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Synthesis and Structure−activity Relationships of Antitubercular 2-Nitroimidazooxazines Bearing Heterocyclic Side Chains

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Recently described biphenyl analogues of the antituberculosis drug PA-824 displayed improved potencies against *M. tuberculosis* but were poorly soluble. Heterobiaryl analogues of these, in which the first phenyl ring was replaced with various 5-membered ring heterocycles, were prepared with the aim of identifying potent new candidates with improved aqueous solubility. The compounds were constructed by coupling the chiral 2-nitroimidazooxazine alcohol with various halomethyl-substituted arylheterocycles, by cycloadditions to a propargyl ether derivative of this alcohol, or by Suzuki couplings on haloheterocyclic methyl ether derivatives. The arylheterocyclic compounds were all more hydrophilic than their corresponding biphenyl analogues, and several showed solubility improvements. 1-Methylpyrazole, 1,3-linked-pyrazole, 2,4-linked-triazole, and tetrazole analogues had 3- to 7-fold higher MIC potencies against replicating *M. tb* than predicted by their lipophilicities. Two pyrazole analogues were >10-fold more efficacious than the parent drug in a mouse model of acute *M. tb* infection, and one displayed a 2-fold higher solubility.

Introduction

Over the last two decades, there has been a global resurgence of tuberculosis (TB[a]), fuelled by an enhanced susceptibility in HIV patients, the increasing incidence of multidrug-resistant (MDR) TB, and the recent emergence of extensively drug resistant (XDR) strains.[1,2] The current second-line drugs used in lengthy combination therapies to treat MDR-TB (typically over 2 years[2]) mostly have reduced potency and/or greater toxicity than existing first-line agents and may be largely ineffective against XDR-TB,[2] underscoring the urgent need for new treatments. In the past decade, the general class of (6*S*)-2-nitroimidazo[2,1-*b*][1,3]oxazines bearing lipophilic side chains at the 6-position, typified by PA-824 (**1**),[3] has shown potent activity against both replicating and nonreplicating cultures of *Mycobacterium tuberculosis* (*M. tb*),[3−6] the causative agent of TB. Recent work suggests that an important component of the activity of these compounds against nonreplicating *M. tb* is due to an unusual route of reductive metabolism of the nitroimidazole ring,[7,8] leading to the release of nitric oxide as a toxic species.[9] Both **1** and the related 6-nitroimidazo[2,1-*b*][1,3]oxazole, OPC-67683 (**2**),[10] are currently in phase II clinical trials for the treatment of drug-susceptible and drug-resistant TB,[11] with the aim of reducing the duration and frequency of drug treatment required. A recent report[12] of a phase IIa early bactericidal activity (EBA) study of **1** given as a single agent to TB patients once daily for 14 days (dosing orally at 200, 600, 1000, or 1200 mg) showed that the drug was essentially equivalent to the standard, four-drug TB treatment protocol in reducing the number of live *M. tb* in the sputum (∼0.1 log decrease in CFUs per day for 14 days) and was well-tolerated (but equally efficacious) at all dose levels. The use of a dry powder inhaler as an alternative drug delivery system for **1** has now been reported to provide increased lung concentrations for longer times than that achieved following oral administration (guinea pig model).[13]

We recently described[6] a structure−activity relationship (SAR) study of biphenyl analogues of **1**, which showed that many derivatives (**I**) (including 3-linked, but particularly 4-linked examples, such as **3**) had improved potencies against both replicating and nonreplicating *M. tb* in culture. Some of these displayed particularly notable efficacies in a mouse model of acute *M. tb* infection (e.g., **3** was >205-fold more effective than **1**). The study also showed that aerobic MIC values correlated positively both with overall lipophilicity and with the electron-withdrawing properties of substituents on the terminal phenyl ring. However, these biphenyl analogues had concomitantly lower aqueous solubilities than **1** (e.g., the solubility of **3** was at least 16-fold less than **1**), which could negatively impact on their oral bioavailability at higher doses. This is likely given that **1** itself is 94% protein bound in human plasma[14] and because absorption issues were noted during

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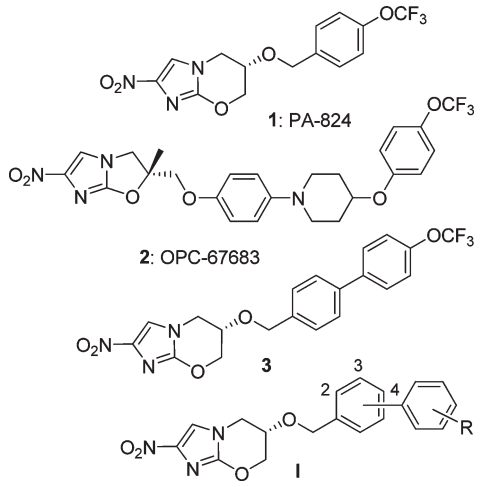
[a] Abbreviations: TB, tuberculosis; MDR, multidrug-resistant; XDR, extensively drug resistant; *M. tb*, *Mycobacterium tuberculosis*; EBA, early bactericidal activity; SAR, structure−activity relationship; MIC, minimum inhibitory concentration; SD, standard deviation; MLB, *meta*-linked biphenyl; CFU, colony forming unit; THP, tetrahydropyranyl; APCI MS, atmospheric pressure chemical ionization mass spectrometry; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; TBAF, tetra-*n*-butylammonium fluoride; DMSO, dimethyl sulfoxide; PAR, peak area ratio; IS, internal standard.

clinical trials of the much more lipophilic **2** that necessitated a change in drug formulation for this compound.[15] Unfortunately, attempts to solubilize the biphenyl class via aminoalkoxy substituents resulted in a dramatic loss in activity, particularly in vivo.[6]



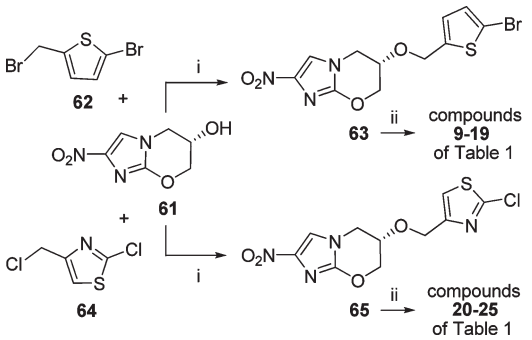
In work aimed at identifying new, potent heterobiaryl analogues of **1** with better aqueous solubilities than the biphenyl class, we now report the synthesis and evaluation of 11 different subseries in which the proximal phenyl ring of **I** was replaced by more hydrophilic 5-membered ring heterocycles.

Chemistry

The 5-arylthiophene and 2-arylthiazole analogues (**9**−**19** and **20**−**25**, respectively) were prepared by base-catalyzed alkylation of the known[16] chiral alcohol **61** with the 2-halo(5- or 4-halomethyl) heterocycles **62**[17] or **64**,[18] followed by Suzuki coupling of the products (**63** and **65**) with appropriate arylboronic acids (Scheme 1). Similar base-catalyzed alkylation of alcohol **61** with (3-bromo-1-propynyl)(*tert*-butyl)dimethylsilane[19] (**87**) gave (after desilylation) the propargyl ether **88**, which underwent cycloaddition[20] with known[21−24] *N*-hydroxy-arylcarboximidoyl chlorides (**89a**−**f**) to give the 3-arylisoxazole derivatives **40**−**45** directly (Scheme 5). Alternatively, treatment of **88** with known[25−28] aromatic azides (**93a**, **93c**−**g**) in the presence of CuI/$Cu(OAc)_2$[29] gave the 1-aryl-1,2,3-triazole derivatives **47**−**52**.

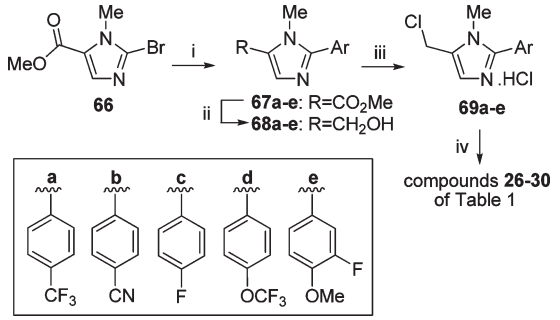
The rest of the compounds were synthesized by the coupling of alcohol **61** with various fully constructed side chains (arylheterocycles bearing a halomethyl substituent). These were prepared by a variety of different routes. The 2-aryl-5-(chloromethyl)-1-methylimidazole hydrochlorides **69a**−**e** required for the synthesis of 2-arylimidazole analogues **26**−**30** were formed by Suzuki coupling of methyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate[30] (**66**) with arylboronic acids, subsequent reduction ($LiAlH_4$) of the resulting esters (**67a**, **67c**−**e**, or $LiPyrrBH_3$[31] reduction in the case of **67b**) to give alcohols **68a**−**e**, and finally chlorination with thionyl chloride (Scheme 2). The 3-aryl-5-(bromomethyl)-1-methylpyrazoles **74a**−**c** employed in the synthesis of 3-arylpyrazole analogues **31**−**33** were constructed by Pd-catalyzed four-component coupling[32] of THP-protected prop-2-yn-1-ol (**70**)[33] with 4-substituted iodobenzenes **71a**−**c**, aqueous methylhydrazine, and carbon monoxide to give the THP-protected 1-methylpyrazole derivatives **72a**−**c** (Scheme 3). Deprotection under forcing conditions (4M HCl/THF/80 °C/16 h) gave alcohols **73a**−**c**, which yielded the desired bromides on treatment with phosphorus tribromide.

Scheme 1[a]



[a] Reagents and conditions: (i) NaH, DMF, 0 °C, 2 h; (ii) $ArB(OH)_2$, toluene, EtOH, 2 M K_2CO_3, $PdCl_2$(dppf) under N_2, reflux, 0.5−1 h.

Scheme 2[a]

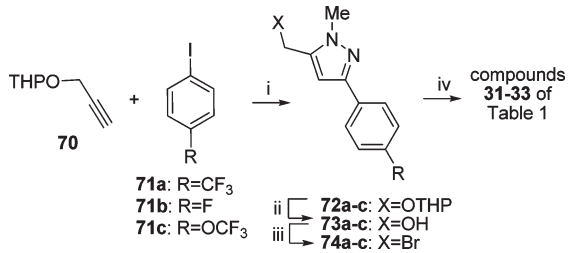


[a] Reagents and conditions: (i) $ArB(OH)_2$, toluene, EtOH, 2 M K_2CO_3, $PdCl_2$(dppf) under N_2, reflux, 2 h; (ii) $LiAlH_4$ or $LiPyrrBH_3$, THF, 0 or 20 °C, 1−2 h; (iii) $SOCl_2$, reflux, 0.5 h; (iv) **61**, NaH, DMF, 0 °C, 2 h.

The synthesis of 1-aryl-4-linked-pyrazoles **34**−**36** began with the condensation of ethyl (2*E*)-2-cyano-3-ethoxy-2-propenoate (**75**) and 4-substituted phenylhydrazines **76a**−**c** to give the expected[34] substituted ethyl 5-amino-1-phenylpyrazole-4-carboxylates (**77a**−**c**) (Scheme 4). Deamination with isoamyl nitrite[35] provided the esters **78a**−**c**, which were successively reduced and brominated as above to furnish the required 1-aryl-4-(bromomethyl)pyrazoles **80a**−**c**. Synthesis of the isomeric 1-aryl-3-linked-pyrazoles **37**−**39** commenced with the reaction of ethyl 2-chloroacetoacetate (**81**) and known[36,37] 4-substituted benzenediazonium tetrafluoroborates (**82a**−**c**) to give[38] the intermediate arylhydrazonoyl chlorides **83a**−**c** (Scheme 4). These underwent a [3 + 2] cycloaddition with bicyclo[2.2.1]hepta-2,5-diene, followed by a retro Diels−Alder reaction (in refluxing xylenes), to form[39,40] the ethyl 1-arylpyrazole-3-carboxylates **84a**−**c**, which were elaborated to the 1-aryl-3-(bromomethyl)pyrazoles **86a**−**c** in similar fashion.

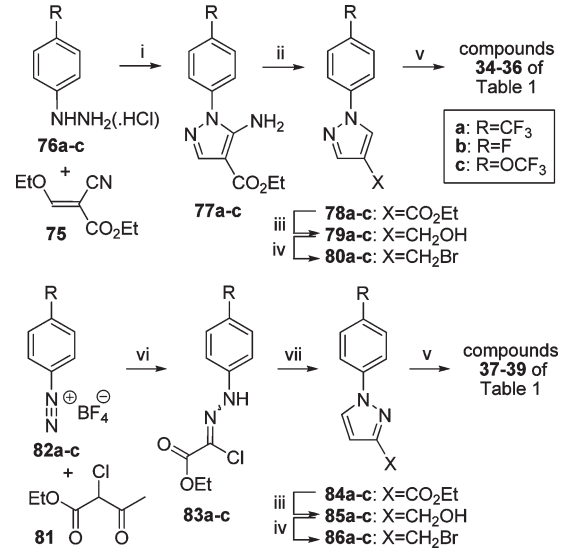
2-(Chloromethyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (**92**), employed in the preparation of the oxadiazole analogue **46**, was prepared directly[41] by chlorination ($POCl_3$) of *N*′-(chloroacetyl)-4-fluorobenzohydrazide[42] (**91**), obtained by chloroacetylation of 4-fluorobenzohydrazide (**90**) (Scheme 5). The 2-aryl-4-(bromomethyl)-1,2,3-triazoles (**99a**−**d**) required for the preparation of 2-aryl-4-linked-1,2,3-triazoles **53**−**56** were synthesized by the condensation of 2-oxopropanedial dioxime[43] (**94**) and arylhydrazines (**95a**−**d**) to give the intermediate dioximes **96a**−**d** (Scheme 6). These dioximes were successively acetylated (Ac_2O), cyclized with cesium carbonate, and treated

Scheme 3[a]



[a] Reagents and conditions: (i) $MeNHNH_2.H_2SO_4$, aq $NaHCO_3$, CuI, $PdCl_2(PPh_3)_2$, THF, 20 °C, 48 h under CO; (ii) 4 M HCl, THF, 80 °C, 16 h; (iii) PBr_3, Et_2O, 0−20 °C, 16 h; (iv) **61**, NaH, DMF, 0 °C, 2 h.

Scheme 4[a]



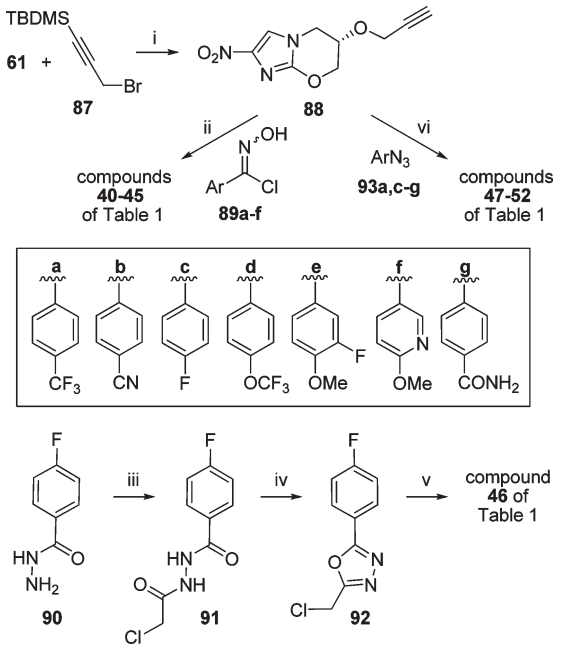
[a] Reagents and conditions: (i) NaOAc, aq AcOH, 100 °C, 15 h; (ii) isoamyl nitrite, THF, reflux, 20 h; (iii) $LiAlH_4$, Et_2O, 0−20 °C or reflux, 1−2 h; (iv) PBr_3, Et_2O, 0−20 °C, 2−17 h; (v) **61**, NaH, DMF, 0 °C, 2 h; (vi) aq pyridine, −5 °C, 0.5 h; (vii) bicyclo[2.2.1]hepta-2,5-diene, Et_3N, toluene, 70 °C, 1 h, then xylenes, reflux, 2 h.

with paraformaldehyde (rather than *s*-trioxane as reported[44]) to give the triazole aldehydes **97a**−**d**, which were further elaborated to the required bromides. Finally, the 2-aryl-5-(bromomethyl)tetraazoles **103a**−**d** needed for the preparation of 2-aryltetrazole analogues **57**−**60** were obtained from the known[45] 2-(2-arylhydrazono)acetic acids (**100a**−**d**) by base-catalyzed reaction[46] with 2-azido-1,3,5-tribromobenzene,[47] followed by esterification with diazomethane, to give 2-aryltetrazole esters **101a**−**d**. Following ester reduction, the alcohols (**102a**−**d**) were brominated using either PBr_3 or NBS/Ph_3P (Scheme 6).

Results and Discussion

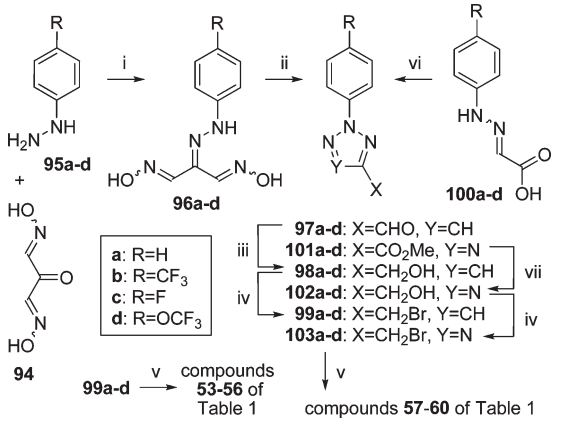
Table 1 provides data on 11 subseries related to the previously described biphenyl analogues, in which the phenyl ring proximal to the 2-nitroimidazooxazine chromophore was replaced by different 5-membered ring heterocycles. These ranged from monoheterocyclic species (thiophene; class A), through various N, mixed N/S, and N/O di- and triheterocycles, to a tetraheterocycle (tetrazole; class K). For comparison, previous data[6] are given for five *meta*-linked biphenyl (MLB) analogues (**4**−**8**) which have the most similar side chain geometry to the new analogues, together with data[6] for **1**

Scheme 5[a]



[a] Reagents and conditions: (i) NaH, DMF, 0 °C, 1 h, then TBAF, THF, 0 °C, 1 h; (ii) Et_3N, THF, 0−20 °C, 16 h; (iii) $ClCH_2COCl$, EtOAc, reflux, 30 min; (iv) $POCl_3$, reflux, 2 h; (v) **61**, NaH, DMF, 0 °C, 0.5 h; (vi) CuI, $Cu(OAc)_2$, THF, 50 °C, 16 h (then, for **48**: TFAA, THF, reflux, 2 h).

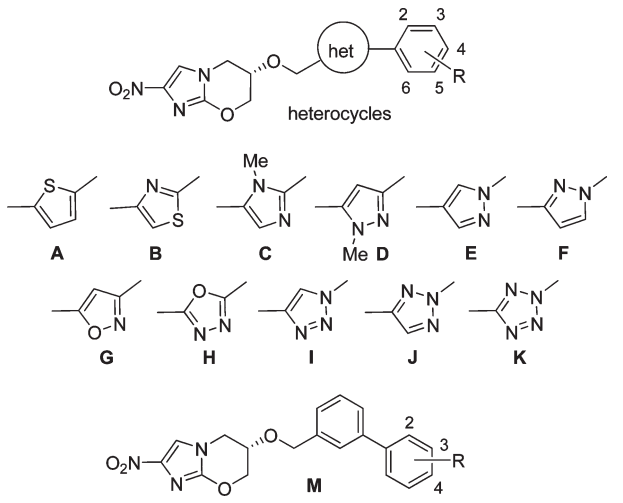
Scheme 6[a]



[a] Reagents and conditions: (i) EtOH, 70 °C, 0.5 h; (ii) Ac_2O, 20 °C, 0.5 h, then Cs_2CO_3, THF, 20 °C, 0.5 h, then $(CH_2O)_n$, 2 M HCl, reflux, 2 h; (iii) $NaBH_4$, MeOH, 20 °C, 0.5 h; (iv) PBr_3, Et_2O, 0−20 °C, 15−16 h or NBS, PPh_3, CH_2Cl_2, −40 °C, 2 h; (v) **61**, NaH, DMF, 0 °C, 1−2 h; (vi) NaOEt, EtOH, 2,4,6-triBrPhN$_3$, reflux, 5 h, then aq HCl, then CH_2N_2, Et_2O, MeOH, 20 °C; (vii) $LiAlH_4$, Et_2O, 0 °C, 1 h.

and **3**. The lipophilicities of the compounds were estimated by CLogP values, calculated using ACD LogP/LogD prediction software (version 8.0, Advanced Chemistry Development Inc., Toronto, Canada), as described for the biphenyl series.[6] The comparative effects of the heterocyclic groups on compound CLogP values were evaluated using the reference set of biphenyl analogues (**4**−**8**) and determining, for each arylheterocyclic subseries, the average difference in CLogP values between compounds in the reference and subseries sets bearing the same substituents (Table 2). All of the arylheterocyclic compounds were more hydrophilic than their MLB

Table 1. Physicochemical Properties and MIC Values for Arylheterocyclic Analogues of **1**



compd	Fm	R	sol[a]	CLogP[b]	MIC (μM)[c] MABA	MIC (μM)[c] LORA
1			19	2.70	0.50 ± 0.30	2.6 ± 1.4
3			1.2	4.36	0.035 ± 0.015	1.3 ± 0.1
4	M	4-CF_3	2.8	4.48	0.12 ± 0.01	2.9 ± 1.4
5	M	4-CN		2.83	0.23 ± 0.01	4.8 ± 1.1
6	M	4-F	1.8	3.44	0.077 ± 0.034	3.8 ± 0.7
7	M	4-OCF_3		4.36	0.11 ± 0.05	2.2 ± 0.5
8	M	3-F, 4-OCH_3		3.30	0.19 ± 0.10	2.2 ± 0.5
9	A	4-CF_3	0.7	4.29	0.16 ± 0	1.0 ± 0.4
10	A	4-CN		2.63	0.055 ± 0.005	1.7 ± 0.6
11	A	4-F		3.25	0.05 ± 0.01	1.9 ± 0.5
12	A	4-OCF_3		4.16	0.85 ± 0.01	2.6 ± 0.5
13	A	3-F, 4-OCH_3		3.10	0.06 ± 0	1.0 ± 0.3
14	A	4-OCF_2H		3.31	0.86 ± 0.01	0.58 ± 0.20
15	A	3-aza, 4-OCH_3	2.2	2.50	0.22 ± 0.02	4.5 ± 0.7
16	A	2-aza, 5-CF_3		2.94	0.28 ± 0.16	1.7 ± 0.2
17	A	3-aza, 4-CF_3	8.9	3.37	0.05 ± 0	4.4 ± 2.3
18	A	3-aza, 4-F		1.99	0.86 ± 0.04	2.3 ± 0.7
19	A	3-aza, 5-F		2.01	0.87 ± 0.05	2.3 ± 0.3
20	B	4-CF_3	2.8	3.74	1.4 ± 0.3	3.0 ± 0.3
21	B	4-CN		2.43	0.67 ± 0.31	3.2 ± 0.3
22	B	4-F		2.99	0.35 ± 0.13	2.8 ± 1.0
23	B	4-OCF_3		3.97	1.2 ± 0.6	1.5 ± 0.1
24	B	3-F, 4-OCH_3		3.14	0.20 ± 0.04	1.7 ± 0.3
25	B	3-aza, 4-OCH_3		2.55	1.4 ± 0.4	4.5 ± 0.9
26	C	4-CF_3	16	2.00	0.65 ± 0.16	9.7 ± 4.0
27	C	4-CN		0.69	2.8 ± 1.1	> 32
28	C	4-F		1.28	1.9 ± 0.1	31 ± 0
29	C	4-OCF_3		2.24	1.1 ± 0.1	7.4 ± 1.2
30	C	3-F, 4-OCH_3		1.40	1.4 ± 0.4	> 32
31	D	4-CF_3	1.4	2.58	0.06 ± 0	4.1 ± 0.2
32	D	4-F		1.54	0.36 ± 0.02	4.0 ± 0.5
33	D	4-OCF_3		2.46	0.06 ± 0	0.58 ± 0.20
34	E	4-CF_3	4.9	2.22	0.54 ± 0.30	2.3 ± 0.6
35	E	4-F		1.70	0.80 ± 0.13	3.9 ± 0.8
36	E	4-OCF_3		2.60	0.15 ± 0.03	1.8 ± 0.2
37	F	4-CF_3	5.4	2.22	0.045 ± 0.005	1.0 ± 0.1
38	F	4-F		1.70	0.11 ± 0.02	7.2 ± 2.4
39	F	4-OCF_3		2.60	0.05 ± 0.01	0.61 ± 0.41
40	G	4-CF_3	0.5	2.19	0.17 ± 0.01	2.6 ± 1.0
41	G	4-CN		0.53	1.4 ± 0.5	6.2 ± 2.1
42	G	4-F		1.15	1.5 ± 0.9	1.9 ± 0.6
43	G	4-OCF_3		2.07	0.55 ± 0.19	1.2 ± 0.5
44	G	3-F, 4-OCH_3		1.00	1.1 ± 0.3	2.0 ± 0
45	G	3-aza, 4-OCH_3		0.40	2.0 ± 1.1	4.1 ± 0.9
46	H	4-F	108	0.65	2.4 ± 0.8	17 ± 0
47	I	4-CF_3	4.6	1.91	0.11 ± 0.02	3.4 ± 0.2
48	I	4-CN		0.77	0.89 ± 0.04	11 ± 5
49	I	4-F		1.39	1.2 ± 0.2	6.9 ± 3.4
50	I	4-OCF_3		2.29	0.075 ± 0.015	3.3 ± 0.2
51	I	3-F, 4-OCH_3		1.25	0.86 ± 0.13	8.7 ± 1.2
52	I	3-aza, 4-OCH_3		0.44	1.6 ± 0.4	12 ± 6
53	J	H		1.34	0.25 ± 0.04	2.2 ± 0.9
54	J	4-CF_3	1.0	1.91	0.05 ± 0.01	2.1 ± 1.2
55	J	4-F		1.39	0.17 ± 0.06	1.4 ± 0.2
56	J	4-OCF_3		2.29	0.03 ± 0	1.6 ± 0.2
57	K	H		1.27	1.2 ± 0.2	5.7 ± 2.4
58	K	4-CF_3	5.0	1.84	0.20 ± 0.03	1.4 ± 0.6
59	K	4-F		1.32	0.29 ± 0.17	3.4 ± 0.1
60	K	4-OCF_3		2.22	0.035 ± 0.005	1.3 ± 0.4

[a] Solubility (μg/mL) in water at pH = 7 and 20 °C, determined by HPLC (see Experimental Section, Method A). [b] CLogP values, calculated using the ACD LogP/LogD prediction software (version 8.0, Advanced Chemistry Development Inc., Toronto, Canada). [c] Minimum inhibitory concentration, determined under aerobic (MABA)[50] or anaerobic (LORA)[49] conditions. Each value is the mean of at least two independent determinations (29 determinations for **1**) ± SD.

analogues, but there was substantial variation across the heterocyclic subseries. The thiophene and thiazole classes (A and B) showed the least lipophilicity differences to MLB analogues, with average ΔCLogP values of −0.20 and −0.43, respectively. All of the other heterocyclic classes were much more hydrophilic and fairly similar, with average ΔCLogPs ranging from −1.90 (3,5-linked-1-methylpyrazole; class D) to −2.79 (2,5-linked-1,3,4-oxadiazole; class H).

The compounds were evaluated for their ability to inhibit *M. tb* in two assays (Table 1) in order to derive SAR for both aerobic and anaerobic activity, as described in previous studies.[4−6] The MABA (aerobic) assay evaluated the activity of compounds against replicating *M. tb* in an 8 day microplate-based assay using Alamar blue reagent (added on day 7).[48] The LORA (anaerobic) assay (luminescence-based low-oxygen-recovery assay) screened for activity against bacteria in a nonreplicating state that models clinical persistence, using an 11 day high-throughput format and *M. tb* containing a plasmid with an acetamidase promoter driving a bacterial luciferase gene, where the bacteria had first been adapted to low oxygen conditions by extended culture.[49] Activity was quantified by the minimum inhibitory concentration (MIC): the lowest compound concentration effecting a growth inhibition of >90%. The values recorded in Table 1 represent the mean of at least two separate determinations (±SD). Because the arylheterocyclic compounds were significantly different in structure from **1** and the biphenyl analogues previously described,[6] assessment of mammalian cell cytotoxicity was also important. This was done[50] using VERO cells (CCL-81, American Type Culture Collection) in a 72 h exposure, using a tetrazolium dye assay, against which all of the compounds were relatively nontoxic, with IC_{50}s >128 μM (data not shown).

The 5-arylthiophene derivatives **9**−**19** (class A) had broadly similar lipophilicities and MIC values to the corresponding MLB analogues (**4**−**8**). The mean MABA and LORA MICs for compounds **9**−**13** were 0.24 and 1.6 μM respectively, compared with 0.15 and 3.2 μM for compounds **4**−**8** (Table 2). However, the 4-CF_3Ph-thiophene **9** showed a 4-fold lower solubility than the corresponding biphenyl analogue **4** (0.7 versus 2.8 μg/mL, Table 1). Therefore, the

Table 2. Summary of Calculated Lipophilicity Differences and Mean MICs for Compound Subsets

				mean MICs (μM)			
				observed		predicted[c]	
compd	subseries	ΔCLogP[a]	n[b]	MABA	LORA	MABA	ratio[c]
4–**8**	M: *m*-linked biphenyl		5	0.15	3.2		
9–**19**	A: (2,5)-thiophene	−0.20[d]	5	0.24	1.6	0.17	1.4
20–**25**	B: (2,4)-thiazole	−0.43[d]	5	0.76	2.4	0.19	4.0
26–**30**	C: (2,5)-1-Me-imidazole	−2.16[d]	5	1.6	>22	0.52	3.1
31–**33**	D: (3,5)-1-Me-pyrazole	−1.90[e]	3	0.16	2.9	0.45	1/2.8
34–**36**	E: (1,4)-pyrazole	−1.92[e]	3	0.50	2.7	0.45	1.1
37–**39**	F: (1,3)-pyrazole	−1.92[e]	3	0.068	2.9	0.45	1/6.6
40–**45**	G: (3,5)-isoxazole	−2.29[d]	5	0.94	2.8	0.56	1.7
46	H: (2,5)-1,3,4-oxadiazole	−2.79[f]	1	2.4	17	0.75	3.2
47–**52**	I: (1,4)-1,2,3-triazole	−2.16[d]	5	0.63	6.7	0.52	1.2
53–**56**	J: (2,4)-1,2,3-triazole	−2.23[e]	3	0.083	1.7	0.54	1/6.5
57–**60**	K: (2,5)-tetrazole	−2.30[e]	3	0.18	2.0	0.56	1/3.1

[a] Mean difference in CLogP values between the heterocyclic subseries and the biphenyl reference compounds. [b] Number of compounds from which mean MICs were calculated. [c] Predicted mean MABA MICs based on eq 1 (see text), using mean observed MABA MIC data for **4**–**8** and ΔCLogP values for each subseries. Ratio is observed/predicted value. [d] Calculations based on data from CF_3, CN, F, OCF_3, and 3-F, 4-OMe analogues. [e] Calculations based on data from CF_3, F, OCF_3 analogues. [f] Calculations based on data from F analogue only.

aza-containing compounds **15**–**19** were also prepared, aiming for compounds of higher solubility. While this objective was achieved (compound **17** displayed a 13-fold higher solubility than **9**), overall, these aza-containing compounds had poorer MICs, with mean MABA and LORA values of 0.46 and 3.0 μM, respectively (the exception being the 3-aza, 4-CF_3 analogue **17**, with an aerobic MABA MIC value of 0.05 μM). The slightly more hydrophilic 2-arylthiazole derivatives **20**–**25** (class B) were comparable to the corresponding MLB analogues in the LORA assay but were overall about 5-fold less potent than the latter in the MABA assay (mean MABA MIC values 0.76 versus 0.15 μM, Table 2). The 4-CF_3Ph derivative **20** was also found to have equivalent aqueous solubility to the MLB analogue **4**. Thus these two classes of arylheterocycles did not offer any significant advantages over the original biphenyl analogues.

The 2-aryl-1-methylimidazole derivatives **26**–**30** (class C) were much more hydrophilic, with a mean ΔCLogP value 2.2 units lower than the reference MLB analogues, and this translated into much higher aqueous solubility (16 μg/mL for the 4-CF_3Ph derivative **26**). However, these compounds had average MIC potencies about an order of magnitude poorer than for MLB analogues (mean MICs: MABA, 1.6 μM, LORA, >22 μM). We have previously shown a negative correlation between hydrophilicity and MABA MIC values for a large set of substituted biphenyls (eq 1).[6]

$$\log(\mathrm{MIC_{MABA}}) = -0.25\mathrm{CLogP} - 0.52\sum\sigma - 0.014 \quad (1)$$

Using this equation, a predicted mean MABA MIC value of 0.52 μM could be estimated for the 2-aryl-1-methylimidazoles (Table 2). This is an average increase, due to their lower lipophilicity, of about 3.5-fold compared with the MLB analogues **4**–**8**. However, the mean measured MABA MIC value (1.6 μM) was about 3-fold poorer than that, suggesting little further interest in these compounds. It is possible that the significantly reduced potency of this particular class (in both assays) may arise from an unfavorable steric effect associated with the *N*-methyl group located between the 5-methylene and 2-aryl substituents (cf. class D below), which could result in a less optimal binding to the nitroreductase; studies are underway to evaluate such effects in more detail.

Three classes of pyrazoles (D–F) of slightly less hydrophilicity (mean ΔCLogP 1.9 units lower than for MLB analogues) showed more promising results. The 3-aryl-1-methylpyrazole derivatives **31**–**33** (class D) were equipotent to the MLB analogues overall (3-fold more active in MABA than expected based on their lipophilicity, Table 2), with one analogue, **33** (4-OCF_3Ph), highly effective in both assays (MICs of 0.06 and 0.58 μM in MABA and LORA, respectively). The 1-aryl-4-linked-pyrazole derivatives **34**–**36** (class E) retained similar LORA potencies but were generally about 3-fold less potent in the MABA assay (average MABA MIC of 0.50 μM, equivalent to their predicted mean potency). The 1-aryl-3-linked-pyrazole derivatives **37**–**39** (class F) displayed the highest average MABA potency of all the 11 subseries (0.068 μM; about 7-fold better than expected based on their lipophilicity), with the 4-OCF_3Ph derivative (**39**) displaying particularly high potencies, similar to **33** in both assays. Encouragingly, the 4-CF_3Ph derivatives in both 1-arylpyrazole classes (E and F: **34** and **37**, respectively) also showed about 2-fold higher solubilities than the biphenyl analogue **4** (whereas **31**, class D, showed a 2-fold lower solubility than **4**).

The 3-arylisoxazole derivatives **40**–**45** (class G) were more hydrophilic than the above pyrazoles (mean CLogP value 2.3 units lower than for MLB analogues), but in this case the aqueous solubility of the 4-CF_3Ph derivative **40** was rather poor (0.5 μg/mL, Table 1). Like the thiazoles (class B), these compounds were significantly less potent overall in the MABA assay (6-fold less than MLB analogues, slightly worse than predicted, Table 2) but retained LORA potency. Only a single 5-aryl-1,3,4-oxadiazole derivative (**46**, 4-FPh, class H) was evaluated. This heterocycle provided the highest hydrophilicity (ΔCLogP −2.79) and the highest aqueous solubility (108 μg/mL) but the poorest activity of all the subseries (the measured MABA MIC was 1.65 μM higher than that estimated by eq 1), so was not investigated further.

Finally, two 1,2,3-triazole-based subseries were evaluated, the 1-aryl-4-linked (**47**–**52**; class I) and the 2-aryl-4-linked (**53**–**56**; class J), together with some 2-aryltetrazole analogues (**57**–**60**; class K). These compounds all showed very similar hydrophilicities to the 2-aryl-1-methylimidazole derivatives **26**–**30** (class C) and the 3-arylisoxazole derivatives **40**–**45** (class G). The class J triazoles were the more active isomer series (mean MICs 2-fold better than for MLB analogues in both assays, about 6.5-fold better than predicted on

lipophilicity grounds and 4- to 8-fold better than for class I), with the 4-OCF_3Ph derivative **56** being the most potent of all the compounds in the MABA assay (MIC 0.03 μM). The 2-aryltetrazoles displayed mean MIC potencies comparable to the MLB analogues (about 3-fold higher than predicted), although 4-OCF_3Ph derivative **60** was essentially as active as triazole **56**. For these three subseries, the 2-aryltetrazole (class K) and 1-aryl-4-linked-1,2,3-triazole (class I) showed modest improvements in aqueous solubility (about 1.6- to 1.8-fold for the 4-CF_3Ph derivatives **47** and **58** over the biphenyl analogue **4**), whereas the 2-aryl-4-linked-triazoles (class J) were less soluble.

Overall then, four heterocyclic subseries (5-arylthiophene, 3-arylisoxazole, 1-aryl-4-linked-pyrazole, and 1-aryl-4-linked-1,2,3-triazole derivatives) showed aerobic (MABA) potencies similar to those expected based on their lipophilicities (Table 2), three subseries (2-arylthiazole, 2-aryl-1-methylimidazole, and 5-aryl-1,3,4-oxadiazole derivatives) showed slightly poorer MABA activities than predicted (3- to 4-fold), while a further four subseries (3-aryl-1-methylpyrazole, 1-aryl-3-linked-pyrazole, 2-aryl-4-linked-triazole, and 2-aryl-5-linked-tetrazole analogues) were 3- to 7-fold more potent than expected (MABA assay). Of these latter four, the 1-aryl-3-linked-pyrazoles, class F, and the 2-aryltetrazoles, class K, provided compounds with both lower lipophilicities and modestly (2-fold) improved aqueous solubilities, compared to the original biphenyl analogues. Interestingly, from an anaerobic (LORA) potency perspective, only two heterocyclic subseries (2-aryl-1-methylimidazole and 5-aryl-1,3,4-oxadiazole derivatives) were significantly different from the MLB analogues (5- to > 7-fold less active). This is consistent with results from previous studies,[4−6] which describe different SAR for aerobic and anaerobic activity with various nitroimidazole analogues and may indicate that a different mechanism of activation applies under aerobic and anaerobic conditions.

Broadly, the results above also suggest that compound lipophilicity (alone) is much less strongly correlated with aerobic potency for this diverse set of heterobiaryl analogues of **1** than for the earlier biphenyl compounds.[6] Indeed, eq 2 shows an identical coefficient to eq 1 (suggesting a similar trend), although the correlation itself had low statistical significance:

$$\log(\mathrm{MIC_{MABA}}) = -0.25\mathrm{CLogP} + 0.059 \qquad (2)$$
$$n = 52 \qquad R = 0.41 \qquad F = 9.9$$

While some uncertainties in the estimated CLogP values and measured MIC data (or possibly, in the case of the 2-aryl-1-methylimidazoles, the influence of subtle steric effects) may in part explain such findings, the unexpectedly high potency of certain nitrogen heterocyclic subseries suggests that there is more to learn about the nature of the proposed[5] hydrophobic binding areas in the nitroreductase, which could be explored in further studies.

The presence of several subsets of compounds bearing the same terminal substituents also permitted an evaluation of the comparative utility of these substituents, especially any differential effects on replicating versus nonreplicating bacteria. Table 3 gives "average" rankings for the up to six common substituent patterns, obtained by ranking the MIC potencies of the compounds bearing them within each subseries (e.g., 1, 2, 3,...), and then averaging these rankings. To compensate for a smaller set of common substituents (3) across five subseries (classes D, E, F, J and K), separate analyses were performed for these and for the five larger-sized subseries (classes A, B, C, G, and I), generating two rankings (A and B). For activity in the MABA assay across the full substituent set (ranking A), 3-F, 4-OCH_3, and 4-CF_3 were slightly better than 4-OCF_3 and 4-F (with 3-aza, 4-OCH_3 clearly the least effective), whereas for the smaller substituent set (ranking B) 4-OCF_3 was slightly superior to 4-CF_3 and 4-F was less effective. The rankings in LORA were more pronounced and consistent, with 4-OCF_3 clearly the best for both substituent set sizes, while 4-CN and 3-aza, 4-OCH_3 were the least effective.

A subset of compounds was evaluated for their stabilities in a metabolism screen with human and mouse liver microsome preparations (Table 4; data for **1** and biphenyl analogue **3** are also provided for comparison). We have previously found at least moderate microsomal stability (> 50% remaining after 1 h) to be a prerequisite to achieve in vivo efficacies better than **1**.[6]

Table 3. Average Ranking of Substituents According to MABA and LORA Activity

	ranking A[a]		ranking B[b]	
substituent	MABA	LORA	MABA	LORA
4-F	3.4	3.0	3.0	2.4
4-OCF_3	3.0	1.8	1.2	1.2
4-CF_3	2.6	2.6	1.6	2.4
3-F, 4-OCH_3	2.6	2.8		
4-CN	3.6	4.6		
3-aza, 4-OCH_3	5.5	5.8		

[a] Value obtained by ranking the MIC potencies of the different substituted compounds in the five largest subseries (1 = most potent, 6 = least potent, for classes A, B, C, G, I) and averaging these "substituent" rankings (see text). [b] Similar value (see footnote a) obtained for the five subseries having only three common substituents (classes D, E, F, J, K).

Table 4. Microsomal Stability and in Vivo Efficacy Data for Selected Analogues

				microsomes (% remaining at 1 h)		
compd	subseries	substituent	TD sol[a]	H[b]	M[c]	in vivo efficacy[d] (ratio vs **1**)
1			11	82	94	1.00
3	*p*-linked biphenyl	OCF_3	< 0.5	97	96	> 205
10	(2,5)-thiophene	CN		85	54	0.02
17	(2,5)-thiophene	3-aza, 4-CF_3		85	77	2.3
33	(3,5)-1-Me-pyrazole	OCF_3	0.88	86	81	12
36	(1,4)-pyrazole	OCF_3		87	64	1.5
39	(1,3)-pyrazole	OCF_3	23	87	67	41
50	(1,4)-1,2,3-triazole	OCF_3		99	74	0.34
60	(2,5)-tetrazole	OCF_3		97	81	4.3

[a] Thermodynamic solubility (μg/mL) in water at pH = 7.4 and 20 °C, determined by HPLC (see Experimental Section, Method B). [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).

All compounds assayed were found to be very stable toward human microsomes (> 80% remaining after incubation at 37 °C for 1 h), and most (except perhaps the thiophene analogue **10**) were adequately stable toward mouse microsomes (although less stable than **1** and **3**). These compounds were further 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.[50] The clinical trial drug **1** was employed as an internal standard, with activity recorded as the ratio of the fold decrease in colony forming units (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 4). Examples derived from six of the 11 heterocyclic subseries were evaluated. The most active compound was the 1-aryl-3-linked-pyrazole **39**, which showed a 41-fold greater efficacy than **1** in this model. Two further compounds, the 3-aryl-1-methylpyrazole **33** and the 2-aryltetrazole **60**, also showed significant in vivo activity in this assay (respectively 12-fold and 4-fold greater than **1**). Finally, accurate (thermodynamic) solubility determinations were obtained on the two best candidates, **39** and **33**, together with reference compounds **1** and **3** (Table 4). The 1-aryl-3-linked-pyrazole **39** was twice as soluble as **1** (23 vs 11 μg/mL) and > 45-fold more soluble than biphenyl analogue **3**. However, 3-aryl-1-methylpyrazole **33** was 12.5-fold less soluble than **1**.

Conclusions

The results of this study showed that heterobiaryl analogues of **1** were more hydrophilic than the related biphenyl series (**I**), as determined by calculated ΔCLogP values, but that there was no overall correlation between hydrophilicity and measured aqueous solubility for the 4-CF_3Ph-substituted analogues across the 10 major subseries. However, six of the heterocycles did provide significant increases in solubility (e.g., 6-fold for the *N*-methylimidazole analogue **26**, 60-fold for the 1,3,4-oxadiazole derivative **46**). A quantitative correlation found previously between MIC potencies against replicating *M. tb* (MABA assay) and compound lipophilicity was employed to calculate the predicted activities of various heterocyclic subseries for comparison with measured values. The results showed that compound lipophilicity was much less strongly correlated with aerobic potency for this diverse set of heterobiaryl analogues of **1** than for the earlier biphenyl series. However, four subseries (3-aryl-1-methylpyrazole, 1-aryl-3-linked-pyrazole, 2-aryl-4-linked-triazole, and 2-aryl-5-linked-tetrazole analogues) were identified from this work as having excellent potencies against both replicating *M. tb* (MABA assay) and nonreplicating *M. tb* (LORA assay). In terms of both retaining good activity and improving solubility, the 1-aryl-3-linked-pyrazole and 2-aryltetrazole subseries seemed to offer the most potential. Representatives of these two classes (pyrazole **39** and tetrazole **60**), together with a 1-methylpyrazole analogue (**33**), showed significantly greater efficacy than **1** (4- to 41-fold) in a mouse model of acute *M. tb* infection, and the best of these (pyrazole **39**) was 2-fold more soluble than **1**.

Experimental Section

Combustion analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal 2300 melting point apparatus and are as read. NMR spectra were obtained 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 ppm and Hz, respectively. 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). 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.

Procedure A. (6*S*)-6-[(5-Bromo-2-thienyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (63) (Scheme 1). NaH (60% w/w, 0.60 g, 15.0 mmol) was added to a solution of (6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-ol[16] (**61**) (2.00 g, 10.8 mmol) and 2-bromo-5-(bromomethyl)-thiophene[17] (**62**) (3.20 g, 12.5 mmol) in anhydrous DMF (40 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then poured onto ice and extracted with EtOAc (2 × 200 mL). The organic layer was dried and evaporated, and then column chromatography of the residue using a gradient (1:1 hexanes: EtOAc to EtOAc) gave **63** (2.985 g, 77%) as a white solid: mp 139−140 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.00 (s, 1 H), 7.11 (d, J = 3.7 Hz, 1 H), 6.95 (d, J = 3.7 Hz, 1 H), 4.79 (d, J = 13.2 Hz, 1 H), 4.76 (d, J = 13.2 Hz, 1 H), 4.60 (dt, J = 12.0, 1.6 Hz, 1 H), 4.44 (d, J = 12.0 Hz, 1 H), 4.25−4.19 (m, 3 H). Anal. ($C_{11}H_{10}BrN_3O_4S$) C, H, N.

Procedure B. (6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)phenyl]-2-thienyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (9). A mixture of **63** (0.205 g, 0.569 mmol) and 4-(trifluoromethyl)phenylboronic acid (0.130 g, 0.684 mmol) in toluene (10 mL), EtOH (6 mL), and aqueous K_2CO_3 (2M, 2 mL) was purged with N_2 for 5 min. $PdCl_2$(dppf) (10 mg, 0.014 mmol) 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 using a gradient (1:1 hexanes:EtOAc to EtOAc) gave **9** (0.161 g, 67%) as a white solid: mp 210−211 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.04 (s, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 7.74 (d, J = 8.3 Hz, 2 H), 7.56 (d, J = 3.7 Hz, 1 H), 7.15 (d, J = 3.7 Hz, 1 H), 4.88 (d, J = 13.8 Hz, 1 H), 4.85 (d, J = 13.8 Hz, 1 H), 4.65 (dt, J = 12.0, 1.3 Hz, 1 H), 4.47 (d, J = 11.5 Hz, 1 H), 4.30−4.22 (m, 3 H). Anal. ($C_{18}H_{14}F_3N_3O_4S$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **10**−**19** from bromothiophene **63**.

(6*S*)-6-[(2-Chloro-1,3-thiazol-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (65) (Scheme 1). Reaction of alcohol **61** with 2-chloro-4-(chloromethyl)-1,3-thiazole[18] (**64**) (1.01 equiv) and NaH in DMF, using procedure A, followed by column chromatography (eluting with EtOAc) gave **65** (27%) as a cream solid: mp 161−163 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.59 (s, 1 H), 4.71−4.61 (m, 3 H), 4.47 (d, J = 12.0 Hz, 1 H), 4.30−4.19 (m, 3 H). APCI MS m/z 317, 319 $[M + H]^+$.

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (20). Reaction of **65** and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure B for 1 h gave **20** (51%) as a white solid: mp 170−172 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (d, J = 8.1 Hz, 2 H), 8.03 (s, 1 H), 7.85 (d, J = 8.1 Hz, 2 H), 7.75 (s, 1 H), 4.84 (dd, J = 12.9, 0.8 Hz, 1 H), 4.80 (dd, J = 12.9, 0.8 Hz, 1 H), 4.69 (dt, J = 12.0, 2.5 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 4.38−4.34 (m, 1 H), 4.32 (dt, J = 13.5, 2.1 Hz, 1 H), 4.25 (dd, J = 13.5, 3.3 Hz, 1 H). Anal. ($C_{17}H_{13}F_3N_4O_4S$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **21**−**25** from chlorothiazole **65**.

Methyl 1-Methyl-2-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-5-carboxylate (67a) (Scheme 2). Reaction of methyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate[30] (**66**) and 4-(trifluoromethyl)phenylboronic acid under the Suzuki coupling conditions described in procedure B for 2 h, followed by column chromatography using a gradient (0−10% EtOAc:CH_2Cl_2), gave **67a** (83%) as cream flakes: mp 100−101 °C. ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.78−7.73 (br s, 4 H), 3.98 (s, 3 H), 3.90 (s, 3 H). APCI MS m/z 285 $[M + H]^+$.

Procedure C. {1-Methyl-2-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-5-yl}methanol (68a). $LiAlH_4$ (0.036 g, 0.95 mmol) was added to a solution of **67a** (0.138 g, 0.486 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then quenched with water and extracted with EtOAc (100 mL). The organic fraction was dried ($MgSO_4$) and evaporated to give **68a** (0.112 g, 90%) as a white solid: mp 158−161 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 7.89 (d, J = 8.2 Hz, 2 H), 7.83 (d, J = 8.2 Hz, 2 H), 6.98 (s, 1 H), 5.13 (t, J = 5.3 Hz, 1 H), 4.51 (d, J = 5.3 Hz, 2 H), 3.73 (s, 3 H). APCI MS m/z 257 $[M + H]^+$.

Procedure D. 5-(Chloromethyl)-1-methyl-2-[4-(trifluoromethyl)-phenyl]-1*H*-imidazole hydrochloride (69a). A solution of **68a** (0.106 g, 0.414 mmol) in $SOCl_2$ (2 mL) was refluxed for 0.5 h and then evaporated. The residue was triturated in Et_2O to give crude **69a** (0.106 g, 83%) as a white solid, which was used directly in the next step. ^{1}H NMR [$(CD_3)_2SO$] δ 8.05−7.99 (br s, 1 H), 7.81 (s, 1 H), 5.09 (s, 2 H), 3.84 (s, 3 H).

(6*S*)-6-({1-Methyl-2-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-5-yl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (26). Reaction of alcohol **61** with **69a** (0.96 equiv) and NaH (3.0 equiv) in DMF, using procedure A, followed by column chromatography (eluting with 95:5 EtOAc:MeOH containing 2% aq NH_3) gave **26** (26%) as a white solid: mp 163−165 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.90 (d, J = 8.4 Hz, 2 H), 7.84 (d, J = 8.4 Hz, 2 H), 7.18 (s, 1 H), 4.78−4.65 (m, 3 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.29−4.20 (m, 3 H), 3.65 (s, 3 H). Anal. ($C_{18}H_{16}F_3N_5O_4 \cdot 0.5H_2O$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **27**−**30** from bromoimidazole **66**, via the intermediates **67b**−**e**, **68b**−**e** and **69b**−**e**.

Procedure E. 1-Methyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazole (72a) (Scheme 3). A solution of 2-(2-propynyloxy)tetrahydro-2*H*-pyran[33] (**70**) (0.758 g, 5.41 mmol), CuI (17 mg, 0.089 mmol), and $PdCl_2(PPh_3)_2$ (0.158 g, 0.225 mmol) in THF (15 mL) was purged with N_2. 1-Iodo-4-(trifluoromethyl)benzene (**71a**) (1.30 g, 4.78 mmol) in THF (10 mL) was added, followed by a solution of methylhydrazine sulfate (1.95 g, 13.5 mmol) and $NaHCO_3$ (2.27 g, 27.0 mmol) in water (25 mL). The mixture was flushed with carbon monoxide and then stirred at room temperature for 2 d under one atmosphere of carbon monoxide. The resulting mixture was partitioned between CH_2Cl_2 and water, the organic fraction was dried and evaporated, and then column chromatography of the residue (eluting with CH_2Cl_2) gave **72a** (0.753 g, 46%) as a brown solid: mp 62−64 °C. ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2 H), 7.62 (d, J = 8.1 Hz, 2 H), 6.58 (s, 1 H), 4.76 (d, J = 12.8 Hz, 1 H), 4.70 (t, J = 3.4 Hz, 1 H), 4.57 (d, J = 12.8 Hz, 1 H), 3.96 (s, 3 H), 3.92−3.84 (m, 1 H), 3.61−3.54 (m, 1 H), 1.88−1.69 (m, 2 H), 1.67−1.49 (m, 4 H). APCI MS m/z 341 $[M + H]^+$.

Procedure F. {1-Methyl-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5-yl}methanol (73a). A solution of **72a** (0.657 g, 1.93 mmol) in HCl (4M, 10 mL) and THF (10 mL) was stirred at 80 °C for 16 h. The THF was evaporated, and the residue was partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was dried and evaporated, and the residue was recrystallized (^{i}Pr$_2$O) to give **73a** (0.371 g, 75%) as a white solid: mp 161−163 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 7.97 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.0 Hz, 2 H), 6.74 (s, 1 H), 5.32 (br s, 1 H), 4.54 (br s, 2 H), 3.86 (s, 3 H). APCI MS m/z 257 $[M + H]^+$.

Procedure G. 5-(Bromomethyl)-1-methyl-3-[4-(trifluoromethyl)-phenyl]-1*H*-pyrazole (74a). PBr_3 (0.15 mL, 1.60 mmol) was added to a solution of **73a** (0.200 g, 0.781 mmol) in Et_2O (10 mL) at 0 °C. The mixture was stirred at room temperature for 16 h, cooled to 0 °C, quenched with ice, and then diluted with Et_2O (100 mL). The organic layer was dried and evaporated, and then column chromatography of the residue (eluting with CH_2Cl_2) gave **74a** (0.212 g, 85%) as a white solid: mp 68−70 °C. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H), 6.62 (s, 1 H), 4.50 (s, 2 H), 3.97 (s, 3 H). APCI MS m/z 319, 321 $[M + H]^+$.

(6*S*)-6-({1-Methyl-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5-yl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (31). Reaction of alcohol **61** with **74a** (1.0 equiv) and NaH (1.6 equiv) in DMF, using procedure A, gave **31** (82%) as a white solid: mp 220−222 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.96 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.0 Hz, 2 H), 6.86 (s, 1 H), 4.78 (d, J = 12.6 Hz, 1 H), 4.73 (d, J = 12.6 Hz, 1 H), 4.70 (dt, J = 12.1, 2.3 Hz, 1 H), 4.48 (d, J = 11.8 Hz, 1 H), 4.32−4.21 (m, 3 H), 3.81 (s, 3 H). Anal. ($C_{18}H_{16}F_3N_5O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **32** and **33** from alkyne **70** and iodobenzenes **71b**,**c**, via the intermediates **72b**,**c**, **73b**,**c**, and **74b**,**c**.

Procedure H. Ethyl 5-Amino-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazole-4-carboxylate (77a) (Scheme 4). A mixture of ethyl (2*E*)-2-cyano-3-ethoxy-2-propenoate (**75**) (0.935 g, 5.53 mmol), 4-(trifluoromethyl)phenylhydrazine (**76a**) (0.881 g, 5.00 mmol), and NaOAc (0.90 g, 11.0 mmol) in AcOH (7.5 mL) and water (2.5 mL) was stirred at 100 °C under N_2 for 15 h. The mixture was poured onto ice, and the precipitate was filtered and recrystallized (MeOH/water) to give **77a** (1.032 g, 69%) as tan needles: mp 122−124 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 7.90 (d, J = 8.6 Hz, 2 H), 7.81 (d, J = 8.6 Hz, 2 H), 7.77 (s, 1 H), 6.52 (br s, 2 H), 4.23 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H). APCI MS m/z 300 $[M + H]^+$.

Procedure I. Ethyl 1-[4-(Trifluoromethyl)phenyl]-1*H*-pyrazole-4-carboxylate (78a). A solution of **77a** (0.925 g, 3.09 mmol) and isoamyl nitrite (0.83 mL, 6.18 mmol) in THF (20 mL) was refluxed for 14 h. Further isoamyl nitrite (0.83 mL, 6.18 mmol) was added, and the solution was refluxed for an additional 6 h. The solvent was then removed under reduced pressure to give a solid which was recrystallized (EtOH) to give **78a** (0.739 g, 84%) as white flakes: mp 140−141 °C. ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1 H), 8.12 (s, 1 H), 7.86 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 1.39 (t, J = 7.1 Hz, 3 H). APCI MS m/z 285 $[M + H]^+$.

Procedure J. {1-[4-(Trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methanol (79a). A mixture of **78a** (0.452 g, 1.59 mmol) and $LiAlH_4$ (0.120 g, 3.16 mmol) in Et_2O (20 mL) was refluxed for 2 h. The resulting mixture was cooled to 0 °C, quenched with ice, diluted with Et_2O (100 mL), and filtered through celite. The organic layer was dried ($MgSO_4$) and evaporated, and then column chromatography of the residue (eluting with 1:1 hexanes:EtOAc) gave **79a** (0.333 g, 86%) as white flakes: mp 80−81 °C. ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 0.5 Hz, 1 H), 7.81 (d, J = 8.5 Hz, 2 H), 7.76 (s, 1 H), 7.71 (d, J = 8.5 Hz, 2 H), 4.71 (d, J = 5.5 Hz, 2 H), 1.59 (t, J = 5.5 Hz, 1 H). APCI MS m/z 243 $[M + H]^+$.

4-(Bromomethyl)-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazole (80a). Bromination of **79a** with PBr_3 (1.0 equiv) for 2 h, using procedure G, gave **80a** (89%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 0.3 Hz, 1 H), 7.80 (d, J = 8.6 Hz, 2 H), 7.77 (s, 1 H), 7.72 (d, J = 8.6 Hz, 2 H), 4.50 (s, 2 H). APCI MS m/z 305, 307 $[M + H]^+$.

(6*S*)-2-Nitro-6-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (34). Reaction of alcohol **61** with **80a** (1.0 equiv) and NaH (1.5 equiv) in DMF, using procedure A, gave **34** (73%) as a white solid: mp 180−181 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (s, 1 H), 8.06−8.01 (m, 3 H), 7.86 (d, J = 8.6 Hz, 2 H), 7.82 (s, 1 H), 4.67−4.58 (m, 3 H), 4.47 (d, J = 11.9 Hz, 1 H), 4.27−4.21 (m, 3 H). Anal. ($C_{17}H_{14}F_3N_5O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **35** and **36** from unsaturated ester **75** and arylhydrazine hydrochlorides **76b**,**c**, via the intermediates **77b**,**c**, **78b**,**c**, **79b**,**c**, and **80b**,**c**.

Procedure K. Ethyl 2-Chloro{[4-(trifluoromethyl)phenyl]-hydrazono}ethanoate (83a) (Scheme 4). 4-(Trifluoromethyl)-benzenediazonium tetrafluoroborate[36] (**82a**) (5.71 g, 22.0 mmol) was added to a solution of ethyl 2-chloroacetoacetate (**81**) (3.29 g, 20.0 mmol) in pyridine (6 mL) and water (6 mL) at −5 °C. The mixture was stirred at −5 °C for 0.5 h, and the resulting precipitate was filtered and washed with ice cold water. Recrystallization from EtOH/water gave **83a** (5.318 g, 90%) as orange needles: mp 140−141 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1 H), 7.68 (d, J = 8.7 Hz, 2 H), 7.51 (d, J = 8.7 Hz, 2 H), 4.31 (t, J = 7.1 Hz, 2 H), 1.31 (q, J = 7.1 Hz, 3 H). APCI MS m/z 293, 295 $[M - H]^-$.

Procedure L. Ethyl 1-[4-(Trifluoromethyl)phenyl]-1*H*-pyrazole-3-carboxylate (84a). A mixture of **83a** (1.47 g, 4.99 mmol), bicyclo[2.2.1]hepta-2,5-diene (2.5 mL, 24.6 mmol) and Et_3N (2.0 mL, 14.3 mmol) in toluene (10 mL) was stirred at 70 °C for 1 h. The resulting mixture was cooled and filtered, the filter cake was washed with toluene (10 mL), and the organic fractions were combined and evaporated. The residue was refluxed in xylenes (30 mL) for 2 h. Column chromatography of the cooled reaction mixture, eluting with hexanes, first gave xylenes, and then further elution with CH_2Cl_2 gave **84a** (1.126 g, 79%) as a white solid: mp 90−91 °C. ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 2.6 Hz, 1 H), 7.90 (d, J = 8.5 Hz, 2 H), 7.76 (d, J = 8.5 Hz, 2 H), 7.03 (d, J = 2.6 Hz, 1 H), 4.45 (q, J = 7.1 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H). APCI MS m/z 285 $[M + H]^+$.

Procedure M. {1-[4-(Trifluoromethyl)phenyl]-1*H*-pyrazol-3-yl}-methanol (85a). $LiAlH_4$ (0.140 g, 3.69 mmol) was added to a stirred solution of **84a** (1.023 g, 3.60 mmol) in Et_2O (20 mL) at 0 °C, and the mixture was warmed to room temperature for 1 h, then cooled to 0 °C and quenched with ice. The resulting mixture was diluted with Et_2O (100 mL) and saturated aqueous sodium potassium tartrate (100 mL) and filtered through celite. The organic layer was dried and evaporated, and then column chromatography of the residue (eluting with 95:5 CH_2Cl_2:EtOAc) gave **85a** (0.760 g, 87%) as cream flakes: mp 72−74 °C. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 2.5 Hz, 1 H), 7.80 (d, J = 8.6 Hz, 2 H), 7.70 (d, J = 8.6 Hz, 2 H), 6.51 (d, J = 2.5 Hz, 1 H), 4.79 (d, J = 5.8 Hz, 2 H), 2.03 (t, J = 5.8 Hz, 1 H). APCI MS m/z 243 $[M + H]^+$.

3-(Bromomethyl)-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazole (86a). Bromination of **85a** with PBr_3 (1.0 equiv) for 17 h, using procedure G, gave **86a** (79%) as a cream solid: mp 81−83 °C. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 2.5 Hz, 1 H), 7.80 (d, J = 8.5 Hz, 2 H), 7.71 (d, J = 8.5 Hz, 2 H), 6.57 (d, J = 2.5 Hz, 1 H), 4.56 (s, 2 H). APCI MS m/z 305, 307 $[M + H]^+$.

(6*S*)-2-Nitro-6-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-3-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (37). Reaction of alcohol **61** with **86a** (1.06 equiv) and NaH (1.5 equiv) in DMF, using procedure A, gave **37** (68%) as a white solid: mp 161−163 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.61 (d, J = 2.6 Hz, 1 H), 8.05 (d, J = 8.5 Hz, 2 H), 8.02 (s, 1 H), 7.85 (d, J = 8.6 Hz, 2 H), 6.58 (d, J = 2.6 Hz, 1 H), 4.76−4.70 (m, 2 H), 4.66 (dt, J = 12.0, 2.4 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.31−4.20 (m, 3 H). Anal. ($C_{17}H_{14}F_3N_5O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **38** and **39** from ester **81** and aryldiazonium tetrafluoroborates **82b**,**c**, via the intermediates **83b**,**c**, **84b**,**c**, **85b**,**c**, and **86b**,**c**.

(6*S*)-2-Nitro-6-(2-propynyloxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*]-[1,3]oxazine (88) (Scheme 5). NaH (60% w/w, 1.40 g, 35.0 mmol) was added to a solution of alcohol **61** (4.53 g, 24.5 mmol) and (3-bromo-1-propynyl)(*tert*-butyl)dimethylsilane[19] (**87**) (6.00 g, 25.7 mmol) in anhydrous DMF (60 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and then quenched with ice. The product was extracted with EtOAc, the extract was dried, and the solvent was evaporated. The oily residue was dissolved in THF (100 mL), cooled to 0 °C, and TBAF (30 mL, 1 M in THF) was added. The solution was stirred at 0 °C for 1 h, and then the THF was evaporated and the residue was partitioned (EtOAc/water). The organic layer was dried and evaporated, and then column chromatography of the residue using gradient elution (1:1 hexanes: EtOAc to EtOAc) gave **88** (4.031 g, 74%) as a white solid: mp 81−82 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 4.60 (d, J = 12.1 Hz, 1 H), 4.46 (d, J = 12.1 Hz, 1 H), 4.33 (d, J = 2.3 Hz, 2 H), 4.30−4.21 (m, 3 H), 3.52 (t, J = 2.3 Hz, 1 H). Anal. ($C_9H_9N_3O_4$) C, H, N.

Procedure N. (6*S*)-2-Nitro-6-({3-[4-(trifluoromethyl)phenyl]-5-isoxazolyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (40). Triethylamine (0.14 mL, 1.01 mmol) was added to a solution of alkyne **88** (0.215 g, 0.963 mmol) and *N*-hydroxy-4-(trifluoromethyl)benzenecarboximidoyl chloride[21] (**89a**) (0.240 g, 1.07 mmol) in anhydrous THF (10 mL) at 0 °C, and the mixture was then stirred at room temperature for 16 h. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was dried and evaporated, and then column chromatography of the residue, eluting with EtOAc, gave **40** (0.295 g, 75%) as a white solid: mp 204−206 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.10 (d, J = 8.1 Hz, 2 H), 8.04 (s, 1 H), 7.89 (d, J = 8.2 Hz, 2 H), 7.18 (s, 1 H), 4.92 (d, J = 14.4 Hz, 1 H), 4.88 (d, J = 14.4 Hz, 1 H), 4.70 (dt, J = 12.1, 2.3 Hz, 1 H), 4.50 (d, J = 12.1 Hz, 1 H), 4.38−4.23 (m, 3 H). Anal. ($C_{17}H_{13}F_3N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **41**−**45** from alkyne **88** and the known[21−24] *N*-hydroxy-arylcarboximidoyl chlorides **89b**−**f**.

***N'*-(Chloroacetyl)-4-fluorobenzohydrazide (91) (Scheme 5).** A solution of chloroacetyl chloride (0.62 mL, 7.78 mmol) in EtOAc (20 mL) was added dropwise to a solution of 4-fluorobenzohydrazide (**90**) (1.00 g, 6.49 mmol) in EtOAc (100 mL) over 5 min. The mixture was refluxed for 30 min, the solvent was removed, and the residue was triturated in hexanes to give **91** (1.455 g, 97%) as a white solid: mp 158−160 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 10.52 (br s, 1 H), 10.35 (br s, 1 H), 7.97−7.92 (m, 2 H), 7.38−7.31 (m, 2 H), 4.19 (s, 2 H). APCI MS m/z 229, 231 $[M - H]^-$.

2-(Chloromethyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (92). A mixture of **91** (0.711 g, 3.08 mmol) and $POCl_3$ (10 mL) was refluxed for 2 h. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was dried and evaporated, and then column chromatography of the residue using gradient elution (0−10% EtOAc:CH_2Cl_2) gave **92** (0.485 g, 74%) as a white solid: mp 74−76 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.10−8.04 (m, 2 H), 7.50−7.44 (m, 2 H), 5.13 (s, 2 H). APCI MS m/z 213, 215 $[M + H]^+$.

(6*S*)-6-{[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (46). Reaction of alcohol **61** with **92** (1.05 equiv) and NaH in DMF for 30 min, using procedure A, gave **46** (36%) as a tan solid: mp 170−171 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.08−8.02 (m, 3 H), 7.48−7.42 (m, 2 H), 5.02 (s, 2 H), 4.70 (dt, J = 12.2, 2.5 Hz, 1 H), 4.51 (d, J = 12.2 Hz, 1 H), 4.45−4.42 (m, 1 H), 4.33 (dt, J = 13.8, 2.0 Hz, 1 H), 4.26 (dd, J = 13.8, 3.2 Hz, 1 H). Anal. ($C_{15}H_{12}FN_5O_5$) C, H, N.

Procedure O. (6*S*)-2-Nitro-6-({1-[4-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*]-[1,3]oxazine (47) (Scheme 5). A mixture of alkyne **88** (0.099 g, 0.44 mmol), 1-azido-4-(trifluoromethyl)benzene (**93a**) (0.198 g, 1.06 mmol), CuI (5 mg, 0.026 mmol), and $Cu(OAc)_2$ (5 mg, 0.028 mmol) in THF (5 mL) was stirred in a sealed tube at 50 °C for 16 h. The resulting mixture was partitioned between EtOAc and water, the organic layer was dried and evaporated, and then column chromatography of the residue using gradient elution (1:1 hexanes:EtOAc to EtOAc) gave **47** (0.095 g, 53%) as a white solid: mp 170−172 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.95 (s, 1 H), 8.16 (d, J = 8.5 Hz, 2 H), 8.03 (s, 1 H), 7.99 (d, J = 8.5 Hz, 2 H), 4.85 (d, J = 12.6 Hz, 1 H), 4.81 (d, J = 12.6 Hz, 1 H), 4.69 (dt, J = 12.0, 2.2 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 4.36−4.22 (m, 3 H). Anal. ($C_{16}H_{13}F_3N_6O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **48**−**52** from alkyne **88** and the known[25−28] arylazides **93c**−**g**.

(6*S*)-2-Nitro-6-[(2-phenyl-2*H*-1,2,3-triazol-4-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (53) (Scheme 6). Reaction of alcohol **61** with 4-(bromomethyl)-2-phenyl-2*H*-1,2,3-triazole[51] (**99a**) (1.0 equiv) and NaH (2.0 equiv) in DMF for 1 h, using procedure A, gave **53** (94%) as a white solid: mp 152−154 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.08 (s, 1 H), 8.03 (s, 1 H), 7.99 (dt, J = 7.6, 1.1 Hz, 2 H), 7.56 (td, J = 8.0, 1.9 Hz, 2 H), 7.43 (tt, J = 7.4, 1.1 Hz, 1 H), 4.87 (d, J = 12.7 Hz, 1 H), 4.83 (d, J = 12.7 Hz, 1 H), 4.69 (dt, J = 12.1, 2.5 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.36−4.22 (m, 3 H). Anal. ($C_{15}H_{14}N_6O_4$) C, H, N.

Procedure P. 2-{[4-(Trifluoromethyl)phenyl]hydrazono}propanedial Dioxime (96b). 4-(Trifluoromethyl)phenylhydrazine (**95b**) (2.64 g, 15.0 mmol) was added to a solution of 2-oxopropanedial dioxime[43] (**94**) (1.74 g, 15.0 mmol) in EtOH (20 mL). The mixture was stirred at 70 °C for 0.5 h, and then water (30 mL) was added. The resulting precipitate was filtered and recrystallized by dissolving in 3:1 toluene:EtOH and refluxing until all of the EtOH had been removed, to give **96b** (1.68 g, 41%) as tan needles: mp 171−173 °C. ^{1}H NMR [$(CD_3)_2CO$] δ 12.18 (s, 1 H), 11.26 (s, 1 H), 10.46 (s, 1 H), 8.38 (s, 1 H), 7.85 (s, 1 H), 7.63 (d, J = 8.6 Hz, 2 H), 7.36 (d, J = 8.6 Hz, 2 H). APCI MS m/z 275 $[M + H]^+$.

Procedure Q. 2-[4-(Trifluoromethyl)phenyl]-2*H*-1,2,3-triazole-4-carbaldehyde (97b). A solution of **96b** (1.66 g, 6.05 mmol) in Ac_2O (15 mL) was stirred at room temperature for 30 min. The reaction solution was diluted with water (60 mL), stirred for a further 30 min, and then the resulting precipitate was collected by filtration. This solid was partitioned between EtOAc and water, and the organic fraction was dried and the solvent was removed under reduced pressure. The resulting crude acetyl oxime was treated with Cs_2CO_3 (2.17 g, 6.66 mmol) in THF (70 mL), stirring at room temperature for 30 min, and the resulting mixture was filtered and the solvent was removed. The residue was dissolved in Et_2O, washed with water, and dried. Removal of the solvent gave a solid which was refluxed with paraformaldehyde (0.38 g, 11.9 mmol) in HCl (2M, 50 mL) for 2 h. The crude product was extracted with Et_2O and washed with water. The organic layer was dried and evaporated, and then column chromatography of the residue (eluting with 1:1 hexanes:CH_2Cl_2) gave **97b** (0.739 g, 51%) as a pale-yellow solid: mp 80−81 °C. ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1 H), 8.30 (s, 1 H), 8.29 (d, J = 8.5 Hz, 2 H), 7.81 (d, J = 8.5 Hz, 2 H). APCI MS m/z 240 $[M - H]^-$.

Procedure R. {2-[4-(Trifluoromethyl)phenyl]-2*H*-1,2,3-triazol-4-yl}methanol (98b). $NaBH_4$ (0.21 g, 5.55 mmol) was added to a solution of **97b** (0.663 g, 2.75 mmol) in MeOH (15 mL). The mixture was stirred at room temperature for 30 min, and then the solvent was evaporated. The residue was dissolved in Et_2O and washed with water. The organic layer was dried and evaporated, and then column chromatography of the residue (eluting with 9:1 CH_2Cl_2:EtOAc) gave **98b** (0.557 g, 83%) as a white solid: mp 103−105 °C. ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.6 Hz, 2 H), 7.84 (s, 1 H), 7.74 (d, J = 8.6 Hz, 2 H), 4.90 (d, J = 6.0 Hz, 2 H), 1.96 (t, J = 6.0 Hz, 1 H). APCI MS m/z 242 $[M - H]^-$.

4-(Bromomethyl)-2-[4-(trifluoromethyl)phenyl]-2*H*-1,2,3-triazole (99b). Bromination of **98b** with PBr_3 (1.0 equiv) for 15 h, using procedure G, gave **99b** (76%) as a white solid, which was used directly in the next step: mp 70−72 °C. ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 2 H), 7.87 (s, 1 H), 7.75 (d, J = 8.5 Hz, 2 H), 4.60 (s, 2 H).

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethyl)phenyl]-2*H*-1,2,3-triazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (54). Reaction of alcohol **61** with **99b** (1.0 equiv) and NaH in DMF for 1 h, using procedure A, gave **54** (84%) as a white solid: mp 209−210 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.20 (d, J = 8.6 Hz, 2 H), 8.18 (s, 1 H), 8.03 (s, 1 H), 7.94 (d, J = 8.6 Hz, 2 H), 4.89 (d, J = 12.8 Hz, 1 H), 4.86 (d, J = 12.8 Hz, 1 H), 4.70 (dt, J = 12.0, 2.5 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 4.37−4.22 (m, 3 H). Anal. ($C_{16}H_{13}F_3N_6O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **55** and **56** from dioxime **94** and arylhydrazines **95c**,**d**, via the intermediates **96c**,**d**, **97c**,**d**, **98c**,**d**, and **99c**,**d**.

5-(Bromomethyl)-2-phenyl-2*H*-tetraazole (103a) (Scheme 6). *N*-Bromosuccinimide (0.184 g, 1.03 mmol) was added to a solution of (2-phenyl-2*H*-tetraazol-5-yl)methanol[52] (**102a**) (0.122 g, 0.692 mmol) and PPh_3 (0.272 g, 1.04 mmol) in CH_2Cl_2 (10 mL) at −40 °C. The mixture was stirred at −40 °C for 2 h and then quenched with aqueous K_2CO_3 and warmed to room temperature. The resulting mixture was extracted with CH_2Cl_2, the extract was dried, and the solvent was removed. Chromatography of the residue (eluting with CH_2Cl_2) gave **103a** (0.123 g, 74%) as a white solid: mp 70−71 °C. ^{1}H NMR ($CDCl_3$) δ 8.14−8.09 (m, 2 H), 7.60−7.48 (m, 3 H), 4.72 (s, 2 H). APCI MS m/z 239, 241 $[M + H]^+$.

(6*S*)-2-Nitro-6-[(2-phenyl-2*H*-tetraazol-5-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (57). Reaction of alcohol **61** with **103a** (1.0 equiv) and NaH (1.4 equiv for 1 h, then extra 1.4 equiv for an additional 1 h) in DMF, using procedure A, gave **57** (81%) as a white solid: mp 169−172 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.10−8.05 (m, 2 H), 8.03 (s, 1 H), 7.59−7.50 (m, 3 H), 5.08 (d, J = 13.2 Hz, 1 H), 5.05 (d, J = 13.2 Hz, 1 H), 4.72 (dt, J = 12.1, 2.6 Hz, 1 H), 4.51 (d, J = 12.1 Hz, 1 H), 4.46−4.42 (m, 1 H), 4.33 (dt, J = 13.7, 2.1 Hz, 1 H), 4.27 (dd, J = 13.6, 3.3 Hz, 1 H). Anal. ($C_{14}H_{13}N_7O_4$) H, N. C: calcd, 48.98; found, 49.72. HPLC purity 100%.

Procedure S. Methyl 2-[4-(Trifluoromethyl)phenyl]-2*H*-tetraazole-5-carboxylate (101b). Sodium (0.19 g, 8.26 mmol) was reacted with absolute ethanol (15 mL) and then 2-{[4-(trifluoromethyl)phenyl]hydrazono}ethanoic acid[45] (**100b**) (0.978 g, 4.21 mmol) and 2-azido-1,3,5-tribromobenzene[47] (1.50 g, 4.22 mmol) were added. The mixture was refluxed for 5 h under nitrogen and then poured onto ice. The tribromoaniline was filtered off, and the filtrate was acidified to pH 1. The resulting precipitate was filtered and then dissolved in MeOH (40 mL). A solution of diazomethane in ether was added, and the mixture was stirred until gas evolution ceased. Removal of the solvent gave the crude product, which was chromatographed using gradient elution (3:1 CH_2Cl_2:hexanes to CH_2Cl_2), to give **101b** (0.127 g, 11%) as a white solid: mp 130−131 °C. ^{1}H NMR ($CDCl_3$) δ 8.37 (d, J = 8.4 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 2 H), 4.12 (s, 3 H). APCI MS m/z 273 $[M + H]^+$.

{2-[4-(Trifluoromethyl)phenyl]-2*H*-tetraazol-5-yl}methanol (102b). Reduction of **101b** with $LiAlH_4$ (2.0 equiv) in Et_2O at 0 °C for 1 h, using procedure M, followed by column chromatography (eluting with 3:1 CH_2Cl_2:EtOAc), gave **102b** (77%) as a white solid: mp 61−62 °C. ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 8.5 Hz, 2 H), 7.84 (d, J = 8.5 Hz, 2 H), 5.08 (d, J = 6.4 Hz, 2 H), 2.28 (t, J = 6.4 Hz, 1 H). APCI MS m/z 245 $[M + H]^+$.

5-(Bromomethyl)-2-[4-(trifluoromethyl)phenyl]-2*H*-tetraazole (103b). Bromination of **102b** with PBr_3, using procedure G, gave **103b** (32%) as a white solid, which was used directly in the next step: mp 60−61 °C. ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 8.5 Hz, 2 H), 7.85 (d, J = 8.5 Hz, 2 H), 4.72 (s, 2 H).

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethyl)phenyl]-2*H*-tetraazol-5-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (58). Reaction of alcohol **61** with **103b** (1.0 equiv) and NaH (1.5 equiv) in DMF, using procedure A, gave **58** (70%) as a white solid: mp 151−153 °C. ^{1}H NMR [$(CD_3)_2SO$] δ 8.32 (d, J = 8.5 Hz, 2 H), 8.06 (d, J = 8.5 Hz, 2 H), 8.03 (s, 1 H), 5.11 (d, J = 13.3 Hz, 1 H), 5.07 (d, J = 13.3 Hz, 1 H), 4.72 (dt, J = 12.1, 2.5 Hz, 1 H), 4.52 (d, J = 12.1 Hz, 1 H), 4.47−4.43 (m, 1 H), 4.34 (dt, J = 13.6, 2.1 Hz, 1 H), 4.27 (dd, J = 13.7, 3.2 Hz, 1 H). Anal. ($C_{15}H_{12}F_3N_7O_4$) C, H, N.

See Supporting Information for details of the syntheses of related compounds **59** and **60** from 2-(2-arylhydrazono)acetic acids **100c**,**d**, via the intermediates **101c**,**d**, **102c**,**d**, and **103c**,**d**.

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. Aliquots of the compound DMSO stocks (10 mM) were transferred to pH 7.4 buffer, Hank's balanced salt solution containing 25 mM HEPES (HBSS), to give target concentrations of 250 μM in compound and 2.5% DMSO. After equilibration at room temperature overnight, the solutions were filtered and the compound concentration was determined by fast gradient HPLC without further dilution of the samples. UV/vis/MS detection was used with reference to 1, 5, 10, 50, 100, and 250 μM analytical standards, prepared from a 500 μM intermediate stock solution, made by diluting 10 μL of the 10 mM sample stocks into 190 μL of 50:50 (v/v) CH_3CN/water. Aliquots of this stock solution (0.4, 2, 4, 20, 40, and 100 μL) were transferred in duplicate into a 96-well plate, with the volumes made up to a total of 200 μL by CH_3CN/water, and the plate was then heat sealed with a foil sheet. Prior to sample filtration, filters were primed with 600 μL of sample to resolve potential adsorption problems. Duplicate determinations were made in all cases, with the average being reported.

The study was conducted by Admetryx, 4717 Campus Drive, Kalamazoo, MI 49008.

Minimum Inhibitory Concentration Assays (MABA and LORA). These were carried out according to the published protocols.[49,50]

Microsomal Stability Assays. These were conducted by MDS Pharma Services, 22011 30th Drive SE, Bothell, WA 98021, using a published protocol.[6] The percentage of compound remaining after 1 h incubation was calculated as:

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

$$\text{where PAR} = \text{analyte/IS peak area ratio}$$

In Vivo Acute TB Infection Assay. Each compound was administered orally to a group of 7 *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.[6,50] 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** itself caused up to 2.5−3 log reductions in CFUs.

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

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