4.54 (s, 2 H); HRESIMS calcd for $C_{12}H_{10}BrFN$ m/z [M + H]$^+$ 267.9955, 265.9975, found 267.9959, 265.9979.

Procedure E. (6*S*)-6-({4-[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]-benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (25). A solution of (6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-ol[23] (**140**) (0.644 g, 3.48 mmol) and bromide **138** (1.217 g, 3.47 mmol) in anhydrous DMF (13 mL) under N_2 at 0 °C was treated with 60% NaH (0.184 g, 4.60 mmol), then quickly degassed, and resealed under N_2. After being stirred at room temperature for 2.5 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), added to brine (100 mL), and extracted with CH_2Cl_2 (7 × 100 mL). The combined extracts were evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 0−1% EtOAc/CH_2Cl_2 first gave foreruns, and then further elution with 7−10% EtOAc/CH_2Cl_2 gave **25** (1.327 g, 84%) as a cream solid: mp (CH_2Cl_2/pentane) 159−160 °C; ^{1}H NMR ($CDCl_3$) δ 8.84 (dd, J = 1.8, 0.7 Hz, 1 H), 8.05 (d, J = 1.6 Hz, 1 H), 7.78 (br d, J = 8.3 Hz, 2 H), 7.45 (br d, J = 8.3 Hz, 2 H), 7.39 (s, 1 H), 4.82 (d, J = 12.4 Hz, 1 H), 4.71 (d, J = 12.4 Hz, 1 H), 4.64 (ddd, J = 12.1, 3.6, 1.9 Hz, 1 H), 4.37 (dd, J = 12.1, 1.3 Hz, 1 H), 4.23−4.11 (m, 3 H). Anal. ($C_{19}H_{14}ClF_3N_4O_4$) C, H, N.

(6*S*)-6-{[4-(5-Fluoro-2-pyridinyl)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (28). Reaction of alcohol **140** with bromide **139** and NaH using procedure E for 135 min, followed by

chromatography of the product on silica gel, eluting with 0−6% EtOAc/CH_2Cl_2 (foreruns) and then with 7−10% EtOAc/CH_2Cl_2, gave crude material, which was further chromatographed, eluting with 0−67% EtOAc/petroleum ether (foreruns) and then with EtOAc and 30% EtOAc/CH_2Cl_2, to give **28** (0.357 g, 74%) as a cream solid: mp (CH_2Cl_2/pentane) 180−181 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 2.9 Hz, 1 H), 7.95 (dt, J = 8.4, 1.9 Hz, 2 H), 7.72 (ddd, J = 8.8, 4.2, 0.4 Hz, 1 H), 7.48 (ddd, J = 8.7, 8.1, 2.9 Hz, 1 H), 7.41 (br d, J = 8.4 Hz, 2 H), 7.37 (s, 1 H), 4.79 (d, J = 12.2 Hz, 1 H), 4.68 (d, J = 12.2 Hz, 1 H), 4.61 (ddd, J = 12.1, 3.7, 1.9 Hz, 1 H), 4.35 (dd, J = 12.1, 1.5 Hz, 1 H), 4.20−4.09 (m, 3 H). Anal. ($C_{18}H_{15}FN_4O_4$) C, H, N.

Compounds of Table 2. 2-Bromo-6-(chloromethyl)pyridine (142) (Scheme 2A). A solution of (6-bromo-2-pyridinyl)methanol (**141**) (3.74 g, 19.9 mmol) in $CHCl_3$ (250 mL) at 0 °C was treated with $SOCl_2$ (26 mL, 356 mmol). The stirred mixture was refluxed for 1 h, then cooled, poured into ice−water, and extracted into iPr$_2$O. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness to give **142**[25] (3.42 g, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.59 (t, J = 7.7 Hz, 1 H), 7.47 (d, J = 7.4 Hz, 1 H), 7.44 (d, J = 7.9 Hz, 1 H), 4.63 (s, 2 H); HREIMS calcd for C_6H_5BrClN m/z (M^+) 208.9244, 206.9273, 204.9294, found 208.9233, 206.9273, 204.9294.

Procedure F. (6*S*)-6-[(6-Bromo-2-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (143). A solution of alcohol **140** (2.65 g, 14.3 mmol) and chloride **142** (3.22 g, 15.7 mmol) in anhydrous DMF (70 mL) at −5 °C was treated with 60% NaH (0.74 g, 18.5 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with water (300 mL) and extracted with EtOAc, and the combined extracts were dried ($MgSO_4$) and evaporated to dryness. Column chromatography of the residue, eluting with 5% MeOH/EtOAc, gave crude **143** (2.56 g, 50%) as a pale brown solid (following Et_2O/EtOAc trituration): mp 163−165 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.75 (t, J = 7.7 Hz, 1 H), 7.56 (d, J = 7.6 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 4.76−4.65 (m, 3 H), 4.49 (br d, J = 12.0 Hz, 1 H), 4.35−4.21 (m, 3 H); HRFABMS calcd for $C_{12}H_{12}BrN_4O_4$ m/z $[M + H]^+$ 357.0022, 355.0042, found 357.0013, 355.0034.

(6*S*)-2-Nitro-6-({6-[4-(trifluoromethyl)phenyl]-2-pyridinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (43). Reaction of bromide **143** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **43** (53%) as a light yellow powder: mp 170−172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.29 (br d, J = 8.1 Hz, 2 H), 8.03 (s, 1 H), 7.99 (dd, J = 7.9, 1.1 Hz, 1 H), 7.95 (t, J = 7.6 Hz, 1 H), 7.85 (br d, J = 8.2 Hz, 2 H), 7.42 (dd, J = 7.4, 1.0 Hz, 1 H), 4.86 (d, J = 13.4 Hz, 1 H), 4.83 (d, J = 13.4 Hz, 1 H), 4.74 (dt, J = 12.0, 2.6 Hz, 1 H), 4.52 (br d, J = 12.0 Hz, 1 H), 4.41−4.33 (m, 2 H), 4.27 (dd, J = 13.2, 2.9 Hz, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_4 \cdot 0.25H_2O$) C, H, N. HPLC purity: 98.9%.

See Supporting Information for details of the syntheses of related compounds **44**−**49** of Table 2 from bromide **143**.

2-Bromo-4-(bromomethyl)pyridine Hydrobromide (145) (Scheme 2B). A solution of (2-bromo-4-pyridinyl)methanol (**144**) (2.00 g, 10.6 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was treated with $SOBr_2$ (0.90 mL, 11.6 mmol). The resulting mixture was stirred at room temperature for 15 h, then the solvent was evaporated, and the residue was crystallized from MeOH/Et_2O, to give **145**[30] (2.77 g, 79%) as a white solid: mp 172−175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.39 (d, J = 5.0 Hz, 1 H), 7.74 (br d, J = 0.9 Hz, 1 H), 7.51 (dd, J = 5.0, 1.4 Hz, 1 H), 4.66 (s, 2 H). APCI MS m/z 254, 252, 250 $[M + H]^+$.

(6*S*)-6-[(2-Bromo-4-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (146). Reaction of alcohol **140** with bromide salt **145** (1.2 equiv) and NaH (2.4 equiv) using procedure F for 1 h, followed by chromatography of the product on silica gel, eluting with 2% MeOH/CH_2Cl_2, gave **146** (65%) as a light yellow solid: mp 150−152 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.34 (dd, J = 5.1, 0.3 Hz, 1 H), 8.02 (s, 1 H), 7.51 (br d, J = 0.5 Hz, 1 H), 7.34 (ddd, J = 5.1, 1.3, 0.6 Hz, 1 H), 4.75 (d, J = 14.1 Hz, 1 H), 4.73−4.64 (m, 2 H), 4.48 (br d, J = 11.9 Hz, 1 H), 4.32−4.20 (m, 3 H); HRESIMS calcd for $C_{12}H_{12}BrN_4O_4$ m/z $[M + H]^+$ 357.0017, 355.0036, found 357.0017, 355.0038.

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethyl)phenyl]-4-pyridinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (50). Reaction of bromide **146** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure A for 6 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **50** (42%) as a white solid: mp 199−202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.68 (dd, J = 5.0, 0.5 Hz, 1 H), 8.26 (br d, J = 8.1 Hz, 2 H), 8.03 (s, 1 H), 7.90 (br s, 1 H), 7.84 (br d, J = 8.2 Hz, 2 H), 7.36 (br d, J = 5.0 Hz, 1 H), 4.83 (d, J = 13.8 Hz, 1 H), 4.79 (d, J = 13.8 Hz, 1 H), 4.72 (dt, J = 12.0, 2.6 Hz, 1 H), 4.51 (br d, J = 11.5 Hz, 1 H), 4.36−4.23 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_4 \cdot 0.25H_2O$) C, H, N. HPLC purity: 100%.

See Supporting Information for details of the syntheses of related compounds **51**−**56** of Table 2 from bromide **146**.

(6*S*)-6-[(5-Bromo-3-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (148) (Scheme 2C). Reaction of alcohol **140** with 3-bromo-5-(chloromethyl)pyridine hydrochloride[26] (**147**) (1.0 equiv) and NaH (2.4 equiv) using procedure F for 16 h, followed by chromatography of the product on silica gel, eluting with 2.5% MeOH/CH_2Cl_2, gave **148** (30%) as a light yellow solid: mp 169−171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (d, J = 2.3 Hz, 1 H), 8.52 (d, J = 1.7 Hz, 1 H), 8.03 (s, 1 H), 7.97 (br t, J = 2.0 Hz, 1 H), 4.73 (d, J = 12.6 Hz, 1 H), 4.70−4.64 (m, 2 H), 4.48 (br d, J = 12.0 Hz, 1 H), 4.32−4.20 (m, 3 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N, Br.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)phenyl]-3-pyridinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (57). Reaction of bromide **148** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with 0−5% MeOH/EtOAc, gave **57** (92%) as a light brown solid: mp 227−229 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.89 (d, J = 2.3 Hz, 1 H), 8.60 (d, J = 1.9 Hz, 1 H), 8.04 (t, J = 2.1 Hz, 1 H), 8.02 (s, 1 H), 7.94 (br d, J = 8.2 Hz, 2 H), 7.85 (br d, J = 8.3 Hz, 2 H), 4.81 (d, J = 12.4 Hz, 1 H), 4.77 (d, J = 12.4 Hz, 1 H), 4.70 (dt, J = 12.0, 2.5 Hz, 1 H), 4.50 (br d, J = 11.9 Hz, 1 H), 4.35−4.22 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_4 \cdot 0.25H_2O$) C, H, N, F. HPLC purity: 99.8%.

See Supporting Information for details of the syntheses of related compounds **58**−**63** of Table 2 from bromide **148**.

(4-Bromo-2-pyridinyl)methanol (150) (Scheme 2D). Protected from moisture, trifluoroacetic anhydride (17 mL, 122 mmol) was carefully and slowly added to 4-bromo-2-methylpyridine 1-oxide[28] (**149**) (4.33 g, 23.0 mmol). The orange mixture was stirred at room temperature for 30 min, refluxed for 30 min, and then cooled. Saturated aqueous $NaHCO_3$ was added (to pH = 8), and the resulting red solution was stirred at room temperature for 16 h. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave **150**[27] (3.38 g, 78%) as a dark orange-brown oil that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 5.3 Hz, 1 H), 7.48 (dd, J = 1.7, 0.7 Hz, 1 H), 7.38 (ddd, J = 5.3, 1.2, 0.7 Hz, 1 H), 4.75 (s, 2 H), 3.32 (s, 1 H).

4-Bromo-2-(chloromethyl)pyridine (151). A solution of **150** (3.38 g, 18.0 mmol) in CH_2Cl_2 (210 mL) at 0 °C was carefully treated with $SOCl_2$ (21 mL, 288 mmol). The mixture was stirred at room temperature for 20 h, and then saturated aqueous $NaHCO_3$ was added. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to dryness to give **151** (2.94 g, 79%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 5.3 Hz, 1 H), 7.68 (d, J = 1.7 Hz, 1 H), 7.42 (dd, J = 5.3, 1.8 Hz, 1 H), 4.64 (s, 2 H); HRFABMS calcd for C_6H_6BrClN m/z $[M + H]^+$ 209.9322, 207.9352, 205.9372, found 209.9319, 207.9356, 205.9368.

(6*S*)-6-[(4-Bromo-2-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (152). Reaction of alcohol **140** with chloride **151** (0.91 equiv) and NaH (1.1 equiv) using procedure F

for 3 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **152** (54%) as a light yellow solid: mp 155−158 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.41 (d, J = 5.3 Hz, 1 H), 8.01 (s, 1 H), 7.59 (dd, J = 5.3, 1.9 Hz, 1 H), 7.55 (d, J = 1.5 Hz, 1 H), 4.77 (d, J = 13.6 Hz, 1 H), 4.72 (d, J = 13.5 Hz, 1 H), 4.70 (dt, J = 12.0, 2.6 Hz, 1 H), 4.50 (br d, J = 12.0 Hz, 1 H), 4.37−4.21 (m, 3 H). Anal. ($C_{12}H_{11}BrN_4O_4 \cdot 0.25H_2O$) C, H, N, Br. HPLC purity: 99.8%.

(6*S*)-2-Nitro-6-({4-[4-(trifluoromethyl)phenyl]-2-pyridinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (64). Reaction of bromide **152** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **64** (87%) as a yellow solid: mp 105−109 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (dd, J = 5.1, 0.4 Hz, 1 H), 8.01 (s, 1 H), 7.95 (br d, J = 8.2 Hz, 2 H), 7.86 (br d, J = 8.3 Hz, 2 H), 7.69 (dd, J = 5.2, 1.9 Hz, 1 H), 7.64 (br s, 1 H), 4.85 (d, J = 13.4 Hz, 1 H), 4.80 (d, J = 13.4 Hz, 1 H), 4.71 (dt, J = 11.8, 2.6 Hz, 1 H), 4.52 (br d, J = 12.0 Hz, 1 H), 4.40 (m, 1 H), 4.35 (dt, J = 13.5, 2.1 Hz, 1 H), 4.26 (dd, J = 13.5, 3.2 Hz, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_4 \cdot H_2O$) C, H, N. HPLC purity: 97.2%.

See Supporting Information for details of the syntheses of related compounds **65**−**70** of Table 2 from bromide **152**.

5-Bromo-2-(bromomethyl)pyridine (154) (Scheme 3A). Bromination of (5-bromo-2-pyridinyl)methanol (**153**) using procedure D (with 1.2 equiv of PPh_3 and NBS) for 3.5 h, followed by chromatography of the product directly on silica gel, eluting with petroleum ether (foreruns) and then with 10−30% Et_2O/petroleum ether, gave **154**[31] (83%) as a lachramatory lilac oil that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.63 (d, J = 2.2 Hz, 1 H), 7.82 (dd, J = 8.3, 2.4 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 4.50 (s, 2 H).

See Supporting Information for details of alternative reaction conditions to provide **154**.

(6*S*)-6-[(5-Bromo-2-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (156). Reaction of alcohol **140** with bromide **154** and NaH (1.4 equiv) using procedure E for 3 h, followed by chromatography of the product on silica gel, eluting with 0−0.5% MeOH/CH_2Cl_2 (foreruns) and then with 0.5−1% MeOH/CH_2Cl_2, gave **156** (81%) as a pale yellow solid: mp 171−172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (dd, J = 2.3, 0.4 Hz, 1 H), 8.04 (dd, J = 8.4, 2.4 Hz, 1 H), 8.02 (s, 1 H), 7.35 (dd, J = 8.4, 0.4 Hz, 1 H), 4.76−4.65 (m, 3 H), 4.49 (br d, J = 12.0 Hz, 1 H), 4.35−4.28 (m, 2 H), 4.24 (dd, J = 13.7, 3.5 Hz, 1 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

See Supporting Information for details of alternative reaction conditions to provide **156**.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (71). Reaction of bromide **156** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **71** (84%) as a light yellow powder: mp 204−207 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.91 (d, J = 1.8 Hz, 1 H), 8.17 (dd, J = 8.1, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.96 (br d, J = 8.2 Hz, 2 H), 7.85 (br d, J = 8.3 Hz, 2 H), 7.50 (d, J = 8.2 Hz, 1 H), 4.83 (d, J = 13.2 Hz, 1 H), 4.79 (d, J = 13.3 Hz, 1 H), 4.73 (dt, J = 12.0, 2.7 Hz, 1 H), 4.52 (br d, J = 12.0 Hz, 1 H), 4.39−4.24 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_4$) C, H, N, F.

See Supporting Information for details of the syntheses of related compounds **72**−**76**, **82**, and **84**−**89** of Table 2 from bromide **156**.

Procedure G. 2-Chloro-4-(trifluoromethoxy)phenylboronic Acid (167) (Scheme 3C). Triisopropyl borate (0.72 mL, 3.12 mmol) and 2-chloro-1-iodo-4-(trifluoromethoxy)benzene (**162**) (0.816 g, 2.53 mmol) were successively added via syringe to a mixture of anhydrous toluene (4 mL) and anhydrous distilled THF (1 mL) under N_2, and the mixture was cooled to −78 °C. *n*BuLi (1.20 mL of a 2.5 M solution in hexanes, 3.00 mmol) was added dropwise over 30 min to the stirred solution (at −78 °C), and the mixture was stirred at −78 °C for an additional 4 h and then slowly warmed to −20 °C (over 2 h). HCl (2 N, 2.6 mL) was added, and the mixture was stirred at room temperature for 40 min and then diluted with water (40 mL) and extracted with EtOAc (5 × 50 mL). The extracts were washed with brine (50 mL) and then evaporated to dryness. The residue was triturated in hexane (∼5 mL), cooled to −20 °C, and rapidly filtered cold (washing with pentane cooled to −20 °C) to give **167**[33] (0.391 g, 64%) as a white solid: mp 150−152 °C (lit.[33] mp 160−162); ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1 H), 7.24 (m, 1 H), 7.18 (ddq, J = 8.4, 2.2, 1.1 Hz, 1 H), 5.25 (s, 2 H).

See Supporting Information for details of the syntheses of related arylboronic acids **168**−**171** from halobenzenes **163**−**166**.

Procedure H. (6*S*)-6-({5-[2-Chloro-4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (77). A stirred mixture of bromide **156** (50.2 mg, 0.141 mmol), boronic acid **167** (63.5 mg, 0.264 mmol), and Pd(dppf)Cl_2 (19.6 mg, 0.027 mmol) in toluene (2 mL) and EtOH (1 mL) was degassed for 5 min (vacuum pump), and then N_2 was added. An aqueous solution of Na_2CO_3 (0.40 mL of 2 M, 0.80 mmol) was added by syringe, the stirred mixture was again degassed for 5 min, and then N_2 was added. The resulting mixture was stirred at 90 °C for 100 min and then cooled, diluted with aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The extracts were evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 0−0.75% MeOH/CH_2Cl_2 first gave foreruns, and then further elution with 0.75% MeOH/CH_2Cl_2 gave **77** (52 mg, 77%) as a cream solid: mp (CH_2Cl_2/pentane) 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (dd, J = 2.3, 0.7 Hz, 1 H), 7.80 (dd, J = 8.0, 2.3 Hz, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.42 (s, 1 H), 7.41 (m, 1 H), 7.37 (d, J = 8.5 Hz, 1 H), 7.25 (m, 1 H), 4.89 (d, J = 13.0 Hz, 1 H), 4.82 (d, J = 13.0 Hz, 1 H), 4.73 (ddd, J = 12.2, 3.4, 2.0 Hz, 1 H), 4.41 (dd, J = 12.2, 1.2 Hz, 1 H), 4.35−4.22 (m, 3 H). Anal. ($C_{19}H_{14}ClF_3N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **78**−**81** of Table 2 from bromide **156**.

{5-[3-Fluoro-4-(trifluoromethoxy)phenyl]-2-pyridinyl}methanol (172) (Scheme 3D). A stirred mixture of bromide **153** (0.753 g, 4.00 mmol), 3-fluoro-4-(trifluoromethoxy)phenylboronic acid (**170**) (1.165 g, 5.20 mmol), and Pd(dppf)Cl_2 (0.366 g, 0.50 mmol) in toluene (40 mL) and EtOH (20 mL) was degassed for 15 min (vacuum pump), and then N_2 was added. An aqueous solution of Na_2CO_3 (10 mL of 2 M, 20.0 mmol) was added by syringe, the stirred mixture was again degassed for 15 min, and then N_2 was added. The resulting mixture was stirred at 89 °C for 2 h and then cooled, diluted with aqueous $NaHCO_3$ (120 mL), and extracted with CH_2Cl_2 (6 × 100 mL). The extracts were evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 50−75% CH_2Cl_2/petroleum ether first gave foreruns, and then further elution with 75% CH_2Cl_2/petroleum ether and 0−0.5% MeOH/CH_2Cl_2 gave **172** (0.687 g, 60%) as a light yellow−brown solid: mp 51−53 °C; ^{1}H NMR ($CDCl_3$) δ 8.76 (br d, J = 1.9 Hz, 1 H), 7.84 (dd, J = 8.1, 2.3 Hz, 1 H), 7.46−7.34 (m, 4 H), 4.83 (d, J = 5.1 Hz, 2 H), 3.47 (t, J = 5.2 Hz, 1 H); HRESIMS calcd for $C_{13}H_{10}F_4NO_2$ m/z $[M + H]^+$ 288.0642, found 288.0641.

2-(Bromomethyl)-5-[3-fluoro-4-(trifluoromethoxy)phenyl]-pyridine (173). Bromination of alcohol **172** using procedure D (with 1.2 equiv of PPh_3 and NBS) for 3 h, followed by chromatography of the product directly on silica gel, eluting with petroleum ether (foreruns) and then with 10−20% Et_2O/pentane, gave **173** (75%) as a white solid that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.76 (dd, J = 2.4, 0.6 Hz, 1 H), 7.84 (dd, J = 8.1, 2.4 Hz, 1 H), 7.54 (dd, J = 8.0, 0.6 Hz, 1 H), 7.46−7.33 (m, 3 H), 4.60 (s, 2 H); HRESIMS calcd for $C_{13}H_9BrF_4NO$ m/z $[M + H]^+$ 351.9778, 349.9798, found 351.9778, 349.9798.

(6*S*)-6-({5-[3-Fluoro-4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (80). Reaction of alcohol **140** with bromide **173** (1.04 equiv) and NaH using procedure E, followed by chromatography of the product on silica gel, eluting with 0−0.75% MeOH/CH_2Cl_2 (foreruns) and then with 0.75−1.5% MeOH/CH_2Cl_2, gave **80** (89%) as a light yellow solid: mp (CH_2Cl_2/pentane) 182−184 °C; ^{1}H NMR

($CDCl_3$) δ 8.74 (dd, J = 2.3, 0.7 Hz, 1 H), 7.86 (dd, J = 8.1, 2.4 Hz, 1 H), 7.48−7.38 (m, 4 H), 7.35 (ddd, J = 8.4, 2.2, 1.0 Hz, 1 H), 4.87 (d, J = 13.0 Hz, 1 H), 4.81 (d, J = 13.0 Hz, 1 H), 4.70 (ddd, J = 12.2, 3.5, 1.5 Hz, 1 H), 4.40 (dd, J = 12.2, 1.4 Hz, 1 H), 4.33−4.20 (m, 3 H). Anal. ($C_{19}H_{14}F_4N_4O_5$) C, H, N.

[5-(Trifluoromethyl)[2,3′-bipyridin]-6′-yl]methanol (175) (Scheme 3E). A stirred mixture of 2-chloro-5-(trifluoromethyl)-pyridine (0.674 g, 3.71 mmol), 6-(hydroxymethyl)-3-pyridinylboronic acid (**174**) (0.124 g, 0.814 mmol), and Pd(dppf)Cl_2 (0.115 g, 0.157 mmol) in toluene (8 mL) and EtOH (4 mL) was degassed for 8 min (vacuum pump), and then N_2 was added. An aqueous solution of Na_2CO_3 (2 mL of 2 M, 4 mmol) was added by syringe, the stirred mixture was again degassed for 8 min, then N_2 was added, and the resulting mixture was stirred at 88 °C for 4 h. The cooled mixture was then diluted with aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (5 × 80 mL). The extracts were evaporated to dryness, and the residue was chromatographed on silica gel. Elution with 0−30% EtOAc/CH_2Cl_2 first gave foreruns, and then further elution with 30−40% EtOAc/CH_2Cl_2 gave the crude product, which was rechromatographed on silica gel, eluting with Et_2O, to give **175** (54 mg, 26%) as a cream solid: mp (CH_2Cl_2/pentane) 99−100 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (d, J = 1.9 Hz, 1 H), 8.98 (dd, J = 1.3, 0.8 Hz, 1 H), 8.39 (dd, J = 8.2, 2.3 Hz, 1 H), 8.03 (dd, J = 8.4, 1.9 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 1 H), 7.41 (dd, J = 8.2, 0.6 Hz, 1 H), 4.86 (d, J = 5.1 Hz, 2 H), 3.55 (t, J = 5.2 Hz, 1 H); HRESIMS calcd for $C_{12}H_{10}F_3N_2O$ m/z $[M + H]^+$ 255.0740, found 255.0735.

6′-(Bromomethyl)-5-(trifluoromethyl)-2,3′-bipyridine (176). Bromination of alcohol **175** using procedure D (with 1.26 equiv of PPh_3 and NBS) for 3 h, followed by chromatography of the product directly on silica gel, eluting with 0−30% Et_2O/petroleum ether (foreruns) and then with 30% Et_2O/petroleum ether, gave **176** (72%) as a lachrymatory white solid that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 9.20 (dd, J = 2.3, 0.6 Hz, 1 H), 8.98 (dd, J = 1.3, 0.9 Hz, 1 H), 8.39 (dd, J = 8.2, 2.3 Hz, 1 H), 8.04 (ddd, J = 8.4, 2.3, 0.4 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 1 H), 7.59 (dd, J = 8.2, 0.7 Hz, 1 H), 4.62 (s, 2 H); HRESIMS calcd for $C_{12}H_9BrF_3N_2$ m/z $[M + H]^+$ 318.9876, 316.9896, found 318.9885, 316.9903.

(6*S*)-2-Nitro-6-{[5-(trifluoromethyl)[2,3′-bipyridin]-6′-yl]-methoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (83). Reaction of alcohol **140** with bromide **176** and NaH (1.6 equiv) using procedure E, followed by chromatography of the product on silica gel, eluting with 0−1.25% MeOH/CH_2Cl_2 (foreruns) and then with 1.5% MeOH/CH_2Cl_2, gave **83** (54%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/pentane) 218 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 9.28 (br d, J = 1.7 Hz, 1 H), 9.08 (dd, J = 1.3, 0.9 Hz, 1 H), 8.52 (dd, J = 8.2, 2.3 Hz, 1 H), 8.34 (dd, J = 8.5, 2.2 Hz, 1 H), 8.28 (d, J = 8.4 Hz, 1 H), 8.04 (s, 1 H), 7.54 (d, J = 8.2 Hz, 1 H), 4.86 (d, J = 13.6 Hz, 1 H), 4.82 (d, J = 13.6 Hz, 1 H), 4.73 (dt, J = 12.0, 2.6 Hz, 1 H), 4.52 (br d, J = 11.9 Hz, 1 H), 4.40−4.33 (m, 2 H), 4.27 (dd, J = 13.8, 3.6 Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_4$) C, H, N.

2-Bromo-5-(bromomethyl)pyridine (158) (Scheme 3B). Bromination of (6-bromo-3-pyridinyl)methanol (**157**) using procedure D for 3.5 h, followed by chromatography of the product directly on silica gel, eluting with petroleum ether (foreruns) and then with 15−25% Et_2O/pentane, gave **158**[32] (91%) as a lachrymatory white solid that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 2.5 Hz, 1 H), 7.59 (dd, J = 8.2, 2.6 Hz, 1 H), 7.48 (d, J = 8.2 Hz, 1 H), 4.42 (s, 2 H).

See Supporting Information for details of alternative reaction conditions to provide **158**.

(6*S*)-6-[(6-Bromo-3-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (160). Reaction of alcohol **140** with bromide **158** and NaH using procedure E, followed by chromatography of the product on silica gel, eluting with 0−1% MeOH/CH_2Cl_2 (foreruns) and then with 1−1.5% MeOH/CH_2Cl_2, gave **160** (88%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 200−203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.35 (dd, J = 2.3, 0.4 Hz, 1 H), 8.02 (s, 1 H), 7.69 (dd, J = 8.2, 2.5 Hz, 1 H), 7.63 (dd, J = 8.1, 0.5 Hz, 1 H), 4.72−4.62 (m, 3 H), 4.47 (br d, J = 11.8 Hz, 1 H), 4.31−4.19 (m, 3 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

See Supporting Information for details of the similar synthesis of chloride **161**.

(6*S*)-2-Nitro-6-({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (90). Reaction of bromide **160** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **90** (51%) as a white solid: mp 267−270 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.67 (d, J = 1.7 Hz, 1 H), 8.30 (br d, J = 8.1 Hz, 2 H), 8.07 (br d, J = 8.1 Hz, 1 H), 8.03 (s, 1 H), 7.87 (dd, J = 8.3, 2.2 Hz, 1 H), 7.85 (br d, J = 8.7 Hz, 2 H), 4.79 (d, J = 12.4 Hz, 1 H), 4.75 (d, J = 12.4 Hz, 1 H), 4.71 (dt, J = 12.0, 2.5 Hz, 1 H), 4.50 (br d, J = 11.7 Hz, 1 H), 4.34−4.22 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_4 \cdot 0.25H_2O$) C, H, N, F. HPLC purity: 98.9%.

See Supporting Information for details of the syntheses of related compounds **91**−**103** of Table 2 from bromide **160** and the alternative synthesis of **93** from chloride **161**.

Compounds of Table 3. (6*S*)-6-[(6-Chloro-3-pyridazinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (178) (Scheme 4A). NaH (60%, 0.304 g, 7.60 mmol) was added to a solution of alcohol **140** (0.893 g, 4.82 mmol) in anhydrous DMF (20 mL) at 0 °C. The mixture was cooled to −42 °C, and a solution of 3-(bromomethyl)-6-chloropyridazine[41] (**177**) (1.05 g, 5.06 mmol) in anhydrous DMF (5 mL) was added. The resulting mixture was stirred at −42 °C for 2 h and then quenched with ice and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$) and evaporated, and then column chromatography of the residue on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **178** (0.843 g, 56%) as a white solid: mp 180−184 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.93 (d, J = 8.8 Hz, 1 H), 7.74 (d, J = 8.9 Hz, 1 H), 4.97 (d, J = 13.2 Hz, 1 H), 4.94 (d, J = 13.2 Hz, 1 H), 4.69 (dt, J = 12.0, 2.6 Hz, 1 H), 4.50 (br d, J = 12.1 Hz, 1 H), 4.39−4.30 (m, 2 H), 4.25 (dd, J = 13.5, 3.3 Hz, 1 H). Anal. ($C_{11}H_{10}ClN_5O_4$) C, H, N.

Procedure I. (6*S*)-2-Nitro-6-({6-[4-(trifluoromethyl)phenyl]-3-pyridazinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (104). A mixture of chloride **178** (0.100 g, 0.32 mmol) and 4-(trifluoromethyl)phenylboronic acid (0.073 g, 0.38 mmol) in toluene (5 mL), EtOH (3 mL), and aqueous K_2CO_3 (2M, 1 mL) was purged with N_2 for 5 min. Pd(dppf)Cl_2 (5 mg, 6.83 μmol) was added, and the mixture was refluxed under N_2 for 0.5 h. The resulting solution was partitioned between EtOAc and water, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue on silica gel, eluting with 1:1 hexanes:EtOAc and 0−5% MeOH/EtOAc, gave **104** (92 mg, 68%) as a white solid: mp 220−224 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.39−8.33 (m, 3 H), 8.03 (s, 1 H), 7.92 (br d, J = 8.3 Hz, 2 H), 7.80 (d, J = 8.8 Hz, 1 H), 5.06 (d, J = 13.2 Hz, 1 H), 5.02 (d, J = 13.2 Hz, 1 H), 4.74 (dt, J = 12.0, 2.6 Hz, 1 H), 4.52 (br d, J = 12.0 Hz, 1 H), 4.44−4.34 (m, 2 H), 4.28 (dd, J = 13.5, 3.2 Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **105**−**111** of Table 3 from chloride **178**.

(5-Chloro-2-pyrazinyl)methanol (180) (Scheme 4B). A solution of 5-oxo-4,5-dihydro-2-pyrazinecarboxylic acid (**179**) (6.70 g, 47.8 mmol) in $SOCl_2$ (40 mL) and DMF (0.4 mL) was refluxed for 1 h. The excess reagent was removed under reduced pressure to give a black oil, which was extracted with refluxing hexanes (500 mL). The hot filtrate was filtered three times through Celite (reheating the filtrate each time) and evaporated to give the crude acid chloride (6.03 g, 71%). A solution of the acid chloride (3.92 g, 22.1 mmol) in dioxane (20 mL) was added slowly to a solution of $NaBH_4$ (2.09 g, 55.2 mmol) in water (150 mL), keeping the temperature of the solution at ∼10 °C. The solution was stirred at room temperature for 1 h and then extracted with EtOAc. The organic portion was dried and evaporated, and the residue was chromatographed on silica gel, eluting with 1:1 CH_2Cl_2:EtOAc, to give **180**[43] (2.18 g, 68%) as a white solid: mp 62−63 °C; ^{1}H

NMR [$(CD_3)_2SO$] δ 8.71 (d, J = 1.3 Hz, 1 H), 8.53 (br d, J = 0.5 Hz, 1 H), 5.65 (t, J = 5.8 Hz, 1 H), 4.64 (d, J = 5.8 Hz, 2 H). APCI MS m/z 147, 145 $[M + H]^+$.

2-Chloro-5-(iodomethyl)pyrazine (181). Mesyl chloride (1.57 mL, 20.3 mmol) was added to a solution of alcohol **180** (1.44 g, 9.98 mmol) and Et_3N (4.17 mL, 29.9 mmol) in anhydrous THF (20 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then partitioned between EtOAc and water. The organic fraction was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a crude mesylate. The mesylate was dissolved in acetone (40 mL), sodium iodide (7.5 g, 50 mmol) was added, and the stirred mixture was refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic portion was dried and evaporated, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2, to give **181** (1.54 g, 61%) as a white solid, which was used immediately due to its instability.

Procedure J. (6*S*)-6-[(5-Chloro-2-pyrazinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (182). NaH (60%, 0.36 g, 9.0 mmol) was added to a solution of alcohol **140** (0.93 g, 5.02 mmol) and iodide **181** (1.54 g, 6.05 mmol) in anhydrous DMF (10 mL) at −78 °C. The mixture was stirred at 0 °C for 1 h and then quenched with ice and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$) and evaporated, and then column chromatography of the residue on silica gel, eluting with 0−5% MeOH/EtOAc, gave **182** (1.02 g, 65%) as a white solid: mp 181−183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.76 (d, J = 1.4 Hz, 1 H), 8.50 (d, J = 1.4 Hz, 1 H), 8.02 (s, 1 H), 4.85 (d, J = 13.7 Hz, 1 H), 4.81 (d, J = 13.7 Hz, 1 H), 4.70 (dt, J = 12.1, 2.6 Hz, 1 H), 4.49 (br d, J = 12.0 Hz, 1 H), 4.38−4.29 (m, 2 H), 4.25 (dd, J = 13.5, 3.3 Hz, 1 H). Anal. ($C_{11}H_{10}ClN_5O_4$) C, H, N.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)phenyl]-2-pyrazinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (112). Reaction of chloride **182** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure I gave **112** (78%) as a white solid: mp 233−236 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.29 (d, J = 1.4 Hz, 1 H), 8.76 (d, J = 1.4 Hz, 1 H), 8.34 (br d, J = 8.2 Hz, 2 H), 8.04 (s, 1 H), 7.90 (br d, J = 8.2 Hz, 2 H), 4.91 (d, J = 13.4 Hz, 1 H), 4.88 (d, J = 13.4 Hz, 1 H), 4.74 (dt, J = 12.1, 2.6 Hz, 1 H), 4.52 (br d, J = 11.9 Hz, 1 H), 4.43−4.33 (m, 2 H), 4.27 (dd, J = 13.5, 3.3 Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **113**−**116** of Table 3 from chloride **182**.

5-Bromo-2-(bromomethyl)pyrimidine (184) (Scheme 4C). A mixture of 5-bromo-2-methylpyrimidine[54] (**183**) (1.34 g, 7.75 mmol), *N*-bromosuccinimide (1.40 g, 7.87 mmol), and AIBN (0.13 g, 0.79 mmol) in CCl_4 (15 mL) was stirred at 60 °C for 3 h. The resulting mixture was filtered, the filter cake was washed with Et_2O (100 mL), and the combined filtrates were concentrated under reduced pressure. Column chromatography of the residue, eluting with 2:1 CH_2Cl_2:hexanes, gave **184**[42] (0.214 g, 11%) as a white solid: mp 55−57 °C; ^{1}H NMR ($CDCl_3$) δ 8.79 (s, 2 H), 4.57 (s, 2 H). Anal. ($C_5H_4Br_2N_2$) C, H, N.

Further elution of the column with 0−5% EtOAc/CH_2Cl_2 gave recovered **183** (0.676 g, 50%).

(6*S*)-6-[(5-Bromo-2-pyrimidinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (185). Reaction of alcohol **140** with bromide **184** (1.24 equiv) and NaH (1.5 equiv), using procedure J for 0.5 h (but quenching with water, filtering the solid, washing with water, then triturating with Et_2O), gave **185** (51%) as a light brown solid: mp >290 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.98 (s, 2 H), 8.04 (s, 1 H), 4.83 (d, J = 13.2 Hz, 1 H), 4.80 (d, J = 13.2 Hz, 1 H), 4.68 (dt, J = 12.0, 2.6 Hz, 1 H), 4.48 (br d, J = 11.9 Hz, 1 H), 4.40−4.36 (m, 1 H), 4.31 (dt, J = 13.5, 2.1 Hz, 1 H), 4.23 (dd, J = 13.5, 3.3 Hz, 1 H). Anal. ($C_{11}H_{10}BrN_5O_4$) C, H. N: calcd, 19.67; found, 19.17.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)phenyl]-2-pyrimidinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (117). Reaction of bromide **185** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure I gave **117** (79%) as a white solid: mp 223−225 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.20 (s, 2 H), 8.05 (s, 1 H), 8.04 (br d, J = 8.3 Hz, 2 H), 7.90 (br d, J = 8.3 Hz, 2 H), 4.93 (d, J = 14.5 Hz, 1 H), 4.89 (d, J = 14.5 Hz, 1 H), 4.73 (dt, J = 11.9, 2.6 Hz, 1 H), 4.52 (br d, J = 11.9 Hz, 1 H), 4.46−4.43 (m, 1 H), 4.36 (dt, J = 13.5, 2.1 Hz, 1 H), 4.27 (dd, J = 13.4, 3.3 Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **118**−**121** of Table 3 from bromide **185**.

[2-(Methylsulfanyl)-5-pyrimidinyl]methanol (187) (Scheme 4D). Isobutyl chloroformate (2.55 mL, 19.7 mmol) was added to a solution of 2-(methylsulfanyl)-5-pyrimidinecarboxylic acid[45] (**186**) (3.33 g, 19.6 mmol) and *N*-methylmorpholine (2.16 mL, 19.6 mmol) in anhydrous DME (100 mL) at 0 °C, and the mixture was stirred at 0 °C for 20 min. The resulting mixture was filtered through Celite, and the filtrate was cooled to 0 °C and then treated with a solution of $NaBH_4$ (0.83 g, 21.9 mmol) in water (10 mL). The mixture was stirred for 10 min, then diluted with water (100 mL), and extracted with EtOAc (200 mL). The organic fraction was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with 1:1 EtOAc:CH_2Cl_2, gave **187** (1.71 g, 56%) as a pale yellow solid: mp 59−61 °C (lit.[47] mp 63−64 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 8.57 (s, 2 H), 5.32 (t, J = 5.6 Hz, 1 H), 4.47 (d, J = 5.6 Hz, 2 H), 2.50 (s, 3 H).

5-(Bromomethyl)-2-(methylsulfanyl)pyrimidine (188). Mesyl chloride (1.38 mL, 17.6 mmol) was added to a solution of alcohol **187** (1.37 g, 8.77 mmol) and Et_3N (3.67 mL, 26.3 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C. The solution was stirred at 0 °C for 0.5 h, then diluted with CH_2Cl_2 (50 mL), and washed with water. The organic fraction was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a crude mesylate. The mesylate was dissolved in acetone (50 mL), LiBr (7.60 g, 87.5 mmol) was added, and the stirred mixture was refluxed for 1 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and water. The organic fraction was dried and evaporated, and then column chromatography of the residue, eluting with 5% EtOAc/CH_2Cl_2, gave **188**[55] (1.511 g, 79%) as a white solid: mp 74−76 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.73 (s, 2 H), 4.70 (s, 2 H), 2.52 (s, 3 H). APCI MS m/z 221, 219 $[M + H]^+$.

(6*S*)-6-{[2-(Methylsulfanyl)-5-pyrimidinyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (189). Reaction of alcohol **140** with bromide **188** and NaH (1.5 equiv), using procedure J, gave **189** (87%) as a cream solid: mp 220−221 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.60 (s, 2 H), 8.01 (s, 1 H), 4.68−4.59 (m, 3 H), 4.46 (br d, J = 11.6 Hz, 1 H), 4.28−4.19 (m, 3 H), 2.51 (s, 3 H). Anal. ($C_{12}H_{13}N_5O_4S$) C, H, N.

Procedure K. (6*S*)-2-Nitro-6-({2-[4-(trifluoromethyl)phenyl]-5-pyrimidinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (122). A mixture of methyl sulfide **189** (0.050 g, 0.16 mmol), tris(2-furyl)phosphine (0.012 g, 52 μmol), copper benzothiophene-2-carboxylate (0.097 g, 0.40 mmol), and 4-(trifluoromethyl)phenylboronic acid (0.067 g, 0.35 mmol) in anhydrous THF (6 mL) was purged with N_2. $Pd_2(dba)_3 \cdot CHCl_3$ (0.013 g, 13 μmol) was added, and the mixture was stirred at 50 °C for 18 h in a sealed tube under N_2. The resulting mixture was diluted with EtOAc (100 mL), filtered through Celite, and washed with water. The organic fraction was dried and evaporated, and then column chromatography of the residue on silica gel, eluting with 0−5% MeOH/EtOAc, gave **122** (26 mg, 40%) as a pale yellow solid: mp (MeOH) 259−263 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.92 (s, 2 H), 8.58 (br d, J = 8.1 Hz, 2 H), 8.03 (s, 1 H), 7.90 (br d, J = 8.1 Hz, 2 H), 4.81 (d, J = 12.8 Hz, 1 H), 4.78 (d, J = 12.8 Hz, 1 H), 4.71 (dt, J = 12.1, 2.5 Hz, 1 H), 4.50 (br d, J = 12.0 Hz, 1 H), 4.36−4.23 (m, 3 H); HRESIMS calcd for $C_{18}H_{15}F_3N_5O_4$ m/z $[M + H]^+$ 422.1071, found 422.1059. HPLC purity: 95.6%.

See Supporting Information for details of the syntheses of related compounds **123**−**126** of Table 3 from methyl sulfide **189**.

5-Bromo-2-[4-(trifluoromethoxy)phenyl]pyrimidine (191) (Scheme 4E). A mixture of 5-bromo-2-iodopyrimidine (**190**) (1.50 g, 5.27 mmol), 4-(trifluoromethoxy)phenylboronic acid

(1.185 g, 5.75 mmol), and Na_2CO_3 (1.11 g, 10.5 mmol) in toluene (120 mL) and water (15 mL) was purged with N_2. $Pd(PPh_3)_4$ (60 mg, 0.052 mmol) was added, and the stirred mixture was refluxed under N_2 for 17.5 h and then partitioned between EtOAc and water. The organic fraction was dried and evaporated, and then column chromatography of the residue on silica gel, eluting with 20% CH_2Cl_2/hexanes, gave **191**[49] (1.26 g, 75%) as a white solid: mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 2 H), 8.46 (d, J = 9.0 Hz, 2 H), 7.31 (br d, J = 9.0 Hz, 2 H). APCI MS m/z 321, 319 $[M + H]^+$.

2-[4-(Trifluoromethoxy)phenyl]-5-pyrimidinecarbaldehyde (192). *n*BuLi (1.88 mL of a 2.5 M solution in hexanes, 4.70 mmol) was added to a stirred solution of bromide **191** (1.252 g, 3.92 mmol) in anhydrous THF (40 mL) at −95 °C. The solution was stirred for 30 s, and then anhydrous DMF (5 mL) was added. The mixture was stirred at −90 °C for 20 min, then quenched with aqueous NH_4Cl, and partitioned between EtOAc and water. The organic fraction was dried and evaporated, and then column chromatography of the residue on silica gel, eluting with 15% EtOAc/hexanes, gave **192** (0.778 g, 74%) as a white solid: mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1 H), 9.22 (s, 2 H), 8.62 (d, J = 9.0 Hz, 2 H), 7.36 (br d, J = 9.0 Hz, 2 H). APCI MS m/z 301 $[M + H + MeOH]^+$, 269 $[M + H]^+$.

{2-[4-(Trifluoromethoxy)phenyl]-5-pyrimidinyl}methanol (193). $NaBH_4$ (0.22 g, 5.82 mmol) was added to a solution of aldehyde **192** (0.776 g, 2.89 mmol) in MeOH (100 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, then quenched with brine, and partitioned between EtOAc and water. Column chromatography of the organic portion on silica gel, eluting with 1:1 EtOAc/hexanes, gave **193** (0.657 g, 84%) as a white solid: mp 84−85 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.86 (s, 2 H), 8.50 (d, J = 8.9 Hz, 2 H), 7.51 (br d, J = 8.9 Hz, 2 H), 5.46 (t, J = 5.5 Hz, 1 H), 4.60 (d, J = 5.5 Hz, 2 H). APCI MS m/z 271 $[M + H]^+$.

5-(Bromomethyl)-2-[4-(trifluoromethoxy)phenyl]pyrimidine (194). Mesyl chloride (0.55 mL, 7.0 mmol) was added to a solution of alcohol **193** (0.951 g, 3.52 mmol) and Et_3N (1.5 mL, 10.8 mmol) in anhydrous THF (40 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then partitioned between EtOAc and water. The organic fraction was dried, and the solvent was removed under reduced pressure to give a crude mesylate. The mesylate was dissolved in acetone (100 mL), LiBr (6.10 g, 70.2 mmol) was added, and the stirred mixture was refluxed under N_2 for 1 h. The resulting mixture was filtered, the solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic fraction was dried and evaporated, and then column chromatography of the residue, eluting with CH_2Cl_2, gave **194** (1.10 g, 94%) as a white solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 2 H), 8.50 (d, J = 9.0 Hz, 2 H), 7.32 (br d, J = 9.0 Hz, 2 H), 4.48 (s, 2 H). APCI MS m/z 335, 333 $[M + H]^+$.

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethoxy)phenyl]-5-pyrimidinyl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (124). Reaction of alcohol **140** with bromide **194** (1.05 equiv) and NaH (1.5 equiv), using procedure J, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **124** (0.512 g, 58%) as a white solid: mp (MeOH) 227−230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.88 (s, 2 H), 8.49 (br d, J = 8.9 Hz, 2 H), 8.03 (s, 1 H), 7.51 (br dd, J = 8.9, 0.8 Hz, 2 H), 4.79 (d, J = 12.6 Hz, 1 H), 4.76 (d, J = 12.6 Hz, 1 H), 4.70 (dt, J = 12.0, 2.5 Hz, 1 H), 4.49 (br d, J = 12.0 Hz, 1 H), 4.35−4.29 (m, 2 H), 4.25 (dd, J = 13.3, 3.1 Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

Solubility Determinations. Method A. The solid compound sample was mixed with water (enough to make a 2 mM solution) in an Eppendorf tube, and the suspension was sonicated for 15 min and then centrifuged at 13000 rpm for 6 min. An aliquot of the clear supernatant was diluted 2-fold with water, and then HPLC was conducted. The solubility was calculated by comparing the peak area obtained with that from a standard solution of the compound in DMSO (after allowing for varying dilution factors and injection volumes).

Method B. The study of most compounds (**1**, **5**, **24**, **32**, **74**, **92**, **93**, **114**) was conducted by Admetryx, 4717 Campus Drive, Suite 600, Kalamazoo, MI 49008, using a published protocol (similar to method C below).[12] For pH 1 determinations, the pH 7.4 solution was replaced by pH 1 buffer.

Method C. The study of the remaining compounds (**80**, **97**, **99**, **107**, and **124**) was conducted by Cerep, 15318 NE 95th St., Redmond, WA 98052. according to the following procedure:

Aliquots of the compound DMSO stocks (10 mM) were transferred to pH 7.4 PBS buffer or simulated gastric fluid (target concentrations were 200 μM in compound and 2% DMSO), and the solutions were equilibrated for 24 h at room temperature. The compound concentrations were determined by fast gradient HPLC (using photodiode array detection) with reference to 200 μM calibration standards. Reported values were the mean of two determinations.

Minimum Inhibitory Concentration Assays (MABA and LORA). These were carried out according to the published protocols.[52,53]

Microsomal Stability Assays. These were conducted by MDS Pharma Services, 22011 30th Drive SE, Bothell, WA 98021, using a published protocol.[10] The percentage of compound remaining after 1 h incubation was calculated as

$$\%\ \text{remaining} = 100(\text{mean PAR}_{T60}/\text{mean PAR}_{T0})$$

where PAR = analyte/IS peak area ratio.

***In Vivo* Acute TB Infection Assay.** Each compound was administered orally to a group of seven *M. tb*-infected BALB/c mice at a standard dose of 100 mg/kg, daily for 5 days a week for 3 weeks, beginning on day 11 postinfection, in accordance with published protocols.[10,53] The results are recorded as the ratio of the average reduction in colony forming units (CFUs) in the compound-treated mice/the average CFU reduction in the mice treated with **1**. In this assay, **1** caused up to 2.5−3 log reductions in CFUs.

***In Vivo* Chronic TB Infection 3 Week Assay.** Compounds were administered orally as described for the acute assay but with treatment beginning ~70 days postinfection. In this assay, **1** caused a ca. 2 log reduction in CFUs, whereas **2** caused a ca. 3 log reduction in CFUs.

***In Vivo* Chronic TB Infection 8 Week Assay.** Each compound was administered orally to a group of seven *M. tb*-infected BALB/c mice at a dose of 30 mg/kg, daily for 5 days a week for 8 weeks, with treatment beginning ~50 days postinfection. In this assay, **2** caused a ca. 3 log reduction in CFUs.

***In Vivo* Mouse Pharmacokinetics.** Compounds were administered orally to CD-1 mice at a standard dose of 40 mg/kg, as a suspension in 0.5% carboxymethylcellulose/0.08% Tween 80 in water. Samples derived from plasma and lungs were analyzed by LC-MS/MS to generate the required pharmacokinetic parameters.

Studies of all compounds except **114** were conducted at Cumbre Pharmaceuticals Inc., Dallas, TX, and UNT Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107-2699. The study of compound **114** (using the same protocol) was conducted by MDS Pharma Services, 22002 26th Ave. SE, Suite 104, Bothell, WA 98021-4444.

***In Vivo* Rat Pharmacokinetics and Oral Bioavailability.** Compounds were administered to male Sprague-Dawley rats both intravenously, at doses of 1 or 5 mg/kg, and orally, at a dose of 20 mg/kg, as 2 mg/mL solutions in 40% hydroxypropyl-β-cyclodextrin/50 mM citrate buffer (pH = 3). Samples derived from plasma were analyzed by LC-MS/MS to generate the required pharmacokinetic parameters.

The study was conducted by Absorption Systems, 436 Creamery Way, Suite 600, Exton, PA 19341-2556.

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Supporting Information Available: Additional experimental procedures and characterizations for compounds in Tables 1−3; combustion analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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