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Synthesis and Structure-activity Relationships of Varied Ether Linker Analogues of the Anti-tubercular 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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[a] Abbreviations: TB, tuberculosis; *M. tb*, *Mycobacterium tuberculosis*; MDR, multidrug-resistant; XDR, extensively drug-resistant; CFU, colony forming unit; SAR, structure-activity relationship; TI, therapeutic index; QSAR, quantitative structure-activity relationship; DMF, *N*,*N*-dimethylformamide; TCT, 2,4,6-trichloro-1,3,5-triazine; THP, tetrahydropyranyl; DIBAL-H, diisobutylaluminium hydride; NBS, *N*-bromosuccinimide; TIPS, triisopropylsilyl; TBDMS, *tert*-butyldimethylsilyl; ee, enantiomeric excess; PMB, *para*-methoxybenzyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MIC, minimum inhibitory concentration; SD, standard deviation; HLM, human liver microsomes; MLM, mouse liver microsomes; AUC, area under the curve; lipE, lipophilic efficiency; 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; TBAF, tetra-*n*-butylammonium fluoride; PAR, peak area ratio; IS, internal standard; DIAD, diisopropyl azodicarboxylate.

Abstract

New analogues of antitubercular drug PA-824 were synthesized, featuring alternative side chain ether linkers of varying size and flexibility, seeking drug candidates with enhanced metabolic stability and high efficacy. Both α-methyl substitution and removal of the benzylic methylene were broadly tolerated *in vitro*, with a biaryl example of the latter class exhibiting an 8-fold better efficacy than the parent drug in a mouse model of acute *Mycobacterium tuberculosis* infection and negligible fragmentation to an alcohol metabolite in liver microsomes. Extended linkers (notably propenyloxy, propynyloxy and pentynyloxy) provided greater potencies against replicating *M. tb* (monoaryl analogues), with propynyl ethers most effective under anaerobic (nonreplicating) conditions (mono/biaryl analogues). For benzyloxybenzyl and biaryl derivatives, aerobic activity was maximal with the original (OCH_2) linker. One propynyloxy-linked compound displayed an 89-fold higher efficacy than the parent drug in the acute model, and was slightly superior to antitubercular drug OPC-67683 in a chronic infection model.

Keywords

Nitroimidazooxazine, tuberculosis drugs, PA-824, OPC-67683, *in vivo* activity, SAR study

Introduction

Tuberculosis (TB) is the second leading cause of death from a single infectious agent (an estimated 1.7 million lives were lost to the disease in 2009).[1] There is no universally effective vaccine against infection by *Mycobacterium tuberculosis* (*M. tb*, the causative pathogen),[2] and an estimated one-third of the world's population already harbours latent TB (of which an estimated 10% will develop active disease during their lifetime), rendering eradication near impossible.[3] The severe challenges to TB control brought by the increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, further exacerbated by HIV coinfection, have culminated in recent reports of emergent strains that are resistant to all known TB drugs.[4] Moreover, of the estimated 440,000 cases of MDR TB in 2008, only about 2% were treated according to World Health Organization standards, reflecting such diverse factors as low diagnosis rates, higher drug costs and longer treatment times, the use of less effective drugs that cause more toxic side effects (leading to patient noncompliance), drug misuse through private sector availability (in many high burden countries), and inadequate health-care oversight.[1,2,4,5] Thus there is an immediate need both for more effective, faster acting new therapies with novel mechanisms of action to simplify or replace the existing drug cocktails required for TB treatment, as well as for improved health infrastructure in endemic countries to better manage their use.

While no new drugs have been introduced in the past 4 decades, a pipeline of several new or redeveloped agents is presently under clinical evaluation.[6,7] Nitroimidazole-based prodrugs PA-824 (**1**)[8] and OPC-67683 (**2**)[9] (Figure 1) were initially characterised as mycolic acid synthesis inhibitors demonstrating high *in vitro* potencies against both susceptible and resistant *M. tb*, and excellent efficacies in animal models, either alone or in combination with other agents.[7] Recent work suggests that intracellular nitric oxide (NO) release is key to their

activity against nonreplicating persistent *M. tb*.[10] Diarylquinoline TMC-207 (**3**)[11] is an inhibitor of mycobacterial ATP synthase that displays high potency against MDR-TB, being particularly efficacious *in vivo*, with a long half life. All three agents are currently in phase II clinical trials for the treatment of both drug-susceptible and drug-resistant TB.[6] Oxazolidinone PNU-100480 (**4**),[12] a protein synthesis inhibitor, shows potent bactericidal activity *in vivo*, particularly in combination therapy, and is now in phase I clinical trials. Diamine SQ-109 (**5**) is an inhibitor of cell wall synthesis, having higher *in vivo* efficacy than the parent anti-TB agent ethambutol (despite poor oral bioavailability[13]), and is also in phase I trials. In addition to these compounds, two known fluoroquinolone antibacterials (gatifloxacin and moxifloxacin) that inhibit DNA gyrase are currently in phase III trials to evaluate their potential to shorten the duration of current combination therapy (from 6-9 months to 4 months).[6]

We have recently reported[14-16] the remarkable utility of various (hetero)biaryl side chains (bearing lipophilic, electron withdrawing substituents at the terminus) to provide analogues of parent drug **1** with enhanced *in vitro* potencies (against both replicating and nonreplicating *M. tb*), and markedly superior *in vivo* efficacies, compared to **1** itself. For example, both biphenyl analogue **6**, and the more soluble, orally bioavailable pyridine derivative **7**, demonstrated an additional 2 log (or more) reduction in colony forming units (CFUs) in the lungs, following oral dosing in a mouse model of acute TB infection.[14,16] The latter compound further exhibited a 6-fold superior efficacy over **2** in a more stringent chronic infection model.[16] In the same study, we also identified the α-trifluoromethylpyridine analogue **8** as being significantly more effective than **1** in both *in vivo* models (suggesting possible additional utility for this terminal aryl group in ongoing work).

The SAR studies described above were directed particularly toward modifications of the benzyl ring of **1** that could enhance *in vivo* efficacy (while retaining appropriate solubility,

metabolic stability, oral bioavailability and pharmacokinetics) as this may assist in reducing the duration of drug treatment required (resulting in improved patient compliance and a lower cost for anti-TB therapy) and in potentially improving the therapeutic index (TI). As part of our overall strategy to develop a second generation analogue of **1** having an improved pharmacological profile, we were also mindful to address any other possible liabilities that may be associated with these compounds. One such consideration was the potential mutagenicity of smaller metabolites formed by oxidative cleavage of the benzyl ether (or picolyl ether) side chain, based on Ames data reported for structurally related 6-nitroimidazooxazoles.[17] These data suggested an increased mutagenicity risk for some analogues having very modest side chain size (e.g. Me, Et groups only), but this was markedly reduced with appropriate substitutions (increased bulk, including heteroatoms).[9,17] Thus compounds such as **1** and **2** are not mutagenic (both *in vitro* and *in vivo*),[8,9] and **1** has demonstrated excellent safety to date in recent clinical trials.[18,19] Nevertheless, we considered that removal of, or substitution on the benzylic methylene moiety should be assessed as alternatives to enhance compound stability and further minimise any possible toxicity risks associated with molecular fragmentation. α-Methyl substitution, in particular, has been described as a possible means to suppress oxidative metabolism of benzyl ethers, and in one case resulted in a markedly improved duration of action *in vivo*.[20]

Regarding other side chain modifications, a recently reported SAR study[21] of 6-amino-linked analogues of **1** found that longer chain alkyl linkers also provided improved potencies *in vitro* against both replicating and nonreplicating *M. tb* (e.g., phenylpropylamino analogue **10** was 4-fold more effective than benzylamino analogue **9** in both assays), although no assessment of the *in vivo* efficacy of the compounds was provided in that report. To account for these results and the similarly enhanced activity observed for benzyloxybenzyl analogues,[21,22] the authors derived a QSAR model that predicted either the presence of two

hydrophobic binding areas (one relatively close and one more distant from the imidazooxazine) or a single (proximal or more distant) hydrophobic pocket in the nitroreductase Ddn responsible for their activation. One previous report[22] had also outlined the improved *in vitro* activity of certain amide, urea, and carbamate-linked analogues of **1** against *Mycobacterium bovis*, but none of these were more effective than **1** *in vivo*. However, there has been no description to date of extended ether linkers as possible alternatives to benzyl, prompting us to report the intriguing findings of such investigations that we conducted in parallel to our other studies.

In this paper, we therefore present the results of a systematic study of both highly flexible and more conformationally restricted extended ether linked variants of **1**, together with α-methylbenzyl and aryl ether analogues, and their biaryl derivatives, seeking second generation candidates with enhanced metabolic stabilities (thus reduced toxicity potential) and improved efficacies in mouse models.

Chemistry

The majority of compounds were obtained from the known[22] chiral alcohol **135** via base-catalysed alkylation reactions (NaH/DMF) with appropriate heteroaryl or other halides, and subsequent Stille, Sonogashira or Suzuki couplings, as required. However, initial attempts to form simple phenyl ether analogues of **1** (such as **11**) directly from **135** via the Mitsunobu reaction with phenols, via copper-catalysed reactions with aryl iodides, or via displacement reactions on iodide or tosylate derivatives of **135** (using phenoxides), were all unsuccessful, due to facile elimination to the alkene (favoured by the adjacent electron-deficient nitroimidazole ring). Racemic analogue **11** was eventually prepared in 7 steps, starting from 3-(benzyloxy)-1,2-propanediol[23] (**121**) (Scheme 1A). A Mitsunobu reaction of the monosilyl ether derivative **122**[24] set up synthesis of the key iodide **125**, which reacted cleanly with 2-

bromo-4-nitroimidazole (**126**) to give **127**. The latter was then elaborated to **11** via methodology described[25] for the synthesis of racemic **1**.

For the preparation of picolyl ether **14**, chloride **131**[26] was acquired by chlorination of the alcohol **130**[27] with TCT/DMF complex,[28] after reaction with thionyl chloride yielded unsatisfactory results. Alcohol **130** was itself obtained via successive lithiation of iodopyridine **129**, DMF quenching, and in situ reduction of the resulting aldehyde (Scheme 1B). The α-methyl benzyl ether **16** (a diastereomeric mixture) was accessed from 1-[4-(trifluoromethoxy)phenyl]ethanol[29] (**133**) (derived from the commercial acetophenone), following bromination with phosphorus tribromide and coupling with **135**. The 4-bromo analogue of **16** (**232**) was similarly prepared (via bromide **231**[30]) and Suzuki coupled with boronic acids to provide biaryl analogues **70-73** (Scheme 6B).

Reactions of alcohol **135** with substituted alkyl iodides provided entry to phenylpropyl ethers **17-19** and phenoxyethyl ethers **20** and **21** (together with related intermediates **153** and **154**; Schemes 2A and 3A), although the yields (particularly in the latter series) were significantly compromised by competing elimination of the halide (see below). The required iodides **142-147** were prepared by iodination of known[21, 31-34] (or commercially available) alcohols **136-141**, readily procured by borane reduction of the inexpensive acids (in the cases of **136** and **137**) or by standard alkylation of the appropriate phenols with 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (K_2CO_3/acetone/reflux, 3-4 days) then THP cleavage[33] (in the cases of **138**, **139** and **141**). For target **19** (Scheme 3A), iodide **165** was synthesised in 4 steps, beginning with a Horner-Wadsworth-Emmons reaction of 6-(trifluoromethyl)nicotinaldehyde (**161**) and triethylphosphonoacetate to form the known[35] conjugated ester **162**. Careful catalytic hydrogenation of **162** (1 mg/mL in EtOAc, 1 atm H_2, 0.1 wt equiv 5% Pd/C) delivered saturated ester **163** (pyridine ring reduction was observed under more forcing conditions), which was reduced to the alcohol **164** ($LiAlH_4$) and iodinated

to furnish **165**. Suzuki couplings of **153** and **154** with boronic acids gave rise to the related biaryl analogues **74-76** and **79-82**, respectively, while a one pot Suzuki method (via *in situ* aryl boronate formation[36]) also permitted the synthesis of pyridine derivatives **77** and **78** from **153** (Scheme 2C).

In an attempt to circumvent the low alkylation yields observed in the syntheses of **20**, **21** and **154**, and to introduce greater side chain structural diversity from a common intermediate, an alternative route to aryloxyethyl ethers was investigated (Scheme 2B). Alkylation of alcohol **135** with (2-iodoethoxy)(triisopropyl)silane[37] and subsequent acidic desilylation[38] gave alcohol **149**, which was readily transformed into the iodide **151** via poorly soluble mesylate **150**. Reaction of **151** with 6-(trifluoromethyl)-3-pyridinol (**152**) (K_2CO_3/acetone) provided ether **23** in excellent yield. However, this method was less useful for preparing phenyl ethers (such as **20**) due to the concomitant formation of small amounts of an inseparable vinyl ether derivative of **1** via elimination. Alkylations of alcohol **149** with reactive heteroaryl halides (**128**, **155** and **157**) were also much less facile than similar reactions with alcohol **135**, but still enabled the synthesis of pyridine **22**, as well as arylbromides **156** and **158** (in order to generate biaryl analogues **83-90**).

An initial alkylation approach to cinnamyl ether derivatives of **1** via cinnamyl bromides was successful for the preparation of **24** and **27** (Scheme 3A). Here, unsaturated esters **166**[39] and **162**[35] were reduced (DIBAL-H) to the allylic alcohols **167**[40] and **169**, respectively, and then converted to the bromides (using NBS/PPh_3), which reacted acceptably well with alcohol **135** under the standard conditions. Biaryl analogues **91-95** were prepared in a similar manner, following initial Suzuki couplings of the 4-bromocinnamate esters **174** or **175** with arylboronic acids and elaboration to the bromides (Scheme 3C), since Suzuki couplings at the final step (on a 4-bromocinnamyl ether derivative of **1**) led to double bond migration and side chain loss (to give **135**).

However, this alkylation strategy proved unviable for the preparation of both **25** and **26**, due either to the apparent instability of the reagent (the unknown 4-benzyloxycinnamyl bromide, iodide, or even the known[41] chloride could not be obtained cleanly from the alcohol by a variety of methods) or its subsequent reaction with strong base (the required bromopropenylpyridine preferentially underwent elimination to the allene, providing impure **26** in only 3% yield). An alternative approach to **25** via a Mizoroki-Heck reaction[42] of the arylboronic acid with the allyl ether derivative of **1** also proved unsatisfactory due to contamination of the product by inseparable side products. Finally, a Stille route, employing (*E*) stannane **173** [derived from (2*E*)-3-(tributylstannyl)-2-propen-1-ol[43] (**171**) via successive bromination to **172**[44] (NBS/PPh_3) and reaction with alcohol **135**; Scheme 3B], together with 1-(benzyloxy)-4-iodobenzene or iodopyridine **129** and $BnPd(PPh_3)_2Cl$ catalyst,[45] allowed the preparation of both **25** and **26** in good yield (~60%).

Sonogashira reactions of known[15] propargyl ether derivative **179** or its 2-carbon homologue, **182** (derived from THP ether **180**,[46] following Br_2/PPh_3 bromination, reaction with **135**, and desilylation) with aryl halides readily generated the alkynyl compounds **28-34** (Scheme 4A). Biaryl analogues of these (**96-105** and **116-120**) were also prepared by Suzuki couplings on appropriate bromophenyl intermediates (**187**, **188** and **194**) derived from known[47-49] alcohol precursors (**183**, **185** and **192**) via similar chemistry (Schemes 4B and 4D). A selective Sonogashira reaction between alkyne **179** and 5-bromo-2-iodopyridine (**190**) (20 °C, 16 h) gave bromide **189**, leading to phenylpyridyl analogues **106-110** by Suzuki coupling, while reversal of the steps (selective Suzuki couplings on **190**, followed by Sonogashira coupling) enabled synthesis of the isomeric compounds **111-115** (Scheme 4C).

Based on the successful synthesis of racemic phenyl ether **11** above (Scheme 1A), a chiral route to biaryl analogue **35** was first proposed (Scheme 5A), starting from (*S*)-glycidol (**195**), but employing TIPS (rather than TBDMS) protection for the primary hydroxyl group of diol

196 to achieve better regioselectivity.[38] Thus, cesium fluoride-promoted ring opening[50] of **195** with benzyl alcohol provided diol **196**,[51] which, after mono-TIPS protection, was reacted with 4'-(trifluoromethoxy)[1,1'-biphenyl]-4-ol[52] (**198**) in a Mitsunobu reaction to form ether **199**. The latter was elaborated to **35**, via iodide **201**, as previously described for **11**. However, chiral HPLC indicated that this product had an ee of only 70%, suggesting that the enantiopurity of commercial **195** may have been inadequate.

The above route was therefore modified by starting from the commercial glycerol acetonide **204**, and preparing the key orthogonally diprotected triol **207** via the known[53] PMB ether **206** (Scheme 5B). Mitsunobu reactions of alcohol **207** with 4-bromophenol or 6-bromo-3-pyridinol (Scheme 5C), followed by selective removal of the PMB group (DDQ), enabled the synthesis of iodides **210** and **216** (from the derived alcohols), which were elaborated to the bromoaryl ethers **213** and **219** as before. Suzuki couplings on these bromides then gave the required biaryl compounds (**36**-**38** and **60**-**63**). Chiral HPLC analysis of **35** resynthesised via this route determined an ee of 99.7%, indicating the superiority of this more general chiral synthesis over the initial approach described above.

Finally, as with **12**, halopyridyl and halopyrimidyl ethers **220**-**225** (Scheme 6A) were conveniently prepared in high yield from alcohol **135** by chemoselective nucleophilic aromatic substitution reactions with reactive fluorohalopyridines or chlorohalopyrimidines under standard alkylation conditions (NaH/DMF). Suzuki couplings on these substrates then provided a more straightforward synthesis of the remaining biaryl analogues of this class (**39**-**59** and **64**-**67**).

Results and Discussion

Tables 1 and 2 present physicochemical and minimum inhibitory concentration (MIC) data for 107 new (and 5 known[14,16,22]) analogues of **1** in which both the ether linker and

mono/biaryl constituents of the side chain have been varied. A total of 8 linker groups (X) were investigated, ranging in both size (from the smallest possible ether, X=O, to the more extended pentynyl ether, $X=O(CH_2)_3C\equiv C$) and conformational mobility (from highly flexible 4 atom linkers, such as propoxy and ethylenedioxy, to more constrained unsaturated analogues, such as propenyl and propynyl ethers). Here, the ethylenedioxy linker, for example, was envisaged as a means to remove a potential metabolism site (methylene attached to phenyl) as well as to introduce more side chain flexibility (to improve solubility) and structural diversity. The parent class ($X=OCH_2$) was additionally compared with α-methyl derivatives (X=OCHMe), obtained as ~1:1 mixtures of the two diastereomers, to investigate steric and metabolic effects, as noted above. In one case (**16**), the diastereomeric mixture of α-methyl derivatives was subsequently separated to enable a more accurate delineation of such effects.

Within these classes, we then applied our recently described[16] solubilisation strategy, incorporating heterocyclic replacements (*viz*. pyridine and pyrimidine) for the phenyl ring proximal to the ether linkage, in order to lower the overall lipophilicities of the compounds but retain high biological activities. Compound lipophilicities were approximated by ClogP values, calculated using ACD Log P/Log D prediction software (version 8.0; Advanced Chemistry Development Inc., Toronto, Canada), as previously described.[14-16] For each subclass in Tables 1 and 2, the combined influence of modifications to the linker (X) and of any heterocyclic replacements (i.e. for the first phenyl ring in biaryl compounds) on compound lipophilicities was assessed by calculating mean differences in ClogP values between compounds in the subclass and parent analogues (having $X=OCH_2$) bearing the same substituents (Table 3). Unsurprisingly, the new (larger) linker groups generally resulted in higher lipophilicities, particularly those incorporating an alkyne (ΔClogP ~1.2-1.3). However, an oxygen (rather than methylene) next to the first phenyl ring gave slightly reduced

lipophilicities in both biaryl classes (X=O and $O(CH_2)_2O$: **35**-**38** and **79**-**82**), and these were successively further lowered upon replacement of this phenyl by pyridine (ΔClogP -0.63 to -0.91) and pyrimidine (ΔClogP -1.27). Interestingly, similar substitution of phenyl by pyridine in the particularly lipophilic propynyl ether class (**106**-**109** and **111**-**114**) provided a much larger decrease in ClogP values (~1.3 units), resulting in lipophilicities comparable to the parent class ($X=OCH_2$). We did not employ *ortho*-substitution in the terminal aryl ring as an alternative strategy to improve solubility in the current study (via disruption of molecular planarity and symmetry[54]) since we have previously found that significantly reduced *in vivo* efficacy results from this modification (6- to 10-fold for 2-Cl, >4-fold for 2-F).[14,16] However, in some cases (X=O: **39**-**55**; $X=OCH_2C{\equiv}C$: **101**-**105**), we did explore reduced symmetry via *meta*-linkage of the biaryl side chain, as previously studied.[14,16]

Solubilities in water at pH=7 were measured for dry powder forms of all (25) of the monoaryl compounds in Table 1 and a representative example (4-OCF_3Ph) of each of the (20) structural subclasses of biaryl analogues described in Table 2. Overall, monopyridine side chains afforded the best solubilities, whereas benzyloxybenzyl and biaryl side chains conferred much poorer results, as expected, based on lipophilicity considerations. Thus, while inherent H-bonding properties and the disruption of crystallinity are recognised as important factors in the aqueous solubility of particular compound samples,[55] it is evident from eq 1 that ClogP values alone provide a good estimation of solubility for the compounds in Table 1 (across a solubility range of ~3100-fold):

$$\text{Log(solubility [}\mu\text{g/mL])} = -0.98\ (\pm 0.12)\ \text{ClogP} + 3.69\ (\pm 0.35) \qquad (1)$$

$$n = 25 \quad R = 0.86 \quad F = 64.6$$

For biaryl compounds (Table 2), replacement of the phenyl ring proximal to the ether linkage by pyrimidine (e.g. **52**, **64** and **87**) gave improved aqueous solubilities at pH=7, but only in one case (**111**) was pyridine similarly effective. However, many of the pyridine derivatives showed enhanced solubilities at pH=1, consistent with their calculated pKa values (up to 1.9 mg/mL for **44**; see Supporting Information, Table S1). The overall impact of linker group variations on compound solubility was evaluated by determining the ratio of mean solubilities for compounds in each linker subclass to the mean solubilities of analogues in the parent class (X=OCH_2) of the same form (I or II) and bearing the same aryl substituents (Table 3). The results suggest that more flexible alkyl ethers generally offer higher solubilities than more conformationally restricted variants, even when their lipophilicities are similar (e.g. propyl versus propenyl ethers). However, in contrast to a recent report,[54] the introduction of a methyl group at the benzylic position of lead compounds **1** and **6** (**16**, **70**) did not significantly improve aqueous solubility.

The *in vitro* antitubercular activity of the compounds was assessed in two assays, MABA[56] and LORA,[57] performed under aerobic and anaerobic conditions, respectively, as previously described.[14] Whereas the former (8 day) assay measures the ability of the compounds to inhibit the growth of replicating *M. tb*, the latter (11 day) assay screens for activity against bacteria in the nonreplicating state that models clinical persistence. Previous studies of related compounds have indicated that derived SAR in such assays can be fundamentally different,[14-16,21] with aerobic activity reportedly correlating better with the efficiency of the compounds to act as substrates for the nitroreductase Ddn;[21,58] it was therefore of some interest to examine whether this could be related to specific *in vivo* effects. The reported MIC values (Tables 1 and 2) represent the lowest concentration of test compound able to effect a >90% inhibition of *M. tb* (H37Rv) growth and each value is the mean of at least two independent determinations (± SD). Most of the compounds (77/107) were also screened for

mammalian cytotoxicity using VERO cells[59] (CCL-81, American Type Culture Collection) in a 72 h tetrazolium dye assay; the compounds were generally non-toxic (IC_{50}s >128 μM, except in three cases where TIs were at least 50; data not shown).

In Table 1, for each of the 8 linker groups described above, the aryl group was varied from 4-trifluoromethoxyphenyl (e.g. **1**) in up to 3 further substitution patterns (4-benzyloxyphenyl and two isomeric trifluoromethylpyridines). The 4-benzyloxybenzyl analogue of **1** (**13**: PA-647)[22] was the most potent compound of this class reported in the original study, being at least 9-fold more potent than **1** against multidrug-resistant *M. tb in vitro* and displaying significant *in vivo* efficacy against *Mycobacterium bovis*.[22] Although this compound was apparently inferior to **1** against *M. tb in vivo* (suggested to result from less optimal pharmacokinetic properties),[8] we considered that its more lipophilic and bulky side chain would be a useful tool to further probe the spatial distribution and steric requirements of proposed[21] hydrophobic binding areas in the activating nitroreductase Ddn, using our different linker groups. The conception of the two isomeric trifluoromethylpyridine moieties as heterocyclic replacements for the aryl groups of **1** and **13** was based largely on the effectiveness of **8** (and its pyridine isomer) *in vivo*, as noted above, as well as the particularly favourable results for related biaryls when the phenyl ring proximal to the ether linkage was pyridine.[16] It was expected that these substitutions would also provide significantly reduced lipophilicity (to offset higher ClogP contributions from extended linker variants) and facilitate further pharmacophore exploration.

The impact of these diverse substitutions on potency against *M. tb* (Table 1) was greatest for the parent linker (X=OCH_2), where compound **13** was clearly superior to **1** (20-fold in MABA but only 2-fold in LORA) and the two pyridyl analogues (**14** and **15**) were significantly less active (3- to 6-fold in MABA and 8- to 18-fold in LORA). In the aryl ether class (X=O), less lipophilic racemate **11** (4-OCF_3) had 2- to 3-fold lower activity than

racemic **1** (MICs: MABA 1.1 μM, LORA 4.4 μM)[25] in both assays, and pyridine analogue **12** was similar (LORA) or slightly less potent than **14** (~2-fold in MABA), despite its higher lipophilicity. The α-methyl derivative of **1**, **16** (X=OCHMe), was also only marginally less active overall (similar in MABA, 3-fold lower in LORA), possibly suggesting a small steric effect. However, upon separation of the diastereomeric mixture, one of the diastereomers was determined to be significantly more potent than the other in both assays (MICs: MABA, 0.23 and 1.8 μM; LORA, 3.2 and 18 μM), though not markedly superior to **1** (~2-fold in MABA).

For all of the more lipophilic extended ether linkers, activity was broadly retained or improved in both assays, compared to the parent class ($X=OCH_2$) (Table 3A), although the exact SAR was found to be dependent on the nature of the aryl group. Thus, for 4-OCF_3Ph (**17**, **20**, **24**, **28**, **32**, compared to **1**), aerobic potency (MABA) increases ranging from a modest 2- to 4-fold (for propyl ether **17** and propynyl ether **28**) to a more significant 10- to 13-fold (surprisingly optimal for the less lipophilic ethylenedioxy compound **20**; MIC 0.04 μM) were observed, but anaerobic potency (LORA) barely changed over this set (<2-fold). For the extended linker 2-pyridine analogues (**22**, **26**, **30**, **33**, in comparison to **14**), even larger enhancements in aerobic potency were found (from 4-fold for ethylenedioxy compound **22**, to an impressive 35-fold for propenyl ether **26**; MIC 0.043 μM), while anaerobic activity (LORA) also generally increased (3- to 4-fold for unsaturated ethers **26**, **30**, and **33**). The less potent 3-pyridine isomers (**19**, **23**, **27**, **31**, **34**, benchmarking against **15**) followed a similar SAR pattern in LORA, with ethylenedioxy compound **23** least effective and propynyl ether **31** the best, but pentynyl ether **34** was superior in the MABA assay. However, for 4-benzyloxybenzyl (**18**, **21**, **25**, **29**), **13** ($X=OCH_2$) remained unsurpassed (by 3- to 20-fold in MABA, and 1- to 4-fold in LORA) and was the most potent of all of the compounds in Table 1.

In summary, from an *in vitro* potency perspective, the structural modifications that we initially designed to improve stability, *viz.* α-methyl benzyl substitution or phenyl ethers, seemed fairly well tolerated. Both highly flexible and more conformationally constrained extended ether linkers generally provided improved potency (Table 3), but the latter classes were more impressive overall. Thus, the moderately lipophilic ethylenedioxy linker class was slightly superior to the propyl class in MABA (whereas the converse was true for LORA), while the propenyl ether class was slightly better than the propynyl and and pentynyl ether analogues in MABA (but the converse was again true for LORA). The best linkers to provide high potencies in both assays appeared to be propynyl and pentynyl (equally), possibly due to their higher lipophilicities. However, a consideration of both aqueous solubility and activity identified two more hydrophilic compounds of particular interest from this study, namely ethylenedioxy compound **20** (2.6-fold more soluble than **1**) and the propenyl ether-linked pyridine **26** (1.5-fold more soluble than **1** at pH=7 and 24-fold more soluble than **1** at low pH).

The unusual results observed for the more bulky benzyloxybenzyl moiety suggest that, in this instance, the parent linker (X=OCH_2) allows the most optimal spatial distribution of the two aryl groups for binding to proposed[21] hydrophobic areas in the activating nitroreductase Ddn. Since the overall activity of longer linked analogues (**18**, **21**, **25**, **29**) is quite similar to their 4-OCF_3Ph counterparts (**17**, **20**, **24**, **28**) this may imply a loss of favourable binding for the terminal phenyl ring of the former set, possibly due to steric or distance constraints. We considered that this hypothesis could be better tested using the more conformationally contrained (hetero-)biaryl groups we employed previously, since these might also provide further potency enhancements for some linkers, heading towards our goal of improved *in vivo* efficacy.

In Table 2, we therefore explored the utility of various biaryl groups (including heterocyclic replacements for phenyl) for each of the 8 linker classes, as described above. Each linker class was further subdivided according to the biaryl geometry (*meta*- or *para*-linked) and the position of any aza atoms in the attached first ring. A minimum of three favoured[14,16] (lipophilic, electron-withdrawing) substituents were selected for the terminal phenyl ring (4-OCF_3, 4-F, 4-CF_3, and, in some cases, 4-OCF_2H), together with the pyridine alternative (3-aza-4-CF_3 pattern) that was effective in **8** (and related compounds).[15,16] This enabled some variation in lipophilicities to be studied across the range of linker variants, as well as a more conclusive evaluation of the merits of each class. In previous studies[14-16] of biaryl compounds in the parent linker class (X=OCH_2) we found that while considerable structural variation was broadly tolerated, a linear geometry (*para*-linkage) for the biaryl group provided the best *in vitro* potencies, microsomal stabilities and *in vivo* efficacies. However, it was not obvious whether such findings would hold true for other linkers of differing size (particularly the shorter aryl ethers, X=O), as these could position the biaryl substituent in different spatial orientations and locations within the activating nitroreductase. Aryl ethers **35**-**67** therefore examined the effects of both geometric and heterocyclic variations. Unfortunately, the potencies of these compounds were generally disappointing (MABA MICs 11- to 139-fold lower than the OCH_2-linked analogues; LORA MICs 5- to >42-fold lower; Table 3B), consistent with less optimal binding (likely steric conflict in some cases). The *para*-linked biaryls were again more effective than the *meta*-linked analogues, with the biphenyl (**35**-**38**) and 5-phenyl-2-pyridyl (**56**-**59**) subclasses slightly preferred in MABA, whereas the 6-phenyl-3-pyridyl (**60**-**63**) analogues gave superior LORA results overall. Compounds **35** and **60** (MABA MICs 0.09, 0.14 μM, respectively) were the best of these aryl ethers (and an order of magnitude better than **11**), and while their aqueous

solubilities at pH=7 were poor (~0.3 μg/mL), **60** showed a markedly improved value (37 μg/mL) at low pH.

Unlike **16**, the α-methyl biaryl compounds **70-73** were ~9-fold less active than the parent class (**6**, **8**, **68** and **69**) in the aerobic assay (suggesting a significant steric effect), although their anaerobic activities were comparable (Table 3B). Of particular interest, however, were the longer chain ethers, since these had been found to result in improved activity above. As before, MABA potencies for the ethylenedioxy analogues (**79-82**) were high, similar to those for the parent class ($X=OCH_2$), and better than results for the propoxy linker class (**74-77**). We therefore examined the effects of replacing the first phenyl ring with pyridine or pyrimidine in this class, seeking improved solubility. Phenylpyridines **83-85** showed excellent potencies in both assays, whereas phenylpyrimidines **87-89**, and the terminal pyridine analogues **86** and **90** in particular, were less effective. Compound **83** also displayed a 72-fold higher aqueous solubility at low pH (57 μg/mL). Surprisingly, the remaining linkers containing unsaturated functionality did not provide compounds with more pronounced activity than the parent class. Propenyl ethers **91-94**, while retaining good aerobic activity (2-fold less than for $X=OCH_2$), generally gave poor results in the LORA assay, whereas propynyl ethers **96-99** were excellent in the latter but less impressive in MABA (5-fold less than for $X=OCH_2$). Recognising that the extended linear aromatic system of these propynyl ethers was sterically demanding, we evaluated an angular form via *meta*-linkage of the biaryl moiety (compounds **101-104**), but these were not significantly different in profile, apart from the 4-fold better aqueous solubility of **101** compared to **96** (consistent with previously described solubility findings[16]). Isomeric pyridine replacements for the first phenyl ring (compounds **106-110** and **111-115**) dramatically lowered lipophilicity, resulting in an improved solubility value for the 3-isomer **111** (0.72 μg/mL at pH=7, 4.0 at pH=1), and some potency improvements, with 2-isomers **106**, **108** and **110** showing notable profiles (MABA

MICs ~0.025 μM, LORA MICs 0.35-0.75 μM). However, the pentynyl analogues **116-120** were mostly ineffective in LORA, and appeared less stable (solubility assay), suggesting little utility.

To better understand these divergent SARs for mono- and biaryl compounds, we compared the relative potencies of 4-OCF_3-substituted analogues across the 8 linker classes (Table 4). The addition of a second phenyl ring increases ClogP values by 1.5-1.7 units. In the parent series (**6** vs **1**), this results in a 14-fold higher aerobic potency (but only a 2-fold improvement in LORA). An assumption that *S*-**11** would be approximately twice as potent as *rac*-**11** (as found for **1**),[14,25] suggests that a similar trend broadly applies for the X=O linker class (**35** over *S*-**11**). For the α-methyl compounds, **70** was only 3- to 5-fold more active than **16** in both assays. However, in the remaining extended linker classes, mono- and biaryl compounds had similar MABA potencies and in two of these (propenyl and pentynyl) anaerobic activity (LORA) for the biaryl analogues was completely lost, illustrating the limitations incurred.

A set of 18 compounds was selected for metabolic stability assessments using human (HLM) and mouse liver microsomes (MLM), primarily on the grounds of high potency in the aerobic *in vitro* assay and being representative of the wide range of different linkers explored (see Table 5; comparative data for **1** and **6** are also provided). Greater emphasis was placed on biaryl analogues (particularly those having a terminal 4-OCF_3 substituent), since these were expected to provide superior metabolic stabilities and higher in vivo efficacies, based on previous results.[14-16] Overall, the compounds were adequately stable toward HLM (>50% remaining after incubation at 37 °C for 1 h), and all except for the benzyloxybenzyl analogue **13** and the pentynyl ether **32** were similarly stable toward MLM (although the remaining monoaryl compounds were also less stable than **1**). Of particular interest, in contrast to the reported results of Swain,[20] the α-methyl derivative of **1** (**16**) appeared to have significantly reduced metabolic stability compared to **1**; subsequent results for the pure diastereomers

(Table S2 in Supporting Information) confirmed this, with the more moderate stabilities in the HLM assay (60% and 73% remaining after 45 min) discouraging further evaluation of these. Importantly, aryl ethers (**35**, **56** and **64**), α-methyl compound **70**, propyl ether **74**, propenyl ether **91**, and propynyl ethers (**96**, **99**, **101**, **106** and **111**) all displayed excellent stabilities toward both HLM and MLM (>80% remaining after 1 h), suggesting that such alternative ether linkers may potentially allow good utility *in vivo*. To verify this, mouse pharmacokinetic data were obtained on 5 examples, including 3 alkynes (using a single oral dose of 40 mg/kg; data for **6** are also provided, Table 6). All except **32** showed excellent plasma half-lives (4-38 h), with **35** and **101** demonstrating very high exposures (superior to **6** in lung, with AUCs >250 μg-hr/mL) and preferential accumulation in lung tissue.

Most of the analogues selected above were further evaluated in a mouse model of acute *M. tb* infection, dosing orally at 100 mg/kg daily for 5 days each week in a standard 3 week assay.[59] To facilitate inter-experiment comparisons, **1** was employed as an internal reference standard, with the activity of new analogues being expressed 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** (Table 5). Removal of the benzylic methylene from **6** (compound **35**) resulted in reduced efficacy (but 8-fold higher than **1**), which was significantly further lowered (48-fold) upon replacement of the first phenyl ring by 2-pyridine (**56**). Unexpectedly, dosing with the α-methyl compound **70** resulted in toxicity (by day 9), preventing further assessment. Surprisingly, the poorly stable pentynyl ether **32** was superior to **1** (~5-fold). Furthermore, the more stable (monoaryl) ethylenedioxy analogue **20** and its biaryl derivative **79** were equally efficacious (~1.3-fold better than **1**), showing that the extra ring provides no additional benefit with this linker. Propyl and propenyl ether-linked biaryls (**74** and **91**) also had similar *in vivo* activities (1.5- to 2-fold greater than **1**) but propynyl ether **96** stood out (89-fold better than **1**), prompting appraisal of potentially more

soluble pyridine analogues (**99**, **106** and **111**). However, only the *meta*-linked analogue of **96** (**101**) showed better efficacy than **1** (just 6-fold, indicating the same preference for *para*-linkage as found in the parent biaryl series). Propynyl ether **96** and its saturated analogue **74** were further compared with the parent biphenyl lead **6** and clinical trial agent **2** in a more stringent mouse model of chronic *M. tb* infection (Table 5). This assay employed the same dosing schedule as above, but commenced ~70 days post infection, when bacteria were in a well established, plateau phase of growth (**2** was ~10-fold more efficacious than **1** in this assay). While **6** was almost as effective as **2**, propyl analogue **74** had poor activity, as expected. However, propynyl ether **96** was slightly superior to **2** (1.6-fold) and was about twice as active as **6**.

A comparison of the above data with earlier *in vitro* results found no obvious correlation of *in vivo* efficacy with either MABA or LORA potency. Nevertheless, reduced molecular flexibility, as measured by the number of rotatable bonds, has been described as an important predictor of good oral bioavailability.[60] While this factor may (at least in part) account for the low efficacies of the more flexible biaryl analogues **74** and **79** (in comparison to **96** and **6**), the similarly modest results for propenyl ether **91** and aryl ether **35** may also suggest that there is a preferred ligand binding conformation for optimal *in vivo* activity that is best attained with an OCH_2 linker between the nitroimidazooxazine and the biaryl moiety (as similarly inferred from *in vitro* results in the benzyloxybenzyl series). Of all the alternative ether linker classes, the linear geometry of the extended π system of the biphenyl propynyl ether **96** allows the closest mimic to the possible binding modes of parent biphenyl **6**. However, with the extended linker, favourable aza substitution effects were not transferable *in vivo*. These results and the SAR above therefore reinforce the hypothesis[14] of a fairly straight, elongated hydrophobic binding pocket in the activating nitroreductase Ddn, having some steric constriction near to the ether oxygen.

Finally, regarding the question of enhancing compound stability to minimize any possible toxicity risks, we investigated the relative tendencies of biaryl analogues **6** (X=OCH_2) and **35** (X=O) to release the alcohol metabolite **135** following HLM and MLM incubations (at 37 °C for 0.5-2 h). The data in Table 7 show first that the percentage formation of alcohol **135** from parent biphenyl **6** was very small, but significant, increasing in a time-dependent manner over 2 h (up to 1.5% in MLM and 0.56% in HLM). In contrast, aryl ether **35** was completely stable over this incubation period (<0.1% **135** after 2 h in HLM and MLM, respectively).

Conclusions

This work investigated a range of possible alternative ether linkages for **1** (and related mono/biaryl analogues), varying in size and flexibility, as a strategy to identify novel candidates with higher metabolic stabilities (reduced toxicity risk) and improved efficacies in mouse models. As potential stabilisation options, both α-methyl substitution and removal of the benzylic methylene were broadly tolerated *in vitro* (monoaryl series; biaryl analogues were up to 12-fold less potent than lead compound **6**), but the former modification (**70**) resulted in unexpected toxicity *in vivo*. An example of the latter class (biaryl **35**) demonstrated excellent pharmacokinetics (high exposures and lengthy half lives in both plasma and lung tissue following oral dosing), superior (8-fold) efficacy compared to **1** in a mouse model of acute *M. tb* infection, and an improved metabolic stability profile compared to **6**, as measured by its negligible fragmentation to alcohol **135** over 2 h in liver microsomes.

Extended ether linkers generally provided improved *in vitro* potencies in the monoaryl series (where trifluoromethylpyridine proved an effective, more soluble substitute for 4-OCF_3Ph), with propenyloxy, propynyloxy and pentynyloxy linkers generally producing the better activities against replicating *M. tb* (aerobic assay), and the latter two linkers affording superior results under anaerobic assay conditions. However, for the more sterically

demanding biaryl series, only the propynyloxy linker furnished improved anaerobic potencies, and furthermore, as with benzyloxybenzyl analogues, none of the alternative linkers could better the level of aerobic activity delivered by the parent (OCH_2) linker. A comparison of 4-OCF_3Ph derivatives further suggested that the overall antitubercular effects of extended linker biaryl examples were not significantly better than their monoaryl counterparts, which was verified for the ethylenedioxy linker in the acute *in vivo* model (efficacies similar to **1**). Whereas propoxy- and propenyloxy-linked analogues were also only similar to **1** *in vivo*, despite excellent microsomal stabilities, propynyl ether **96** displayed an 89-fold higher efficacy than **1** in the acute model, and was slightly superior to both the original lead **6** (1.9-fold) and clinical trial drug **2** (1.6-fold) in a more stringent mouse model of chronic *M. tb* infection. However, potentially more soluble pyridine analogues of **96** were not effective. The results provide additional insight into possible ligand binding interactions at the active site of the nitroreductase responsible for triggering the antitubercular effects of these compounds, which may be of utility in further studies.

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 ppm 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 ionisation (HRESIMS) and atmospheric pressure chemical ionisation (HRAPCIMS) mass spectra were determined on a Bruker micrOTOF-Q II mass spectrometer.

Low-resolution atmospheric pressure chemical ionisation (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 aluminium-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 and 2 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

1-(Benzyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-propanol (122) (Scheme 1A). A solution of *tert*-butyl(chloro)dimethylsilane (7.29 g, 48.4 mmol) in anhydrous DMF (15 mL) was added dropwise (over 2 h) to a stirred solution of 3-(benzyloxy)-1,2-propanediol[23] (**121**) (8.40 g, 46.1 mmol) and imidazole (6.75 g, 99.1 mmol) in anhydrous DMF (35 mL) at 0 °C. The mixture was stirred at 0 °C for a further 3 h, and then at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic extract was washed with water and brine, and then dried and evaporated, and the residue was chromatographed on silica gel. Elution with 10% EtOAc/petroleum ether gave **122**[24] (8.25 g, 60%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5 H), 4.55 (s, 2 H), 3.85 (m, 1 H), 3.68 (dd, *J* = 10.1, 5.0 Hz, 1 H), 3.64 (dd, *J* = 10.1, 5.8 Hz, 1 H), 3.54 (dd, *J* = 9.6, 5.0 Hz, 1 H), 3.51 (dd, *J* = 9.8, 5.8 Hz, 1 H), 2.47 (br d, *J* = 5.0 Hz, 1 H), 0.89 (s, 9 H), 0.06 (s, 6 H). APCI MS *m/z* 297 $[M + H]^+$.

Procedure A. {3-(Benzyloxy)-2-[4-(trifluoromethoxy)phenoxy]propoxy}(*tert*-butyl)dimethylsilane (123). Diisopropyl azodicarboxylate (2.46 mL, 12.7 mmol) was added

dropwise to a stirred solution of alcohol **122** (3.00 g, 10.1 mmol), 4-(trifluoromethoxy)phenol (1.35 mL, 10.4 mmol) and PPh_3 (3.30 g, 12.6 mmol) in anhydrous benzene (10 mL) at 0 °C. After being stirred at room temperature for 18 h, the mixture was evaporated onto silica gel and chromatographed on silica gel. Elution with 5% EtOAc/petroleum ether gave **123** (2.97 g, 64%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.36-7.25 (m, 5 H), 7.10 (br d, *J* = 9.1 Hz, 2 H), 6.95 (br d, *J* = 9.1 Hz, 2 H), 4.56 (s, 2 H), 4.42 (m, 1 H), 3.84 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.80 (dd, *J* = 10.8, 5.5 Hz, 1 H), 3.73 (dd, *J* = 10.4, 4.5 Hz, 1 H), 3.66 (dd, *J* = 10.4, 5.4 Hz, 1 H), 0.86 (s, 9 H), 0.04, 0.02 (2 s, 6 H). APCI MS *m/z* 457 $[M + H]^+$.

Procedure B. 3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[4-(trifluoromethoxy)phenoxy]-1-propanol (124). A mixture of benzyl ether **123** (2.97 g, 6.51 mmol) and 5% Pd-C (300 mg) in 1:1 EtOAc/EtOH (60 mL) was hydrogenated at 60 psi for 4 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure to give **124** (2.25 g, 94%) as a viscous oil; ^{1}H NMR ($CDCl_3$) δ 7.13 (br d, *J* = 9.1 Hz, 2 H), 6.96 (br d, *J* = 9.1 Hz, 2 H), 4.37 (m, 1 H), 3.94-3.78 (m, 4 H), 2.09 (br s, 1 H), 0.88 (s, 9 H), 0.06, 0.04 (2 s, 6 H). APCI MS *m/z* 367 $[M + H]^+$.

Procedure C. *tert*-Butyl{3-iodo-2-[4-(trifluoromethoxy)phenoxy]propoxy}dimethylsilane (125). Iodine (2.01 g, 7.92 mmol) was added in portions to a vigorously stirred solution of alcohol **124** (2.24 g, 6.11 mmol), PPh_3 (2.08 g, 7.93 mmol) and imidazole (0.82 g, 12.0 mmol) in benzene (60 mL) and the mixture was stirred at room temperature for 1 h. After dilution with EtOAc, the mixture was sequentially washed with water, 2 M Na_2SO_3, and water. The organic extract was dried and evaporated and the residue was chromatographed on silica gel. Elution with 5% EtOAc/petroleum ether gave **125** (2.59 g, 89%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.14 (br d, *J* = 8.7 Hz, 2 H), 6.95 (br d, *J* = 9.1 Hz, 2 H), 4.20 (m, 1 H), 3.89 (dd, *J* = 10.7, 5.0 Hz,

1 H), 3.81 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.45 (dd, *J* = 10.6, 5.6 Hz, 1 H), 3.37 (dd, *J* = 10.6, 4.9 Hz, 1 H), 0.89 (s, 9 H), 0.09, 0.06 (2 s, 6 H). APCI MS *m/z* 477 $[M + H]^+$.

Procedure D. 2-Bromo-1-{3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-(trifluoromethoxy)phenoxy]propyl}-4-nitro-1*H*-imidazole (127). A mixture of 2-bromo-4-nitroimidazole (**126**) (0.945 g, 4.92 mmol), iodide **125** (2.58 g, 5.42 mmol) and K_2CO_3 (0.82 g, 5.93 mmol) in anhydrous DMF (15 mL) under N_2 was stirred at 87 °C for 20 h. The resulting mixture was partitioned between EtOAc and brine, and the organic extract was washed with brine and then evaporated to give an oil, which was chromatographed on silica gel. Elution with 10% EtOAc/petroleum ether gave foreruns, and then further elution with 50% EtOAc/petroleum ether gave **127** (1.33 g, 50%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.13 (br d, *J* = 9.0 Hz, 2 H), 6.83 (br d, *J* = 9.1 Hz, 2 H), 4.54-4.47 (m, 2 H), 4.30 (dd, *J* = 15.1, 8.3 Hz, 1 H), 3.85 (dd, *J* = 11.1, 3.9 Hz, 1 H), 3.73 (dd, *J* = 11.1, 6.3 Hz, 1 H), 0.92 (s, 9 H), 0.09, 0.07 (2 s, 6 H). APCI MS *m/z* 542, 540 $[M + H]^+$.

Procedure E. 2-Nitro-6-[4-(trifluoromethoxy)phenoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (11). Tetra-*n*-butylammonium fluoride (2.72 mL of a 1 M solution in THF, 2.72 mmol) was added to a solution of silyl ether **127** (0.761 g, 1.41 mmol) in THF (10 mL) under N_2 and the mixture was stirred at room temperature for 1 h. After dilution with EtOAc, the solution was sequentially washed with saturated aqueous $NaHCO_3$ solution and water, and then dried and evaporated to give an oil, which was chromatographed on silica gel. Elution with 20% EtOAc/petroleum ether gave foreruns, and then further elution with EtOAc gave the deprotected alcohol as a crude oil. This material was dissolved in anhydrous DMF (10 mL) and the solution was cooled to 0 °C and treated with 60% NaH (0.300 g, 7.50 mmol). After being stirred at room temperature for 30 min, the reaction was quenched and diluted with water, and the mixture was extracted with EtOAc. The extract was washed with brine and then evaporated to dryness and the residue was chromatographed on silica gel.

Elution with 1:1 EtOAc/petroleum ether gave foreruns, and then further elution with 2:1 EtOAc/petroleum ether gave **11** (0.145 g, 30%) as a pale yellow powder: mp 151-153 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (s, 1 H), 7.33 (br d, *J* = 9.0 Hz, 2 H), 7.16 (br d, *J* = 9.2 Hz, 2 H), 5.25 (m, 1 H), 4.67 (dt, *J* = 12.5, 2.2 Hz, 1 H), 4.63 (br d, *J* = 12.0 Hz, 1 H), 4.40 (dd, *J* = 13.8, 3.2 Hz, 1 H), 4.32 (br d, *J* = 14.0 Hz, 1 H). Anal. ($C_{13}H_{10}F_3N_3O_5$) C, H, N.

Procedure F. (6*S*)-2-Nitro-6-{[5-(trifluoromethyl)-2-pyridinyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (12) (Scheme 1B). A solution of (6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-ol[22] (**135**) (116 mg, 0.627 mmol) and 2-chloro-5-(trifluoromethyl)pyridine (**128**) (374 mg, 2.06 mmol) in anhydrous DMF (2.5 mL) under N_2 at 0 °C was treated with 60% NaH (40 mg, 1.00 mmol), then quickly degassed, and resealed under N_2. After being stirred at room temperature for 3 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL), and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 1-2% EtOAc/CH_2Cl_2 gave **12** (177 mg, 86%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 138-140 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (m, 1 H), 7.88 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.44 (s, 1 H), 6.90 (d, *J* = 8.7 Hz, 1 H), 5.81 (m, 1 H), 4.82 (dt, *J* = 12.4, 2.6 Hz, 1 H), 4.55 (dd, *J* = 12.4, 1.3 Hz, 1 H), 4.43 (dd, *J* = 13.5, 3.7 Hz, 1 H), 4.37 (dt, *J* = 13.6, 2.1 Hz, 1 H). Anal. ($C_{12}H_9F_3N_4O_4$) C, H, N.

See Supporting Information for details of the syntheses of **13-15** (Table 1).

Procedure G. 1-(1-Bromoethyl)-4-(trifluoromethoxy)benzene (134). Phosphorous tribromide (5.54 mL, 58.9 mmol) was added dropwise to stirred 1-[4-(trifluoromethoxy)phenyl]ethanol[29] (**133**) (6.08 g, 29.5 mmol) at 5 °C. After being stirred at room temperature for 2 h, the reaction was carefully quenched with excess saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with Et_2O. The extract was washed with

water, dried, and evaporated, to give **134** (7.91 g, 100%) as a lachramatory colourless oil, that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.46 (br d, *J* = 8.7 Hz, 2 H), 7.18 (br d, *J* = 8.4 Hz, 2 H), 5.19 (q, *J* = 6.9 Hz, 1 H), 2.03 (d, *J* = 6.9 Hz, 3 H).

Procedure H. (6*S*)-2-Nitro-6-{1-[4-(trifluoromethoxy)phenyl]ethoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (16). A solution of alcohol **135** (1.52 g, 8.21 mmol) and bromide **134** (2.43 g, 9.03 mmol) in anhydrous DMF (15 mL) under N_2 at 0 °C was treated with 60% NaH (0.65 g, 16.3 mmol). After being stirred under N_2 at room temperature for 45 min, the reaction was quenched and diluted with water, and the mixture was extracted with EtOAc. The extract was evaporated to dryness and the residue was chromatographed on silica gel. Elution with 20% EtOAc/petroleum ether gave foreruns, and then further elution with EtOAc gave **16** (0.74 g, 24%), a ~1:1 mixture of diastereomers, as a cream powder: mp 130-132 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05, 7.92 (2 s, 1 H), 7.49, 7.45 (2 br d, *J* = 8.7 Hz, 2 H), 7.35, 7.33 (2 br d, *J* = 8.7 Hz, 2 H), 4.88, 4.84 (2 q, *J* = 6.4 Hz, 1 H), 4.66 (dt, *J* = 12.0, 2.7 Hz, 0.5 H), 4.40 (d, *J* = 12.0 Hz, 0.5 H), 4.37 (m, 1 H), 4.29 (br dd, *J* = 13.4, 1.5 Hz, 0.5 H), 4.18 (dd, *J* = 13.4, 3.2 Hz, 0.5 H), 4.14 (dd, *J* = 13.0, 3.1 Hz, 0.5 H), 4.09-3.97 (m, 1.5 H), 1.35, 1.33 (2 d, *J* = 6.4 Hz, 3 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the separation of the diastereomers of **16**, the synthesis of ether **232** from alcohol **230**, via bromide **231** (Scheme 6B), and for the preparation of **70-73** (Table 2).

Procedure I. 1-(3-Iodopropyl)-4-(trifluoromethoxy)benzene (142) (Scheme 2A). Chlorodiphenylphosphine (0.460 mL, 2.49 mmol) was added to a mixture of 3-[4-(trifluoromethoxy)phenyl]-1-propanol[21] (**136**) (416 mg, 1.89 mmol) and imidazole (288 mg, 4.23 mmol) in toluene (20 mL) under N_2. After stirring at room temperature for 5 min, a solution of iodine (626 mg, 2.47 mmol) in toluene (3x 4 mL, then 1 mL to rinse) was added, and then the mixture was stirred at room temperature for 6 h. The resulting mixture was washed

with saturated aqueous Na_2CO_3 (50 mL) and water (2x 50 mL), and the aqueous washes were back-extracted with toluene (40 mL). The combined extracts were dried (Na_2SO_4) and evaporated to dryness and the residue was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, and then further elution with 0-10% CH_2Cl_2/petroleum ether gave **142** (466 mg, 75%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.21 (br d, J = 8.6 Hz, 2 H), 7.13 (br d, J = 8.2 Hz, 2 H), 3.16 (t, J = 6.8 Hz, 2 H), 2.74 (t, J = 7.3 Hz, 2 H), 2.12 (quintet, J = 7.1 Hz, 2 H); HREIMS calcd for $C_{10}H_{10}F_3IO$ m/z (M^+) 329.9729, found 329.9728.

See Supporting Information for details of the syntheses of iodides **143** and **146** from alcohols **137** and **140**.

Procedure J. 1-(2-Iodoethoxy)-4-(trifluoromethoxy)benzene (144). A solution of iodine (0.91 g, 3.59 mmol) in anhydrous CH_2Cl_2 (5x 5 mL) was added to a mixture of 2-[4-(trifluoromethoxy)phenoxy]ethanol[32] (**138**) (0.634 g, 2.87 mmol), imidazole (0.809 g, 11.9 mmol) and PPh_3 (0.928 g, 3.54 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2. After being stirred at room temperature for 5 h, the mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, and then further elution with 10% CH_2Cl_2/petroleum ether gave **144** (0.862 g, 91%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.15 (br d, J = 9.1 Hz, 2 H), 6.89 (br d, J = 9.1 Hz, 2 H), 4.24 (t, J = 6.8 Hz, 2 H), 3.41 (t, J = 6.8 Hz, 2 H); HRFABMS calcd for $C_9H_8F_3IO_2$ m/z (M^+) 331.9521, found 331.9521.

See Supporting Information for details of the syntheses of iodides **145**, **147** and **165** from alcohols **139**, **141** and **164**.

Procedure K. (6*S*)-2-Nitro-6-{3-[4-(trifluoromethoxy)phenyl]propoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (17). A solution of alcohol **135** (200 mg, 1.08 mmol) in anhydrous DMF (6.5 mL) under N_2 at 0 °C was treated with 60% NaH (65 mg, 1.63 mmol), then quickly degassed and resealed under N_2. After stirring at 0 °C for 10 min, a solution of

iodide **142** (462 mg, 1.40 mmol) in anhydrous DMF (3x 1.5 mL) was added dropwise, and then the mixture was stirred at room temperature for 5 h. The resulting mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL) and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 0-1% EtOAc/CH_2Cl_2 gave **17** (145 mg, 35%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 99-101 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.15 (br d, *J* = 8.9 Hz, 2 H), 7.12 (br d, *J* = 9.0 Hz, 2 H), 4.56 (ddd, *J* = 12.1, 3.7, 2.2 Hz, 1 H), 4.31 (dd, *J* = 12.1, 1.4 Hz, 1 H), 4.17 (dd, *J* = 12.7, 3.9 Hz, 1 H), 4.07 (dt, *J* = 12.8, 2.5 Hz, 1 H), 3.97 (m, 1 H), 3.62 (dt, *J* = 8.8, 6.2 Hz, 1 H), 3.51 (dt, *J* = 8.8, 6.1 Hz, 1 H), 2.67 (t, *J* = 7.5 Hz, 2 H), 1.91 (m, 2 H). Anal. ($C_{16}H_{16}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the syntheses of **18** and **19** (Table 1).

Procedure L. (6*S*)-2-Nitro-6-{2-[4-(trifluoromethoxy)phenoxy]ethoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (20). A solution of alcohol **135** (368 mg, 1.99 mmol) in anhydrous DMF (8 mL) under N_2 at room temperature was treated with 60% NaH (116 mg, 2.90 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 5 min, a solution of iodide **144** (855 mg, 2.57 mmol) in anhydrous DMF (2 mL, then 3x 1 mL to rinse) was added, and then the mixture was stirred at room temperature for 4 h. The resulting mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), added to brine (100 mL) and extracted with CH_2Cl_2 (6x 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 firstly gave foreruns, and then further elution with 1-3% EtOAc/CH_2Cl_2 gave **20** (60 mg, 8%) as a pale yellow solid: mp (Et_2O/pentane) 71-73 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.14 (br d, *J* = 8.5 Hz, 2 H), 6.87 (br d, *J* = 9.1 Hz, 2 H), 4.63 (ddd, *J* = 12.1, 3.6, 2.1

Hz, 1 H), 4.38 (br d, *J* = 12.2 Hz, 1 H), 4.26-4.08 (m, 5 H), 4.01 (ddd, *J* = 11.1, 4.7, 3.6 Hz, 1 H), 3.94 (ddd, *J* = 11.2, 6.1, 3.7 Hz, 1 H). Anal. ($C_{15}H_{14}F_3N_3O_6$) C, H, N.

See Supporting Information for details of the syntheses of **21** (Table 1) and iodide **154**.

(6*S*)-2-Nitro-6-{2-[(triisopropylsilyl)oxy]ethoxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (148) (Scheme 2B). Reaction of alcohol **135** with (2-iodoethoxy)(triisopropyl)silane[37] (1.39 equiv) and NaH (1.40 equiv), using Procedure F for 6 h, followed by chromatography of the product on silica gel, eluting with 0-33% EtOAc/petroleum ether (foreruns) and then with 33-67% EtOAc/petroleum ether, gave **148** (18%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 119-120 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 4.59 (ddd, *J* = 12.0, 4.0, 1.9 Hz, 1 H), 4.35 (dd, *J* = 12.2, 1.4 Hz, 1 H), 4.23-4.10 (m, 3 H), 3.86 (m, 2 H), 3.75 (dt, *J* = 10.7, 4.4 Hz, 1 H), 3.68 (ddd, *J* = 10.7, 5.5, 4.6 Hz, 1 H), 1.14-1.00 (m, 21 H). Anal. ($C_{17}H_{31}N_3O_5Si$) C, H, N.

2-{[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}ethanol (149). A suspension of silyl ether **148** (1.508 g, 3.91 mmol) in a solution of 1% HCl in 95% EtOH[38] (50 mL) was stirred at room temperature for 25 h. The resulting solution was cooled (CO_2/acetone), neutralised by dropwise addition of 7M NH_3 in MeOH (7 mL) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 2-3% MeOH/CH_2Cl_2 gave **149** (880 mg, 98%) as a pale yellow solid (after prolonged freezing of the initial oil and pentane trituration): mp 100-102 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (s, 1 H), 4.68 (t, *J* = 5.4 Hz, 1 H), 4.58 (ddt, *J* = 12.0, 2.3, 1.0 Hz, 1 H), 4.42 (dd, *J* = 11.8, 0.7 Hz, 1 H), 4.19 (m, 2 H), 4.15 (m, 1 H), 3.63-3.45 (m, 4 H). Anal. ($C_8H_{11}N_3O_5$) C, H, N.

(6*S*)-2-Nitro-6-(2-{[5-(trifluoromethyl)-2-pyridinyl]oxy}ethoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (22). Reaction of alcohol **149** with 2-chloro-5-(trifluoromethyl)pyridine (**128**) (4.0 equiv) and NaH (1.53 equiv), using Procedure F for 4 h,

followed by chromatography of the product on silica gel, eluting with 0-0.33% MeOH/CH_2Cl_2 (foreruns) and then with 0.33% MeOH/CH_2Cl_2, gave **22** (8%) as a cream solid: mp (CH_2Cl_2/pentane) 142-144 °C; ^{1}H NMR ($CDCl_3$) δ 8.41 (m, 1 H), 7.79 (ddd, *J* = 8.7, 2.5, 0.3 Hz, 1 H), 7.40 (s, 1 H), 6.83 (br d, *J* = 8.7 Hz, 1 H), 4.62 (ddd, *J* = 12.1, 3.7, 2.2 Hz, 1 H), 4.56 (ddd, *J* = 12.1, 5.4, 4.0 Hz, 1 H), 4.52 (ddd, *J* = 12.1, 5.8, 3.8 Hz, 1 H), 4.37 (dd, *J* = 12.1, 1.4 Hz, 1 H), 4.22 (br dd, *J* = 13.3, 4.6 Hz, 1 H), 4.18-4.12 (m, 2 H), 4.02 (ddd, *J* = 11.0, 5.4, 3.8 Hz, 1 H), 3.93 (ddd, *J* = 11.0, 5.8, 4.0 Hz, 1 H). Anal. ($C_{14}H_{13}F_3N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of **23** (Table 1) and bromides **156** and **158** from alcohol **149**, and for the preparation of **83-90** (Table 2).

Procedure M. (2*E*)-3-[4-(Trifluoromethoxy)phenyl]-2-propen-1-ol (167) (Scheme 3A). A solution of DIBAL-H (20% w/w in toluene, 4.5 mL, 5.44 mmol) was added dropwise over 45 min to a solution of methyl (2*E*)-3-[4-(trifluoromethoxy)phenyl]-2-propenoate[39] (**166**) (509 mg, 2.07 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2 at -78 °C. The mixture was stirred at -78 °C for 4 h, and then quenched with 2.5M NaOH (2.3 mL, 5.75 mmol) and warmed to room temperature. The resulting mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (4x 50 mL), and the combined extracts were evaporated. Column chromatography of the residue on silica gel, eluting with petroleum ether and 33% Et_2O/petroleum ether, firstly gave foreruns, and then further elution with 33-50% Et_2O/petroleum ether gave **167**[40] (440 mg, 98%) as a white solid: mp 40-41 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (br d, *J* = 8.7 Hz, 2 H), 7.16 (br d, *J* = 8.0 Hz, 2 H), 6.61 (br d, *J* = 15.9 Hz, 1 H), 6.34 (dt, *J* = 15.9, 5.6 Hz, 1 H), 4.34 (td, *J* = 5.7, 1.6 Hz, 2 H), 1.45 (t, *J* = 5.9 Hz, 1 H); HRESIMS calcd for $C_{10}H_8F_3O$ *m/z* $[M + H - H_2O]^+$ 201.0522, found 201.0515.

Procedure N. 1-[(1*E*)-3-Bromo-1-propenyl]-4-(trifluoromethoxy)benzene (168). A solution of alcohol **167** (138 mg, 0.633 mmol) and PPh_3 (201 mg, 0.764 mmol) in anhydrous

CH_2Cl_2 (7 mL) was carefully treated with recrystallized *N*-bromosuccinimide (135 mg, 0.759 mmol), and the mixture was stirred at room temperature for 3 h. The resulting solution was concentrated under a stream of dry N_2 and then added to excess pentane at the top of a silica gel column (12 g in petroleum ether), rinsing on with minimal extra CH_2Cl_2. Elution with pentane firstly gave foreruns and then **168** (170 mg, 96%) as a lachramatory colourless oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.40 (br d, *J* = 8.6 Hz, 2 H), 7.17 (br d, *J* = 8.1 Hz, 2 H), 6.63 (br d, *J* = 15.6 Hz, 1 H), 6.37 (dt, *J* = 15.6, 7.7 Hz, 1 H), 4.14 (dd, *J* = 7.7, 0.9 Hz, 2 H).

(6*S*)-2-Nitro-6-({(2*E*)-3-[4-(trifluoromethoxy)phenyl]-2-propenyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (24). Reaction of alcohol **135** with bromide **168** (0.94 equiv) and NaH (1.39 equiv), using Procedure F for 1 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **24** (62%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 156-158 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1 H), 7.39 (br d, *J* = 8.7 Hz, 2 H), 7.17 (br d, *J* = 8.0 Hz, 2 H), 6.60 (br d, *J* = 16.0 Hz, 1 H), 6.22 (dt, *J* = 15.9, 6.0 Hz, 1 H), 4.61 (ddd, *J* = 12.1, 3.8, 2.1 Hz, 1 H), 4.37 (dd, *J* = 12.0, 1.5 Hz, 1 H), 4.35 (ddd, *J* = 12.7, 5.9, 1.5 Hz, 1 H), 4.27 (ddd, *J* = 12.7, 6.2, 1.4 Hz, 1 H), 4.22 (br dd, *J* = 13.2, 4.5 Hz, 1 H), 4.18-4.12 (m, 2 H). Anal. ($C_{16}H_{14}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the synthesis of **27** (Table 1) from ester **162**.

[(1*E*)-3-Bromo-1-propenyl](tributyl)stannane (172) (Scheme 3B). Bromination of (2*E*)-3-(tributylstannyl)-2-propen-1-ol[43] (**171**) with NBS/PPh_3, using Procedure N for 4 h, gave **172**[44] (69%) as a lachramatory oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 6.29 (dt, *J* = 18.6, 0.8 Hz, 1 H), 6.12 (dt, *J* = 18.6, 6.7 Hz, 1 H), 3.95 (dd, *J* = 6.7, 0.9 Hz, 2 H), 1.61-1.39 (m, 6 H), 1.38-1.21 (m, 6 H), 1.01-0.82 (m, 15 H).

(6*S*)-2-Nitro-6-{[(2*E*)-3-(tributylstannyl)-2-propenyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (173). Reaction of alcohol **135** with bromide **172** (1.05 equiv) and NaH (1.39 equiv) using Procedure F for 100 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1% EtOAc/CH_2Cl_2, gave **173** (70%) as a cream solid: mp (CH_2Cl_2/pentane) 95-96 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 6.27 (dt, *J* = 19.1, 1.4 Hz, 1 H), 6.01 (dt, *J* = 19.1, 5.3 Hz, 1 H), 4.55 (ddd, *J* = 12.0, 4.1, 2.0 Hz, 1 H), 4.34 (dd, *J* = 12.0, 1.6 Hz, 1 H), 4.23-4.05 (m, 5 H), 1.60-1.38 (m, 6 H), 1.36-1.25 (m, 6 H), 1.00-0.82 (m, 15 H). Anal. ($C_{21}H_{37}N_3O_4Sn$) C, H, N.

Procedure O. (6*S*)-6-({(2*E*)-3-[4-(Benzyloxy)phenyl]-2-propenyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (25). A stirred mixture of stannane **173** (94.2 mg, 0.183 mmol), 1-(benzyloxy)-4-iodobenzene (65.3 mg, 0.211 mmol) and *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (1.18 mg, 1.56 μmol) in anhydrous DMF (2.2 mL) was degassed for 2 min (vacuum pump) and then N_2 was added. The resulting mixture was stirred at 82 °C for 23 h, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (5x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Successive elution with petroleum ether, 33-50% EtOAc/petroleum ether, petroleum ether, and CH_2Cl_2 firstly gave foreruns, and then further elution with 0.5% MeOH/CH_2Cl_2 gave **25** (42 mg, 56%) as a pale yellow solid: mp (CH_2Cl_2/EtOAc/pentane) 192-195 °C; ^{1}H NMR ($CDCl_3$) δ 7.44-7.29 (m, 8 H), 6.94 (br d, *J* = 8.8 Hz, 2 H), 6.56 (d, *J* = 15.9 Hz, 1 H), 6.10 (dt, *J* = 15.9, 6.4 Hz, 1 H), 5.07 (s, 2 H), 4.58 (ddd, *J* = 12.0, 3.6, 2.4 Hz, 1 H), 4.36 (dd, *J* = 12.0, 1.3 Hz, 1 H), 4.32 (ddd, *J* = 12.4, 6.2, 1.3 Hz, 1 H), 4.24 (ddd, *J* = 12.4, 6.6, 1.2 Hz, 1 H), 4.19 (dd, *J* = 14.5, 5.6 Hz, 1 H), 4.16-4.09 (m, 2 H). Anal. ($C_{22}H_{21}N_3O_5$) C, H, N.

See Supporting Information for details of the synthesis of **26** (Table 1) from stannane **173**.

(6*S*)-2-Nitro-6-({3-[4-(trifluoromethoxy)phenyl]-2-propynyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (28) (Scheme 4A). A mixture of (6*S*)-2-nitro-6-(2-propynyloxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine[15] (**179**) (0.108 g, 0.484 mmol), 1-iodo-4-(trifluoromethoxy)benzene (0.167 g, 0.580 mmol) and CuI (2 mg, 0.01 mmol) in Et_3N (5 mL) and THF (5 mL) was purged with N_2. $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) was added, and the stirred mixture was refluxed under N_2 for 10 min, then cooled, and 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 **28** (0.115 g, 62%) as a cream solid: mp 144-146 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.60 (br d, *J* = 8.8 Hz, 2 H), 7.39 (br d, *J* = 8.8 Hz, 2 H), 4.66 (dt, *J* = 12.1, 2.4 Hz, 1 H), 4.59 (s, 2 H), 4.50 (br d, *J* = 12.0 Hz, 1 H), 4.39 (m, 1 H), 4.31 (dt, *J* = 13.6, 2.0 Hz, 1 H), 4.25 (dd, *J* = 13.6, 3.2 Hz, 1 H). Anal. ($C_{16}H_{12}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the synthesis of **29** (Table 1) from alkyne **179**.

Procedure P. (6*S*)-2-Nitro-6-({3-[5-(trifluoromethyl)-2-pyridinyl]-2-propynyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (30). A mixture of alkyne **179** (0.050 g, 0.224 mmol), 2-iodo-5-(trifluoromethyl)pyridine (**129**) (0.082 g, 0.299 mmol) and CuI (4 mg, 0.02 mmol) in DMF (1.5 mL) and Et_3N (1.5 mL) was purged with N_2. $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) was added and the mixture was stirred at 70 °C for 1 h under N_2, then cooled, and 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 **30** (0.059 g, 72%) as a white solid: mp 174-177 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (m, 1 H), 8.25 (dd, *J* = 8.2, 2.1 Hz, 1 H), 8.03 (s, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 4.70-4.65 (m, 3 H), 4.51 (br d, *J* = 12.2 Hz, 1 H), 4.41 (m, 1 H), 4.32 (dt, *J* = 13.6, 2.0 Hz, 1 H), 4.26 (dd, *J* = 13.6, 3.2 Hz, 1 H). Anal. ($C_{15}H_{11}F_3N_4O_4$) C, H, N.

See Supporting Information for details of the synthesis of **31** (Table 1) from alkyne **179**.

Procedure Q. (5-Bromo-1-pentynyl)(*tert*-butyl)dimethylsilane (181). A solution of Br_2 (8.83 g, 55.2 mmol) in CH_2Cl_2 (50 mL) was added to a solution of PPh_3 (15.2 g, 58.0 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The solution was stirred at 0 °C for 15 min and then a solution of *tert*-butyl(dimethyl)[5-(tetrahydro-2*H*-pyran-2-yloxy)-1-pentynyl]silane[46] (**180**) (15.6 g, 55.2 mmol) in CH_2Cl_2 (50 mL) was added. The mixture was warmed to room temperature and stirred for 20 h, and then diluted with pentane (300 mL) and filtered. The filtrate was concentrated under reduced pressure, triturated with pentane, and refiltered; this procedure was repeated twice, and the solvent was removed. Column chromatography of the residue, eluting with hexanes, gave **181** (9.74 g, 52%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.52 (t, *J* = 6.5 Hz, 2 H), 2.43 (t, *J* = 6.8 Hz, 2 H), 2.05 (quintet, *J* = 6.7 Hz, 2 H), 0.93 (s, 9 H), 0.08 (s, 6 H).

(6*S*)-2-Nitro-6-(4-pentynyloxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (182). NaH (60% w/w, 0.65 g, 16.3 mmol) was added to a solution of alcohol **135** (2.00 g, 10.8 mmol) and bromide **181** (3.38 g, 12.9 mmol) in anhydrous DMF (60 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, and then quenched with water and extracted with EtOAc. The organic layer was dried and evaporated, and the residue was dissolved in THF (100 mL) and treated with TBAF (20 mL of a 1 M solution in THF, 20 mmol). The solution was stirred at room temperature for 1.5 h, and then evaporated, and the residue was 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 **182** (0.487 g, 18%) as a gum; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 4.56 (br d, *J* = 11.9 Hz, 1 H), 4.42 (d, *J* = 11.9 Hz, 1 H), 4.23-4.14 (m, 2 H), 4.11 (m, 1 H), 3.66-3.56 (m, 2 H), 2.74 (t, *J* = 2.6 Hz, 1 H), 2.16 (td, *J* = 7.1, 2.6 Hz, 2 H), 1.66 (quintet, *J* = 6.6 Hz, 2 H). Anal. ($C_{11}H_{13}N_3O_4$) C, H, N.

See Supporting Information for details of the synthesis of ether **194** from alcohol **192** (Scheme 4D) and for the preparation of **116-120** (Table 2).

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethoxy)phenyl]-4-pentynyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (32). Reaction of alkyne **182** and 1-iodo-4-(trifluoromethoxy)benzene (1.5 equiv) under the Sonogashira coupling conditions described in Procedure P (but refluxing for 1 h) gave **32** (49%) as a white solid: mp 140-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.51 (br d, *J* = 8.8 Hz, 2 H), 7.33 (br d, *J* = 8.8 Hz, 2 H), 4.59 (dt, *J* = 11.9, 1.2 Hz, 1 H), 4.44 (br d, *J* = 11.8 Hz, 1 H), 4.25-4.17 (m, 2 H), 4.15 (m, 1 H), 3.73-3.62 (m, 2 H), 2.44 (t, *J* = 7.1 Hz, 2 H), 1.76 (quintet, *J* = 6.6 Hz, 2 H). Anal. ($C_{18}H_{16}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the syntheses of **33** and **34** (Table 1) from alkyne **182**.

Compounds of Table 2

Procedure R. (2*R*)-1-[(4-Methoxybenzyl)oxy]-3-[(triisopropylsilyl)oxy]-2-propanol (207) (Scheme 5B). Chloro(triisopropyl)silane (26.1 mL, 0.122 mol) was added dropwise to a stirred solution of (2*S*)-3-[(4-methoxybenzyl)oxy]-1,2-propanediol[53] (**206**) (24.7 g, 0.116 mol) and imidazole (11.9 g, 0.175 mol) in anhydrous DMF (300 mL) and the mixture was stirred at room temperature for 16 h. Most of the DMF was removed by evaporation under reduced pressure and the residue was partitioned between EtOAc and water. The organic extract was washed well with water, then brine, and evaporated to give an oil, which was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, and then further elution with 5-10% EtOAc/petroleum ether gave **207** (93%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.25 (br d, *J* = 8.7 Hz, 2 H), 6.87 (br d, *J* = 8.7 Hz, 2 H), 4.48 (s, 2 H), 3.85 (m, 1 H), 3.80 (s, 3 H), 3.75 (dd, *J* = 9.8, 4.9 Hz, 1 H), 3.72 (dd, *J* = 9.8, 5.8 Hz, 1 H), 3.54

(dd, J = 9.6, 5.1 Hz, 1 H), 3.50 (dd, J = 9.6, 5.8 Hz, 1 H), 2.54 (d, J = 5.1 Hz, 1 H), 1.15-1.02 (m, 21 H); $[\alpha]_D^{23}$ -0.86° (*c* 3.47, $CHCl_3$); HRESIMS calcd for $C_{20}H_{36}NaO_4Si$ *m/z* $[M + Na]^+$ 391.2275, found 391.2286.

({(2*S*)-2-(4-Bromophenoxy)-3-[(4-methoxybenzyl)oxy]propyl}oxy)(triisopropyl)silane (208). Mitsunobu coupling of alcohol **207** and 4-bromophenol, using Procedure A for 17 h, followed by precipitation of PPh_3O with petroleum ether, filtration, and chromatography of the concentrated filtrate on silica gel, eluting with petroleum ether (foreruns) and then with 3% EtOAc/petroleum ether, gave **208** (70%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.33 (br d, J = 9.0 Hz, 2 H), 7.21 (br d, J = 8.7 Hz, 2 H), 6.87-6.82 (m, 4 H), 4.48 (s, 2 H), 4.40 (m, 1 H), 3.92-3.84 (m, 2 H), 3.80 (s, 3 H), 3.73 (dd, J = 10.4, 4.5 Hz, 1 H), 3.64 (dd, J = 10.4, 5.4 Hz, 1 H), 1.12-1.00 (m, 21 H). APCI MS *m/z* 525, 523 $[M + H]^+$.

Procedure S. (2*S*)-2-(4-Bromophenoxy)-3-[(triisopropylsilyl)oxy]-1-propanol (209). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (5.19 g, 22.9 mmol) was added to a solution of PMB ether **208** (9.97 g, 19.0 mmol) in CH_2Cl_2 (150 mL) and water (150 mL) and the mixture was stirred at room temperature for 1 h. The resulting solution was washed with portions of saturated aqueous $NaHCO_3$ until the washings were colourless. The organic layer was evaporated to give an oil, which was chromatographed on silica gel. Elution with 5% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 15% EtOAc/petroleum ether gave crude **209** (7.7 g) as an oil, that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.36 (br d, J = 9.0 Hz, 2 H), 6.85 (br d, J = 9.0 Hz, 2 H), 4.37 (m, 1 H), 3.97-3.84 (m, 4 H), 2.13 (t, J = 6.4 Hz, 1 H), 1.15-1.01 (m, 21 H). APCI MS *m/z* 405, 403 $[M + H]^+$.

{[(2*R*)-2-(4-Bromophenoxy)-3-iodopropyl]oxy}(triisopropyl)silane (210). Iodine (6.34 g, 25.0 mmol) was added in portions to a vigorously stirred solution of crude alcohol **209** (7.7 g), PPh_3 (6.56 g, 25.0 mmol) and imidazole (2.59 g, 38.0 mmol) in benzene (100 mL) and the

mixture was stirred at room temperature for 30 min. The same quantities of iodine, PPh_3 and imidazole were then added to the mixture, and stirring was continued at room temperature for a further 1 h. After dilution with EtOAc, the resulting mixture was sequentially washed with water, 5% aqueous Na_2SO_3, and water. The organic extract was evaporated to dryness, and the residue was chromatographed on silica gel. Elution with petroleum ether gave **210** (7.34 g, 75% from **208**) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.37 (br d, *J* = 9.0 Hz, 2 H), 6.84 (br d, *J* = 9.0 Hz, 2 H), 4.19 (m, 1 H), 3.98 (dd, *J* = 10.4, 4.8 Hz, 1 H), 3.89 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.49 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.39 (dd, *J* = 10.5, 4.8 Hz, 1 H), 1.16-1.02 (m, 21 H). APCI MS *m/z* 515, 513 $[M + H]^+$.

2-Bromo-1-{(2*S*)-2-(4-bromophenoxy)-3-[(triisopropylsilyl)oxy]propyl}-4-nitro-1*H*-imidazole (211). Reaction of 2-bromo-4-nitroimidazole (**126**) with iodide **210** and K_2CO_3 (2.2 equiv), using Procedure D for 16 h, followed by chromatography of the product on silica gel, eluting with 10% EtOAc/petroleum ether (foreruns) and then with 33% EtOAc/petroleum ether, gave **211** (74%) as a viscous oil; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.37 (br d, *J* = 9.0 Hz, 2 H), 6.71 (br d, *J* = 9.0 Hz, 2 H), 4.56 (dd, *J* = 14.3, 3.2 Hz, 1 H), 4.49 (m, 1 H), 4.29 (dd, *J* = 14.3, 7.6 Hz, 1 H), 3.95 (dd, *J* = 10.9, 4.0 Hz, 1 H), 3.80 (dd, *J* = 10.8, 6.7 Hz, 1 H), 1.18-1.01 (m, 21 H). APCI MS *m/z* 580, 578, 576 $[M + H]^+$.

(6*S*)-6-(4-Bromophenoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (213). Desilylation of silyl ether **211** with TBAF (for 3 h), followed by reaction of the resulting alcohol **212** with NaH (2.0 equiv; reacting at 0 °C for 20 min only), using Procedure E, followed by chromatography of the product on silica gel, eluting with 10% EtOAc/petroleum ether (foreruns) and then with a gradient of 50% EtOAc/petroleum ether to EtOAc, gave **213** (37%) as a yellow solid: mp (CH_2Cl_2/Et_2O) 184 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (s, 1 H), 7.50 (br d, *J* = 9.1 Hz, 2 H), 7.03 (br d, *J* = 9.1 Hz, 2 H), 5.22 (m, 1 H), 4.68-4.60 (m, 2 H),

4.39 (dd, *J* = 13.8, 3.2 Hz, 1 H), 4.30 (br dd, *J* = 13.9, 1.1 Hz, 1 H); $[\alpha]_D^{25}$ -26.6° (*c* 1.09, DMF). Anal. ($C_{12}H_{10}BrN_3O_4 \cdot 0.5H_2O$) C, H, N.

Procedure T. (6*S*)-2-Nitro-6-{[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (35). A stirred mixture of bromide **213** (200 mg, 0.588 mmol) and 4-(trifluoromethoxy)phenylboronic acid (140 mg, 0.680 mmol) in toluene (8.0 mL), EtOH (3.0 mL), and aqueous Na_2CO_3 (2 M, 2.0 mL) was purged with N_2. $Pd(dppf)Cl_2$ (30 mg, 0.041 mmol) was added, and the stirred mixture was refluxed under N_2 for 30 min. The resulting mixture was partitioned between EtOAc and water, the organic layer was evaporated, and the residue was chromatographed on silica gel. Elution with 50% EtOAc/petroleum ether firstly gave foreruns, and then further elution with EtOAc gave **35** (139 mg, 56%) as a cream solid: mp 216-217 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07 (s, 1 H), 7.75 (br d, *J* = 8.8 Hz, 2 H), 7.66 (br d, *J* = 8.8 Hz, 2 H), 7.42 (br d, *J* = 8.1 Hz, 2 H), 7.15 (br d, *J* = 8.8 Hz, 2 H), 5.29 (m, 1 H), 4.69 (dt, *J* = 12.4, 2.0 Hz, 1 H), 4.66 (br d, *J* = 12.5 Hz, 1 H), 4.42 (dd, *J* = 13.8, 3.1 Hz, 1 H), 4.34 (br d, *J* = 13.9 Hz, 1 H); $[\alpha]_D^{25}$ -19.6° (*c* 1.12, acetone). Anal. ($C_{19}H_{14}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the alternative synthesis of **35** from (*S*)-glycidol (**195**) (Scheme 5A), the syntheses of **36**-**38** (Table 2) from bromide **213** (Scheme 5B), and the preparation of **60**-**63** (Table 2) from alcohol **207** (Scheme 5C).

(6*S*)-6-[(6-Bromo-2-pyridinyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (220) (Scheme 6A). Reaction of alcohol **135** with 2-bromo-6-fluoropyridine (**226**) (1.51 equiv) and NaH (1.53 equiv), using Procedure F for 3.5 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave **220** (90%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 134-136 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (t, *J* = 7.9 Hz, 1 H), 7.44 (s, 1 H), 7.18 (d, *J* = 7.5 Hz, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 5.74 (m, 1 H), 4.80 (dt, *J* = 12.4, 2.6 Hz, 1 H), 4.53 (dd, *J* = 12.4, 1.2 Hz, 1 H),

4.42 (dd, *J* = 13.6, 3.7 Hz, 1 H), 4.35 (dt, *J* = 13.6, 2.2 Hz, 1 H). Anal. ($C_{11}H_9BrN_4O_4$) C, H, N.

See Supporting Information for details of the syntheses of halides **222** and **225** from alcohol **135**.

Procedure U. (6*S*)-2-Nitro-6-({6-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (39). A stirred mixture of bromide **220** (40.1 mg, 0.118 mmol), 4-(trifluoromethoxy)phenylboronic acid (38.9 mg, 0.189 mmol) and Pd(dppf)Cl_2 (13.1 mg, 0.018 mmol) in toluene (1.7 mL) and EtOH (0.7 mL) was degassed for 5 min (vacuum pump) and then N_2 was added. An aqueous solution of Na_2CO_3 (0.30 mL of 2 M, 0.60 mmol) was added by syringe and the stirred mixture was again degassed for 5 min, and then N_2 was added. The resulting mixture was stirred at 90 °C for 60 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-0.5% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 0.5-1% EtOAc/CH_2Cl_2 gave **39** (93%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 175-177 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (br d, *J* = 8.8 Hz, 2 H), 7.74 (dd, *J* = 8.0, 7.7 Hz, 1 H), 7.44 (s, 1 H), 7.42 (br d, *J* = 7.3 Hz, 1 H), 7.32 (br d, *J* = 8.8 Hz, 2 H), 6.77 (d, *J* = 7.9 Hz, 1 H), 5.91 (m, 1 H), 4.87 (ddd, *J* = 12.2, 2.8, 1.7 Hz, 1 H), 4.59 (dd, *J* = 12.2, 1.4 Hz, 1 H), 4.46 (dd, *J* = 13.4, 3.5 Hz, 1 H), 4.42 (dt, *J* = 13.4, 2.3 Hz, 1 H). Anal. ($C_{18}H_{13}F_3N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of **40**-**43**, **52**-**55** and **64**-**67** (Table 2) from halides **220**, **225** and **222**, respectively.

Procedure V. (6*S*)-6-[(2-Chloro-4-pyridinyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (224). A solution of alcohol **135** (501 mg, 2.71 mmol) in anhydrous DMF (10 mL) under N_2 at 0 °C was treated with 60% NaH (171 mg, 4.28 mmol), then quickly degassed and resealed under N_2. After stirring at 0 °C for 5 min, 2-chloro-4-fluoropyridine (**228**) (545 mg,

4.14 mmol) was added (syringe), and then the mixture was stirred at room temperature for 3 h. The resulting mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), added to brine (80 mL) and extracted with CH_2Cl_2 (6x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-25% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 25-50% EtOAc/CH_2Cl_2 gave **224** (668 mg, 83%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 220-221 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.25 (d, *J* = 5.8 Hz, 1 H), 8.04 (s, 1 H), 7.33 (d, *J* = 2.3 Hz, 1 H), 7.11 (dd, *J* = 5.8, 2.3 Hz, 1 H), 5.44 (m, 1 H), 4.68 (m, 2 H), 4.43 (dd, *J* = 14.1, 3.2 Hz, 1 H), 4.35 (br d, *J* = 14.2 Hz, 1 H). Anal. ($C_{11}H_9ClN_4O_4$) C, H, N.

See Supporting Information for details of the syntheses of bromides **221** and **223** from alcohol **135**.

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethoxy)phenyl]-4-pyridinyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (44). Reaction of chloride **224** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure U (but using 0.33 equiv Pd(dppf)Cl_2 for 100 min), followed by chromatography of the product on silica gel, eluting with 0-10% EtOAc/CH_2Cl_2 (foreruns) and then with 10-12% EtOAc/CH_2Cl_2, gave **44** (67%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 240-241 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (d, *J* = 5.7 Hz, 1 H), 8.25 (br d, *J* = 8.9 Hz, 2 H), 8.06 (s, 1 H), 7.69 (d, *J* = 2.3 Hz, 1 H), 7.46 (br d, *J* = 8.8 Hz, 2 H), 7.10 (dd, *J* = 5.7, 2.4 Hz, 1 H), 5.55 (m, 1 H), 4.75 (dt, *J* = 12.5, 2.1 Hz, 1 H), 4.71 (br d, *J* = 12.8 Hz, 1 H), 4.48 (dd, *J* = 14.0, 3.2 Hz, 1 H), 4.39 (br d, *J* = 14.1 Hz, 1 H). Anal. ($C_{18}H_{13}F_3N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of **45**, **46**, **48-51** and **56-59** (Table 2) from halides **224**, **223** and **221**, respectively.

Procedure W. (6*S*)-2-Nitro-6-{[6'-(trifluoromethyl)[2,3'-bipyridin]-4-yl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (47). A stirred mixture of chloride **224** (50.2 mg,

0.169 mmol), 6-(trifluoromethyl)-3-pyridinylboronic acid (70.5 mg, 0.369 mmol) and Pd(dppf)Cl_2 (51.5 mg, 0.070 mmol) in DMF (1.5 mL), toluene (1.0 mL) and EtOH (0.6 mL) was degassed for 6 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 and the stirred mixture was again degassed for 6 min, and then N_2 was added. The resulting mixture was stirred at 90 °C for 5 h, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (4x 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 firstly gave foreruns, and then further elution with 0.75% MeOH/CH_2Cl_2 gave **47** (50 mg, 73%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 284-286 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.47 (d, *J* = 1.9 Hz, 1 H), 8.75 (dd, *J* = 8.2, 1.7 Hz, 1 H), 8.62 (d, *J* = 5.8 Hz, 1 H), 8.07 (s, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.89 (d, *J* = 2.4 Hz, 1 H), 7.22 (dd, *J* = 5.7, 2.4 Hz, 1 H), 5.57 (m, 1 H), 4.77 (dt, *J* = 12.4, 2.2 Hz, 1 H), 4.73 (br d, *J* = 12.4 Hz, 1 H), 4.50 (dd, *J* = 14.1, 3.2 Hz, 1 H), 4.41 (br d, *J* = 14.2 Hz, 1 H). Anal. ($C_{17}H_{12}F_3N_5O_4$) C, H, N.

(6*S*)-6-[3-(4-Bromophenyl)propoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (153) (Scheme 2A). Reaction of alcohol **135** with iodide **146** and NaH, using Procedure K for 5.5 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1.5% EtOAc/CH_2Cl_2, gave **153** (38%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 148-150 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.39 (br d, *J* = 8.4 Hz, 2 H), 7.01 (br d, *J* = 8.4 Hz, 2 H), 4.55 (ddd, *J* = 12.1, 3.7, 2.2 Hz, 1 H), 4.31 (dd, *J* = 12.0, 1.4 Hz, 1 H), 4.16 (dd, *J* = 12.7, 3.9 Hz, 1 H), 4.06 (dt, *J* = 12.8, 2.5 Hz, 1 H), 3.95 (m, 1 H), 3.59 (dt, *J* = 8.8, 6.2 Hz, 1 H), 3.49 (dt, *J* = 8.8, 6.1 Hz, 1 H), 2.62 (t, *J* = 7.4 Hz, 2 H), 1.89 (m, 2 H). Anal. ($C_{15}H_{16}BrN_3O_4$) C, H, N.

See Supporting Information for details of the syntheses of **74-76** (Table 2) from bromide **153**.

Procedure X. (6*S*)-2-Nitro-6-(3-{4-[6-(trifluoromethyl)-3-pyridinyl]phenyl}propoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (77) (Scheme 2C). A stirred mixture of bromide **153** (50.0 mg, 0.131 mmol), bis(pinacolato)diboron (38.9 mg, 0.153 mmol), KOAc (47 mg, 0.479 mmol) and Pd(dppf)Cl_2 (19.3 mg, 0.026 mmol) in anhydrous DMF (0.8 mL) was degassed for 5 min (vacuum pump) and then N_2 was added. After being stirred at 90 °C for 5 h, the mixture was cooled, and 5-bromo-2-(trifluoromethyl)pyridine (**159**) (55 mg, 0.243 mmol), Pd(dppf)Cl_2 (10.4 mg, 0.014 mmol), and aqueous Na_2CO_3 (2 M, 0.35 mL) were added. The resulting mixture was degassed for 5 min (vacuum pump) and N_2 was added. After being stirred at 90 °C for 60 min, the mixture was cooled, diluted with aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-4% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 4-6% EtOAc/CH_2Cl_2 gave the crude product; impure fractions were combined and further chromatographed on silica gel. Elution with 0-0.25% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 0.25-0.5% MeOH/CH_2Cl_2 gave additional product; impure fractions were rechromatographed using this method and the purified material was combined to give **77** (23 mg, 39%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 198-200 °C; ^{1}H NMR ($CDCl_3$) δ 8.93 (d, *J* = 1.9 Hz, 1 H), 8.02 (dd, *J* = 8.1, 1.9 Hz, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.52 (br d, *J* = 8.2 Hz, 2 H), 7.41 (s, 1 H), 7.28 (br d, *J* = 8.1 Hz, 2 H), 4.59 (ddd, *J* = 12.1, 3.5, 2.2 Hz, 1 H), 4.33 (br d, *J* = 12.7 Hz, 1 H), 4.19 (dd, *J* = 12.8, 3.8 Hz, 1 H), 4.11 (dt, *J* = 12.8, 2.4 Hz, 1 H), 4.00 (m, 1 H), 3.65 (dt, *J* = 8.8, 6.2 Hz, 1 H), 3.55 (dt, *J* = 8.8, 6.1 Hz, 1 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 1.97 (m, 2 H). Anal. ($C_{21}H_{19}F_3N_4O_4$) C, H, N.

See Supporting Information for details of the synthesis of **78** (Table 2) from bromide **153**.

Procedure Y. Methyl (2*E*)-3-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-2-propenoate (176a) (Scheme 3C). A mixture of methyl (2*E*)-3-(4-bromophenyl)-2-propenoate (**174**)

(0.500 g, 2.07 mmol) and 4-(trifluoromethoxy)phenylboronic acid (0.612 g, 2.97 mmol) in dioxane (40 mL) and aqueous K_2CO_3 (2 M, 10 mL) was purged with N_2. $Pd(dppf)Cl_2$ (0.050 g, 0.07 mmol) was added, and the stirred mixture was refluxed under N_2 for 1 h. The resulting mixture was concentrated 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 on silica gel, eluting with a gradient of hexanes to CH_2Cl_2, gave **176a** (0.567 g, 85%) as a white solid: mp 134-136 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, *J* = 16.0 Hz, 1 H), 7.63-7.56 (m, 6 H), 7.30 (br d, *J* = 8.8 Hz, 2 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 3.82 (s, 3 H). APCI MS *m/z* 323 $[M + H]^+$.

Procedure Z. (2*E*)-3-[4'-(Trifluoromethoxy)[1,1'-biphenyl]-4-yl]-2-propen-1-ol (177a). A solution of DIBAL-H (20% w/w in toluene, 2.0 mL, 2.42 mmol) was added to a slurry of ester **176a** (0.396 g, 1.23 mmol) in toluene (12 mL) at -78 °C. The mixture was warmed to room temperature, stirred for 1 h, and then poured into ice cold aqueous NH_4Cl (50 mL). The resulting mixture was diluted with CH_2Cl_2 (100 mL) and filtered through Celite, and then the organic layer was dried and evaporated. Column chromatography of the residue on silica gel, eluting with a gradient of 0-5% EtOAc/CH_2Cl_2, gave **177a** (0.195 g, 54%) as a white solid: mp 86-90 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.60 (br d, *J* = 8.7 Hz, 2 H), 7.53 (br d, *J* = 8.4 Hz, 2 H), 7.47 (br d, *J* = 8.4 Hz, 2 H), 7.28 (br d, *J* = 8.1 Hz, 2 H), 6.66 (br d, *J* = 15.9 Hz, 1 H), 6.42 (dt, *J* = 15.9, 5.7 Hz, 1 H), 4.36 (td, *J* = 5.8, 1.5 Hz, 2 H), 1.44 (t, *J* = 5.9 Hz, 1 H); HRAPCIMS calcd for $C_{16}H_{12}F_3O$ *m/z* $[M + H - H_2O]^+$ 277.0835, found 277.0832.

Procedure AA. 4-[(1*E*)-3-Bromo-1-propenyl]-4'-(trifluoromethoxy)-1,1'-biphenyl (178a). PBr_3 (26 μL, 0.28 mmol) was added to a solution of alcohol **177a** (0.159 g, 0.540 mmol) in Et_2O (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, and then quenched with ice, and extracted with Et_2O. The organic layer was dried and evaporated, and then column chromatography of the residue on silica gel, eluting with CH_2Cl_2, gave **178a**

(0.123 g, 64%) as a white solid: mp 125-127 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (br d, *J* = 8.8 Hz, 2 H), 7.53 (br d, *J* = 8.4 Hz, 2 H), 7.46 (br d, *J* = 8.3 Hz, 2 H), 7.28 (br d, *J* = 8.8 Hz, 2 H), 6.69 (d, *J* = 15.6 Hz, 1 H), 6.45 (dt, *J* = 15.6, 7.8 Hz, 1 H), 4.18 (dd, *J* = 7.8, 0.9 Hz, 2 H); HRAPCIMS calcd for $C_{16}H_{12}F_3O$ *m/z* $[M + H - HBr]^+$ 277.0835, found 277.0832.

Procedure BB. (6*S*)-2-Nitro-6-({(2*E*)-3-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-2-propenyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (91). NaH (60% w/w, 0.016 g, 0.40 mmol) was added to a solution of alcohol **135** (0.050 g, 0.27 mmol) and bromide **178a** (0.100 g, 0.28 mmol) in anhydrous DMF (6 mL) at -78 °C. The mixture was stirred at 0 °C for 1 h, and then quenched with ice, and 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 **91** (0.079 g, 63%) as a white solid: mp 224-225 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.04 (s, 1 H), 7.80 (br d, *J* = 8.8 Hz, 2 H), 7.66 (br d, *J* = 8.4 Hz, 2 H), 7.55 (br d, *J* = 8.4 Hz, 2 H), 7.44 (br d, *J* = 8.0 Hz, 2 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.43 (dt, *J* = 16.0, 5.9 Hz, 1 H), 4.65 (br d, *J* = 11.9 Hz, 1 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.35-4.21 (m, 5 H). Anal. ($C_{22}H_{18}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the syntheses of **92-95** (Table 2) from esters **174** and **175**.

(6*S*)-6-{[3-(4-Bromophenyl)-2-propynyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (187) (Scheme 4B). Reaction of alcohol **135** with 1-bromo-4-(3-bromo-1-propynyl)benzene[47] (**184**) and NaH (1.30 equiv), using Procedure BB, gave **187** (77%) as a white solid: mp 170-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.60 (br d, *J* = 8.5 Hz, 2 H), 7.42 (br d, *J* = 8.5 Hz, 2 H), 4.66 (dt, *J* = 12.1, 2.4 Hz, 1 H), 4.57 (s, 2 H), 4.49 (br d, *J* = 12.0 Hz, 1 H), 4.38 (m, 1 H), 4.30 (dt, *J* = 13.6, 2.1 Hz, 1 H), 4.25 (dd, *J* = 13.6, 3.2 Hz, 1 H). Anal. ($C_{15}H_{12}BrN_3O_4$) C, H, N.

See Supporting Information for details of the similar synthesis of bromide **188**.

Procedure CC. (6*S*)-2-Nitro-6-({3-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-2-propynyl}oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (96). A mixture of bromide **187** (0.200 g, 0.529 mmol) and 4-(trifluoromethoxy)phenylboronic acid (0.131 g, 0.636 mmol) in toluene (10 mL), EtOH (6 mL) and aqueous K_2CO_3 (2 M, 2 mL) was purged with N_2. $Pd(dppf)Cl_2$ (10 mg, 0.014 mmol) was added, and the stirred mixture was refluxed under N_2 for 0.5 h. The resulting mixture was partitioned between EtOAc and water, and the organic layer was dried, and then evaporated under reduced pressure. Column chromatography of the residue on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **96** (0.174 g, 72%) as a white solid: mp 178-180 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.04 (s, 1 H), 7.83 (br d, *J* = 8.8 Hz, 2 H), 7.72 (br d, *J* = 8.4 Hz, 2 H), 7.58 (br d, *J* = 8.4 Hz, 2 H), 7.46 (br d, *J* = 8.1 Hz, 2 H), 4.68 (dt, *J* = 12.1, 2.4 Hz, 1 H), 4.61 (s, 2 H), 4.51 (br d, *J* = 12.0 Hz, 1 H), 4.40 (m, 1 H), 4.32 (dt, *J* = 13.6, 1.9 Hz, 1 H), 4.27 (dd, *J* = 13.6, 3.2 Hz, 1 H). Anal. ($C_{22}H_{16}F_3N_3O_5$) C, H, N.

See Supporting Information for details of the syntheses of **97**-**105** (Table 2) from bromides **187** and **188**.

(6*S*)-6-{[3-(5-Bromo-2-pyridinyl)-2-propynyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (189) (Scheme 4C). A mixture of alkyne **179** (0.324 g, 1.45 mmol), 5-bromo-2-iodopyridine (**190**) (0.500 g, 1.76 mmol) and CuI (7 mg, 0.04 mmol) in DMF (5 mL) and Et_3N (5 mL) was purged with N_2. $Pd(PPh_3)_2Cl_2$ (0.023 g, 0.031 mmol) was added, and the mixture was stirred at room temperature for 16 h under N_2. The resulting mixture was partitioned between EtOAc and water, and the organic layer was dried, and then evaporated under reduced pressure. Column chromatography of the residue on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **189** (0.412 g, 75%) as a tan solid: mp 190-191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.70 (dd, *J* = 2.4, 0.4 Hz, 1 H), 8.09 (dd, *J* = 8.4, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.54 (dd, *J* = 8.3, 0.4 Hz, 1 H), 4.67 (dt, *J* = 12.1, 2.4 Hz, 1

H), 4.62 (s, 2 H), 4.50 (br d, J = 12.1 Hz, 1 H), 4.39 (m, 1 H), 4.31 (dt, J = 13.7, 2.0 Hz, 1 H), 4.26 (dd, J = 13.7, 3.2 Hz, 1 H). Anal. ($C_{14}H_{11}BrN_4O_4$) C, H, N.

See Supporting Information for details of the syntheses of **106-110** (Table 2) from bromide **189**.

Procedure DD. 5-Bromo-2-[4-(trifluoromethoxy)phenyl]pyridine (191a). A mixture of 5-bromo-2-iodopyridine (**190**) (0.568 g, 2.00 mmol) and 4-(trifluoromethoxy)phenylboronic acid (0.412 g, 2.00 mmol) in THF (20 mL) and aqueous K_2CO_3 (2 M, 10 mL) was purged with N_2. $Pd(PPh_3)_4$ (0.070 g, 0.06 mmol) was added and the stirred mixture was refluxed under N_2 at 80 °C for 24 h. The resulting mixture was partitioned between EtOAc and water, and the organic layer was dried, and then evaporated under reduced pressure. Column chromatography of the residue on silica gel, eluting with 1:3 CH_2Cl_2:hexanes, gave **191a** (0.525 g, 83%) as a white solid: mp 52-53 °C; ^{1}H NMR ($CDCl_3$) δ 8.74 (dd, J = 2.4, 0.6 Hz, 1 H), 8.00 (br d, J = 8.9 Hz, 2 H), 7.88 (dd, J = 8.5, 2.4 Hz, 1 H), 7.60 (dd, J = 8.5, 0.7 Hz, 1 H), 7.31 (br d, J = 8.9 Hz, 2 H). APCI MS m/z 320, 318 $[M + H]^+$.

(6*S*)-2-Nitro-6-[(3-{6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}-2-propynyl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (111). Reaction of alkyne **179** and bromide **191a** (1.06 equiv) under the Sonogashira coupling conditions described in Procedure P for 0.5 h gave **111** (59%) as a white solid: mp 183-186 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.78 (dd, J = 2.1, 0.8 Hz, 1 H), 8.24 (br d, J = 8.9 Hz, 2 H), 8.05 (dd, J = 8.3, 0.9 Hz, 1 H), 8.05 (s, 1 H), 8.01 (dd, J = 8.3, 2.1 Hz, 1 H), 7.49 (br d, J = 8.8 Hz, 2 H), 4.68 (dt, J = 12.1, 2.5 Hz, 1 H), 4.65 (s, 2 H), 4.51 (br d, J = 12.1 Hz, 1 H), 4.42 (m, 1 H), 4.33 (dt, J = 13.7, 2.0 Hz, 1 H), 4.27 (dd, J = 13.6, 3.2 Hz, 1 H). Anal. ($C_{21}H_{15}F_3N_4O_5$) C, H, N.

See Supporting Information for details of the syntheses of **112-115** (Table 2) from iodide **190**.

Solubility determinations. The solid compound sample was mixed with water or 0.1 M HCl (enough to make a 2 mM solution) in an Eppendorf tube and the suspension was sonicated for 15 min, and then centrifuged at 13,000 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).

Minimum Inhibitory Concentration Assays (MABA and LORA). These were carried out according to the published protocols.[57,59]

Microsomal stability assays. These were conducted by MDS Pharma Services, 22011 30th Drive SE, Bothell, WA 98021-4444, using a published protocol.[14] The percentage of compound remaining after a 1 h incubation was calculated as:

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

where PAR = analyte/IS peak area ratio

Additional studies on the pure diastereomers of **16** were conducted by Cyprotex Discovery Ltd, 13-15 Beech Lane, Macclesfield, Cheshire SK10 2DR, United Kingdom, using the following similar protocol:

Compounds (1 μM) were singularly incubated with pooled human or CD-1 mouse liver microsome preparations (0.5 mg/mL final protein concentration) and NADPH (1.0 mM) in phosphate buffer (0.1 M, pH 7.4), with a final volume of 25 μL. Compounds were dissolved in DMSO such that the final DMSO concentration was 0.25%. Positive controls (dextromethorphan and verapamil for HLM, diazepam and diphenhydramine for MLM) were treated similarly; negative controls (minus NADPH or minus compound) were also included in each experiment. Incubation was at 37 °C, and reactions were stopped at 0 and 45 min by the addition of MeOH (50 μL) containing internal standard. The incubation plates were centrifuged at 2,500 rpm for 20 min at 4 °C, prior to analysis by LC-MS/MS.

Alcohol metabolite assay. Compounds (5 μM) were incubated with human or mouse liver microsomes (2 mg/mL) at 37 °C for up to 2 h, in the presence of NADPH (3 mM) and $MgCl_2$ (5 mM). Reactions were terminated by the addition of ice-cold MeCN and then the MeCN extracts were evaporated, mixed with 0.1% aqueous HCOOH, and analysed by LC-MS/MS to determine the concentrations of alcohol metabolite (**135**) present (and thus % formation data).

The studies were conducted by XenoBiotic Laboratories, Inc., 107 Morgan Lane, Plainsboro, NJ 08536.

***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 post-infection, in accordance with published protocols.[14,59] 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 assay.** Compounds were administered orally as described for the acute assay but with treatment beginning ~70 days post-infection. In this assay, **1** caused a ca. 2 log reduction in CFUs, whereas **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.

The study of compounds **6**, **32**, **74** and **96** was conducted by Cumbre Pharmaceuticals Inc., 1502 Viceroy Dr., Dallas, TX 75235-2304. The study of compounds **35** and **101** (using the same protocol) was conducted by MDS Pharma Services, 22011 30th Drive SE, Bothell, WA 98021-4444.

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Supporting Information Available: Additional experimental procedures and characterizations for compounds in Tables 1 and 2; solubility data at pH=1; microsomal stability data for the diastereomers of **16**; ligand efficiency and lipophilic efficiency data; combustion analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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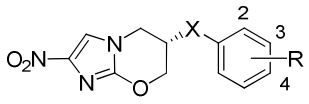
Table 1. Physicochemical properties and MIC values for monoaryl and benzyloxybenzyl analogues of **1** having various ether linkers

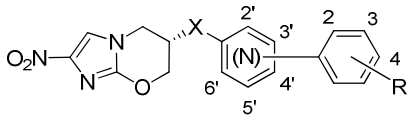


					MIC (μM)[c]	
compd	X	R	sol[a]	CLogP[b]	MABA	LORA
11	O (*rac.*)[d]	4-OCF_3	12	2.48	2.9 ± 1.0	9.6 ± 3.0
12	O	2-aza, 4-CF_3	83	2.33	2.9 ± 1.0	16 ± 4
1	OCH_2	4-OCF_3	19	2.70	0.50 ± 0.30	2.6 ± 1.4
13[e]	OCH_2	4-OCH_2Ph	0.76	3.32	0.025 ± 0.005	1.3 ± 0.6
14	OCH_2	2-aza, 4-CF_3	188	1.23	1.5 ± 0.5	22 ± 6
15	OCH_2	3-aza, 4-CF_3	68	1.23	3.0 ± 1.0	50 ± 4
16	OCH(Me)	4-OCF_3	25	3.05	0.60 ± 0.31	7.7 ± 3.9
17	$O(CH_2)_3$	4-OCF_3	11	3.34	0.22 ± 0.08	3.2 ± 1.3
18	$O(CH_2)_3$	4-OCH_2Ph	3.8	3.96	0.50 ± 0.10	3.7 ± 0.8
19	$O(CH_2)_3$	3-aza, 4-CF_3	168	1.87	0.51 ± 0.27	12 ± 3
20	$O(CH_2)_2O$	4-OCF_3	50	2.49	0.04 ± 0.01	5.1 ± 1.3
21	$O(CH_2)_2O$	4-OCH_2Ph	1.7	3.11	0.085 ± 0.035	5.5 ± 1.3
22	$O(CH_2)_2O$	2-aza, 4-CF_3	42	2.34	0.38 ± 0.14	26 ± 4
23	$O(CH_2)_2O$	3-aza, 4-CF_3	58	2.09	0.79 ± 0.24	59 ± 12
24	$OCH_2CH{=}CH$	4-OCF_3	1.5	3.20	0.05 ± 0.01	4.3 ± 0.4
25	$OCH_2CH{=}CH$	4-OCH_2Ph	0.06[f]	3.82	0.16 ± 0.01	1.3 ± 0.3
26	$OCH_2CH{=}CH$	2-aza, 4-CF_3	29	2.22	0.043 ± 0.017	3.8 ± 1.7
27	$OCH_2CH{=}CH$	3-aza, 4-CF_3	45	2.33	0.15 ± 0.06	21 ± 1
28	$OCH_2C{\equiv}C$	4-OCF_3	0.77[f]	3.94	0.12 ± 0	3.4 ± 0.3
29	$OCH_2C{\equiv}C$	4-OCH_2Ph	0.43[f]	4.56	0.09 ± 0.01	3.5 ± 1.5

30	$OCH_2C{\equiv}C$	2-aza, 4-CF_3	8.4	2.47	0.12 ± 0.01	3.3 ± 0.7
31	$OCH_2C{\equiv}C$	3-aza, 4-CF_3	11	2.47	0.18 ± 0.06	8.9 ± 3.0
32	$O(CH_2)_3C{\equiv}C$	4-OCF_3	0.09[f]	3.98	0.05 ± 0.01	1.9 ± 0
33	$O(CH_2)_3C{\equiv}C$	2-aza, 4-CF_3	28	2.51	0.19 ± 0.01	3.5 ± 0.8
34	$O(CH_2)_3C{\equiv}C$	3-aza, 4-CF_3	16	2.51	0.12 ± 0.01	9.2 ± 2.2

[a]Solubility (μg/mL) in water at pH=7 and 20 °C, determined by HPLC (see Experimental Section). [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)[59] or anaerobic (LORA)[57] conditions. Each value is the mean of at least two independent determinations ± SD. [d]Racemic compound. [e]Ref 22. [f]Unstable in assay (<50% parent observed).

Table 2. Physicochemical properties and MIC values for biaryl analogues of **1** having various ether linkers



							MIC (μM)[c]	
compd	link	aza	X	R	sol[a]	CLogP[b]	MABA	LORA
35	4′		O	4-OCF_3	0.33	3.98	0.090 ± 0.057	1.1 ± 0.4
36	4′		O	4-F		3.07	0.31 ± 0.13	1.2 ± 0.2
37	4′		O	4-CF_3		4.10	0.39 ± 0.07	>128
38	4′		O	3-aza, 4-CF_3		3.19	0.51 ± 0.26	4.1 ± 1.2
39	3′	2′	O	4-OCF_3	0.12	3.27	0.24 ± 0.01	3.3 ± 0.1
40	3′	2′	O	4-F		2.35	3.2 ± 1.1	27 ± 11
41	3′	2′	O	4-CF_3		3.39	0.55 ± 0.26	35 ± 7
42	3′	2′	O	3-aza, 4-CF_3		2.48	5.7 ± 2.0	>128
43	3′	2′	O	4-OCF_2H		2.41	0.52 ± 0.03	4.4 ± 1.0
44	3′	4′	O	4-OCF_3	0.53	2.95	0.30 ± 0.02	2.6 ± 0.5
45	3′	4′	O	4-F		2.03	0.67 ± 0.18	8.5 ± 2.2
46	3′	4′	O	4-CF_3		3.07	0.65 ± 0.19	>128
47	3′	4′	O	3-aza, 4-CF_3		2.15	14 ± 6	>128
48	3′	6′	O	4-OCF_3	0.13[d]	3.23	5.1 ±1 .8	87 ± 25
49	3′	6′	O	4-F		2.31	5.2 ± 1.7	28 ± 17
50	3′	6′	O	4-CF_3		3.35	0.88 ± 0.22	32 ± 12
51	3′	6′	O	3-aza, 4-CF_3		2.44	3.0 ± 0.7	27 ± 2
52	3′	4′,6′	O	4-OCF_3	0.88[d]	2.79	2.1 ± 0.2	21 ± 5
53	3′	4′,6′	O	4-F		1.87	0.99 ± 0.04	15 ± 8
54	3′	4′,6′	O	4-CF_3		2.91	0.80 ± 0.12	17 ± 8

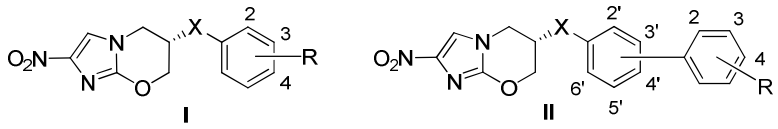
55	3′	4′,6′	O	3-aza, 4-CF_3		1.99	3.0 ± 0.7	62 ± 0
56	4′	2′	O	4-OCF_3	0.24	3.35	0.39 ± 0.01	12 ± 1
57	4′	2′	O	4-F		2.43	0.37 ± 0.06	15 ± 1
58	4′	2′	O	4-CF_3		3.47	0.10 ± 0.05	12 ± 1
59	4′	2′	O	3-aza, 4-CF_3		2.56	0.42 ± 0.20	14 ± 1
60	4′	3′	O	4-OCF_3	0.27	3.07	0.14 ± 0.08	1.5 ± 0.4
61	4′	3′	O	4-F		2.15	0.50 ± 0.20	5.6 ± 2.4
62	4′	3′	O	4-CF_3		3.19	0.78 ± 0.40	1.2 ± 0.7
63	4′	3′	O	3-aza, 4-CF_3		2.28	0.45 ± 0.22	17 ± 8
64	4′	2′,6′	O	4-OCF_3	1.7	2.71	0.22 ± 0.03	5.2 ± 0.2
65	4′	2′,6′	O	4-F		1.80	1.6 ± 0.4	7.4 ± 0.1
66	4′	2′,6′	O	4-CF_3		2.84	0.21 ± 0.01	3.0 ± 0.9
67	4′	2′,6′	O	3-aza, 4-CF_3		1.92	1.3 ± 0.3	17 ± 10
6[e]	4′		OCH_2	4-OCF_3	1.2	4.36	0.035 ± 0.015	1.3 ± 0.1
68[e]	4′		OCH_2	4-F		3.44	0.015 ± 0.005	1.4 ± 0.5
69[e]	4′		OCH_2	4-CF_3		4.48	0.03 ± 0.01	1.4 ± 0.5
8[f]	4′		OCH_2	3-aza, 4-CF_3		3.57	0.03 ± 0	2.1 ± 0.2
70	4′		OCH(Me)	4-OCF_3	0.84	4.71	0.19 ± 0.03	1.5 ± 0.4
71	4′		OCH(Me)	4-F		3.79	0.22 ± 0.02	1.3 ± 0.4
72	4′		OCH(Me)	4-CF_3		4.83	0.18 ± 0.05	2.2 ± 0.9
73	4′		OCH(Me)	3-aza, 4-CF_3		3.91	0.39 ± 0.11	4.3 ± 0.9
74	4′		$O(CH_2)_3$	4-OCF_3	1.7	4.99	0.15 ± 0.04	3.8 ± 1.3
75	4′		$O(CH_2)_3$	4-F		4.08	0.045 ± 0.005	0.92 ± 0.39
76	4′		$O(CH_2)_3$	4-CF_3		5.12	0.043 ± 0.005	>128
77	4′		$O(CH_2)_3$	3-aza, 4-CF_3		4.20	0.07 ± 0	1.9 ± 0.8
78	4′		$O(CH_2)_3$	2-aza, 4-CF_3		4.17	0.055 ± 0.005	3.0 ± 0.4
79	4′		$O(CH_2)_2O$	4-OCF_3	0.68	3.99	0.055 ± 0.005	1.6 ± 0.5
80	4′		$O(CH_2)_2O$	4-F		3.08	0.04 ± 0.01	3.4 ± 0.1

81	4′		$O(CH_2)_2O$	4-CF_3		4.12	0.04 ± 0	104 ± 9
82	4′		$O(CH_2)_2O$	3-aza, 4-CF_3		3.20	0.025 ± 0.005	4.1 ± 0.4
83	4′	2′	$O(CH_2)_2O$	4-OCF_3	0.79[d]	3.36	0.04 ± 0.02	2.5 ± 0.6
84	4′	2′	$O(CH_2)_2O$	4-F		2.44	0.02 ± 0	2.4 ± 1.1
85	4′	2′	$O(CH_2)_2O$	4-CF_3		3.48	0.02 ± 0	3.0 ± 0.1
86	4′	2′	$O(CH_2)_2O$	3-aza, 4-CF_3		2.57	0.22 ± 0.01	10 ± 6
87	4′	2′,6′	$O(CH_2)_2O$	4-OCF_3	21	2.72	0.13 ± 0.01	2.1 ± 0.7
88	4′	2′,6′	$O(CH_2)_2O$	4-F		1.81	0.13 ± 0.01	13 ± 0
89	4′	2′,6′	$O(CH_2)_2O$	4-CF_3		2.85	0.12 ± 0.01	5.4 ± 1.1
90	4′	2′,6′	$O(CH_2)_2O$	3-aza, 4-CF_3		1.93	0.63 ± 0.20	56 ± 10
91	4′		$OCH_2CH=CH$	4-OCF_3	0.50	4.83	0.063 ± 0.040	>128
92	4′		$OCH_2CH=CH$	4-F		3.91	0.09 ± 0	3.1 ± 0.2
93	4′		$OCH_2CH=CH$	4-CF_3		4.95	0.045 ± 0.015	43 ± 17
94	4′		$OCH_2CH=CH$	3-aza, 4-CF_3		4.03	0.02 ± 0	15 ± 1
95	4′		$OCH_2CH=CH$	4-OCF_2H		3.97	0.08 ± 0	4.3 ± 1.3
96	4′		$OCH_2C\equiv C$	4-OCF_3	0.07	5.60	0.16 ± 0.02	0.99 ± 0.49
97	4′		$OCH_2C\equiv C$	4-F		4.68	0.035 ± 0.005	2.7 ± 1.2
98	4′		$OCH_2C\equiv C$	4-CF_3		5.72	0.22 ± 0.09	0.86 ± 0.36
99	4′		$OCH_2C\equiv C$	3-aza, 4-CF_3		4.80	0.15 ± 0.01	1.2 ± 0.5
100	4′		$OCH_2C\equiv C$	4-OCF_2H		4.74	0.14 ± 0.05	1.8 ± 0.8
101	3′		$OCH_2C\equiv C$	4-OCF_3	0.27	5.60	0.11 ± 0.02	1.3 ± 0.5
102	3′		$OCH_2C\equiv C$	4-F		4.68	0.04 ± 0.02	0.88 ± 0.10
103	3′		$OCH_2C\equiv C$	4-CF_3		5.72	0.27 ± 0.13	1.3 ± 0.4
104	3′		$OCH_2C\equiv C$	3-aza, 4-CF_3		4.80	0.12 ± 0.06	0.96 ± 0.03
105	3′		$OCH_2C\equiv C$	4-OCF_2H		4.74	0.09 ± 0.03	1.4 ± 0.6
106	4′	2′	$OCH_2C\equiv C$	4-OCF_3	0.05	4.28	0.025 ± 0.005	0.35 ± 0.12
107	4′	2′	$OCH_2C\equiv C$	4-F		3.36	0.05 ± 0.01	0.85 ± 0
108	4′	2′	$OCH_2C\equiv C$	4-CF_3		4.40	0.02 ± 0	0.75 ± 0.04

109	4′	2′	$OCH_2C{\equiv}C$	3-aza, 4-CF_3		3.49	0.44 ± 0.03	6.6 ± 1.9
110	4′	2′	$OCH_2C{\equiv}C$	4-OCF_2H		3.42	0.025 ± 0.005	0.44 ± 0.26
111	4′	3′	$OCH_2C{\equiv}C$	4-OCF_3	0.72	4.25	0.09 ± 0.03	0.52 ± 0.26
112	4′	3′	$OCH_2C{\equiv}C$	4-F		3.33	0.05 ± 0.03	1.0 ± 0.1
113	4′	3′	$OCH_2C{\equiv}C$	4-CF_3		4.37	0.07 ± 0.03	0.58 ± 0.19
114	4′	3′	$OCH_2C{\equiv}C$	3-aza, 4-CF_3		3.46	0.12 ± 0.01	3.7 ± 1.4
115	4′	3′	$OCH_2C{\equiv}C$	4-OCF_2H		3.39	0.08 ± 0.02	0.61 ± 0.14
116	4′		$O(CH_2)_3C{\equiv}C$	4-OCF_3	0[d]	5.64	0.055 ± 0.015	>128
117	4′		$O(CH_2)_3C{\equiv}C$	4-F		4.73	0.07 ± 0.02	1.6 ± 0.2
118	4′		$O(CH_2)_3C{\equiv}C$	4-CF_3		5.76	0.085 ± 0.035	>128
119	4′		$O(CH_2)_3C{\equiv}C$	3-aza, 4-CF_3		4.85	0.11 ± 0.02	63 ± 3
120	4′		$O(CH_2)_3C{\equiv}C$	4-OCF_2H		4.79	0.035 ± 0.005	39 ± 19

[a-c]As for Table 1. [d]Unstable in assay (<50% parent observed; for **116** no parent was detected). [e]Data from ref 14. [f]Data from ref 16.

Table 3. Summary of relative mean solubilities, calculated lipophilicity differences, and mean MICs for compound subsets

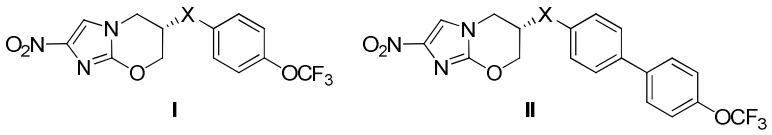


compds	link	X	sol. ratio[a]	ΔCLogP[b]	mean MICs (μM) MABA	mean MICs (μM) LORA	ratio[c] (X/OCH_2) MABA	ratio[c] (X/OCH_2) LORA
*A: compounds **I** of Table 1*								
11,12		O	0.46	0.44	2.2[d]	10[d]	1.7[d]	0.53[d]
1,**13-15**		OCH_2	1.0	0	1.3	19	1.0	1.0
16		OCH(Me)	1.3	0.35	0.60	7.7	0.46	0.41
17-19		$O(CH_2)_3$	2.1	0.64	0.41	6.3	0.32	0.33
20-23		$O(CH_2)_2O$	0.55	0.39	0.32	24	0.25	1.3
24-27		$OCH_2CH{=}CH$	0.27	0.77	0.10	7.6	0.08	0.40
28-31		$OCH_2C{\equiv}C$	0.07	1.24	0.13	4.8	0.10	0.25
32-34		$O(CH_2)_3C{\equiv}C$	0.16	1.28	0.12	4.9	0.09	0.26
*B: compounds **II** of Table 2*								
35-38	4′	O	0.28	-0.38	0.33	>34	12	>21
39-42	3′	O (2′-aza)	0.10	-1.09	2.4	>48	86	>30
44-47	3′	O (4′-aza)	0.44	-1.41	3.9	>67	139	>42
48-51	3′	O (6′-aza)	0.11	-1.13	3.5	44	125	28
52-55	3′	O (4′,6′-diaza)	0.73	-1.57	1.7	29	61	18
56-59	4′	O (2′-aza)	0.20	-1.01	0.32	13	11	8.1
60-63	4′	O (3′-aza)	0.23	-1.29	0.47	6.3	17	3.9
64-67	4′	O (2′,6′-diaza)	1.4	-1.65	0.83	8.2	30	5.1
6,**8**,**68**,**69**	4′	OCH_2	1.0	0	0.028	1.6	1.0	1.0
70-73	4′	OCH(Me)	0.70	0.35	0.25	2.3	8.9	1.4

74-77	4′	$O(CH_2)_3$	1.4	0.64	0.077	>34	2.8	>21
79-82	4′	$O(CH_2)_2O$	0.57	-0.37	0.040	28	1.4	18
83-86	4′	$O(CH_2)_2O$ (2′-aza)	0.66	-1.00	0.075	4.5	2.7	2.8
87-90	4′	$O(CH_2)_2O$ (2′,6′-diaza)	18	-1.64	0.25	19	8.9	12
91-94	4′	$OCH_2CH{=}CH$	0.42	0.47	0.055	>47	2.0	>29
96-99	4′	$OCH_2C{\equiv}C$	0.06	1.24	0.14	1.4	5.0	0.88
101-104	3′	$OCH_2C{\equiv}C$	0.23	1.24	0.14	1.1	5.0	0.69
106-109	4′	$OCH_2C{\equiv}C$ (2′-aza)	0.04	-0.08	0.13	2.1	4.6	1.3
111-114	4′	$OCH_2C{\equiv}C$ (3′-aza)	0.60	-0.11	0.083	1.5	3.0	0.94
116-119	4′	$O(CH_2)_3C{\equiv}C$	0	1.28	0.080	>80	2.9	>50

[a]Ratio of mean aqueous solubility values (X/OCH_2) for the various linker subclasses of the same form (I or II) bearing the same aryl substituents. [b]Mean difference in CLogP values between the linker subclass X and the OCH_2–linked compounds of that form (I or II) bearing the same substituents. [c]Ratio of mean MICs (X/OCH_2) for the various linker subclasses of the same form (I or II). [d]Estimated value by assuming *S*-**11** is twice as potent as *rac*-**11** (as approximately found for **1**, refs 14 and 25).

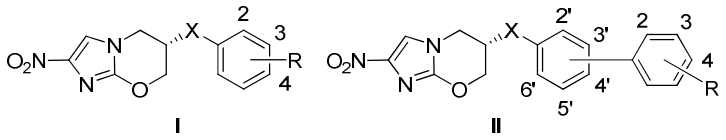
Table 4. Comparative activities of mono- and biphenyl analogues of **1** having various ether linkers



compds				MIC (μM) MABA		MIC (μM) LORA		MIC ratio[b] (I/II)	
I	II	X	ΔCLogP[a]	I	II	I	II	MABA	LORA
11	**35**	O	-0.22/-0.38	2.9	0.09	9.6	1.1	32	8.7
1	**6**	OCH_2	0	0.50	0.035	2.6	1.3	14	2.0
16	**70**	OCH(Me)	0.35	0.60	0.19	7.7	1.5	3.2	5.1
17	**74**	$O(CH_2)_3$	0.64/0.63	0.22	0.15	3.2	3.8	1.5	0.84
20	**79**	$O(CH_2)_2O$	-0.21/-0.37	0.04	0.055	5.1	1.6	0.73	3.2
24	**91**	$OCH_2CH{=}CH$	0.50/0.47	0.05	0.063	4.3	>128	0.79	<0.034
28	**96**	$OCH_2C{\equiv}C$	1.24	0.12	0.16	3.4	0.99	0.75	3.4
32	**116**	$O(CH_2)_3C{\equiv}C$	1.28	0.05	0.055	1.9	>128	0.91	<0.015

[a]Difference in CLogP values between compounds in the linker subclass X and OCH_2–linked analogues of the same form (I or II). [b]Ratio of MICs for mono- vs biphenyl compounds (I/II) for the various linker subclasses.

Table 5. Microsomal stability and *in vivo* efficacy data for selected analogues



					microsomes (% remaining at 1 h)		*in vivo* efficacy (ratio vs **1** or **2**)	
compd	Fm	link	X	R	H[a]	M[b]	Acute[c]	Chronic[d]
1	I		OCH_2	4-OCF_3	82	94	1.0	0.14
6	II	4′	OCH_2	4-OCF_3	97	96	>205	0.86
13	I		OCH_2	4-OCH_2Ph	59	44		
16	I		OCH(Me)	4-OCF_3	73	75		
20	I		$O(CH_2)_2O$	4-OCF_3	85	66	1.3	
24	I		$OCH_2CH{=}CH$	4-OCF_3	99	71		
32	I		$O(CH_2)_3C{\equiv}C$	4-OCF_3	69	24	4.9	
35	II	4′	O	4-OCF_3	99	97	8.1	
56	II	4′	O (2′-aza)	4-OCF_3	96	93	0.17	
64	II	4′	O (2′,6′-diaza)	4-OCF_3	88	95		
70	II	4′	OCH(Me)	4-OCF_3	100	92	toxic	
74	II	4′	$O(CH_2)_3$	4-OCF_3	88	91	1.5	0.025
76	II	4′	$O(CH_2)_3$	4-CF_3	73	81	0.05	
79	II	4′	$O(CH_2)_2O$	4-OCF_3	90	70	1.4	
91	II	4′	$OCH_2CH{=}CH$	4-OCF_3	100	95	2.0	
96	II	4′	$OCH_2C{\equiv}C$	4-OCF_3	93	85	89	1.6
99	II	4′	$OCH_2C{\equiv}C$	3-aza, 4-CF_3	82	90	0.01	
101	II	3′	$OCH_2C{\equiv}C$	4-OCF_3	94	89	6.4	
106	II	4′	$OCH_2C{\equiv}C$ (2′-aza)	4-OCF_3	89	86	0.91	
111	II	4′	$OCH_2C{\equiv}C$ (3′-aza)	4-OCF_3	93	90	1.0	

[a]Pooled human liver microsomes. [b]Pooled CD-1 mouse liver microsomes. [c]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). [d]Fold reduction in lung CFUs for compound compared with the fold CFU reduction for **2** in a mouse model of chronic TB infection (see text).

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-hr/mL)	C_{max} (μg/mL)	$t_{1/2}$ (h)	$AUC_{0\text{-}inf}$[a] (μg-hr/mL)	C_{max} (μg/mL)	$t_{1/2}$ (h)	AUC ratio[b]
6	198	7.4	14.4	218	9.0	12.8	1.1
32	12.6	2.54	1.6	7.57	2.72	1.4	0.60
35	102	1.86	37.9	347	15.8	15.3	3.4
74	13.3	0.99	4.4	29.5	10.1	-[c]	2.2
96	10.0	0.57	7.5	13.6	0.76	12.3	1.4
101	35.8	1.66	14.7	257	12.9	14.1	7.2

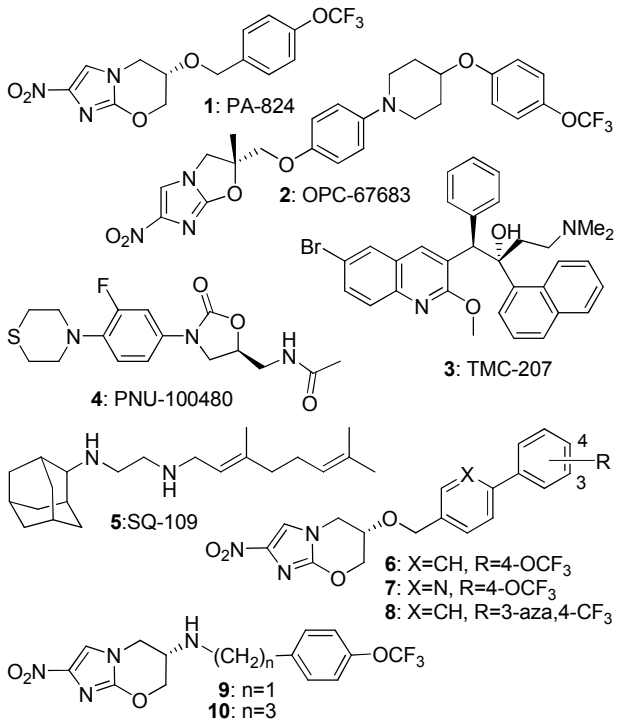
[a]Area under the curve, extrapolated to infinity. [b]Lung AUC/plasma AUC. [c]Not calculable.

Table 7. Metabolite formation data for selected analogues

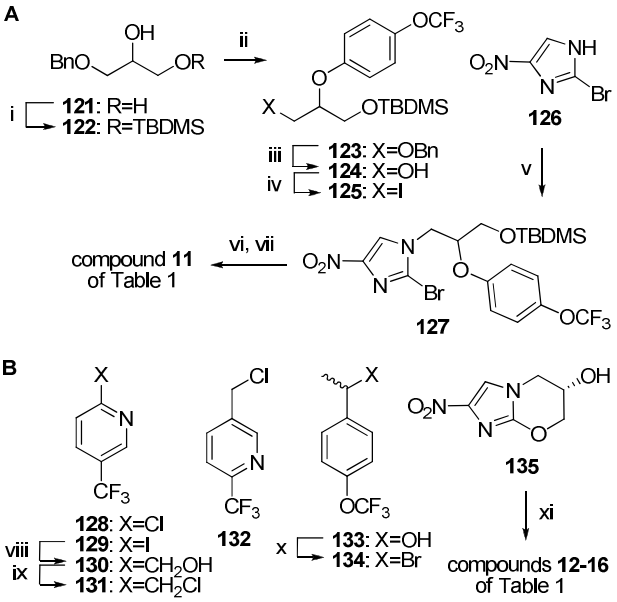
	HLM (% **135**)[a]				MLM (% **135**)[a]			
compd	0 h	0.5 h	1 h	2 h	0 h	0.5 h	1 h	2 h
6	0.10	0.20	0.36	0.56	0.06	0.80	1.04	1.50
35	0.06	0.08	0.07	0.07	0.05	0.06	0.07	0.06

[a]Percent of test compound (at 5 μM) isolated as alcohol metabolite **135** following incubation with human or mouse liver microsomes.

Figure 1. Structures of antitubercular agents

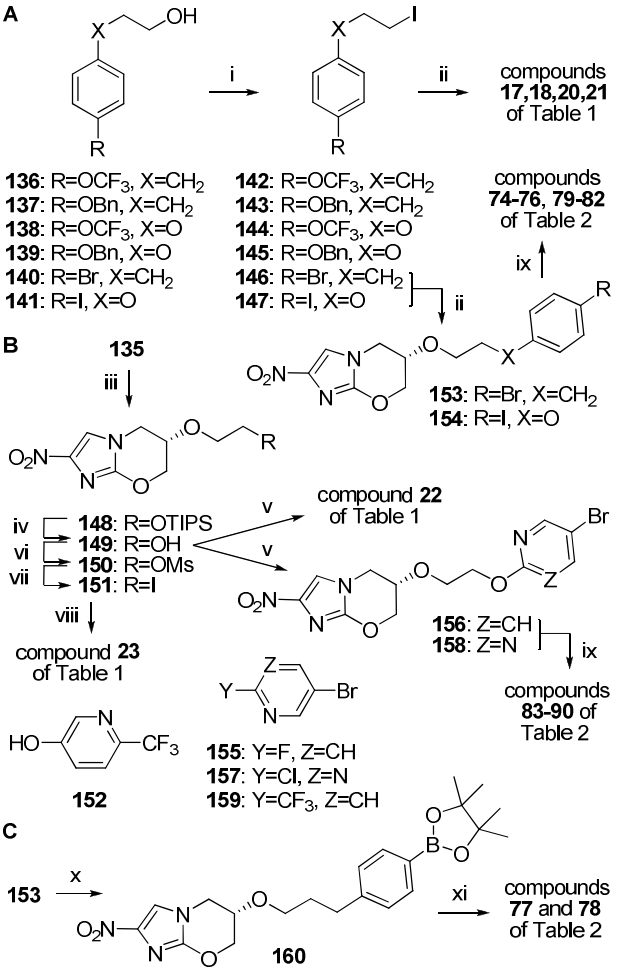


Scheme 1[a]



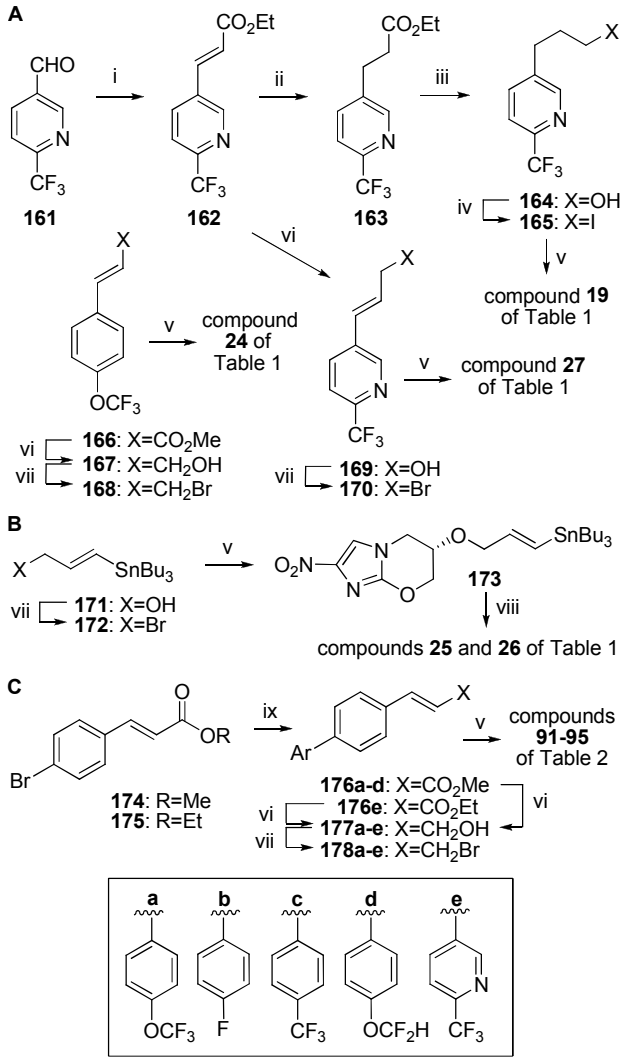
[a] Reagents and conditions: (i) TBDMSCl, imidazole, DMF, 0 °C, 3 h, then 20 °C, 16 h; (ii) 4-OCF_3PhOH, DIAD, PPh_3, benzene, 0-20 °C, 18 h; (iii) H_2, 5% Pd-C, EtOAc, EtOH, 60 psi, 20 °C, 4 h; (iv) I_2, PPh_3, imidazole, benzene, 20 °C, 1 h; (v) **125**, K_2CO_3, DMF, 87 °C, 20 h; (vi) TBAF, THF, 20 °C, 1 h; (vii) NaH, DMF, 0-20 °C, 30 min; (viii) *n*BuLi, $PhCH_3$, -78 °C, 15 min, then DMF, -78 °C, 1 h, then $NaBH_4$, MeOH, -78 to 20 °C, 30 min; (ix) TCT/DMF, CH_2Cl_2, 20 °C, 36 h, then reflux, 24 h; (x) PBr_3, 5-20 °C, 2 h; (xi) ArX or RX (**128**, **131**, **132**, **134** or 4-BnOBnCl), NaH, DMF, 0-20 °C, 0.75-18 h.

Scheme 2[a]



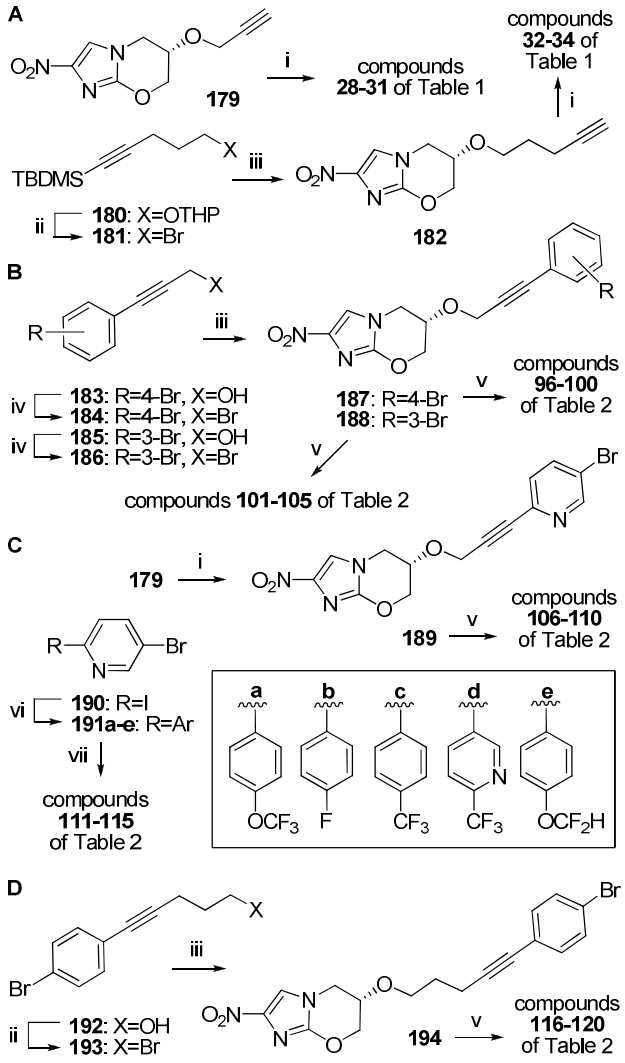
[a]Reagents and conditions: (i) I_2, PPh_2Cl or PPh_3, imidazole, toluene or CH_2Cl_2, 20 °C, 5-22 h; (ii) **135**, NaH, DMF, 0-20 °C, 2.5-5.5 h; (iii) $I(CH_2)_2OTIPS$, NaH, DMF, 0-20 °C, 6 h; (iv) 1% HCl in 95% EtOH, 20 °C, 25 h; (v) ArX (**128**, **155** or **157**), NaH, DMF, 0-20 °C, 4-4.5 h; (vi) MsCl, Et_3N, DMAP, THF, pyridine, 0-20 °C, 18 h; (vii) NaI, Me_2CO, 59 °C, 5 h; (viii) **152**, K_2CO_3, Me_2CO, 56 °C, 29 h; (ix) $ArB(OH)_2$, toluene, EtOH, 2 M Na_2CO_3, $Pd(dppf)Cl_2$ under N_2, 90 °C, 0.75-2 h; (x) bis(pinacolato)diboron, KOAc, DMF, $Pd(dppf)Cl_2$ under N_2, 90 °C, 5 h; (xi) ArX (**128** or **159**), 2 M Na_2CO_3, DMF, $Pd(dppf)Cl_2$ under N_2, 90 °C, 1-1.5 h.

Scheme 3[a]



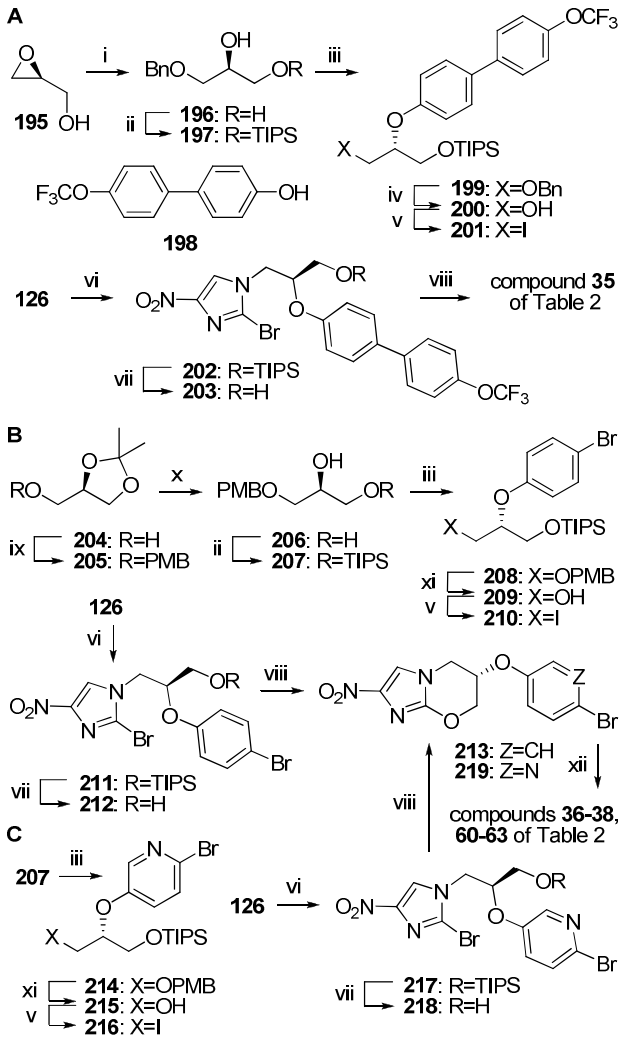
[a]Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 20 °C, 3 h; (ii) H_2, 5% Pd-C, EtOAc, 1 atm, 20 °C, 4 h; (iii) $LiAlH_4$, THF, 0-20 °C, 35 h; (iv) I_2, PPh_3, imidazole, CH_2Cl_2, 20 °C, 8 h; (v) **135**, NaH, DMF, 0-20 °C, 1-2 h, or -78 to 0 °C, 1 h; (vi) DIBAL-H, toluene, (CH_2Cl_2), -78 °C, 3-6 h, or -78 to 20 °C, 1 h; (vii) NBS, PPh_3, CH_2Cl_2, 20 °C, 2.5-4 h, or PBr_3, Et_2O, 0-20 °C, 1-3 h (for **177a-d**); (viii) 4-BnOPhI or **129**, DMF, $BnPd(PPh_3)_2Cl$ under N_2, 82 °C, 13-23 h; (ix) $ArB(OH)_2$, dioxane (or toluene, EtOH), 2 M K_2CO_3 (or Na_2CO_3), $Pd(dppf)Cl_2$ under N_2, 90-100 °C, 1-1.5 h.

Scheme 4[a]



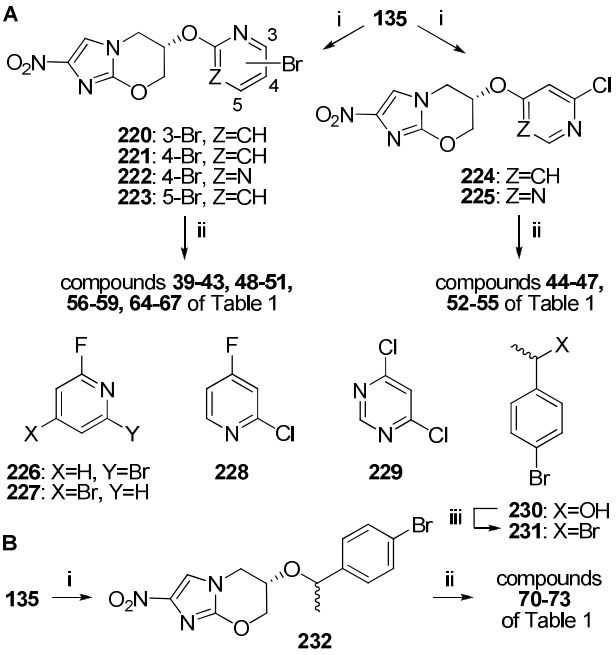
[a]Reagents and conditions: (i) ArX, CuI, Et_3N, (THF or DMF), $Pd(PPh_3)_2Cl_2$ under N_2, 50-90 °C, 10-120 min or 20 °C, 16 h (for **189**); (ii) Br_2, PPh_3, CH_2Cl_2, 0-20 °C, 16-20 h; (iii) **135**, NaH, DMF, -78 to 0 °C, 0.5-2 h (then TBAF, THF, 20 °C, 1.5 h for **182**); (iv) PBr_3, Et_2O, pyridine, 0-20 °C, 2.5 h; (v) $ArB(OH)_2$, toluene, EtOH, 2 M K_2CO_3, $Pd(dppf)Cl_2$ under N_2, reflux, 5-30 min; (vi) $ArB(OH)_2$, THF, 2 M K_2CO_3, $Pd(PPh_3)_4$ under N_2, reflux, 24 h; (vii) **179**, CuI, Et_3N, DMF, $Pd(PPh_3)_2Cl_2$ under N_2, 70 °C, 0.5 h.

Scheme 5[a]



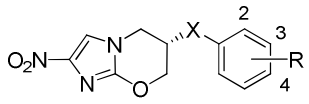
[a]Reagents and conditions: (i) BnOH, CsF, 120 °C, 16 h; (ii) TIPSCl, imidazole, DMF, 20 °C, 16 h; (iii) ArOH (**198**, 4-BrPhOH or 6-Br-3-pyridinol), DIAD, PPh_3, benzene, 0-20 °C, 17-18 h; (iv) H_2, 5% Pd-C, EtOAc, EtOH, 60 psi, 20 °C, 4 h; (v) I_2, PPh_3, imidazole, benzene, 20 °C, 1-1.5 h; (vi) RI (**201**, **210** or **216**), K_2CO_3, DMF, 81-92 °C, 16-46 h; (vii) TBAF, THF, 20 °C, 1-3 h; (viii) NaH, DMF, 0-20 °C, 0.33-2.5 h; (ix) PMBCl, KO*t*Bu, THF, 0-20 °C, 18 h; (x) 1 M HCl, MeOH, 20 °C, 1 h; (xi) DDQ, CH_2Cl_2, water, 20 °C, 1-5 h; (xii) $ArB(OH)_2$, toluene, EtOH, (DMF), 2 M Na_2CO_3, $Pd(dppf)Cl_2$ under N_2, 90 °C, 0.5-3.5 h.

Scheme 6[a]

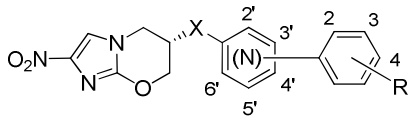


[a]Reagents and conditions: (i) ArX or RX (**155**, **157**, **226**, **227**, **228**, **229** or **231**), NaH, DMF, 0-20 °C, 0.75-3.5 h; (ii) $ArB(OH)_2$, toluene, EtOH, (DMF), 2 M Na_2CO_3, $Pd(dppf)Cl_2$ under N_2, 85-90 °C, 0.33-5 h; (iii) PBr_3, 5-20 °C, 2 h.

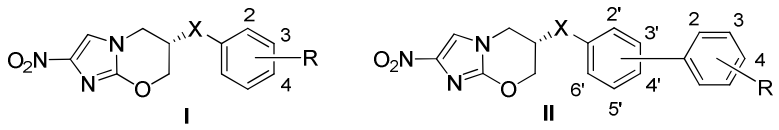
Formulae for Tables



Formula for Table 1



Formula for Table 2



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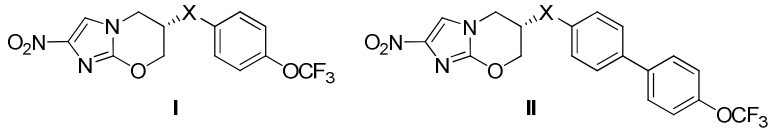

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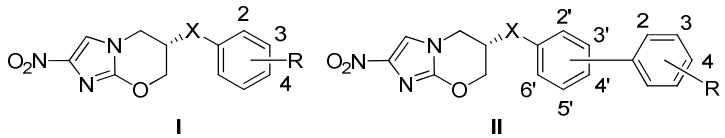

Formula for Table 5

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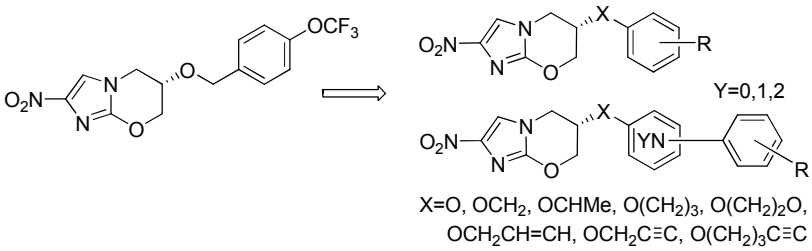

X=O, OCH_2, OCHMe, $O(CH_2)_3$, $O(CH_2)_2O$, $OCH_2CH{=}CH$, $OCH_2C{\equiv}C$, $O(CH_2)_3C{\equiv}C$