

Supporting Information

Synthesis and structure-activity studies of biphenyl analogues of the tuberculosis 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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Table S1 Mean CFU data from acute in vivo assays (pp S24-S25)

Tables S2-S5 Combustion analysis data (pp S26-S31)

Preparation of biphenyl analogues from iodobenzyl ethers and arylboronic acids (Scheme 1).

General method for Suzuki coupling. Iodides **124**, **126** or **128** (1 equiv.) and arylboronic acids (1.3 equiv.) were suspended in toluene/EtOH (5 mL/2 mL per 100 mg iodide) and then aqueous K₂CO₃ (1 mL of 2M per 100 mg iodide) was added. The resulting mixture was purged with N₂, treated with Pd(dppf)Cl₂ (5 mol%), and heated under reflux in an N₂ atmosphere for 20 min (or longer if noted). The mixture was diluted with water and extracted with EtOAc (3x). The dried (MgSO₄) organic layers were adsorbed onto silica gel and chromatographed, eluting firstly with EtOAc/hexane (1:1) and then with EtOAc to give the product. For more polar compounds, EtOAc/MeOH (95:5) or CH₂Cl₂/MeOH (95:5) was used. Trituration of the product in Et₂O gave the pure compounds.

(6S)-6-([1,1'-Biphenyl]-2-ylmethoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (7). From **124** and phenylboronic acid (81%), light brown solid: mp 153-156 °C; ¹H NMR δ 7.99 (s, 1 H), 7.45-7.36 (m, 6 H), 7.34-7.31 (m, 2 H), 7.27-7.24 (m, 1 H), 4.55-4.48 (m, 3 H), 4.41 (d, *J* = 11.8 Hz, 1 H), 4.20-4.10 (m, 3 H). Anal. (C₁₉H₁₇N₃O₄) C, H, N.

(6S)-2-Nitro-6-([2'-(trifluoromethoxy)[1,1'-biphenyl]-2-yl]methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (8). From **124** and 2-(trifluoromethoxy)phenylboronic acid (79%), yellow solid: mp 82-96 °C; ¹H NMR δ 7.95 (br d, *J* = 7.6 Hz, 1 H), 7.61-7.25 (m, 7 H), 7.24-7.07 (m, 1 H), 4.53-4.22 (m, 4 H), 4.18-3.95 (m, 3 H). Anal. (C₂₀H₁₆F₃N₃O₅) C, H, N, F.

2'-([[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-3-carbonitrile (9). From **124** and 3-cyanophenylboronic acid (55%), yellow solid: mp 107-110 °C; ¹H NMR δ 7.97 (s, 1 H), 7.85 (dt, *J* = 7.6, 1.5 Hz, 1 H), 7.82 (br t, *J* = 1.6, 1 H), 7.67 (dt, *J* = 7.9, 1.6 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.50-7.46 (m, 1 H), 7.45-7.40

(m, 2 H), 7.31-7.28 (m, 1 H), 4.56 (d, $J = 11.4$ Hz, 1 H), 4.53-4.48 (m, 2 H), 4.40 (d, $J = 11.8$ Hz, 1 H), 4.18-4.00 (m, 3 H). Anal. ($C_{20}H_{16}N_4O_4 \cdot 0.25EtOAc$) C, H, N.

(6*S*)-6-[(3'-Fluoro[1,1'-biphenyl]-2-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (10). From **124** and 3-fluorophenylboronic acid (77%), yellow solid: mp 127-129 °C; 1H NMR δ 7.98 (s, 1 H), 7.47-7.38 (m, 4 H), 7.29-7.26 (m, 1 H), 7.21-7.15 (m, 3 H), 4.56 (d, $J = 11.3$ Hz, 1 H), 4.54-4.49 (m, 2 H), 4.41 (d, $J = 11.9$ Hz, 1 H), 4.19-4.11 (m, 3 H). Anal. ($C_{19}H_{16}FN_3O_4$) C, H, N.

(6*S*)-2-Nitro-6-[[3'-(trifluoromethoxy)[1,1'-biphenyl]-2-yl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (11). From **124** and 3-(trifluoromethoxy)phenylboronic acid (65%), yellow solid: mp 81-85 °C; 1H NMR δ 7.98 (s, 1 H), 7.55 (t, $J = 8.0$ Hz, 1 H), 7.49-7.47 (m, 1 H), 7.44-7.37 (m, 4 H), 7.34 (br s, 1 H), 7.31-7.29 (m, 1 H), 4.56 (d, $J = 11.2$ Hz, 1 H), 4.54-4.48 (m, 2 H), 4.41 (d, $J = 11.9$ Hz, 1 H), 4.20-4.10 (m, 3 H). Anal. ($C_{20}H_{16}F_3N_3O_5 \cdot 0.25Et_2O$) C, H, N, F.

(6*S*)-6-[[3'-(Methylsulfanyl)[1,1'-biphenyl]-2-yl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (12). From **124** and 3-(methylsulfanyl)phenylboronic acid for 30 min (64%), yellow solid: mp 121-127 °C; 1H NMR δ 8.01 (s, 1 H), 7.47-7.44 (m, 1 H), 7.40-7.36 (m, 2 H), 7.33 (d, $J = 7.7$ Hz, 1 H), 7.29-7.26 (m, 2 H), 7.19 (t, $J = 1.7$ Hz, 1 H), 7.09 (dt, $J = 7.6, 1.3$ Hz, 1 H), 4.54 (d, $J = 11.2$ Hz, 1 H), 4.52-4.48 (m, 2 H), 4.41 (d, $J = 11.8$ Hz, 1 H), 4.22-4.08 (m, 3 H), 2.49 (s, 3 H). Anal. ($C_{20}H_{19}N_3O_4S$) C, H, N, S.

1-[2'-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)[1,1'-biphenyl]-4-yl]ethanone (13). From **124** and 4-acetylphenylboronic acid (64%), yellow solid: mp 118-121 °C; 1H NMR δ 7.99 (s, 1 H), 7.99-7.97 (m, 2 H), 7.51-7.44 (m, 3 H), 7.44-7.41 (m, 2 H), 7.31-7.29 (m, 1 H), 4.56-4.49 (m, 3 H), 4.42 (d, $J = 11.8$ Hz, 1 H), 4.19-4.12 (m, 3 H), 2.62 (s, 3 H). Anal. ($C_{21}H_{19}N_3O_5$) C, H, N.

2'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-carbonitrile (14). From **124** and 4-cyanophenylboronic acid for 30 min (69%), light yellow solid: mp 173-176 °C; ¹H NMR δ 8.00 (s, 1 H), 7.86 (dt, *J* = 8.5, 1.9 Hz, 2 H), 7.54 (dt, *J* = 8.2, 1.9 Hz, 2 H), 7.51-7.47 (m, 1 H), 7.46-7.41 (m, 2 H), 7.31-7.28 (m, 1 H), 4.54-4.47 (m, 3 H), 4.41 (d, *J* = 11.9 Hz, 1 H), 4.20-4.09 (m, 3 H). Anal. (C₂₀H₁₆N₄O₄·0.25H₂O) C, H, N.

(6*S*)-6-[(4'-Fluoro[1,1'-biphenyl]-2-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (15). From **124** and 4-fluorophenylboronic acid (80%), light brown powder: mp 156-158 °C; ¹H NMR δ 8.00 (s, 1 H), 7.47-7.44 (m, 1 H), 7.39-7.34 (m, 4 H), 7.26-7.19 (m, 3 H), 4.55-4.46 (m, 3 H), 4.42 (d, *J* = 11.8 Hz, 1 H), 4.19-4.12 (m, 3 H). Anal. (C₁₉H₁₆FN₃O₄·H₂O) C, H, N.

(6*S*)-2-Nitro-6-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-2-yl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (16). From **124** and 4-(trifluoromethoxy)phenylboronic acid (76%), beige solid: mp 147-150 °C; ¹H NMR δ 7.99 (s, 1 H), 7.49-7.45 (m, 3 H), 7.42-7.37 (m, 4 H), 7.30-7.28 (m, 1 H), 4.53-4.47 (m, 3 H), 4.42 (d, *J* = 11.8 Hz, 1 H), 4.17 (s, 3 H). Anal. (C₂₀H₁₆F₃N₃O₅) C, H, N.

(6*S*)-6-[[4'-(Methylsulfanyl)[1,1'-biphenyl]-2-yl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (17). From **124** and 4-(methylsulfanyl)phenylboronic acid (64%), yellow solid: mp 81-84 °C; ¹H NMR δ 8.01 (s, 1 H), 7.47-7.44 (m, 1 H), 7.40-7.33 (m, 2 H), 7.28-7.24 (m, 5 H), 4.57-4.47 (m, 3 H), 4.44 (d, *J* = 11.9 Hz, 1 H), 4.18 (s, 3 H), 2.51 (s, 3 H). Anal. (C₂₀H₁₉N₃O₄S) C, H, N: calcd, 10.57; found, 10.06. HPLC purity: 95.7%.

(6*S*)-6-[(3'-Fluoro-4'-methoxy[1,1'-biphenyl]-2-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (18). From **124** and 3-fluoro-4-methoxyphenylboronic acid (81%), yellow solid: mp 83-87 °C; ¹H NMR δ 8.00 (s, 1 H), 7.46-7.43 (m, 1 H), 7.37-7.34 (m, 2 H), 7.26-7.19 (m, 2 H), 7.18 (t, *J* = 8.6 Hz, 1 H), 7.09 (br dd, *J* = 8.5, 2.0 Hz, 1 H),

4.56-4.53 (m, 3 H), 4.43 (d, $J = 11.8$ Hz, 1 H), 4.18 (s, 3 H), 3.88 (s, 3 H). Anal. ($C_{20}H_{18}FN_3O_5 \cdot 0.25H_2O$) C, H, N, F.

(6S)-6-{[2-(2-Naphthyl)benzyl]oxy}-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (19). From **124** and naphthalen-2-ylboronic acid (69%), yellow solid: mp 108-110 °C; 1H NMR δ 7.94 (s, 1 H), 7.96-7.91 (m, 3 H), 7.88 (m, 1 H), 7.56-7.53 (m, 2 H), 7.51-7.48 (m, 2 H), 7.43-7.38 (m, 3 H), 4.60 (d, $J = 11.1$ Hz, 1 H), 4.58-4.51 (m, 2 H), 4.40 (d, $J = 11.8$ Hz, 1 H), 4.15 (s, 3 H). Anal. ($C_{23}H_{19}N_3O_4 \cdot 0.25H_2O$) C, H, N.

(6S)-6-([1,1'-Biphenyl]-3-ylmethoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (20). From **126** and phenylboronic acid (78%), white solid: mp 118-120 °C; 1H NMR δ 8.02 (s, 1 H), 7.64-7.59 (m, 4 H), 7.58-7.56 (m, 3 H), 7.48-7.30 (m, 2 H), 4.74 (d, $J = 12.1$ Hz, 1 H), 4.70-4.66 (m, 2 H), 4.49 (d, $J = 11.8$ Hz, 1 H), 4.29-4.24 (m, 3 H). Anal. ($C_{19}H_{17}N_3O_4 \cdot 0.25H_2O$) C, H, N.

(6S)-2-Nitro-6-{[2'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (21). From **126** and 2-(trifluoromethoxy)phenylboronic acid (75%), yellow solid: mp 100-102 °C; 1H NMR δ 8.03 (s, 1 H), 7.53-7.44 (m, 5 H), 7.44-7.35 (m, 3 H), 4.73 (d, $J = 12.2$ Hz, 1 H), 4.71-4.65 (m, 2 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.20 (m, 3 H); HRFABMS calcd for $C_{20}H_{17}F_3N_3O_5$ m/z $[M + H]^+$ 436.1120, found 436.1129. HPLC purity: 99.8%.

(6S)-2-Nitro-6-{[3'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]methoxy}-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (22). From **126** and 3-(trifluoromethyl)phenylboronic acid (95%), yellow oil; 1H NMR δ 8.01 (s, 1 H), 7.95 (br d, $J = 10.1$ Hz, 2 H), 7.75-7.66 (m, 4 H), 7.49 (br t, $J = 7.7$ Hz, 1 H), 7.39 (d, $J = 7.7$ Hz, 1 H), 4.76 (d, $J = 12.1$ Hz, 1 H), 4.73-4.66 (m, 2 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.21 (m, 3 H); HRFABMS calcd for $C_{20}H_{17}F_3N_3O_4$ m/z $[M + H]^+$ 420.1171, found 420.1174. HPLC purity: 98.6%.

3'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl)[1,1'-biphenyl]-3-carbonitrile (23). From **126** and 3-cyanophenylboronic acid (99%), yellow solid: mp 93-96 °C; ¹H NMR δ 8.14 (t, *J* = 1.6 Hz, 1 H), 8.01 (s, 1 H), 7.99 (ddd, *J* = 8.0, 1.9, 1.2 Hz, 1 H), 7.83 (dt, *J* = 7.9, 1.3 Hz, 1 H), 7.69-7.64 (m, 3 H), 7.49 (br t, *J* = 7.7 Hz, 1 H), 7.39 (br d, *J* = 7.7 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.72-4.66 (m, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. (C₂₀H₁₆N₄O₄·0.75H₂O) C, H, N.

(6*S*)-6-[(3'-Fluoro[1,1'-biphenyl]-3-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (24). From **126** and 3-fluorophenylboronic acid (94%), brown solid: mp 82-84 °C; ¹H NMR δ 8.01 (s, 1 H), 7.63 (d, *J* = 8.6 Hz, 2 H), 7.50-7.43 (m, 4 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.22-7.17 (m, 1 H), 4.74 (d, *J* = 12.1 Hz, 1 H), 4.71-4.66 (m, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. (C₁₉H₁₆FN₃O₄·0.25H₂O) C, H, N.

(6*S*)-2-Nitro-6-[(3'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (26). From **126** and 3-(trifluoromethoxy)phenylboronic acid (85%), cream solid: mp (Et₂O/pentane) 66-69 °C; ¹H NMR δ 8.01 (s, 1 H), 7.70-7.57 (m, 5 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 4.75 (d, *J* = 12.2 Hz, 1 H), 4.72-4.66 (m, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.21 (m, 3 H). Anal. (C₂₀H₁₆F₃N₃O₅) C, H, N.

(6*S*)-6-[(3'-(Methylsulfanyl)[1,1'-biphenyl]-3-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (29). From **126** and 3-(methylsulfanyl)phenylboronic acid (79%), yellow solid: mp 59-62 °C; ¹H NMR δ 8.04 (s, 1 H), 7.60 (br d, *J* = 7.4 Hz, 2 H), 7.46-7.37 (m, 4 H), 7.33 (d, *J* = 7.6 Hz, 1 H), 7.28-7.25 (m, 1 H), 4.74 (d, *J* = 12.1 Hz, 1 H), 4.70-4.65 (m, 2 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 4.27-4.22 (m, 3 H), 2.53 (s, 3 H). Anal. (C₂₀H₁₉N₃O₄S) C, H, N, S.

1-[3'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl)[1,1'-biphenyl]-4-yl]ethanone (30). From **126** and 4-acetylphenylboronic acid (84%), light yellow solid: mp 149-151 °C; ¹H NMR δ 8.04-8.02 (m, 2 H), 8.02 (s, 1 H), 7.79 (dt, *J* = 8.6, 1.8 Hz,

2 H), 7.68-7.64 (m, 2 H), 7.48 (t, $J = 7.6$ Hz, 1 H), 7.34 (br d, $J = 7.6$ Hz, 1 H), 4.76 (d, $J = 12.2$ Hz, 1 H), 4.73-4.66 (m, 2 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.32-4.22 (m, 3 H), 2.61 (s, 3 H). Anal. ($C_{21}H_{19}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6S)-2-Nitro-6-([4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (31). From **126** and 4-(trifluoromethyl)phenylboronic acid (79%), white solid: mp 140-141 °C; 1H NMR δ 8.01 (s, 1 H), 7.86 (d, $J = 8.3$ Hz, 2 H), 7.80 (d, $J = 8.4$ Hz, 2 H), 7.65 (br t, $J = 7.6$ Hz, 2 H), 7.50 (t, $J = 7.6$ Hz, 1 H), 7.39 (d, $J = 7.6$ Hz, 1 H), 4.76 (d, $J = 12.2$ Hz, 1 H), 4.73-4.66 (m, 2 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.32-4.22 (m, 3 H). Anal. ($C_{20}H_{16}F_3N_3O_4$) C, H, N.

3'-([[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-carbonitrile (32). From **126** and 4-cyanophenylboronic acid for 30 min (83%), light yellow solid: mp 150-154 °C; 1H NMR δ 8.01 (s, 1 H), 7.92 (dt, $J = 8.6, 2.0$ Hz, 2 H), 7.85 (dt, $J = 8.6, 2.1$ Hz, 2 H), 7.69-7.65 (m, 2 H), 7.50 (t, $J = 7.6$ Hz, 1 H), 7.40 (br d, $J = 7.7$ Hz, 1 H), 4.75 (d, $J = 12.2$ Hz, 1 H), 4.73-4.65 (m, 2 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($C_{20}H_{16}N_4O_4$) C, H, N.

(6S)-6-[(4'-Fluoro[1,1'-biphenyl]-3-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (33). From **126** and 4-fluorophenylboronic acid (86%), beige powder: mp 140-141 °C; 1H NMR δ 8.02 (s, 1 H), 7.67 (dd, $J = 8.7, 5.5$ Hz, 2 H), 7.58-7.54 (m, 2 H), 7.44 (t, $J = 7.6$ Hz, 1 H), 7.32-7.25 (m, 3 H), 4.72-4.66 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.28-4.22 (m, 3 H). Anal. ($C_{19}H_{16}FN_3O_4 \cdot 0.75H_2O$) C, H, N, F.

3'-([[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-ol (34). From **126** and 4-hydroxyphenylboronic acid (80%), tan solid: mp 239-242 °C; 1H NMR δ 9.51 (s, 1 H), 8.02 (s, 1 H), 7.51-7.46 (m, 2 H), 7.44 (d, $J = 8.7$ Hz, 2 H), 7.37 (t, $J = 7.6$ Hz, 1 H), 7.21 (d, $J = 7.6$ Hz, 1 H), 6.83 (d, $J = 8.7$ Hz, 2 H), 4.73-4.63 (m, 3 H), 4.47 (d, $J = 11.9$ Hz, 1 H), 4.32-4.20 (m, 3 H). Anal. ($C_{19}H_{17}N_3O_5 \cdot 0.25EtOAc$) C, H, N.

(6*S*)-2-Nitro-6-([4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (35). From **126** and 4-(trifluoromethoxy)phenylboronic acid for 15 min (76%), white powder: mp 118-120 °C; ¹H NMR δ 8.02 (s, 1 H), 7.75 (br d, *J* = 8.8 Hz, 2 H), 7.61-7.57 (m, 2 H), 7.48-7.42 (m, 3 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 4.75 (d, *J* = 12.2 Hz, 1 H), 4.72-4.66 (m, 2 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.28-4.24 (m, 3 H). Anal. (C₂₀H₁₆F₃N₃O₅·H₂O) C, H, N.

(6*S*)-6-([4'-(Methylsulfanyl)[1,1'-biphenyl]-3-yl]methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (39). From **126** and 4-(methylsulfanyl)phenylboronic acid for 30 min (85%), light yellow powder: mp 159-161 °C; ¹H NMR δ 8.02 (s, 1 H), 7.60-7.54 (m, 4 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 6.09 (dt, *J* = 8.5, 2.3 Hz, 2 H), 7.29 (br d, *J* = 7.7 Hz, 1 H), 4.73 (d, *J* = 12.1 Hz, 1 H), 4.70-4.65 (m, 2 H), 4.49 (d, *J* = 11.8 Hz, 1 H), 4.32-4.24 (m, 3 H), 2.51 (s, 3 H). Anal. (C₂₀H₁₉N₃O₄S·0.25H₂O) C, H, N, S.

(6*S*)-6-[(3'-Fluoro-4'-methoxy[1,1'-biphenyl]-3-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (40). From **126** and 3-fluoro-4-methoxyphenylboronic acid (67%), beige powder: mp 150-152 °C; ¹H NMR δ 8.01 (s, 1 H), 7.59-7.52 (m, 2 H), 7.50 (d, *J* = 2.2 Hz, 1 H), 7.44-7.41 (m, 2 H), 7.29 (br d, *J* = 7.6 Hz, 1 H), 7.23 (t, *J* = 8.8 Hz, 1 H), 4.72 (d, *J* = 12.1 Hz, 1 H), 4.70-4.65 (m, 2 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.31-4.24 (m, 3 H), 3.88 (s, 3 H). Anal. (C₂₀H₁₈FN₃O₅·H₂O) C, H, N.

(6*S*)-6-([3-(2-Naphthyl)benzyl]oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (41). From **126** and naphthalen-2-ylboronic acid for 15 min (64%), white powder: mp 129-131 °C; ¹H NMR δ 8.19 (d, *J* = 1.4 Hz, 1 H), 8.03 (s, 1 H), 8.01-7.81 (m, 3 H), 7.82 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.79-7.74 (m, 2 H), 7.55-7.47 (m, 3 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 4.78 (d, *J* = 12.1 Hz, 1 H), 4.73-4.68 (m, 2 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.30-4.26 (m, 3 H). Anal. (C₂₃H₁₉N₃O₄·0.5H₂O) C, H, N.

(6S)-6-([1,1'-Biphenyl]-4-ylmethoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (42). From **128** and phenylboronic acid (68%), white solid: mp 202-204 °C; ¹H NMR δ 8.03 (s, 1 H), 7.66-7.62 (m, 4 H), 7.46 (br t, *J* = 7.3 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.36 (tt, *J* = 7.4, 1.2 Hz, 1 H), 4.73-4.65 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.23 (m, 3 H). Anal. (C₁₉H₁₇N₃O₄·0.25H₂O) C, H, N.

(6S)-2-Nitro-6-([2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (43). From **128** and 2-(trifluoromethyl)phenylboronic acid, oil; ¹H NMR δ 8.03 (s, 1 H), 7.82 (d, *J* = 7.7 Hz, 1 H), 7.71 (br t, *J* = 7.1 Hz, 1 H), 7.61 (br t, *J* = 7.7 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 3 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 4.74 (d, *J* = 12.1 Hz, 1 H), 4.72-4.69 (m, 2 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.34-4.24 (m, 3 H); HRFABMS calcd for C₂₀H₁₇F₃N₃O₄ *m/z* [M + H]⁺ 420.1171, found 420.1175. HPLC purity: 98.6%.

4'-([[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-2-carbaldehyde (44). From **128** and 2-formylphenylboronic acid for 15 min (77%), beige powder: mp 138-140 °C; ¹H NMR δ 9.88 (s, 1 H), 8.03 (s, 1 H), 7.92 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.75 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.58 (br t, *J* = 7.6 Hz, 1 H), 7.51-7.41 (m, 5 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.74 (m, 2 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.30-4.26 (m, 3 H). Anal. (C₂₀H₁₇N₃O₅·0.25H₂O) C, H, N.

(6S)-6-([2'-Fluoro[1,1'-biphenyl]-4-yl]methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (45). From **128** and 2-fluorophenylboronic acid (74%), yellow solid: mp 110-112 °C; ¹H NMR δ 8.03 (s, 1 H), 7.54-7.49 (m, 3 H), 7.43-7.39 (m, 3 H), 7.32-7.27 (m, 2 H), 4.72 (d, *J* = 12.2 Hz, 1 H), 4.70-4.67 (m, 2 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.32-4.22 (m, 3 H). Anal. (C₁₉H₁₆FN₃O₄·0.25H₂O) C, H, N, F.

(6S)-6-([2'-Chloro[1,1'-biphenyl]-4-yl]methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (46). From **128** and 2-chlorophenylboronic acid, oil; ¹H NMR δ 8.03 (s, 1 H), 7.57-7.54 (m, 1 H), 7.43-7.37 (m, 7 H), 4.73 (d, *J* = 12.0 Hz, 1 H), 4.71-4.67 (m, 2 H), 4.50

(d, $J = 11.8$ Hz, 1 H), 4.33-4.23 (m, 3 H); HRFABMS calcd for $C_{19}H_{17}^{35}ClN_3O_4$ m/z $[M + H]^+$ 386.0908, found 396.0901; calcd for $C_{19}H_{17}^{37}ClN_3O_4$ m/z $[M + H]^+$ 388.0878, found 388.0883. HPLC purity: 95.8%.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-2-ol (47). From **128** and 2-hydroxyphenylboronic acid (81%), beige solid: mp 93-95 °C; 1H NMR δ 9.51 (s, 1 H), 8.05 (s, 1 H), 7.51 (d, $J = 8.2$ Hz, 2 H), 7.33 (d, $J = 8.2$ Hz, 2 H), 7.22 (dd, $J = 7.5, 1.7$ Hz, 1 H), 7.14 (ddd, $J = 8.4, 7.4, 1.7$ Hz, 1 H), 6.92 (dd, $J = 8.1, 1.0$ Hz, 1 H), 6.85 (td, $J = 7.5, 1.2$ Hz, 1 H), 4.72-4.61 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($C_{19}H_{17}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6*S*)-6-[(2'-Methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (48). From **128** and 2-methoxyphenylboronic acid, brown solid: mp 148-150 °C; 1H NMR δ 8.03 (s, 1 H), 7.44 (br d, $J = 8.2$ Hz, 2 H), 7.36-7.31 (m, 3 H), 7.26 (dd, $J = 7.5, 1.7$ Hz, 1 H), 7.10 (br d, $J = 7.7$ Hz, 1 H), 7.02 (dt, $J = 7.4, 1.0$ Hz, 1 H), 4.71-4.64 (m, 3 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.32-4.22 (m, 3 H), 3.75 (s, 3 H). Anal. ($C_{20}H_{19}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6*S*)-6-[(2'-Ethoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (49). From **128** and 2-ethoxyphenylboronic acid, beige foam; 1H NMR δ 8.03 (s, 1 H), 7.48 (br d, $J = 8.2$ Hz, 2 H), 7.35-7.26 (m, 4 H), 7.08 (br d, $J = 7.6$ Hz, 1 H), 7.00 (dt, $J = 7.5, 1.0$ Hz, 1 H), 4.71-4.64 (m, 3 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.32-4.23 (m, 3 H), 4.03 (q, $J = 7.0$ Hz, 2 H), 1.25 (t, $J = 7.0$ Hz, 3 H); HRFABMS calcd for $C_{21}H_{22}N_3O_5$ m/z $[M + H]^+$ 396.1560, found 396.1553. HPLC purity: 99.5%.

(6*S*)-2-Nitro-6-[[2'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (51). From **128** and 2-(trifluoromethoxy)phenylboronic acid, brown solid: mp 77-80 °C; 1H NMR δ 8.22 (s, 1 H), 7.54-7.40 (m, 8 H), 4.74 (d, $J = 12.1$ Hz,

1 H), 4.71-4.68 (m, 2 H), 4.50 (d, $J = 11.9$ Hz, 1 H), 4.33-4.23 (m, 3 H); HRFABMS calcd for $C_{20}H_{17}F_3N_3O_5$ m/z $[M + H]^+$ 436.1120, found 436.1122. HPLC purity: 98.9%.

(6S)-2-Nitro-6-[(2'-phenoxy[1,1'-biphenyl]-4-yl)methoxy]-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (52). From **128** and 2-phenoxyphenylboronic acid (83%), yellow powder: mp 132-134 °C; 1H NMR δ 8.03 (s, 1 H), 7.51-7.33 (m, 3 H), 7.32-7.27 (m, 6 H), 7.04-6.98 (m, 2 H), 6.89-6.87 (m, 2 H), 4.67-4.63 (m, 3 H), 4.46 (d, $J = 11.9$ Hz, 1 H), 4.25-4.20 (m, 3 H). Anal. ($C_{25}H_{21}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6S)-6-[(2'-(Methylsulfanyl)[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (53). From **128** and 2-(methylsulfanyl)phenylboronic acid, light brown solid: mp 161-163 °C; 1H NMR δ 8.03 (s, 1 H), 7.38-7.32 (m, 6 H), 7.23-7.15 (m, 2 H), 4.74-4.66 (m, 3 H), 4.50 (d, $J = 11.9$ Hz, 1 H), 4.33-4.23 (m, 3 H), 2.35 (s, 3 H). Anal. ($C_{20}H_{19}N_3O_4S$) C, H, N.

(6S)-6-[(3'-Isopropyl[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (54). From **128** and 3-isopropylphenylboronic acid, pink solid: mp 120-122 °C; 1H NMR δ 8.03 (s, 1 H), 7.63 (br d, $J = 8.2$ Hz, 2 H), 7.49 (br s, 1 H), 7.45-7.35 (m, 4 H), 7.24 (br d, $J = 7.6$ Hz, 1 H), 4.73-4.65 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H), 2.96 (sept, $J = 6.9$ Hz, 1 H), 1.25 (d, $J = 6.9$ Hz, 6 H). Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

(6S)-2-Nitro-6-([1,1':3',1''-terphenyl]-4-ylmethoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (55). From **128** and 3-biphenylboronic acid for 15 min (79%), yellow solid: mp 160-162 °C; 1H NMR δ 8.03 (s, 1 H), 7.88 (t, $J = 1.7$ Hz, 1 H), 7.76-7.73 (m, 4 H), 7.66-7.63 (m, 2 H), 7.57-7.37 (m, 6 H), 4.73 (d, $J = 12.0$ Hz, 1 H), 4.70-4.67 (m, 2 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.29-4.23 (m, 3 H). Anal. ($C_{25}H_{21}N_3O_4 \cdot 0.5EtOAc$) C, H, N.

(6S)-2-Nitro-6-[(3'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methoxy]-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (56). From **128** and 3-(trifluoromethyl)phenylboronic acid, pink

solid: mp 148-150 °C; ^1H NMR δ 8.03 (s, 1 H), 7.99-7.94 (m, 2 H), 7.74-7.68 (m, 4 H), 7.44 (d, J = 8.3 Hz, 2 H), 4.73 (d, J = 12.1 Hz, 1 H), 4.71-4.67 (m, 2 H), 4.49 (d, J = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_4$) C, H, N.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-3-carbaldehyde (57). From **128** and 3-formylphenylboronic acid for 15 min (71%), yellow powder: mp 169-171 °C; ^1H NMR δ 10.09 (s, 1 H), 8.19 (t, J = 1.6 Hz, 1 H), 8.03 (s, 1 H), 8.01 (ddd, J = 7.7, 1.8, 1.2 Hz, 1 H), 7.90 (dt, J = 7.6, 1.3 Hz, 1 H), 7.75-7.71 (m, 3 H), 7.45 (d, J = 8.3 Hz, 2 H), 4.74 (d, J = 12.1 Hz, 1 H), 4.72-4.65 (m, 2 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.35-4.19 (m, 3 H). Anal. ($\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_5 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-3-carbonitrile (58). From **128** and 3-cyanophenylboronic acid (74%), light yellow powder: mp 182-184 °C; ^1H NMR δ 8.14 (t, J = 1.6 Hz, 1 H), 8.03 (s, 1 H), 8.03-7.99 (m, 1 H), 7.82 (dt, J = 7.8, 1.3 Hz, 1 H), 7.74 (br d, J = 8.3 Hz, 2 H), 7.66 (t, J = 7.8 Hz, 1 H), 7.44 (d, J = 8.3 Hz, 2 H), 4.73 (d, J = 12.2 Hz, 1 H), 4.70-4.67 (m, 2 H), 4.49 (d, J = 11.6 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_4 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-3-carboxamide (59). From **128** and 3-aminocarbonylphenylboronic acid (94%), cream solid: mp 186 °C (dec); ^1H NMR δ 8.14 (s, 1 H), 8.06-8.03 (m, 1 H), 8.03 (s, 1 H), 7.85 (d, J = 7.6 Hz, 1 H), 7.81 (d, J = 7.8 Hz, 1 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.53 (t, J = 7.7 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.39 (s, 1 H), 4.71-4.67 (m, 3 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.27-4.25 (m, 3 H); HRFABMS calcd for $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_5$ m/z $[\text{M} + \text{H}]^+$ 395.1355, found 395.1357. HPLC purity: 100%.

(6*S*)-6-[(3'-Fluoro[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (60). From **128** and 3-fluorophenylboronic acid, brown solid: mp 189-191 °C; ^1H NMR δ 7.94 (s, 1 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.49-7.37 (m, 3 H), 7.38 (d, J = 8.3 Hz, 2

H), 7.18-7.11 (m, 1 H), 4.68-4.61 (m, 3 H), 4.42 (d, $J = 12.0$ Hz, 1 H), 4.29-4.17 (m, 3 H).

Anal. ($C_{19}H_{16}FN_3O_4 \cdot 0.25H_2O$) C, H, N.

(6S)-6-[(3'-Chloro[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (61). From **128** and 3-chlorophenylboronic acid, cream solid: mp 192-194 °C; 1H NMR δ 8.03 (s, 1 H), 7.71 (t, $J = 1.9$ Hz, 1 H), 7.68 (dt, $J = 8.3, 1.9$ Hz, 2 H), 7.63 (dt, $J = 7.8, 1.4$ Hz, 1 H), 7.48 (t, $J = 7.9$ Hz, 1 H), 7.43-7.40 (m, 3 H), 4.72 (d, $J = 12.1$ Hz, 1 H), 4.70-4.66 (m, 2 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.31-4.21 (m, 3 H). Anal. ($C_{19}H_{16}ClN_3O_4$) C, H, N.

4'-{[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl}[1,1'-biphenyl]-3-ol (62). From **128** and 3-hydroxyphenylboronic acid (77%), tan powder: mp 169-171 °C; 1H NMR δ 9.48 (s, 1 H), 8.02 (s, 1 H), 7.56 (br d, $J = 8.3$ Hz, 2 H), 7.38 (br d, $J = 8.3$ Hz, 2 H), 7.23 (t, $J = 7.9$ Hz, 1 H), 7.04 (ddd, $J = 7.7, 1.6, 1.0$ Hz, 1 H), 7.00 (t, $J = 2.1$ Hz, 1 H), 6.75 (ddd, $J = 8.1, 2.4, 0.9$ Hz, 1 H), 4.72-4.62 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.32-4.22 (m, 3 H). Anal. ($C_{19}H_{17}N_3O_5$) C, H, N.

(6S)-6-[(3'-Methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (63). From **128** and 3-methoxyphenylboronic acid, light brown solid: mp 152-154 °C; 1H NMR δ 8.03 (s, 1 H), 7.64 (br d, $J = 8.3$ Hz, 2 H), 7.40 (d, $J = 8.3$ Hz, 2 H), 7.34 (t, $J = 8.0$ Hz, 1 H), 7.22 (ddd, $J = 7.7, 1.5, 1.0$ Hz, 1 H), 7.17 (t, $J = 2.1$ Hz, 1 H), 6.93 (ddd, $J = 8.2, 2.5, 0.8$ Hz, 1 H), 4.72-4.65 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H), 3.82 (s, 3 H). Anal. ($C_{20}H_{19}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6S)-2-Nitro-6-{[3'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (67). From **128** and 3-(trifluoromethoxy)phenylboronic acid, pink solid: mp 110-112 °C; 1H NMR δ 8.03 (s, 1 H), 7.72-7.68 (m, 3 H), 7.61-7.57 (m, 2 H), 7.43 (d, $J = 8.3$ Hz, 2 H), 7.37-7.34 (m, 1 H), 4.73 (d, $J = 12.2$ Hz, 1 H), 4.70-4.67 (m, 2 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($C_{20}H_{16}F_3N_3O_5$) C, H, N.

(6S)-6-[[3'-(Benzyloxy)[1,1'-biphenyl]-4-yl]methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (68). From **128** and 3-(benzyloxy)phenylboronic acid, tan solid: mp 131-133 °C; ¹H NMR δ 8.03 (s, 1 H), 7.64 (d, *J* = 8.2 Hz, 2 H), 7.48 (br d, *J* = 7.1 Hz, 2 H), 7.42-7.31 (m, 6 H), 7.27 (t, *J* = 2.0 Hz, 1 H), 7.23 (br d, *J* = 7.7 Hz, 1 H), 7.01 (dd, *J* = 8.1, 1.9 Hz, 1 H), 5.18 (s, 2 H), 4.73-4.65 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.21 (m, 3 H). Anal. (C₂₆H₂₃N₃O₅) C, H, N.

(6S)-6-[[3'-(Methylsulfanyl)[1,1'-biphenyl]-4-yl]methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (69). From **128** and 3-(methylsulfanyl)phenylboronic acid, light brown solid: mp 120-121 °C; ¹H NMR δ 8.03 (s, 1 H), 7.65 (br d, *J* = 8.3 Hz, 2 H), 7.48-7.47 (m, 1 H), 7.42-7.37 (m, 4 H), 7.26 (dt, *J* = 6.5, 2.2 Hz, 1 H), 4.72 (d, *J* = 12.1 Hz, 1 H), 4.69-4.65 (m, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H), 2.53 (s, 3 H). Anal. (C₂₀H₁₉N₃O₄S·0.5H₂O) C, H, N.

4'-{[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl[1,1'-biphenyl]-3-amine (70). From **128** and 3-aminophenylboronic acid (34%), yellow powder: mp 223-226 °C; ¹H NMR δ 8.03 (s, 1 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 6.82 (br s, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 6.55 (dd, *J* = 7.9, 1.4 Hz, 1 H), 5.11 (s, 2 H), 4.71-4.63 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.27-4.22 (m, 3 H). Anal. (C₁₉H₁₈N₄O₄·H₂O) C, H, N: calcd, 14.58; found, 13.99. HPLC purity: 97.9%.

(6S)-2-Nitro-6-[(3'-nitro[1,1'-biphenyl]-4-yl)methoxy]-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (71). From **128** and 3-nitrophenylboronic acid (72%), light brown powder: mp 179-181 °C; ¹H NMR δ 8.43 (t, *J* = 2.0 Hz, 1 H), 8.22 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1 H), 8.14 (ddd, *J* = 8.1, 1.7, 1.0 Hz, 1 H), 8.03 (s, 1 H), 7.79-7.74 (m, 3 H), 7.47 (d, *J* = 8.3 Hz, 2 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.72-4.67 (m, 2 H), 4.49 (d, *J* = 11.7 Hz, 1 H), 4.32-4.22 (m, 3 H); HRFABMS calcd for C₁₉H₁₇N₄O₆ *m/z* [M + H]⁺ 397.1148, found 397.1150. HPLC purity: 98.8%.

(6S)-6-[(4'-Isopropyl[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (72). From **128** and 4-isopropylphenylboronic acid, light brown solid: mp 241 °C; ¹H NMR δ 8.03 (s, 1 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 7.56 (br d, *J* = 8.3 Hz, 2 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 4.72- 4.64 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H), 2.92 (sept, *J* = 6.9 Hz, 1 H), 1.23 (d, *J* = 6.9 Hz, 6 H). Anal. (C₂₂H₂₃N₃O₄·0.25H₂O) C, H, N.

(6S)-6-[(4'-*tert*-Butyl[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (73). From **128** and 4-*tert*-butylphenylboronic acid (59%), pink solid: mp 254 °C; ¹H NMR δ 8.03 (s, 1 H), 7.62 (d, *J* = 8.2 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 4.72-4.64 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H), 1.31 (s, 9 H). Anal. (C₂₃H₂₅N₃O₄) C, H, N.

(6S)-2-Nitro-6-([1,1':4',1''-terphenyl]-4-ylmethoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (74). From **128** and 4-biphenylboronic acid (54%), light yellow solid: mp 270-273 °C; ¹H NMR δ 8.03 (s, 1 H), 7.76 (s, 4 H), 7.73-7.69 (m, 4 H), 7.49 (br t, *J* = 7.4 Hz, 2 H), 6.43 (d, *J* = 8.2 Hz, 2 H), 7.38 (br t, *J* = 7.4 Hz, 1 H), 4.71-4.67 (m, 3 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.29-4.26 (m, 3 H); HRFABMS calcd for C₂₅H₂₂N₃O₄ *m/z* [M + H]⁺ 428.1610, found 428.1609. HPLC purity: 99.0%.

(6S)-2-Nitro-6-[[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methoxy]-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (75). From **128** and 4-(trifluoromethyl)phenylboronic acid, light yellow-brown solid: mp 151-153 °C; ¹H NMR δ 8.03 (s, 1 H), 7.89 (d, *J* = 8.2 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 2 H), 7.45 (d, *J* = 8.3 Hz, 2 H), 4.74 (d, *J* = 12.2 Hz, 1 H), 4.71 (m, 2 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.32-4.23 (m, 3 H). Anal. (C₂₀H₁₆F₃N₃O₄) C, H, N.

[4'-({[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)[1,1'-biphenyl]-4-yl]methanol (76). From **128** and 4-(hydroxymethyl)phenylboronic acid, pale

pink solid: mp 201 °C; ¹H NMR δ 8.03 (s, 1 H), 7.64 (d, *J* = 8.3 Hz, 2 H), 7.61 (d, *J* = 8.3 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 4 H), 5.17 (t, *J* = 5.8 Hz, 1 H), 4.72-4.64 (m, 3 H), 4.53 (d, *J* = 5.7 Hz, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. (C₂₀H₁₉N₃O₅·0.25EtOAc) C, H, N.

(6*S*)-6-([4'-(*tert*-Butoxymethyl)[1,1'-biphenyl]-4-yl]methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (77). From **128** and 4-(*tert*-butoxymethyl)phenylboronic acid for 15 min (68%), light-yellow powder: mp 232-235 °C; ¹H NMR δ 8.03 (s, 1 H), 7.64-7.59 (m, 4 H), 7.41-7.37 (m, 4 H), 4.70-4.65 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.44 (s, 2 H), 4.28-4.25 (m, 3 H), 1.24 (s, 9 H). Anal. (C₂₄H₂₇N₃O₅·H₂O) C, H, N.

***N*-{[4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-yl]methyl}aniline (78).** From **128** and 4-[(phenylamino)methyl]phenylboronic acid (45%), white solid: mp 200-202 °C; ¹H NMR δ 8.03 (s, 1 H), 7.61 (t, *J* = 8.6 Hz, 4 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 7.04 (br t, *J* = 8.4 Hz, 2 H), 6.58 (d, *J* = 7.7 Hz, 2 H), 6.50 (t, *J* = 7.3 Hz, 1 H), 6.22 (t, *J* = 6.1 Hz, 1 H), 4.72-4.64 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.30-4.21 (m, 3 H), 4.29 (d, *J* = 6.1 Hz, 2 H). Anal. (C₂₆H₂₄N₄O₄) C, H, N.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-carbaldehyde (79). From **128** and 4-formylphenylboronic acid for 15 min (49%), yellow powder: mp (CH₂Cl₂/hexane) 194-197 °C; ¹H NMR δ 10.05 (s, 1 H), 8.03 (s, 1 H), 7.99 (br d, *J* = 8.5 Hz, 2 H), 7.91 (br d, *J* = 8.3 Hz, 2 H), 7.76 (br d, *J* = 8.3 Hz, 2 H), 7.45 (d, *J* = 8.3 Hz, 2 H), 4.74 (d, *J* = 12.2 Hz, 1 H), 4.71-4.67 (m, 2 H), 4.49 (d, *J* = 11.8 Hz, 1 H), 4.29-4.23 (m, 3 H). Anal. (C₂₀H₁₇N₃O₅·H₂O) C, H, N: calcd, 10.57; found, 10.13. HPLC purity: 98.8%.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-carbonitrile (80). From **128** and 4-cyanophenylboronic acid (79%), white

powder: mp 177-180 °C; ^1H NMR δ 8.03 (s, 1 H), 7.92 (br d, J = 8.6 Hz, 2 H), 7.87 (br d, J = 8.7 Hz, 2 H), 7.74 (br d, J = 8.3 Hz, 2 H), 7.45 (d, J = 8.3 Hz, 2 H), 4.74 (d, J = 12.2 Hz, 1 H), 4.71-4.67 (m, 2 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_4 \cdot 0.25\text{H}_2\text{O}$) C, H, N.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-carboxamide (81). From **128** and 4-aminocarbonylphenylboronic acid (54%), light brown solid: mp 249-252 °C; ^1H NMR δ 8.03 (s, 1 H), 7.98-7.94 (m, 3 H), 7.74-7.69 (m, 4 H), 7.43 (d, J = 8.2 Hz, 2 H), 7.34 (br s, 1 H), 4.73 (d, J = 12.4 Hz, 1 H), 4.70-4.67 (m, 2 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.31-4.22 (m, 3 H); HRFABMS calcd for $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_5$ m/z $[\text{M} + \text{H}]^+$ 395.1355, found 395.1362. HPLC purity: 99.8%.

1-[4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-yl]ethanone (82). From **128** and 4-acetylphenylboronic acid (61%), light brown solid: mp 227-230 °C; ^1H NMR δ 8.04-8.02 (m, 3 H), 7.82 (br d, J = 8.5 Hz, 2 H), 7.74 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 4.73 (d, J = 12.2 Hz, 1 H), 4.71-4.68 (m, 2 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.32-4.22 (m, 3 H), 2.61 (s, 3 H); HRFABMS calcd for $\text{C}_{21}\text{H}_{20}\text{N}_3\text{O}_5$ m/z $[\text{M} + \text{H}]^+$ 394.1403, found 394.1407. HPLC purity: 98.4%.

(6*S*)-6-[(4'-Fluoro[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (83). From **128** and 4-fluorophenylboronic acid, cream solid: mp 199-201 °C; ^1H NMR δ 8.03 (s, 1 H), 7.72-7.66 (m, 2 H), 7.62 (br d, J = 8.3 Hz, 2 H), 7.40 (d, J = 8.3 Hz, 2 H), 7.28 (tt, J = 8.9, 2.6 Hz, 2 H), 4.72-4.65 (m, 3 H), 4.47 (d, J = 11.9 Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($\text{C}_{19}\text{H}_{16}\text{FN}_3\text{O}_4$) C, H, N.

(6*S*)-6-[(4'-Chloro[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (84). From **128** and 4-chlorophenylboronic acid, pale brown solid: mp 243-246 °C; ^1H NMR δ 8.03 (s, 1 H), 7.68 (dt, J = 8.6, 2.4 Hz, 2 H), 7.65 (br d, J = 8.3 Hz, 2 H),

7.51 (dt, $J = 8.6, 2.3$ Hz, 2 H), 7.41 (d, $J = 8.3$ Hz, 2 H), 4.71 (d, $J = 12.2$ Hz, 1 H), 4.68-4.65 (m, 2 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($C_{19}H_{16}ClN_3O_4$) C, H, N.

4'-([[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-ol (85). From **128** and 4-hydroxyphenylboronic acid (77%), white solid: mp 190-192 °C; 1H NMR δ 9.51 (br s, 1 H), 8.02 (s, 1 H), 7.54 (d, $J = 8.3$ Hz, 2 H), 7.46 (d, $J = 8.7$ Hz, 2 H), 7.34 (d, $J = 8.3$ Hz, 2 H), 6.83 (d, $J = 8.7$ Hz, 2 H), 4.69-4.61 (m, 3 H), 4.46 (d, $J = 11.9$ Hz, 1 H), 4.30-4.20 (m, 3 H). Anal. ($C_{19}H_{17}N_3O_5$) C, H, N.

(6*S*)-6-[(4'-Methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (86). From **128** and 4-methoxyphenylboronic acid, beige solid: mp 218-220 °C; 1H NMR δ 8.03 (s, 1 H), 7.59 (br d, $J = 8.6$ Hz, 4 H), 7.37 (d, $J = 8.2$ Hz, 2 H), 7.01 (dt, $J = 8.8, 2.6$ Hz, 2 H), 4.69-4.62 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.29-4.20 (m, 3 H), 3.79 (s, 3 H). Anal. ($C_{20}H_{19}N_3O_5 \cdot 0.25EtOAc$) C, H, N.

(6*S*)-6-[(4'-Isopropoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (87). From **128** and 4-isopropoxyphenylboronic acid, light brown solid: mp 231 °C; 1H NMR δ 8.02 (s, 1 H), 7.59-7.54 (m, 4 H), 7.36 (d, $J = 8.2$ Hz, 2 H), 6.98 (dt, $J = 8.8, 2.5$ Hz, 2 H), 4.70-4.61 (m, 4 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.30-4.21 (m, 3 H), 1.28 (d, $J = 6.0$ Hz, 6 H). Anal. ($C_{22}H_{23}N_3O_5$) C, H, N.

(6*S*)-2-Nitro-6-[(4'-phenoxy[1,1'-biphenyl]-4-yl)methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (88). From **128** and 4-phenoxyphenylboronic acid for 15 min (40%), pink solid: mp 173-175 °C; 1H NMR δ 8.03 (s, 1 H), 7.67 (dt, $J = 8.8, 2.6$ Hz, 2 H), 7.63 (d, $J = 8.3$ Hz, 2 H), 7.44-7.38 (m, 4 H), 7.19-7.14 (m, 1 H), 7.10-7.05 (m, 4 H), 4.72-4.65 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($C_{25}H_{21}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6*S*)-2-Nitro-6-[[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (93). From **128** and 4-(trifluoromethoxy)phenylboronic acid

(86%), cream solid: mp (CH₂Cl₂/hexane) 199-201 °C; ¹H NMR δ 8.03 (s, 1 H), 7.78 (dt, *J* = 8.8, 2.6 Hz, 2 H), 7.66 (br d, *J* = 8.3 Hz, 2 H), 7.43 (br t, *J* = 8.5 Hz, 4 H), 4.72 (d, *J* = 12.2 Hz, 1 H), 4.70-4.66 (m, 2 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.31-4.21 (m, 3 H). Anal. (C₂₀H₁₆F₃N₃O₅) C, H, N.

(6*S*)-6-{[4'-(Methylsulfanyl)[1,1'-biphenyl]-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (94). From **128** and 4-(methylsulfanyl)phenylboronic acid, brown solid: mp 248-250 °C; ¹H NMR δ 8.03 (s, 1 H), 7.64-7.59 (m, 4 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 4.72-4.63 (m, 3 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.21 (m, 3 H), 2.51 (s, 3 H). Anal. (C₂₀H₁₉N₃O₄S·0.5H₂O) C, H, N.

(6*S*)-6-{[4'-(Methylsulfonyl)[1,1'-biphenyl]-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (95). From **128** and 4-(methylsulfonyl)phenylboronic acid for 15 min (24%), cream powder: mp 238-240 °C; ¹H NMR δ 8.03 (s, 1 H), 7.99 (br d, *J* = 8.6 Hz, 2 H), 7.93 (br d, *J* = 8.6 Hz, 2 H), 7.74 (d, *J* = 8.3 Hz, 2 H), 7.46 (d, *J* = 8.3 Hz, 2 H), 4.74 (d, *J* = 12.2 Hz, 1 H), 4.71-4.67 (m, 2 H), 4.49 (d, *J* = 11.8 Hz, 1 H), 4.28-4.23 (m, 3 H), 3.24 (s, 3 H). Anal. (C₂₀H₁₉N₃O₆S·H₂O) C, N, H: calcd, 4.73; found, 4.32. HPLC purity: 99.3%.

4'-{[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl}[1,1'-biphenyl]-4-amine (96). From **128** and 4-aminophenylboronic acid for 2.5 h (47%), orange solid: mp 214-216 °C; ¹H NMR δ 8.03 (s, 1 H), 7.50 (d, *J* = 8.3 Hz, 2 H), 7.35-7.29 (m, 4 H), 6.63 (br d, *J* = 8.6 Hz, 2 H), 5.19 (s, 2 H), 4.67-4.62 (m, 3 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.25-4.22 (m, 3 H); HRFABMS calcd for C₁₉H₁₉N₄O₄ *m/z* [M + H]⁺ 367.1406, found 367.1406. HPLC purity: 99.5%.

(6*S*)-6-{[2'-Chloro-4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (97). From **128** and 2-chloro-4-(trifluoromethyl)phenylboronic acid for 10 min (71%), white solid: mp 133-136 °C; ¹H NMR δ 8.03 (s, 1 H), 7.97 (d, *J* = 1.1 Hz, 1 H), 7.79 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz,

1 H), 7.47-7.42 (m, 4 H), 4.75 (d, $J = 12.1$ Hz, 1 H), 4.77-4.68 (m, 2 H), 4.50 (d, $J = 11.8$ Hz, 1 H), 4.33-4.23 (m, 3 H). Anal. ($C_{20}H_{15}ClF_3N_3O_4$) C, H, N, F.

(6S)-6-[(2'-Chloro-6'-methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (99). From **128** and 2-chloro-6-methoxyphenylboronic acid, beige solid: mp 169-171 °C; 1H NMR δ 8.03 (s, 1 H), 7.46 (br d, $J = 8.2$ Hz, 2 H), 7.38 (dd, $J = 8.8, 2.7$ Hz, 1 H), 7.35 (br d, $J = 8.3$ Hz, 2 H), 7.30 (d, $J = 2.7$ Hz, 1 H), 7.13 (d, $J = 8.9$ Hz, 1 H), 4.72-4.64 (m, 3 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H), 3.75 (s, 3 H). Anal. ($C_{20}H_{18}ClN_3O_5$) C, H, N, Cl.

(6S)-6-[(2'-Fluoro-6'-methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (101). From **128** and 2-fluoro-6-methoxyphenylboronic acid (77%), light yellow powder: mp 148-151 °C; 1H NMR δ 8.03 (s, 1 H), 7.39-7.33 (m, 3 H), 7.31 (br d, $J = 8.2$ Hz, 2 H), 6.96 (d, $J = 8.5$ Hz, 1 H), 6.88 (br t, $J = 8.5$ Hz, 1 H), 4.72-4.65 (m, 3 H), 4.49 (d, $J = 11.9$ Hz, 1 H), 4.29-4.24 (m, 3 H), 3.72 (s, 3 H). Anal. ($C_{20}H_{18}FN_3O_5 \cdot 0.25H_2O$) C, H, N.

(6S)-6-[(2',6'-Dimethyl[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (102). From **128** and 2,6-dimethylphenylboronic acid, white solid: mp 72-75 °C; 1H NMR δ 8.03 (s, 1 H), 7.39 (d, $J = 8.1$ Hz, 2 H), 7.16-7.08 (m, 5 H), 4.74 (d, $J = 12.0$ Hz, 1 H), 4.71-4.64 (m, 2 H), 4.50 (d, $J = 11.8$ Hz, 1 H), 4.34-4.24 (m, 3 H), 1.94 (s, 6 H). Anal. ($C_{21}H_{21}N_3O_4 \cdot 0.25 H_2O$) C, H, N.

(6S)-6-[(2',6'-Dimethoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (103). From **128** and 2,6-dimethoxyphenylboronic acid (57%), brown solid: mp 150-152 °C; 1H NMR δ 8.03 (s, 1 H), 7.31-7.26 (m, 3 H), 7.17 (br d, $J = 8.2$ Hz, 2 H), 6.73 (d, $J = 8.4$ Hz, 2 H), 4.73-4.62 (m, 3 H), 4.50 (d, $J = 11.9$ Hz, 1 H), 4.33-4.23 (m, 3 H), 3.64 (s, 6 H). Anal. ($C_{21}H_{21}N_3O_6 \cdot H_2O$) C, H, N.

(6S)-6-[(3',4'-Difluoro[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (104). From **128** and 3,4-difluorophenylboronic acid (69%), white powder: mp (hexane/EtOAc) 158-160 °C; ¹H NMR δ 8.02 (s, 1 H), 7.78-7.72 (m, 1 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.53-7.48 (m, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 4.71 (d, *J* = 12.2 Hz, 1 H), 4.69-4.65 (m, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.31-4.21 (m, 3 H). Anal. (C₁₉H₁₅F₂N₃O₄) C, H, N.

(6S)-6-[[3'-Chloro-4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (105). A stirred mixture of bromide **132** (40.1 mg, 0.113 mmol), 3-chloro-4-(trifluoromethyl)phenylboronic acid (38.3 mg, 0.171 mmol) and Pd(dppf)Cl₂ (12.8 mg, 0.0175 mmol) in toluene (2 mL) and EtOH (1 mL) was degassed for 4 min (vacuum pump) and then N₂ was added. Aqueous Na₂CO₃ (0.3 mL of 2M, 0.6 mmol) was added by syringe and the stirred mixture was again degassed for 4 min, and then N₂ was added. The resulting mixture was stirred at 88 °C for 100 min and then cooled, diluted with aqueous NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1.5% EtOAc/CH₂Cl₂ gave foreruns, and then elution with 1.5-2.5% EtOAc/CH₂Cl₂ gave **105** (45.5 mg, 89%) as a cream solid: mp (CH₂Cl₂/pentane) 192-194 °C; ¹H NMR (CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 1 H), 7.70 (br d, *J* = 0.9 Hz, 1 H), 7.58 (dt, *J* = 8.3, 1.8 Hz, 2 H), 7.54 (dq, *J* = 8.2, 0.9 Hz, 1 H), 7.42 (br d, *J* = 8.3 Hz, 2 H), 7.39 (s, 1 H), 4.79 (d, *J* = 12.1 Hz, 1 H), 4.68 (d, *J* = 12.1 Hz, 1 H), 4.64 (ddd, *J* = 12.1, 3.7, 2.1 Hz, 1 H), 4.37 (dd, *J* = 12.1, 1.4 Hz, 1 H), 4.24-4.12 (m, 3 H). Anal. (C₂₀H₁₅ClF₃N₃O₄) C, H, N.

(6S)-6-[[4'-Chloro-3'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (108). From **128** and 4-chloro-3-(trifluoromethyl)phenylboronic acid for 10 min (82%), white solid: mp 155-158 °C; ¹H NMR δ 8.03 (d, *J* = 2.2 Hz, 1 H), 8.02 (s, 1 H), 7.98 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz,

1 H), 7.74 (d, $J = 8.3$ Hz, 2 H), 7.44 (d, $J = 8.3$ Hz, 2 H), 4.75-4.65 (m, 3 H), 4.49 (d, $J = 11.8$ Hz, 1 H), 4.31-4.22 (m, 3 H). Anal. ($C_{20}H_{15}ClF_3N_3O_4$) C, H, N, F.

(6S)-6-[(3'-Fluoro-4'-methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (110). From **128** and 3-fluoro-4-methoxyphenylboronic acid, pale pink solid: mp 200 °C; 1H NMR δ 8.03 (s, 1 H), 7.63 (d, $J = 8.3$ Hz, 2 H), 7.54 (dd, $J = 13.0, 2.2$ Hz, 1 H), 7.46 (ddd, $J = 8.5, 2.2, 1.0$ Hz, 1 H), 7.37 (d, $J = 8.3$ Hz, 2 H), 7.24 (t, $J = 8.8$ Hz, 1 H), 4.72-4.64 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.21 (m, 3 H), 3.87 (s, 3 H). Anal. ($C_{20}H_{18}FN_3O_5 \cdot 0.25H_2O$) C, H, N.

(6S)-6-[(4'-Fluoro-3'-methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (112). From **128** and 4-fluoro-3-methoxyphenylboronic acid for 5 min (77%), yellow solid: mp 132-135 °C; 1H NMR δ 8.02 (s, 1 H), 7.65 (br d, $J = 8.3$ Hz, 2 H), 7.40-7.36 (m, 1 H), 7.39 (d, $J = 8.4$ Hz, 2 H), 7.27 (dd, $J = 11.3, 8.4$ Hz, 1 H), 7.19 (ddd, $J = 8.4, 4.5, 2.2$ Hz, 1 H), 4.71 (d, $J = 12.1$ Hz, 1 H), 4.69-4.65 (m, 2 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.34-4.18 (m, 3 H), 3.92 (s, 3 H). Anal. ($C_{20}H_{18}FN_3O_5$) C, H, N.

(6S)-6-[(3',5'-Dimethoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (115). From **128** and 3,5-dimethoxyphenylboronic acid, brown solid: mp 52-55 °C; 1H NMR δ 8.02 (s, 1 H), 7.64 (d, $J = 8.3$ Hz, 2 H), 7.38 (d, $J = 8.2$ Hz, 2 H), 6.76 (d, $J = 2.3$ Hz, 2 H), 6.50 (t, $J = 2.2$ Hz, 1 H), 4.72-4.65 (m, 3 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.30-4.21 (m, 3 H), 3.80 (s, 6 H); HRFABMS calcd for $C_{21}H_{22}N_3O_6$ m/z $[M + H]^+$ 412.1509, found 412.1507. HPLC purity: 96.2%.

(6S)-6-[(3',5'-Difluoro-2'-methoxy[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (116). From **128** and 3,5-difluoro-2-methoxyphenylboronic acid for 15 min (85%), light yellow powder: mp 129-131 °C; 1H NMR δ 8.03 (s, 1 H), 7.52 (br d, $J = 8.3$ Hz, 2 H), 7.40 (d, $J = 8.3$ Hz, 2 H), 7.34 (ddd, $J = 11.4, 8.7, 3.1$ Hz, 1 H), 7.07

(ddd, $J = 9.3, 3.0, 1.9$ Hz, 1 H), 4.73 (d, $J = 12.1$ Hz, 1 H), 4.70-4.67 (m, 2 H), 4.50 (d, $J = 11.8$ Hz, 1 H), 4.29-4.23 (m, 3 H), 3.60 (s, 3 H). Anal. ($C_{20}H_{17}F_2N_3O_5$) C, H, N, F.

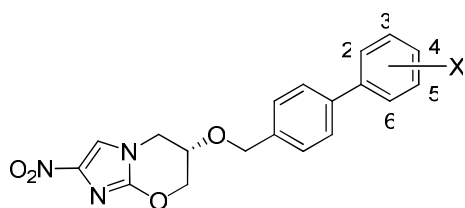
(6S)-6-[(4'-Methoxy-2',6'-dimethyl[1,1'-biphenyl]-4-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (117). From **128** and 2,6-dimethyl-4-methoxyphenylboronic acid, white solid: mp 77 °C; 1H NMR δ 8.02 (s, 1 H), 7.63 (d, $J = 8.1$ Hz, 2 H), 7.08 (d, $J = 8.1$ Hz, 2 H), 6.68 (s, 2 H), 4.74-4.64 (m, 3 H), 4.50 (d, $J = 11.9$ Hz, 1 H), 4.33-4.24 (m, 3 H), 3.74 (s, 3 H), 1.92 (s, 6 H). Anal. ($C_{22}H_{23}N_3O_5$) C, H, N.

(6S)-2-Nitro-6-[(3',4',5'-trifluoro[1,1'-biphenyl]-4-yl)methoxy]-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (118). From **128** and 3,4,5-trifluorophenylboronic acid (82%), beige powder: mp 150-152 °C; 1H NMR δ 8.02 (s, 1 H), 7.72-7.65 (m, 2 H), 7.71 (d, $J = 8.4$ Hz, 2 H), 7.41 (d, $J = 8.3$ Hz, 2 H), 4.72 (d, $J = 12.1$ Hz, 1 H), 4.69-4.66 (m, 2 H), 4.48 (d, $J = 11.9$ Hz, 1 H), 4.31-4.22 (m, 3 H); HRFABMS calcd for $C_{19}H_{15}F_3N_3O_4$ m/z $[M + H]^+$ 406.1015, found 406.1012. HPLC purity: 98.5%.

3,5-Dimethyl-4'-([[(6S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl][1,1'-biphenyl]-4-ol (119). From **128** and 3,5-dimethyl-4-hydroxyphenylboronic acid (82%), pale yellow solid: mp 179-182 °C; 1H NMR δ 8.70 (br s, 1 H), 8.02 (s, 1 H), 7.54 (d, $J = 8.3$ Hz, 2 H), 7.33 (d, $J = 8.3$ Hz, 2 H), 7.21 (s, 2 H), 4.68-4.64 (m, 3 H), 4.47 (d, $J = 11.9$ Hz, 1 H), 4.25-4.23 (m, 3 H), 2.21 (s, 6 H). Anal. ($C_{21}H_{21}N_3O_5 \cdot 0.25H_2O$) C, H, N.

(6S)-6-{[4-(2-Naphthyl)benzyl]oxy}-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (121). From **128** and 2-naphthylboronic acid (72%), tan solid: mp 227-228 °C; 1H NMR δ 8.21 (br d, $J = 1.4$ Hz, 1 H), 8.04 (s, 1 H), 8.02-7.97 (m, 2 H), 7.96-7.92 (m, 1 H), 7.84 (dd, $J = 8.6, 1.9$ Hz, 1 H), 7.81 (d, $J = 1.8$ Hz, 2 H), 7.57-7.49 (m, 2 H), 7.45 (d, $J = 8.3$ Hz, 2 H), 4.76-4.67 (m, 3 H), 4.50 (d, $J = 11.9$ Hz, 1 H), 4.34-4.23 (m, 3 H). Anal. ($C_{23}H_{19}N_3O_4$) C, H, N.

Table S1. Mean CFU data from various acute in vivo assays



		CFU/mouse (lungs) ^a			
Compd	X	T10 Control	T31 Control	1	Test compd
49	2-OEt	99,000	840,000	79,000	540,000
50	2-O(CH ₂) ₃ OH	13,000	2,200,000	3,900	1,100,000
68	3-OCH ₂ Ph	99,000	840,000	79,000	120,000
75	4-CF ₃	99,000	840,000	79,000	1,100
78	4-CH ₂ NHPh	96,000	900,000	16,000	500,000
80	4-CN	96,000	900,000	16,000	4,500
82	4-COMe	1,300	230,000	230	110,000
83	4-F	96,000	900,000	16,000	5,400
88	4-OPh	1,300	230,000	230	330,000
91	4-O(CH ₂) ₃ Nmorph ^b	96,000	900,000	16,000	310,000
92	4-OCF ₂ H	15,000	3,300,000	9,300	1,100
93	4-OCF ₃	3,000	170,000	410	<2
97	2-Cl, 4-CF ₃	13,000	2,200,000	3,900	540
98	2-Cl, 4-OCF ₃	9,900	480,000	9,100	390
100	2-F, 4-OCF ₃	81,000	700,000	1,800	39
101	2-F, 6-OMe	99,000	840,000	79,000	1,100,000
106	3-Cl, 4-OCF ₃	81,000	700,000	1,800	6.4
107	3-OCF ₃ , 4-Cl	7,900	1,100,000	3,500	360
108	3-CF ₃ , 4-Cl	1,300	230,000	230	30
110	3-F, 4-OMe	96,000	900,000	16,000	850,000
111	3-F, 4-OCF ₃	81,000	700,000	1,800	4.3

113	3-OCF ₂ H, 4-Cl	18,000	630,000	1,500	150
116	2-OMe, 3,5-diF	99,000	840,000	79,000	200,000

^aMean CFU/mouse data for groups of 7 or 8 control mice at start (T10) and end (T31) of treatment or for similar groups of mice treated with either the test compound or compound **1** (PA-824) as internal standard in the same head-to-head assay (CFU values vary between different assays). ^b*N*-Morpholinyl

Table S2. Combustion analyses for the compounds of Table 1.

No.	Calculated				Found			
	C	H	N	other	C	H	N	other
7	64.95	4.88	11.96		64.69	5.02	11.84	
8	55.18	3.70	9.65	F: 13.09	55.33	3.94	9.43	F: 12.87
9	63.31	4.55	14.06		63.35	4.37	14.22	
10	61.79	4.37	11.38		61.46	4.51	11.24	
11	55.57	4.11	9.26	F: 12.56	55.83	4.14	9.30	F: 12.92
12	60.44	4.82	10.57	S: 8.07	60.24	5.11	10.24	S: 7.69
13	64.12	4.87	10.68		63.95	5.08	10.45	
14	63.07	4.37	14.71		62.93	4.13	14.55	
15	58.91	4.68	10.85		58.93	4.41	10.68	
16	55.18	3.70	9.65		54.88	3.90	9.45	
17	60.44	4.82	10.57		60.41	5.18	10.06	
18	59.48	4.62	10.40	F: 4.70	59.29	4.72	10.26	F: 4.71
19	68.06	4.84	10.35		68.26	5.15	10.05	

Table S3. Combustion analyses for the compounds of Table 2.

No.	Calculated				Found			
	C	H	N	other	C	H	N	other
20	64.13	4.96	11.81		64.25	4.97	11.86	
23	61.61	4.52	14.37		61.92	4.28	14.21	
24	61.04	4.45	11.24		60.81	4.28	10.84	
25	61.69	4.92	10.79		61.51	4.76	10.82	
26	55.18	3.70	9.65		55.12	3.64	9.71	
28	62.02	6.21	11.13		62.26	6.16	10.85	
29	60.44	4.82	10.57	S: 8.07	60.20	5.06	10.46	S: 8.06
30	63.39	4.94	10.56		63.20	5.05	10.32	
31	57.28	3.85	10.02		57.11	3.86	10.06	
32	63.82	4.28	14.89		63.46	4.37	14.62	
33	59.61	4.61	10.98	F: 4.96	59.58	4.33	10.80	F: 5.20
34	61.69	4.92	10.79		61.32	4.89	10.71	
35	52.98	4.00	9.27		52.76	3.72	9.28	
36	57.56	4.11	10.07		57.79	4.23	10.20	
37	62.11	5.45	9.88		61.98	5.53	9.76	
38	63.15	6.11	11.33		63.45	6.25	11.37	
39	59.76	4.89	10.45	S: 7.98	59.77	4.82	10.48	S: 7.87
40	57.55	4.83	10.07		57.50	4.49	10.01	
41	67.31	4.91	10.24		67.58	4.87	10.20	

Table S4. Combustion analyses for the compounds of Table 3.

No.	Calculated				Found			
	C	H	N	other	C	H	N	other
42	64.13	4.96	11.81		64.28	5.18	11.71	
44	62.58	4.59	10.95		62.61	4.51	10.89	
45	61.04	4.45	11.24	F: 5.08	61.11	4.25	10.99	F: 5.31
47	61.37	4.74	11.30		61.21	5.02	11.14	
48	62.25	5.09	10.89		62.23	5.13	10.63	
52	67.03	4.84	9.38		67.27	4.82	9.03	
53	60.44	4.82	10.57		60.51	4.96	10.37	
54	67.16	5.89	10.68		67.20	6.01	10.69	
55	68.78	5.34	8.91		68.79	5.08	9.06	
56	57.28	3.85	10.02		57.08	3.92	9.86	
57	61.85	4.67	10.82		61.82	4.55	10.66	
58	62.33	4.45	14.54		62.23	4.33	14.49	
60	61.04	4.45	11.24		60.81	4.55	11.07	
61	59.15	4.18	10.89		59.39	4.39	10.90	
62	62.12	4.66	11.44		61.92	4.61	11.24	
63	62.25	5.09	10.89		62.30	5.11	10.82	
66	61.73	6.08	12.52		62.02	5.93	12.53	
67	55.18	3.70	9.65		55.21	3.84	9.28	
68	68.26	5.07	9.19		68.40	5.15	8.97	
69	59.10	4.96	10.34		59.44	4.75	10.13	
70	59.37	5.24	14.58		59.42	4.88	13.99	
72	66.40	5.95	10.56		66.50	5.92	10.39	
73	67.80	6.18	10.31		67.50	5.94	10.15	

75	57.28	3.85	10.02		57.04	3.77	9.85	
76	62.52	5.25	10.42		62.74	5.14	10.08	
77	63.28	6.42	9.22		63.31	6.19	8.99	
78	68.41	5.30	12.27		68.40	5.42	12.20	
79	60.45	4.82	10.57		60.35	4.50	10.13	
80	63.07	4.37	14.71		63.11	4.29	14.64	
83	61.79	4.37	11.38		61.81	4.62	11.19	
84	59.15	4.18	10.89		59.08	4.29	10.62	
85	62.12	4.66	11.44		61.82	4.76	11.10	
86	62.52	5.25	10.42		62.18	5.27	10.42	
87	64.54	5.66	10.26		64.43	5.92	10.03	
88	67.03	4.84	9.38		67.14	4.93	9.28	
89	61.31	5.14	10.21		61.35	5.24	10.20	
90	62.11	5.45	9.88		61.90	5.49	9.74	
91	62.58	6.16	11.23		62.51	6.31	11.14	
92	57.56	4.11	10.07		57.74	4.20	10.13	
93	55.18	3.70	9.65		55.16	3.83	9.47	
94	59.10	4.96	10.34		59.31	4.76	9.98	
95	53.68	4.73	9.39		53.36	4.32	9.04	
97	52.93	3.33	9.26	F:12.56	52.88	3.41	9.21	F: 12.64
98	51.13	3.22	8.94		51.34	3.34	8.92	
99	57.77	4.36	10.11	Cl: 8.53	57.55	4.32	9.87	Cl: 8.20
100	52.99	3.34	9.27		53.28	3.40	9.28	
101	59.48	4.62	10.40		59.52	4.43	10.24	
102	65.70	5.64	10.95		65.59	5.55	10.92	
103	58.74	5.40	9.79		58.85	5.07	9.43	
104	58.92	3.90	10.85		58.95	3.99	10.85	
105	52.93	3.33	9.26		53.17	3.35	9.22	

106	51.13	3.22	8.94		51.27	3.27	8.91	
107	51.13	3.22	8.94		51.33	3.22	8.93	
108	52.93	3.33	9.26	F:12.56	52.95	3.39	9.30	F: 12.82
109	50.01	3.15	11.66		50.24	3.30	11.59	
110	59.48	4.62	10.40		59.80	4.61	10.09	
111	52.99	3.34	9.27		52.92	3.37	9.21	
112	60.15	4.54	10.52		60.34	4.71	10.15	
113	53.17	3.57	9.30		53.25	3.84	9.24	
114	56.80	4.01	10.46		56.59	4.27	10.09	
116	57.56	4.11	10.07	F: 9.10	57.31	4.21	10.02	F: 9.12
117	64.54	5.66	10.26		64.43	5.63	9.98	
119	63.07	5.42	10.51		62.99	5.08	10.40	
120	57.56	4.11	10.07		57.84	4.15	10.05	
121	68.82	4.77	10.47		68.84	4.76	10.19	

Table S5. Combustion analyses for new intermediates, in order of their appearance in the Experimental Section.

No.	Calculated				Found			
	C	H	N	other	C	H	N	other
124	38.92	3.02	10.47	I: 31.63	39.08	2.99	10.47	I: 31.81
126	39.74	3.33	9.93		39.50	3.16	10.26	
128	38.92	3.02	10.47		39.23	3.22	10.19	
130	44.09	3.42	11.86		44.40	3.39	11.73	
132	44.09	3.42	11.86		44.28	3.37	11.75	
133	56.88	6.03	10.47		57.04	6.24	10.65	
134	56.88	6.03	10.47		56.79	6.08	10.50	