

Supporting Information

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

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(6*S*)-6-([2-(6-Fluoro-3-pyridinyl)benzyl]oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (10) (Scheme 1A). Reaction of (6*S*)-6-[(2-iodobenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine¹ (**127**) and 6-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 10 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **10** (83%) as a light yellow powder: mp 140-142 °C; ¹H NMR [(CD₃)₂SO] δ 8.20 (d, *J* = 2.5 Hz, 1 H), 7.98 (s, 1 H), 7.94 (td, *J* = 8.2, 2.6 Hz, 1 H), 7.52-7.47 (m, 1 H), 7.45-7.40 (m, 2 H), 7.32-7.28 (m, 1 H), 7.19 (dd, *J* = 8.4, 2.5 Hz, 1 H), 4.57-4.49 (m, 3 H), 4.41 (br d, *J* = 11.8 Hz, 1 H), 4.21-4.11 (m, 3 H). Anal. (C₁₈H₁₅FN₄O₄) C, H, N, F.

(6*S*)-6-([2-(6-Methoxy-3-pyridinyl)benzyl]oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (11). Reaction of iodide **127** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **11** (78%) as a light yellow powder: mp 128-130 °C; ¹H NMR [(CD₃)₂SO] δ 8.12 (d, *J* = 2.0 Hz, 1 H), 7.99 (s, 1 H), 7.67 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.50-7.44 (m, 1 H), 7.42-7.35 (m, 2 H), 7.29-7.24 (m, 1 H), 6.83 (d, *J* = 8.6 Hz, 1 H), 4.57-4.49 (m, 3 H), 4.43 (br d, *J* = 11.8 Hz, 1 H), 4.17 (br s, 3 H), 3.90 (s, 3 H). Anal. (C₁₉H₁₈N₄O₅·0.5H₂O) C, H, N. HPLC purity: 96.3%.

(6*S*)-6-([2-[6-(Benzyloxy)-3-pyridinyl]benzyl]oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (12). Reaction of iodide **127** and 2-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine under the Suzuki coupling conditions described in Procedure A for 10 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **12** (89%) as a light yellow powder: mp 133-137 °C; ¹H NMR [(CD₃)₂SO] δ 8.13 (d, *J* = 2.2 Hz, 1 H), 7.99 (s, 1 H), 7.70 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.51-7.45 (m, 3 H), 7.44-7.25 (m, 6 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 5.40 (s, 2 H),

4.58-4.49 (m, 3 H), 4.43 (br d, $J = 11.8$ Hz, 1 H), 4.17 (br s, 3 H). Anal. ($C_{25}H_{22}N_4O_5 \cdot 0.25H_2O$) C, H, N: calcd, 12.10; found, 11.65. HPLC purity: 97.2%.

(6*S*)-2-Nitro-6-([2-(4-pyridinyl)benzyl]oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (13). Reaction of iodide **127** and 4-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 2 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **13** (19%) as a brown powder: mp 98-101 °C; 1H NMR [$(CD_3)_2SO$] δ 8.59 (dd, $J = 4.4, 1.6$ Hz, 2 H), 7.99 (s, 1 H), 7.52-7.47 (m, 1 H), 7.46-7.41 (m, 2 H), 7.36 (dd, $J = 4.4, 1.6$ Hz, 2 H), 7.33-7.28 (m, 1 H), 4.58-4.50 (m, 3 H), 4.42 (br d, $J = 11.9$ Hz, 1 H), 4.20-4.11 (m, 3 H); HRFABMS calcd for $C_{18}H_{17}N_4O_4$ m/z $[M + H]^+$ 353.1250, found 353.1256. HPLC purity: 99.2%.

(6*S*)-2-Nitro-6-([3-[5-(trifluoromethyl)-2-pyridinyl]benzyl]oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (15) (Scheme 1B). Reaction of (6*S*)-2-nitro-6-([3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine¹ (**130**) and 2-chloro-5-(trifluoromethyl)pyridine under the Suzuki coupling conditions described in Procedure B gave **15** (69%) as a white solid: mp 162-164 °C; 1H NMR [$(CD_3)_2SO$] δ 9.02 (dd, $J = 1.4, 0.7$ Hz, 1 H), 8.27 (dd, $J = 8.4, 2.0$ Hz, 1 H), 8.17 (d, $J = 8.4$ Hz, 1 H), 8.11-8.06 (m, 2 H), 8.01 (s, 1 H), 7.53 (t, $J = 8.2$ Hz, 1 H), 7.47 (br d, $J = 7.6$ Hz, 1 H), 4.78 (d, $J = 12.1$ Hz, 1 H), 4.74 (d, $J = 12.1$ Hz, 1 H), 4.69 (dt, $J = 12.0, 2.5$ Hz, 1 H), 4.49 (br d, $J = 11.8$ Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-([3-(3-pyridinyl)benzyl]oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (17). Reaction of (6*S*)-6-[(3-iodobenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine¹ (**128**) and 3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 35 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **17** (75%) as a light brown powder: mp 109-111 °C; 1H NMR [$(CD_3)_2SO$] δ 8.87 (d, $J = 1.9$ Hz, 1 H), 8.58

(dd, $J = 4.7, 1.5$ Hz, 1 H), 8.04 (dt, $J = 8.0, 1.7$ Hz, 1 H), 8.01 (s, 1 H), 7.67-7.61 (m, 2 H), 7.52-7.44 (m, 2 H), 7.38 (br d, $J = 7.6$ Hz, 1 H), 4.77-4.65 (m, 3 H), 4.48 (br d, $J = 11.9$ Hz, 1 H), 4.32-4.20 (m, 3 H). HPLC purity: 98.0%.

(6S)-2-Nitro-6-([3-[6-(trifluoromethyl)-3-pyridinyl]benzyl]oxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (18). Reaction of boronate ester **130** and 5-bromo-2-(trifluoromethyl)pyridine under the Suzuki coupling conditions described in Procedure B gave **18** (64%) as a cream solid: mp 181-183 °C; ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 9.07 (d, $J = 2.2$ Hz, 1 H), 8.33 (dd, $J = 8.2, 1.7$ Hz, 1 H), 8.01 (s, 1 H), 7.97 (dd, $J = 8.2, 0.4$ Hz, 1 H), 7.79-7.71 (m, 2 H), 7.54 (t, $J = 7.7$ Hz, 1 H), 7.44 (br d, $J = 7.7$ Hz, 1 H), 4.77 (d, $J = 12.2$ Hz, 1 H), 4.73 (d, $J = 12.2$ Hz, 1 H), 4.69 (dt, $J = 11.9, 2.4$ Hz, 1 H), 4.48 (br d, $J = 11.7$ Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. ($\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_4\text{O}_4$) C, H, N.

(6S)-6-([3-(6-Fluoro-3-pyridinyl)benzyl]oxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (19). Reaction of iodide **128** and 6-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **19** (68%) as a light brown powder: mp 106-108 °C; ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 8.53 (d, $J = 2.6$ Hz, 1 H), 8.25 (td, $J = 8.4, 2.6$ Hz, 1 H), 8.01 (s, 1 H), 7.66-7.61 (m, 2 H), 7.48 (t, $J = 7.6$ Hz, 1 H), 7.38 (br d, $J = 7.6$ Hz, 1 H), 7.27 (dd, $J = 8.4, 2.7$ Hz, 1 H), 4.75 (d, $J = 12.2$ Hz, 1 H), 4.72-4.65 (m, 2 H), 4.48 (br d, $J = 11.9$ Hz, 1 H), 4.31-4.20 (m, 3 H). Anal. ($\text{C}_{18}\text{H}_{15}\text{FN}_4\text{O}_4 \cdot 1.25\text{H}_2\text{O}$) C, N, F. H: calcd, 4.49; found, 4.01. HPLC purity: 98.7%.

(6S)-6-([3-(6-Methoxy-3-pyridinyl)benzyl]oxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (20). Reaction of iodide **128** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **20** (65%) as a pale pink solid: mp 111-113 °C; ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 8.45 (d, J

= 2.2 Hz, 1 H), 8.01 (s, 1 H), 8.79 (dd, J = 8.6, 2.6 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.31 (br d, J = 7.8 Hz, 1 H), 6.90 (dd, J = 8.7, 0.4 Hz, 1 H), 4.75-4.65 (m, 3 H), 4.48 (br d, J = 11.9 Hz, 1 H), 4.32-4.20 (m, 3 H), 3.90 (s, 3 H). HPLC purity: 97.2%.

(6S)-6-({3-[6-(Benzyloxy)-3-pyridinyl]benzyl}oxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (21). Reaction of iodide **128** and 2-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine under the Suzuki coupling conditions described in Procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with a gradient of 1:1 hexanes:EtOAc to EtOAc, gave **21** (80%) as a pale brown powder: mp 150-152 °C; ^1H NMR [(CD₃)₂SO] δ 8.46 (d, J = 2.2 Hz, 1 H), 8.01 (s, 1 H), 8.00 (dd, J = 8.7, 2.6 Hz, 1 H), 7.59 (br d, J = 8.9 Hz, 2 H), 7.50-7.28 (m, 7 H), 6.97 (dd, J = 8.6, 0.4 Hz, 1 H), 5.47 (s, 2 H), 4.75-4.65 (m, 3 H), 4.48 (br d, J = 11.9 Hz, 1 H), 4.32-4.20 (m, 3 H). Anal. (C₂₅H₂₂N₄O₅·0.25H₂O) C, H, N.

(6S)-2-Nitro-6-({3-(4-pyridinyl)benzyl}oxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (22). Reaction of iodide **128** and 4-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 40 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **22** (72%) as a brown solid: mp 69-73 °C; ^1H NMR [(CD₃)₂SO] δ 8.63 (dd, J = 4.5, 1.6 Hz, 2 H), 8.02 (s, 1 H), 7.75-7.67 (m, 2 H), 7.67 (dd, J = 4.5, 1.7 Hz, 2 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.42 (br d, J = 7.6 Hz, 1 H), 4.78-4.65 (m, 3 H), 4.49 (br d, J = 11.9 Hz, 1 H), 4.34-4.21 (m, 3 H); HRFABMS calcd for C₁₈H₁₇N₄O₄ m/z [M + H]⁺ 353.1250, found 353.1244. HPLC purity: 94.8%.

(6S)-2-Nitro-6-({4-(2-pyridinyl)benzyl}oxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (23). Reaction of (6S)-2-nitro-6-({4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl}oxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine¹ (**131**) and 2-bromopyridine under the Suzuki coupling conditions described in Procedure B gave **23** (50%) as a white solid: mp 190-192 °C; ^1H NMR [(CD₃)₂SO] δ 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1 H), 8.06 (br

d, $J = 8.3$ Hz, 2 H), 8.03 (s, 1 H), 7.94 (dt, $J = 8.0, 1.0$ Hz, 1 H), 7.87 (td, $J = 7.4, 1.8$ Hz, 1 H), 7.43 (br d, $J = 8.3$ Hz, 2 H), 7.35 (ddd, $J = 7.4, 4.8, 1.2$ Hz, 1 H), 4.76-4.66 (m, 3 H), 4.49 (br d, $J = 11.9$ Hz, 1 H), 4.33-4.28 (m, 3 H). Anal. ($C_{18}H_{16}N_4O_4$) C, H, N.

(6*S*)-2-Nitro-6-([4-[5-(trifluoromethyl)-2-pyridinyl]benzyl]oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (24). Reaction of boronate ester **131** and 2-chloro-5-(trifluoromethyl)pyridine under the Suzuki coupling conditions described in Procedure B for 45 min gave **24** (62%) as a white solid: mp 252-254 °C; 1H NMR [$(CD_3)_2SO$] δ 9.03 (br s, 1 H), 8.27 (dd, $J = 8.5, 2.1$ Hz, 1 H), 8.18 (d, $J = 8.4$ Hz, 1 H), 8.15 (br d, $J = 8.3$ Hz, 2 H), 8.03 (s, 1 H), 7.48 (br d, $J = 8.3$ Hz, 2 H), 4.78-4.66 (m, 3 H), 4.49 (br d, $J = 11.8$ Hz, 1 H), 4.33-4.23 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_4$) C, H, N.

6-[4-([(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl]phenyl]nicotinonitrile (26). Reaction of boronate ester **131** and 6-bromonicotinonitrile under the Suzuki coupling conditions described in Procedure B gave **26** (52%) as a white solid: mp 215-218 °C; 1H NMR [$(CD_3)_2SO$] δ 9.08 (dd, $J = 2.2, 0.7$ Hz, 1 H), 8.37 (dd, $J = 8.4, 2.2$ Hz, 1 H), 8.20-8.13 (m, 3 H), 8.03 (s, 1 H), 7.48 (br d, $J = 8.4$ Hz, 2 H), 4.78-4.66 (m, 3 H), 4.49 (br d, $J = 11.8$ Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{19}H_{15}N_5O_4$) C, H, N.

(6*S*)-6-{[4-(6-Fluoro-2-pyridinyl)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (27). Reaction of (6*S*)-6-[(4-iodobenzyl)oxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine¹ (**129**) and 2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine under the Suzuki coupling conditions described in Procedure A for 1.5 h gave **27** (99%) as a white solid: mp 199-201 °C; 1H NMR [$(CD_3)_2SO$] δ 8.10-8.01 (m, 4 H), 7.92 (dd, $J = 7.5, 2.7$ Hz, 1 H), 7.45 (br d, $J = 8.4$ Hz, 2 H), 7.13 (dd, $J = 8.1, 2.8$ Hz, 1 H), 4.76-4.65 (m, 3 H), 4.49 (br d, $J = 11.9$ Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. ($C_{18}H_{15}FN_4O_4$) C, H, N.

(6S)-6-({4-[5-(Difluoromethoxy)-2-pyridinyl]benzyl}oxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (29). Reaction of boronate ester **131** and 2-bromo-5-(difluoromethoxy)pyridine² (**133**) under the Suzuki coupling conditions described in Procedure B gave **29** (71%) as a white solid: mp 187-189 °C; ¹H NMR [(CD₃)₂SO] δ 8.55 (d, *J* = 2.8 Hz, 1 H), 8.06-8.00 (m, 4 H), 7.75 (dd, *J* = 8.7, 2.9 Hz, 1 H), 7.43 (br d, *J* = 8.3 Hz, 2 H), 7.34 (t, *J*_{H-F} = 73.5 Hz, 1 H), 4.75-4.65 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. (C₁₉H₁₆F₂N₄O₅) C, H, N.

(6S)-6-{{4-[5-Methoxy-2-pyridinyl]benzyl}oxy}-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (30). Reaction of boronate ester **131** and 2-bromo-5-methoxypyridine under the Suzuki coupling conditions described in Procedure B for 1 h gave **30** (81%) as a white solid: mp 188-190 °C; ¹H NMR [(CD₃)₂SO] δ 8.37 (d, *J* = 2.6 Hz, 1 H), 8.03 (s, 1 H), 7.98 (br d, *J* = 8.4 Hz, 2 H), 7.89 (dd, *J* = 8.7, 0.3 Hz, 1 H), 7.46 (dd, *J* = 8.7, 3.0 Hz, 1 H), 7.39 (br d, *J* = 8.4 Hz, 2 H), 4.73-4.64 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.31-4.21 (m, 3 H), 3.87 (s, 3 H). Anal. (C₁₉H₁₈N₄O₅) C, H, N.

(6S)-2-Nitro-6-{{4-[3-pyridinyl]benzyl}oxy}-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (31). Reaction of iodide **129** and 3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with 0-7% MeOH/EtOAc, gave **31** (75%) as a pink solid: mp 180 °C; ¹H NMR [(CD₃)₂SO] δ 8.88 (dd, *J* = 2.3, 0.6 Hz, 1 H), 8.57 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.06 (ddd, *J* = 8.0, 2.3, 1.7 Hz, 1 H), 8.03 (s, 1 H), 7.71 (br d, *J* = 8.3 Hz, 2 H), 7.48 (ddd, *J* = 7.9, 4.8, 0.7 Hz, 1 H), 7.45 (br d, *J* = 8.3 Hz, 2 H), 4.75-4.66 (m, 3 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. (C₁₈H₁₆N₄O₄) C, H, N.

(6S)-2-Nitro-6-({4-[6-(trifluoromethyl)-3-pyridinyl]benzyl}oxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (32). Reaction of boronate ester **131** and 5-bromo-2-(trifluoromethyl)pyridine under the Suzuki coupling conditions described in Procedure B

gave **32** (64%) as a white solid: mp 221-222 °C; ¹H NMR [(CD₃)₂SO] δ 9.08 (d, *J* = 2.1 Hz, 1 H), 8.35 (dd, *J* = 8.1, 1.9 Hz, 1 H), 8.03 (s, 1 H), 7.97 (d, *J* = 8.1 Hz, 1 H), 7.81 (br d, *J* = 8.3 Hz, 2 H), 7.48 (br d, *J* = 8.3 Hz, 2 H), 4.77-4.67 (m, 3 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. (C₁₉H₁₅F₃N₄O₄) C, H, N.

5-[4-(((6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl)phenyl]-2-pyridinecarbonitrile (33**).** Reaction of iodide **129** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinecarbonitrile under the Suzuki coupling conditions described in Procedure A for 40 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **33** (73%) as a light yellow powder: mp 208-210 °C; ¹H NMR [(CD₃)₂SO] δ 9.10 (dd, *J* = 2.3, 0.7 Hz, 1 H), 8.34 (dd, *J* = 8.2, 2.3 Hz, 1 H), 8.12 (dd, *J* = 8.2, 0.7 Hz, 1 H), 8.02 (s, 1 H), 7.83 (br d, *J* = 8.3 Hz, 2 H), 7.48 (br d, *J* = 8.3 Hz, 2 H), 4.75 (d, *J* = 12.3 Hz, 1 H), 4.73-4.66 (m, 2 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. (C₁₉H₁₅N₅O₄·0.5H₂O) C, H, N. HPLC purity: 98.8%.

(6*S*)-6-{[4-(6-Fluoro-3-pyridinyl)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (34**).** Reaction of iodide **129** and 6-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **34** (50%) as a tan powder: mp 149-151 °C; ¹H NMR [(CD₃)₂SO] δ 8.54 (d, *J* = 2.6 Hz, 1 H), 8.27 (td, *J* = 8.4, 2.6 Hz, 1 H), 8.03 (s, 1 H), 7.70 (br d, *J* = 8.3 Hz, 2 H), 7.44 (br d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.6, 2.8 Hz, 1 H), 4.74-4.65 (m, 3 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. (C₁₈H₁₅FN₄O₄) C, H, N.

(6*S*)-6-{[4-(5-Fluoro-3-pyridinyl)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (35**).** Reaction of iodide **129** and 5-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 10 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **35** (65%)

as a yellow solid: mp 162-165 °C; ¹H NMR [(CD₃)₂SO] δ 8.79 (t, *J* = 1.8 Hz, 1 H), 8.57 (d, *J* = 2.7 Hz, 1 H), 8.05 (ddd, *J* = 10.4, 2.7, 1.9 Hz, 1 H), 8.02 (s, 1 H), 7.76 (br d, *J* = 8.5 Hz, 2 H), 7.45 (br d, *J* = 8.3 Hz, 2 H), 4.74 (d, *J* = 12.2 Hz, 1 H), 4.72-4.66 (m, 2 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. (C₁₈H₁₅FN₄O₄·0.25H₂O) C, H, N: calcd, 14.95; found, 14.53. HPLC purity: 95.3%.

5-[4-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)phenyl]-2-pyridinamine (36). Reaction of iodide **129** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinylamine under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **36** (71%) as a white solid: mp 180-182 °C; ¹H NMR [(CD₃)₂SO] δ 8.23 (d, *J* = 2.1 Hz, 1 H), 8.02 (s, 1 H), 7.68 (dd, *J* = 8.6, 2.6 Hz, 1 H), 7.54 (br d, *J* = 8.3 Hz, 2 H), 7.34 (br d, *J* = 8.3 Hz, 2 H), 6.51 (dd, *J* = 8.6, 0.5 Hz, 1 H), 6.02 (s, 2 H), 4.69-4.60 (m, 3 H), 4.47 (br d, *J* = 11.9 Hz, 1 H), 4.30-4.19 (m, 3 H). Anal. (C₁₈H₁₇N₅O₄·0.25H₂O) C, H, N: calcd, 18.83; found, 18.28. HPLC purity: 98.8%.

(6*S*)-6-({4-[6-(Difluoromethoxy)-3-pyridinyl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (37). Reaction of boronate ester **131** and 5-bromo-2-(difluoromethoxy)pyridine³ (**134**) under the Suzuki coupling conditions described in Procedure B, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **37** (50%) as a light yellow powder: mp 148-150 °C; ¹H NMR [(CD₃)₂SO] δ 8.56 (d, *J* = 2.5 Hz, 1 H), 8.21 (dd, *J* = 8.6, 2.6 Hz, 1 H), 8.02 (s, 1 H), 7.73 (t, *J*_{H-F} = 72.9 Hz, 1 H), 7.69 (br d, *J* = 8.2 Hz, 2 H), 7.43 (br d, *J* = 8.3 Hz, 2 H), 7.18 (d, *J* = 8.5 Hz, 1 H), 4.74-4.65 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. (C₁₉H₁₆F₂N₄O₅) C, H, N.

(6*S*)-6-{{4-[6-(Methoxy-3-pyridinyl)benzyl]oxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (38). Reaction of iodide **129** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by

chromatography of the product on silica gel, eluting with 0-5% MeOH/EtOAc, gave **38** (69%) as a tan powder: mp 181-183 °C; ¹H NMR [(CD₃)₂SO] δ 8.47 (d, *J* = 2.2 Hz, 1 H), 8.02 (s, 1 H), 8.00 (dd, *J* = 8.6, 2.6 Hz, 1 H), 7.64 (br d, *J* = 8.3 Hz, 2 H), 7.40 (br d, *J* = 8.2 Hz, 2 H), 6.90 (dd, *J* = 8.5, 0.4 Hz, 1 H), 4.72-4.64 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H), 3.89 (s, 3 H). Anal. (C₁₉H₁₈N₄O₅) C, H, N.

(6*S*)-6-({4-[6-(Benzyloxy)-3-pyridinyl]benzyl}oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (39). Reaction of iodide **129** and 2-(benzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine under the Suzuki coupling conditions described in Procedure A for 20 min gave **39** (56%) as a tan powder: mp 221 °C; ¹H NMR [(CD₃)₂SO] δ 8.48 (dd, *J* = 2.5, 0.4 Hz, 1 H), 8.02 (dd, *J* = 8.6, 2.6 Hz, 1 H), 8.02 (s, 1 H), 7.65 (br d, *J* = 8.3 Hz, 2 H), 7.47 (br d, *J* = 7.0 Hz, 2 H), 7.43-7.30 (m, 5 H), 6.97 (dd, *J* = 8.6, 0.6 Hz, 1 H), 5.40 (s, 2 H), 4.73-4.64 (m, 3 H), 4.48 (br d, *J* = 11.9 Hz, 1 H), 4.32-4.21 (m, 3 H). Anal. (C₂₅H₂₂N₄O₅·0.25H₂O) C, H, N.

(6*S*)-2-Nitro-6-([4-(4-pyridinyl)benzyl]oxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (40). Reaction of iodide **129** and 4-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with 0-7% MeOH/EtOAc, gave **40** (60%) as a light brown solid: mp 208-211 °C; ¹H NMR [(CD₃)₂SO] δ 8.62 (dd, *J* = 4.5, 1.6 Hz, 2 H), 8.03 (s, 1 H), 7.79 (br d, *J* = 8.3 Hz, 2 H), 7.69 (dd, *J* = 4.5, 1.6 Hz, 2 H), 7.46 (br d, *J* = 8.3 Hz, 2 H), 4.76-4.66 (m, 3 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. (C₁₈H₁₆N₄O₄) C, H, N.

(6*S*)-6-([4-(3-Fluoro-4-pyridinyl)benzyl]oxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (41). Reaction of iodide **129** and 3-fluoro-4-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 3 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **41** (82%) as a white solid: mp 208-210 °C; ¹H NMR [(CD₃)₂SO] δ 8.65 (d, *J* = 2.7 Hz, 1 H), 8.50 (dd, *J* = 4.9, 0.9 Hz, 1 H),

8.03 (s, 1 H), 7.66 (br dd, $J = 8.2, 1.4$ Hz, 2 H), 7.62 (dd, $J = 7.0, 5.0$ Hz, 1 H), 7.48 (br d, $J = 8.3$ Hz, 2 H), 4.75 (d, $J = 12.4$ Hz, 1 H), 4.73-4.67 (m, 2 H), 4.49 (br d, $J = 11.8$ Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{18}H_{15}FN_4O_4 \cdot 0.25H_2O$) C, H, N. HPLC purity: 99.4%.

(6S)-6-[[4-(2-Fluoro-4-pyridinyl)benzyl]oxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (42). Reaction of iodide **129** and 2-fluoro-4-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **42** (61%) as a cream solid: mp 159-161 °C; 1H NMR [$(CD_3)_2SO$] δ 8.30 (d, $J = 5.3$ Hz, 1 H), 8.03 (s, 1 H), 7.85 (br d, $J = 8.3$ Hz, 2 H), 7.69 (dt, $J = 5.3, 1.9$ Hz, 1 H), 7.51 (br s, 1 H), 7.47 (br d, $J = 8.3$ Hz, 2 H), 4.75 (d, $J = 12.4$ Hz, 1 H), 4.73-4.66 (m, 2 H), 4.49 (br d, $J = 11.8$ Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. ($C_{18}H_{15}FN_4O_4 \cdot 0.25H_2O$) C, H, N. HPLC purity: 96.7%.

4-[6-({[(6S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)-2-pyridinyl]benzonitrile (44) (Scheme 2A). Reaction of (6S)-6-[(6-bromo-2-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (**143**) and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave the crude product, which was further chromatographed, eluting with 5% MeOH/ CH_2Cl_2 , to give **44** (59%) as a light yellow powder: mp 239-240 °C; 1H NMR [$(CD_3)_2SO$] δ 8.27 (dt, $J = 8.6, 1.8$ Hz, 2 H), 8.02 (s, 1 H), 8.01 (br d, $J = 8.1$ Hz, 1 H), 7.98-7.92 (m, 3 H), 7.43 (br d, $J = 7.4$ Hz, 1 H), 4.86 (d, $J = 13.4$ Hz, 1 H), 4.82 (d, $J = 13.4$ Hz, 1 H), 4.73 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.52 (br d, $J = 11.9$ Hz, 1 H), 4.40-4.32 (m, 2 H), 4.27 (dd, $J = 13.4, 3.2$ Hz, 1 H). HPLC purity: 95.8%.

(6S)-6-[[6-(4-Fluorophenyl)-2-pyridinyl]methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (45). Reaction of bromide **143** with 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 10 min, followed by

chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **45** (77%) as a yellow powder: mp 155-157 °C; ¹H NMR [(CD₃)₂SO] δ 8.12 (ddt, *J* = 9.0, 5.6, 2.6 Hz, 2 H), 8.03 (s, 1 H), 7.90-7.85 (m, 2 H), 7.35-7.28 (m, 3 H), 4.83 (d, *J* = 13.3 Hz, 1 H), 4.79 (d, *J* = 13.3 Hz, 1 H), 4.73 (dt, *J* = 13.0, 2.6 Hz, 1 H), 4.52 (br d, *J* = 11.9 Hz, 1 H), 4.39-4.32 (m, 2 H), 4.27 (dd, *J* = 13.4, 3.1 Hz, 1 H). Anal. (C₁₈H₁₅FN₄O₄·0.5H₂O) C, H, N. HPLC purity: 98.2%.

(6S)-2-Nitro-6-({6-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (46). Reaction of bromide **143** with 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with EtOAc, gave the crude product, which was further chromatographed, eluting with 2.5% MeOH/CH₂Cl₂, to give **46** (60%) as a light yellow solid: mp 131-133 °C; ¹H NMR [(CD₃)₂SO] δ 8.18 (dt, *J* = 8.9, 2.5 Hz, 2 H), 8.03 (s, 1 H), 7.94-7.88 (m, 2 H), 7.48 (br d, *J* = 8.8 Hz, 2 H), 7.39-7.34 (m, 1 H), 4.84 (d, *J* = 13.2 Hz, 1 H), 4.81 (d, *J* = 13.3 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.52 (br d, *J* = 12.0 Hz, 1 H), 4.40-4.33 (m, 2 H), 4.27 (dd, *J* = 13.2, 3.0 Hz, 1 H). Anal. (C₁₉H₁₅F₃N₄O₅) H, N, F. C: calcd, 52.30; found, 52.98. HPLC purity: 99.3%.

(6S)-6-({6-[4-(Difluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (47). Reaction of bromide **143** with 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **47** (70%) as a light yellow solid: mp 82-84 °C; ¹H NMR [(CD₃)₂SO] δ 8.14 (dt, *J* = 8.9, 2.5 Hz, 2 H), 8.03 (s, 1 H), 7.91-7.85 (m, 2 H), 7.36-7.26 (m, 3 H), 7.31 (t, *J*_{H-F} = 74.0 Hz, 1 H), 4.83 (d, *J* = 13.3 Hz, 1 H), 4.80 (d, *J* = 13.3 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H),

4.52 (br d, $J = 12.0$ Hz, 1 H), 4.40-4.33 (m, 2 H), 4.27 (dd, $J = 13.2, 3.0$ Hz, 1 H). Anal. ($C_{19}H_{16}F_2N_4O_5$) C, H, N.

(6*S*)-6-[[6-(3-Fluoro-4-methoxyphenyl)-2-pyridinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (48). Reaction of bromide **143** with 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **48** (64%) as a light yellow solid: mp 110-112 °C; 1H NMR[(CD_3) $_2$ SO] δ 8.02 (s, 1 H), 7.94-7.82 (m, 4 H), 7.32-7.23 (m, 2 H), 4.82 (d, $J = 13.3$ Hz, 1 H), 4.78 (d, $J = 13.4$ Hz, 1 H), 4.73 (dt, $J = 12.0, 2.9$ Hz, 1 H), 4.52 (br d, $J = 12.0$ Hz, 1 H), 4.39-4.32 (m, 2 H), 4.27 (dd, $J = 13.4, 3.2$ Hz, 1 H), 3.90 (s, 3 H). Anal. ($C_{19}H_{17}FN_4O_5$) C, H, N: calcd, 13.99; found, 13.45. HPLC purity: 96.1%.

(6*S*)-6-[(6'-Methoxy[2,3'-bipyridin]-6-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (49). Reaction of bromide **143** with 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 10 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **49** (74%) as a white powder: mp 188-190 °C; 1H NMR [(CD_3) $_2$ SO] δ 8.86 (dd, $J = 2.5, 0.6$ Hz, 1 H), 8.35 (dd, $J = 8.7, 2.5$ Hz, 1 H), 8.03 (s, 1 H), 7.90-7.83 (m, 2 H), 7.34-7.28 (m, 1 H), 6.93 (dd, $J = 8.7, 0.6$ Hz, 1 H), 4.82 (d, $J = 13.1$ Hz, 1 H), 4.79 (d, $J = 13.3$ Hz, 1 H), 4.73 (dt, $J = 11.9, 2.6$ Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.42-4.32 (m, 2 H), 4.27 (dd, $J = 13.4, 3.2$ Hz, 1 H), 3.92 (s, 3 H). Anal. ($C_{18}H_{17}N_5O_5$) C, H, N.

4-[4-([(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl]-2-pyridinyl]benzonitrile (51) (Scheme 2B). Reaction of (6*S*)-6-[(2-bromo-4-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**146**) with 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 5 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **51**

(26%) as a white powder: mp 199-201 °C; ¹H NMR [(CD₃)₂SO] δ 8.68 (dd, *J* = 4.9, 0.4 Hz, 1 H), 8.24 (dt, *J* = 8.6, 1.8 Hz, 2 H), 8.03 (s, 1 H), 7.97-7.92 (m, 3 H), 7.36 (br d, *J* = 5.0 Hz, 1 H), 4.83 (d, *J* = 13.8 Hz, 1 H), 4.78 (d, *J* = 13.8 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 11.7 Hz, 1 H), 4.35-4.23 (m, 3 H). Anal. (C₁₉H₁₅N₅O₄·0.5H₂O) C, H, N. HPLC purity: 99.6%.

(6*S*)-6-([2-(4-Fluorophenyl)-4-pyridinyl]methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (52). Reaction of bromide **146** with 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **52** (46%) as a white powder: mp 136-139 °C; ¹H NMR [(CD₃)₂SO] δ 8.61 (d, *J* = 4.9 Hz, 1 H), 8.09 (ddt, *J* = 8.9, 5.6, 2.6 Hz, 2 H), 8.03 (s, 1 H), 7.79 (br s, 1 H), 7.33-7.24 (m, 3 H), 4.80 (d, *J* = 13.7 Hz, 1 H), 4.76 (d, *J* = 13.8 Hz, 1 H), 4.71 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.36-4.22 (m, 3 H). Anal. (C₁₈H₁₅FN₄O₄·0.75H₂O) C, H, N. HPLC purity: 100%.

(6*S*)-2-Nitro-6-([2-[4-(trifluoromethoxy)phenyl]-4-pyridinyl]methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (53). Reaction of bromide **146** with 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **53** (48%) as a white powder: mp 140-141 °C; ¹H NMR [(CD₃)₂SO] δ 8.64 (dd, *J* = 4.9, 0.4 Hz, 1 H), 8.16 (dt, *J* = 8.9, 2.5 Hz, 2 H), 8.03 (s, 1 H), 7.84 (br s, 1 H), 7.46 (br d, *J* = 8.8 Hz, 2 H), 7.31 (br d, *J* = 5.0 Hz, 1 H), 4.82 (d, *J* = 13.7 Hz, 1 H), 4.77 (d, *J* = 13.7 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.36-4.23 (m, 3 H). Anal. (C₁₉H₁₅F₃N₄O₅·0.25H₂O) C, H, N. HPLC purity: 100%.

(6*S*)-6-([2-[4-(Difluoromethoxy)phenyl]-4-pyridinyl]methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (54). Reaction of bromide **146** with 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in

Procedure A for 1.5 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **54** (79%) as a light yellow powder: mp 122-124 °C; ¹H NMR [(CD₃)₂SO] δ 8.61 (dd, *J* = 4.9, 0.5 Hz, 1 H), 8.10 (dt, *J* = 8.9, 2.5 Hz, 2 H), 8.04 (s, 1 H), 7.80 (br s, 1 H), 7.31 (t, *J*_{H-F} = 74.0 Hz, 1 H), 7.30-7.25 (m, 3 H), 4.81 (d, *J* = 13.7 Hz, 1 H), 4.76 (d, *J* = 13.7 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 11.8 Hz, 1 H), 4.36-4.23 (m, 3 H). Anal. (C₁₉H₁₆F₂N₄O₅) C, H, N.

(6*S*)-6-[[2-(3-Fluoro-4-methoxyphenyl)-4-pyridinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (55). Reaction of bromide **146** with 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **55** (68%) as a white powder: mp 171-173 °C; ¹H NMR [(CD₃)₂SO] δ 8.58 (dd, *J* = 5.0, 0.4 Hz, 1 H), 8.03 (s, 1 H), 7.91-7.82 (m, 2 H), 7.79 (br s, 1 H), 7.28-7.21 (m, 2 H), 4.79 (d, *J* = 13.6 Hz, 1 H), 4.76-4.68 (m, 2 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.35-4.22 (m, 3 H), 3.90 (s, 3 H). Anal. (C₁₉H₁₇FN₄O₅·0.25H₂O) C, H, N. HPLC purity: 99.5%.

(6*S*)-6-[(6'-Methoxy[2,3'-bipyridin]-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (56). Reaction of bromide **146** with 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **56** (73%) as a light brown solid: mp 89-91 °C; ¹H NMR [(CD₃)₂SO] δ 8.84 (dd, *J* = 2.5, 0.6 Hz, 1 H), 8.60 (dd, *J* = 4.9, 0.4 Hz, 1 H), 8.32 (dd, *J* = 8.7, 2.5 Hz, 1 H), 8.03 (s, 1 H), 7.80 (br s, 1 H), 7.26 (dd, *J* = 5.1, 1.4 Hz, 1 H), 6.92 (dd, *J* = 8.7, 0.6 Hz, 1 H), 4.82-4.69 (m, 3 H), 4.50 (br d, *J* = 11.6 Hz, 1 H), 4.36-4.22 (m, 3 H), 3.92 (s, 3 H). Anal. (C₁₈H₁₇N₅O₅·0.5H₂O) C, H, N: calcd, 17.85; found, 16.75. HPLC purity: 92.0%.

4-[5-([(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl]-3-pyridinyl]benzonitrile (58) (Scheme 2C). Reaction of (6*S*)-6-[(5-bromo-3-

pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**148**) with 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **58** (92%) as a light yellow solid: mp 192-194 °C; ¹H NMR [(CD₃)₂SO] δ 8.90 (d, *J* = 2.3 Hz, 1 H), 8.61 (d, *J* = 1.9 Hz, 1 H), 8.06 (t, *J* = 2.1 Hz, 1 H), 8.01 (s, 1 H), 7.99-7.91 (m, 4 H), 4.81 (d, *J* = 12.4 Hz, 1 H), 4.78 (d, *J* = 12.4 Hz, 1 H), 4.70 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.49 (br d, *J* = 12.0 Hz, 1 H), 4.34-4.21 (m, 3 H). Anal. (C₁₉H₁₅N₅O₄·0.5H₂O) C, H, N. HPLC purity: 99.5%.

(6*S*)-6-([5-(4-Fluorophenyl)-3-pyridinyl]methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (59**)**. Reaction of bromide **148** with 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **59** (96%) as a light brown solid: mp 169-171 °C; ¹H NMR [(CD₃)₂SO] δ 8.81 (d, *J* = 2.3 Hz, 1 H), 8.53 (d, *J* = 1.9 Hz, 1 H), 8.02 (s, 1 H), 7.95 (t, *J* = 2.1 Hz, 1 H), 7.75 (ddt, *J* = 8.9, 5.4, 2.7 Hz, 2 H), 7.33 (tt, *J* = 8.9, 2.7 Hz, 2 H), 4.79 (d, *J* = 12.3 Hz, 1 H), 4.75 (d, *J* = 12.3 Hz, 1 H), 4.70 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.49 (br d, *J* = 11.9 Hz, 1 H), 4.34-4.21 (m, 3 H). Anal. (C₁₈H₁₅FN₄O₄) C, H, F, N: calcd, 15.13; found, 14.45. HPLC purity: 100%.

(6*S*)-2-Nitro-6-([5-[4-(trifluoromethoxy)phenyl]-3-pyridinyl]methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (60**)**. Reaction of bromide **148** with 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 0-5% MeOH/EtOAc, gave **60** (95%) as a white solid: mp 152-155 °C; ¹H NMR [(CD₃)₂SO] δ 8.84 (d, *J* = 2.2 Hz, 1 H), 8.56 (d, *J* = 1.7 Hz, 1 H), 8.02 (s, 1 H), 7.98 (t, *J* = 1.9 Hz, 1 H), 7.84 (br d, *J* = 8.7 Hz, 2 H), 7.49 (br d, *J* = 8.3 Hz, 2 H), 4.80 (d, *J* = 13.2 Hz, 1 H), 4.76 (d, *J* =

13.2 Hz, 1 H), 4.70 (dt, $J = 12.0, 2.4$ Hz, 1 H), 4.44 (br d, $J = 12.0$ Hz, 1 H), 4.34-4.21 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_5 \cdot 0.25H_2O$) C, H, N, F. HPLC purity: 99.9%.

(6S)-6-({5-[4-(Difluoromethoxy)phenyl]-3-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (61). Reaction of bromide **148** with 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1.5 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **61** (63%) as a light yellow solid: mp 158-160 °C; 1H NMR [$(CD_3)_2SO$] δ 8.82 (d, $J = 2.3$ Hz, 1 H), 8.53 (d, $J = 2.0$ Hz, 1 H), 8.02 (s, 1 H), 7.96 (t, $J = 2.1$ Hz, 1 H), 7.77 (dt, $J = 8.8, 2.5$ Hz, 2 H), 7.30 (t, $J_{H-F} = 74.0$ Hz, 1 H), 7.30 (dt, $J = 8.7, 2.5$ Hz, 2 H), 4.79 (d, $J = 12.3$ Hz, 1 H), 4.75 (d, $J = 12.3$ Hz, 1 H), 4.70 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.49 (br d, $J = 11.9$ Hz, 1 H), 4.34-4.22 (m, 3 H). Anal. ($C_{19}H_{16}F_2N_4O_5$) C, H, N.

(6S)-6-[[5-(3-Fluoro-4-methoxyphenyl)-3-pyridinyl]methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (62). Reaction of bromide **148** with 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **62** (92%) as a light yellow solid: mp 181-183 °C; 1H NMR [$(CD_3)_2SO$] δ 8.82 (d, $J = 2.3$ Hz, 1 H), 8.50 (d, $J = 1.9$ Hz, 1 H), 8.01 (s, 1 H), 7.96 (t, $J = 2.1$ Hz, 1 H), 7.64 (dd, $J = 12.8, 2.2$ Hz, 1 H), 7.52 (ddd, $J = 8.5, 2.2, 1.1$ Hz, 1 H), 7.27 (t, $J = 8.8$ Hz, 1 H), 4.77 (d, $J = 12.3$ Hz, 1 H), 4.75-4.67 (m, 2 H), 4.49 (br d, $J = 11.5$ Hz, 1 H), 4.33-4.21 (m, 3 H), 3.89 (s, 3 H). Anal. ($C_{19}H_{17}FN_4O_5 \cdot H_2O$) C, H, N, F. HPLC purity: 98.2%.

(6S)-6-[(6'-Methoxy[3,3'-bipyridin]-5-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (63). Reaction of bromide **148** with 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 15 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **63** (92%) as a light brown solid: mp 170-172 °C; 1H NMR [$(CD_3)_2SO$] δ

8.83 (d, $J = 2.3$ Hz, 1 H), 8.54-8.51 (m, 2 H), 8.06 (dd, $J = 8.7, 2.6$ Hz, 1 H), 8.01 (s, 1 H), 7.97 (t, $J = 2.1$ Hz, 1 H), 6.94 (dd, $J = 8.7, 0.6$ Hz, 1 H), 4.78 (d, $J = 12.3$ Hz, 1 H), 4.74 (d, $J = 12.4$ Hz, 1 H), 4.70 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.49 (br d, $J = 12.0$ Hz, 1 H), 4.34-4.22 (m, 3 H), 3.91 (s, 3 H). Anal. ($C_{18}H_{17}N_5O_5 \cdot 0.75H_2O$) C, H, N. HPLC purity: 100%.

4-[2-(((6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl)oxy)methyl)-4-pyridinyl]benzonitrile (65) (Scheme 2D). Reaction of (6*S*)-6-[(4-bromo-2-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**152**) with 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **65** (25%) as a beige powder: mp 173 °C (dec); 1H NMR [$(CD_3)_2SO$] δ 8.65 (br d, $J = 5.1$ Hz, 1 H), 8.00 (s, 1 H), 7.99-7.92 (m, 4 H), 7.70 (dd, $J = 5.2, 1.8$ Hz, 1 H), 7.65 (br s, 1 H), 4.84 (d, $J = 13.3$ Hz, 1 H), 4.80 (d, $J = 13.3$ Hz, 1 H), 4.71 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.51 (br d, $J = 12.0$ Hz, 1 H), 4.41-4.31 (m, 2 H), 4.25 (dd, $J = 13.5, 3.2$ Hz, 1 H). Anal. ($C_{19}H_{15}N_5O_4 \cdot 0.75H_2O$) C, H, N: calcd, 17.92; found, 17.47. HPLC purity: 99.8%.

(6*S*)-6-[[4-(4-Fluorophenyl)-2-pyridinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (66). Reaction of bromide **152** with 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **66** (86%) as a white solid: mp 170 °C (dec); 1H NMR [$(CD_3)_2SO$] δ 8.57 (br d, $J = 5.3$ Hz, 1 H), 8.01 (s, 1 H), 7.80 (ddt, $J = 8.9, 5.4, 2.7$ Hz, 2 H), 7.61 (dd, $J = 5.2, 1.8$ Hz, 1 H), 7.58 (br s, 1 H), 7.33 (tt, $J = 8.8, 2.6$ Hz, 2 H), 4.82 (d, $J = 13.3$ Hz, 1 H), 4.79 (d, $J = 13.3$ Hz, 1 H), 4.72 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.51 (br d, $J = 12.0$ Hz, 1 H), 4.40-4.31 (m, 2 H), 4.25 (dd, $J = 13.4, 3.2$ Hz, 1 H). Anal. ($C_{18}H_{15}FN_4O_4 \cdot 0.25H_2O$) C, H, N, F. HPLC purity: 95.7%.

(6*S*)-2-Nitro-6-({4-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (67). Reaction of bromide **152** with 4-

(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **67** (70%) as an orange solid: mp 74-77 °C; ¹H NMR [(CD₃)₂SO] δ 8.61 (dd, *J* = 5.1, 0.3 Hz, 1 H), 8.01 (s, 1 H), 7.87 (dt, *J* = 8.8, 2.1 Hz, 2 H), 7.64 (dd, *J* = 5.0, 1.8 Hz, 1 H), 7.60 (br s, 1 H), 7.49 (br d, *J* = 8.0 Hz, 2 H), 4.83 (d, *J* = 13.3 Hz, 1 H), 4.79 (d, *J* = 13.3 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 12.5 Hz, 1 H), 4.41-4.23 (m, 3 H); HRFABMS calcd for C₁₉H₁₆F₃N₄O₅ *m/z* [M + H]⁺ 437.1073, found 437.1073. HPLC purity: 96.1%.

(6*S*)-6-({4-[4-(Difluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (68). Reaction of bromide **152** with 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **68** (79%) as a light yellow oil; ¹H NMR [(CD₃)₂SO] δ 8.58 (dd, *J* = 5.1, 0.4 Hz, 1 H), 8.02 (s, 1 H), 7.81 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.62 (dd, *J* = 5.2, 1.8 Hz, 1 H), 7.59 (br s, 1 H), 7.32 (t, *J*_{H-F} = 73.8 Hz, 1 H), 7.30 (dt, *J* = 8.7, 2.4 Hz, 2 H), 4.81 (d, *J* = 13.3 Hz, 1 H), 4.78 (d, *J* = 13.4 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.40-4.23 (m, 3 H); HRFABMS calcd for C₁₉H₁₇F₂N₄O₅ *m/z* [M + H]⁺ 419.1167, found 419.1173. HPLC purity: 95.4%.

(6*S*)-6-[[4-(3-Fluoro-4-methoxyphenyl)-2-pyridinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (69). Reaction of bromide **152** with 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure A for 45 min, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **69** (76%) as a beige powder: mp 110-112 °C; ¹H NMR [(CD₃)₂SO] δ 8.54 (dd, *J* = 5.3, 0.4 Hz, 1 H), 8.01 (s, 1 H), 7.68 (dd, *J* = 12.8, 2.3 Hz, 1 H), 7.62 (dd, *J* = 5.2, 1.9 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.27 (t, *J* = 8.8 Hz, 1 H), 4.80 (d, *J* = 13.2 Hz, 1 H),

4.77-4.69 (m, 2 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.39-4.22 (m, 3 H), 3.90 (s, 3 H). Anal. ($C_{19}H_{17}FN_4O_5$) C, H, N.

(6S)-6-[(6-Methoxy[3,4'-bipyridin]-2'-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (70). Reaction of bromide **152** with 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **70** (77%) as a beige powder: mp 139-141 °C; 1H NMR [$(CD_3)_2SO$] δ 8.60 (dd, $J = 2.6$, 0.5 Hz, 1 H), 8.56 (dd, $J = 5.2$, 0.6 Hz, 1 H), 8.08 (dd, $J = 8.7$, 2.7 Hz, 1 H), 8.01 (s, 1 H), 7.64 (dd, $J = 5.2$, 1.9 Hz, 1 H), 7.61 (br s, 1 H), 6.94 (dd, $J = 8.7$, 0.6 Hz, 1 H), 4.81 (d, $J = 13.3$ Hz, 1 H), 4.76 (d, $J = 13.3$ Hz, 1 H), 4.72 (dt, $J = 12.0$, 2.6 Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.39-4.22 (m, 3 H), 3.92 (s, 3 H). Anal. ($C_{18}H_{17}N_5O_5 \cdot 0.25H_2O$) C, H, N. HPLC purity: 99.6%.

Procedure L. 5-Bromo-2-(bromomethyl)pyridine (154) (Scheme 3A; alternative method). Mesyl chloride (0.84 mL, 10.7 mmol) was added to a solution of (5-bromo-2-pyridinyl)methanol (**153**) (1.00 g, 5.32 mmol) and Et_3N (2.22 mL, 15.9 mmol) in anhydrous THF (15 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, and then partitioned between EtOAc and water. The organic layer was dried and concentrated to give a crude mesylate. The mesylate was dissolved in acetone (20 mL), LiBr (2.0 g, 23 mmol) was added, and the stirred mixture was refluxed under N_2 for 1 h. The cooled mixture was filtered and evaporated, and the residue was diluted with water and extracted with CH_2Cl_2 . The organic fraction was dried and evaporated, and then column chromatography of the residue, eluting with 5% EtOAc/ CH_2Cl_2 , gave **154**⁴ (1.28 g, 96%) as a lachramatory lilac oil that was used directly in the next step.

(6S)-6-[(5-Bromo-2-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (156) (alternative method). A solution of alcohol **140** (1.87 g, 10.1 mmol)

and 5-bromo-2-(chloromethyl)pyridine⁵ (**155**) (2.50 g, 12.1 mmol) in anhydrous DMF (40 mL) at 0 °C was treated with 60% NaH (0.525 g, 13.1 mmol). The resulting mixture was stirred at room temperature for 2 h, and then quenched with water (300 mL). The precipitate was filtered, washed with water, and triturated with Et₂O, to give **156** (3.09 g, 86%) as a light brown solid that was sufficiently pure to use directly in the next step.

4-[6-([(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl]-3-pyridinyl]benzonitrile (72**). Reaction of bromide **156** and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **72** (81%) as light yellow powder: mp 172 °C; ¹H NMR [(CD₃)₂SO] δ 8.92 (dd, *J* = 2.3, 0.4 Hz, 1 H), 8.18 (dd, *J* = 8.2, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.98-7.92 (m, 4 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 4.83 (d, *J* = 13.3 Hz, 1 H), 4.79 (d, *J* = 13.3 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 12.0 Hz, 1 H), 4.39-4.24 (m, 3 H). Anal. (C₁₉H₁₅N₅O₄·0.5H₂O) C, H, N. HPLC purity: 97.1%.**

(6*S*)-6-([5-(4-Fluorophenyl)-2-pyridinyl]methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (73**). Reaction of bromide **156** and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1.5 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/CH₂Cl₂, gave **73** (89%) as a white solid: mp 157-159 °C; ¹H NMR [(CD₃)₂SO] δ 8.82 (d, *J* = 1.8 Hz, 1 H), 8.06 (dd, *J* = 8.1, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.76 (ddt, *J* = 8.9, 5.4, 2.7 Hz, 2 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 7.33 (tt, *J* = 8.9, 2.7 Hz, 2 H), 4.82-4.74 (m, 2 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 12.0 Hz, 1 H), 4.38-4.23 (m, 3 H). Anal. (C₁₈H₁₅FN₄O₄·0.5H₂O) C, H, N, F. HPLC purity: 99.9%.**

(6*S*)-2-Nitro-6-([5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl]methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (74**). Reaction of bromide **156** and 4-**

(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1.5 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **74** (79%) as a white solid: mp 157-159 °C; ¹H NMR [(CD₃)₂SO] δ 8.85 (d, *J* = 2.0 Hz, 1 H), 8.11 (dd, *J* = 8.1, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.85 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.51-7.44 (m, 3 H), 4.81 (d, *J* = 13.2 Hz, 1 H), 4.77 (d, *J* = 13.2 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 12.0 Hz, 1 H), 4.38-4.23 (m, 3 H). Anal. (C₁₉H₁₅F₃N₄O₅) C, H, N, F.

(6S)-6-({5-[4-(Difluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (75). Reaction of bromide **156** and 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **75** (78%) as a white solid: mp 166-169 °C; ¹H NMR [(CD₃)₂SO] δ 8.83 (dd, *J* = 2.4, 0.6 Hz, 1 H), 8.07 (dd, *J* = 8.1, 1.4 Hz, 1 H), 8.04 (s, 1 H), 7.78 (dt, *J* = 8.8, 2.6 Hz, 2 H), 7.46 (br d, *J* = 8.2 Hz, 1 H), 7.30 (br d, *J* = 8.7 Hz, 2 H), 7.29 (t, *J*_{H-F} = 74.0 Hz, 1 H), 4.81 (d, *J* = 13.1 Hz, 1 H), 4.77 (d, *J* = 13.1 Hz, 1 H), 4.72 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.38-4.23 (m, 3 H). Anal. (C₁₉H₁₆F₂N₄O₅) C, H, N.

(6S)-6-{[5-(3-Fluoro-4-methoxyphenyl)-2-pyridinyl]methoxy}-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (76). Reaction of bromide **156** and 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **76** (65%) as a beige powder: mp 161 °C; ¹H NMR [(CD₃)₂SO] δ 8.84 (d, *J* = 2.0 Hz, 1 H), 8.11 (dd, *J* = 8.2, 2.3 Hz, 1 H), 8.03 (s, 1 H), 7.66 (dd, *J* = 12.8, 2.2 Hz, 1 H), 7.54 (ddd, *J* = 8.6, 2.2, 1.1 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.28 (t, *J* = 8.9 Hz, 1 H), 4.80 (d, *J* = 13.1 Hz, 1 H), 4.76 (d, *J* = 13.1 Hz, 1 H), 4.71 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 11.9 Hz, 1 H), 4.37-4.23 (m, 3 H), 3.89 (s, 3 H). Anal. (C₁₉H₁₇FN₄O₅·1.5H₂O) C, H, N. HPLC purity: 100%.

3-Chloro-4-(trifluoromethoxy)phenylboronic acid (168) (Scheme 3C). Reaction of 2-chloro-4-iodo-1-(trifluoromethoxy)benzene¹ (**163**), triisopropyl borate (1.3 equiv.) and *n*BuLi (1.07 equiv.) at -78 °C, using Procedure G, followed by trituration of the product in pentane (~3-4 mL) (cooling to -78 °C, filtering rapidly and washing with pentane cooled to -78 °C), gave **168**⁶ (76%) as a white solid (a 1:1 mixture of the trimeric boroxine and the boronic acid by NMR): mp 202-204 °C; ¹H NMR (CDCl₃) δ 8.26 (d, *J* = 1.5 Hz, 3 H, boroxine), 8.12 (dd, *J* = 8.2, 1.5 Hz, 3 H, boroxine), 7.85 (d, *J* = 1.5 Hz, 1 H, boronic acid), 7.65 (dd, *J* = 8.2, 1.6 Hz, 1 H, boronic acid), 7.48 (dq, *J* = 8.2, 1.5 Hz, 3 H, boroxine), 7.35 (dq, *J* = 8.2, 1.5 Hz, 1 H, boronic acid), 4.57 (s, 2 H, boronic acid).

2-Fluoro-4-(trifluoromethoxy)phenylboronic acid (169). Reaction of 1-bromo-2-fluoro-4-(trifluoromethoxy)benzene (**164**), triisopropyl borate and *n*BuLi at -78 °C, using Procedure G, followed by trituration of the product in cold pentane, gave **169**⁷ (75%) as a pale pink solid: mp 114-116 °C (lit.⁷ mp 89-93 °C); ¹H NMR (CDCl₃) δ 7.89 (t, *J* = 8.0 Hz, 1 H), 7.08 (ddq, *J* = 8.4, 2.2, 1.1 Hz, 1 H), 6.94 (ddq, *J* = 11.0, 1.9, 0.9 Hz, 1 H), 4.97, 4.99 (2 s, 2 H).

3-Fluoro-4-(trifluoromethoxy)phenylboronic acid (170). Reaction of 4-bromo-2-fluoro-1-(trifluoromethoxy)benzene (**165**), triisopropyl borate (1.3 equiv.) and *n*BuLi (1.05 equiv.) at -78 °C, using Procedure G, followed by trituration of the product in pentane (~3-4 mL) (cooling to -78 °C, filtering rapidly and washing with pentane cooled to -78 °C), gave **170**⁸ (71%) as a white solid (a 1:3 mixture of the trimeric boroxine and the boronic acid by NMR): mp 141-143 °C; ¹H NMR (CDCl₃) δ 8.03-7.95 (m, 6 H, boroxine), 7.58 (dd, *J* = 10.4, 1.4 Hz, 3x 1 H, boronic acid), 7.52 (br d, *J* = 8.2 Hz, 3x 1 H, boronic acid), 7.46 (ddq, *J* = 8.2, 7.1, 1.3 Hz, 3 H, boroxine), 7.33 (ddq, *J* = 8.4, 7.1, 1.3 Hz, 3x 1 H, boronic acid), 4.61 (s, 3x 2 H, boronic acid).

4-Chloro-3-(trifluoromethoxy)phenylboronic acid (171). Reaction of 4-bromo-1-chloro-2-(trifluoromethoxy)benzene (**166**), triisopropyl borate and *n*BuLi at -78 °C, using Procedure

G, followed by trituration of the product in pentane (~3-4 mL) (cooling to -78 °C, filtering rapidly and washing with pentane cooled to -78 °C), gave **171**⁹ (73%) as a white solid (initially a 1:2.5 mixture of the trimeric boroxine and the boronic acid by NMR): mp 177-179 °C; ¹H NMR (CDCl₃) δ 8.07 (m, 3 H, boroxine), 8.03 (dd, *J* = 7.9, 1.4 Hz, 3 H, boroxine), 7.69 (m, 2.5x 1 H, boronic acid), 7.65 (d, *J* = 7.9 Hz, 3 H, boroxine), 7.60 (dd, *J* = 8.0, 1.4 Hz, 2.5x 1 H, boronic acid), 7.51 (d, *J* = 7.9 Hz, 2.5x 1 H, boronic acid), 4.59 (s, 2.5x 2 H, boronic acid).

(6S)-6-({5-[3-Chloro-4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (78) (Scheme 3A). Reaction of bromide **156** and 3-chloro-4-(trifluoromethoxy)phenylboronic acid (**168**) (1.6 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.6% MeOH/CH₂Cl₂ (foreruns) and then with 0.6% MeOH/CH₂Cl₂, gave **78** (72%) as a pale yellow solid: mp (CH₂Cl₂/pentane) 162-163 °C; ¹H NMR (CDCl₃) δ 8.74 (dd, *J* = 2.3, 0.7 Hz, 1 H), 7.87 (dd, *J* = 8.1, 2.4 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 7.51-7.43 (m, 3 H), 7.42 (s, 1 H), 4.87 (d, *J* = 13.0 Hz, 1 H), 4.81 (d, *J* = 13.0 Hz, 1 H), 4.72 (ddd, *J* = 12.3, 3.3, 1.8 Hz, 1 H), 4.40 (dd, *J* = 12.2, 1.2 Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. (C₁₉H₁₄ClF₃N₄O₅) C, H, N.

(6S)-6-({5-[2-Fluoro-4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (79). Reaction of bromide **156** and 2-fluoro-4-(trifluoromethoxy)phenylboronic acid (**169**) (1.5 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.75% MeOH/CH₂Cl₂ (foreruns) and then with 0.75-1% MeOH/CH₂Cl₂, gave **79** (87%) as a pale orange solid: mp (CH₂Cl₂/pentane) 161-162 °C; ¹H NMR (CDCl₃) δ 8.70 (m, 1 H), 7.86 (dt, *J* = 8.2, 1.9 Hz, 1 H), 7.46 (t, *J* = 8.5 Hz, 1 H), 7.46 (d, *J* = 7.9 Hz, 1 H), 7.39 (s, 1 H), 7.15 (m, 1 H), 7.11 (m,

1 H), 4.87 (d, $J = 13.0$ Hz, 1 H), 4.81 (d, $J = 13.0$ Hz, 1 H), 4.70 (ddd, $J = 12.2, 3.5, 1.7$ Hz, 1 H), 4.40 (dd, $J = 12.2, 1.4$ Hz, 1 H), 4.33-4.20 (m, 3 H). Anal. ($C_{19}H_{14}F_4N_4O_5$) C, H, N.

(6S)-6-({5-[3-Fluoro-4-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (80) (alternative method). Reaction of bromide **156** and 3-fluoro-4-(trifluoromethoxy)phenylboronic acid (**170**) (1.6 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.75% MeOH/ CH_2Cl_2 (foreruns) and then 0.75% MeOH/ CH_2Cl_2 (**80**: ~26 mg) and then 0.75-2% MeOH/ CH_2Cl_2 , gave impure product (~40 mg), which was rechromatographed on silica gel, as above, and the pure product fractions from both columns were combined to give **80** (64%) as a light yellow solid: mp (CH_2Cl_2 /pentane) 182-184 °C; 1H NMR ($CDCl_3$) δ 8.74 (dd, $J = 2.3, 0.7$ Hz, 1 H), 7.86 (dd, $J = 8.1, 2.4$ Hz, 1 H), 7.48-7.38 (m, 4 H), 7.35 (ddd, $J = 8.4, 2.2, 1.0$ Hz, 1 H), 4.87 (d, $J = 13.0$ Hz, 1 H), 4.81 (d, $J = 13.0$ Hz, 1 H), 4.70 (ddd, $J = 12.2, 3.5, 1.5$ Hz, 1 H), 4.40 (dd, $J = 12.2, 1.4$ Hz, 1 H), 4.33-4.20 (m, 3 H). Anal. ($C_{19}H_{14}F_4N_4O_5$) C, H, N.

(6S)-6-({5-[4-Chloro-3-(trifluoromethoxy)phenyl]-2-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (81). Reaction of bromide **156** and 4-chloro-3-(trifluoromethoxy)phenylboronic acid (**171**) (1.5 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.75% MeOH/ CH_2Cl_2 (foreruns) and then with 0.75-1% MeOH/ CH_2Cl_2 , gave **81** (85%) as a pale orange solid: mp (CH_2Cl_2 /pentane) 149-150 °C; 1H NMR ($CDCl_3$) δ 8.74 (br d, $J = 1.9$ Hz, 1 H), 7.86 (dd, $J = 8.1, 2.4$ Hz, 1 H), 7.59 (d, $J = 8.3$ Hz, 1 H), 7.51 (quintet, $J = 1.5$ Hz, 1 H), 7.46 (br d, $J = 8.0$ Hz, 1 H), 7.45 (dd, $J = 8.3, 2.1$ Hz, 1 H), 7.40 (s, 1 H), 4.86 (d, $J = 13.0$ Hz, 1 H), 4.81 (d, $J = 13.0$ Hz, 1 H), 4.69 (ddd, $J = 12.2, 3.4, 1.5$ Hz, 1 H), 4.39 (dd, $J = 12.2, 1.2$ Hz, 1 H), 4.32-4.20 (m, 3 H). Anal. ($C_{19}H_{14}ClF_3N_4O_5$) C, H, N.

(6*S*)-6-[(6-Fluoro[2,3'-bipyridin]-6'-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (82). Reaction of bromide **156** and 2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine under the Suzuki coupling conditions described in Procedure A for 3 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **82** (70%) as a white solid: mp 171-173 °C; ¹H NMR [(CD₃)₂SO] δ 9.18 (dd, *J* = 2.3, 0.6 Hz, 1 H), 8.42 (dd, *J* = 8.2, 2.3 Hz, 1 H), 8.14 (q, *J* = 8.1 Hz, 1 H), 8.04 (s, 1 H), 8.02 (dd, *J* = 7.4, 2.5 Hz, 1 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 7.20 (dd, *J* = 8.2, 2.7 Hz, 1 H), 4.84 (d, *J* = 13.5 Hz, 1 H), 4.80 (d, *J* = 13.5 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.51 (br d, *J* = 12.0 Hz, 1 H), 4.39-4.23 (m, 3 H). Anal. (C₁₇H₁₄FN₅O₄) C, H, N.

(6*S*)-2-Nitro-6-[[6'-(trifluoromethyl)[3,3'-bipyridin]-6-yl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (84). Reaction of bromide **156** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine under the Suzuki coupling conditions described in Procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **84** (18%) as a white solid: mp 212-214 °C; ¹H NMR [(CD₃)₂SO] δ 9.15 (d, *J* = 2.1 Hz, 1 H), 8.98 (dd, *J* = 2.2, 0.4 Hz, 1 H), 8.44 (dd, *J* = 8.0, 1.8 Hz, 1 H), 8.26 (dd, *J* = 8.2, 2.4 Hz, 1 H), 8.04 (s, 1 H), 8.03 (d, *J* = 7.7 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 1 H), 4.84 (d, *J* = 13.4 Hz, 1 H), 4.81 (d, *J* = 13.4 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.52 (br d, *J* = 12.0 Hz, 1 H), 4.40-4.24 (m, 3 H); HRFABMS calcd for C₁₈H₁₅F₃N₅O₄ *m/z* [M + H]⁺ 422.1076, found 422.1070. HPLC purity: 98.1%.

(6*S*)-6-[(6'-Fluoro[3,3'-bipyridin]-6-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (85). Reaction of bromide **156** and 6-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **85** (61%) as a pale yellow solid: mp 188-190 °C; ¹H NMR [(CD₃)₂SO] δ 8.89 (d, *J* = 1.9 Hz, 1 H), 8.61 (d, *J* = 2.5 Hz, 1 H), 8.35 (td, *J* = 8.2, 2.6 Hz, 1 H), 8.15 (dd, *J* = 8.1, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.48 (d, *J*

= 8.2 Hz, 1 H), 7.33 (dd, J = 8.6, 2.8 Hz, 1 H), 4.82 (d, J = 13.2 Hz, 1 H), 4.78 (d, J = 13.3 Hz, 1 H), 4.72 (dt, J = 12.0, 2.6 Hz, 1 H), 4.51 (br d, J = 11.9 Hz, 1 H), 4.39-4.23 (m, 3 H); HRFABMS calcd for $C_{17}H_{15}FN_5O_4$ m/z $[M + H]^+$ 372.1108, found 372.1110. HPLC purity: 98.5%.

(6S)-6-[(5'-Fluoro[3,3'-bipyridin]-6-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (86). Reaction of bromide **156** and 5-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 21 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **86** (55%) as a brown powder: mp 187 °C (dec); 1H NMR $[(CD_3)_2SO]$ δ 8.95 (br d, J = 1.9 Hz, 1 H), 8.86 (t, J = 1.8 Hz, 1 H), 8.63 (d, J = 2.7 Hz, 1 H), 8.22 (dd, J = 8.1, 2.4 Hz, 1 H), 8.17 (ddd, J = 10.2, 2.6, 1.9 Hz, 1 H), 8.03 (s, 1 H), 7.50 (d, J = 8.2 Hz, 1 H), 4.83 (d, J = 13.3 Hz, 1 H), 4.79 (d, J = 13.3 Hz, 1 H), 4.73 (dt, J = 12.0, 2.6 Hz, 1 H), 4.51 (br d, J = 11.9 Hz, 1 H), 4.39-4.24 (m, 3 H). Anal. ($C_{17}H_{14}FN_5O_4 \cdot 0.25H_2O$) C, H, N: calcd, 18.63; found, 18.15. HPLC purity: 99.2%.

(6S)-6-[(6'-Methoxy[3,3'-bipyridin]-6-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (87). Reaction of bromide **156** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 6 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **87** (59%) as a light yellow powder: mp 187-189 °C; 1H NMR $[(CD_3)_2SO]$ δ 8.83 (d, J = 2.0 Hz, 1 H), 8.54 (d, J = 2.5 Hz, 1 H), 8.10-8.04 (m, 2 H), 8.03 (s, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 4.79 (d, J = 13.1 Hz, 1 H), 4.76 (d, J = 13.1 Hz, 1 H), 4.71 (dt, J = 12.0, 2.6 Hz, 1 H), 4.51 (br d, J = 11.9 Hz, 1 H), 4.37-4.23 (m, 3 H), 3.90 (s, 3 H). Anal. ($C_{18}H_{17}N_5O_5$) C, H, N.

(6S)-6-[(3'-Fluoro[3,4'-bipyridin]-6-yl)methoxy]-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (88). Reaction of bromide **156** and 3-fluoro-4-pyridinylboronic acid under the

Suzuki coupling conditions described in Procedure A for 6.5 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **88** (31%) as a light yellow solid: mp 160-162 °C; ¹H NMR [(CD₃)₂SO] δ 8.82 (br s, 1 H), 8.70 (d, *J* = 2.5 Hz, 1 H), 8.55 (dd, *J* = 4.9, 0.8 Hz, 1 H), 8.12 (dt, *J* = 8.6, 1.5 Hz, 1 H), 8.04 (s, 1 H), 7.71 (dd, *J* = 6.8, 5.0 Hz, 1 H), 7.54 (d, *J* = 8.2 Hz, 1 H), 4.85 (d, *J* = 13.6 Hz, 1 H), 4.81 (d, *J* = 13.6 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.52 (br d, *J* = 11.9 Hz, 1 H), 4.40-4.24 (m, 3 H); HRFABMS calcd for C₁₇H₁₅FN₅O₄ *m/z* [M + H]⁺ 372.1108, found 372.1108. HPLC purity: 96.5%.

(6*S*)-6-[(2'-Fluoro[3,4'-bipyridin]-6-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (89). Reaction of bromide **156** and 2-fluoro-4-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 4 h, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **89** (26%) as a light yellow solid: mp 188 °C (dec.); ¹H NMR [(CD₃)₂SO] δ 9.02 (d, *J* = 1.8 Hz, 1 H), 8.35 (d, *J* = 5.3 Hz, 1 H), 8.28 (dd, *J* = 8.2, 2.4 Hz, 1 H), 8.03 (s, 1 H), 7.77 (dt, *J* = 5.2, 1.8 Hz, 1 H), 7.63 (br s, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 4.84 (d, *J* = 13.6 Hz, 1 H), 4.80 (d, *J* = 13.6 Hz, 1 H), 4.73 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.52 (br d, *J* = 12.0 Hz, 1 H), 4.39-4.24 (m, 3 H). HPLC purity: 97.1%.

2-Bromo-5-(bromomethyl)pyridine (158) (Scheme 3B; alternative method). Mesylation of (6-bromo-3-pyridinyl)methanol (**157**), followed by treatment with LiBr, using Procedure L above (see **154**), gave **158**¹⁰ (86%) as a lachrymatory white solid that was used directly in the next step.

(6*S*)-6-[(6-Chloro-3-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (161). A solution of alcohol **140** (2.073 g, 11.2 mmol) and 2-chloro-5-(chloromethyl)pyridine (**159**) (2.00 g, 12.3 mmol) in anhydrous DMF (40 mL) at 5 °C was treated with 60% NaH (0.584 g, 14.6 mmol). The resulting mixture was stirred at room

temperature for 16 h, and then quenched with water (150 mL). The precipitate was filtered, washed with water, and dried to give **161** (3.39 g, 97%) as a light yellow solid that was sufficiently pure to use directly in the next step: mp 191-193 °C; ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 8.37 (dd, $J = 2.3, 0.4$ Hz, 1 H), 8.02 (s, 1 H), 7.79 (dd, $J = 8.3, 2.4$ Hz, 1 H), 7.51 (br d, $J = 8.2$ Hz, 1 H), 4.74 (d, $J = 12.4$ Hz, 1 H), 4.69-4.64 (m, 2 H), 4.47 (br d, $J = 11.8$ Hz, 1 H), 4.30-4.20 (m, 3 H); HRESIMS calcd for $\text{C}_{12}\text{H}_{12}\text{ClN}_4\text{O}_4$ m/z $[\text{M} + \text{H}]^+$ 313.0513, 311.0542, found 313.0518, 311.0545.

4-[5-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl}-2-pyridinyl]benzonitrile (91**).** Reaction of (6*S*)-6-[(6-bromo-3-pyridinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**160**) and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **91** (74%) as a white solid: mp 188-190 °C; ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 8.68 (d, $J = 1.7$ Hz, 1 H), 8.28 (dt, $J = 8.7, 1.8$ Hz, 2 H), 8.09 (dd, $J = 8.2, 0.5$ Hz, 1 H), 8.03 (s, 1 H), 7.96 (dt, $J = 8.6, 1.9$ Hz, 2 H), 7.88 (dd, $J = 8.2, 2.2$ Hz, 1 H), 4.79 (d, $J = 12.4$ Hz, 1 H), 4.75 (d, $J = 12.4$ Hz, 1 H), 4.70 (dt, $J = 12.0, 2.5$ Hz, 1 H), 4.50 (br d, $J = 11.6$ Hz, 1 H), 4.34-4.22 (m, 3 H). Anal. ($\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_4$) C, H, N.

(6*S*)-6-{{[6-(4-Fluorophenyl)-3-pyridinyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (92**).** Reaction of bromide **160** and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **92** (84%) as a white solid: mp 194-196 °C; ^1H NMR $[(\text{CD}_3)_2\text{SO}]$ δ 8.60 (d, $J = 1.7$ Hz, 1 H), 8.13 (ddt, $J = 9.0, 5.6, 2.5$ Hz, 2 H), 8.03 (s, 1 H), 7.95 (dd, $J = 8.2, 0.6$ Hz, 1 H), 7.81 (dd, $J = 8.2, 2.3$ Hz, 1 H), 7.31 (tt, $J = 8.9, 2.5$ Hz, 2 H), 4.75 (d, $J = 12.2$ Hz, 1 H), 4.71 (d, $J = 12.2$ Hz, 1 H), 4.69

(dt, $J = 12.0, 2.5$ Hz, 1 H), 4.49 (br d, $J = 11.7$ Hz, 1 H), 4.33-4.21 (m, 3 H). Anal. ($C_{18}H_{15}FN_4O_4 \cdot 1.5H_2O$) C, N, F, H: calcd, 4.57; found, 3.87. HPLC purity: 99.4%.

(6S)-2-Nitro-6-({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (93).

1) *via bromide 160*: Reaction of bromide **160** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **93** (70%) as a cream solid: mp 217-219 °C; 1H NMR [$(CD_3)_2SO$] δ 8.63 (d, $J = 1.7$ Hz, 1 H), 8.20 (dt, $J = 8.9, 2.5$ Hz, 2 H), 8.03 (s, 1 H), 7.99 (dd, $J = 8.2, 0.5$ Hz, 1 H), 7.84 (dd, $J = 8.2, 2.2$ Hz, 1 H), 7.47 (br d, $J = 8.8$ Hz, 2 H), 4.77 (d, $J = 12.3$ Hz, 1 H), 4.74-4.67 (m, 2 H), 4.49 (br d, $J = 11.7$ Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

2) *via chloride 161*: Chloride **161** (1.00 g, 3.22 mmol) and 4-(trifluoromethoxy)phenylboronic acid (0.788 g, 3.83 mmol) were suspended in DME (50 mL) and an aqueous solution of K_2CO_3 (2M, 15 mL) was added. The mixture was purged with N_2 and then treated with $Pd(dppf)Cl_2$ (50 mg, 0.068 mmol) and stirred at 85 °C in an N_2 atmosphere for 18 h. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The dried ($MgSO_4$) organic layers were adsorbed onto silica gel and chromatographed, eluting with EtOAc, to give impure **93** (containing a small amount of chloride **161**). This crude **93** was further reacted with 4-(trifluoromethoxy)phenylboronic acid (0.400 g, 1.94 mmol), aqueous K_2CO_3 (2M, 8 mL) and $Pd(dppf)Cl_2$ (100 mg, 0.137 mmol) in DME (50 mL) at 85 °C in an N_2 atmosphere for 1 h. The resulting mixture was worked up as before and chromatographed on silica gel, eluting with EtOAc, to give pure **93** (0.788 g, 57%).

(6S)-6-({6-[4-(Difluoromethoxy)phenyl]-3-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (94). Reaction of bromide **160** with 4-

(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure A for 1 h, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **94** (74%) as a light yellow powder: mp 199-201 °C; ¹H NMR [(CD₃)₂SO] δ 8.60 (d, *J* = 1.8 Hz, 1 H), 8.14 (dt, *J* = 8.9, 2.5 Hz, 2 H), 8.03 (s, 1 H), 7.95 (d, *J* = 8.1 Hz, 1 H), 7.81 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.31 (t, *J*_{H-F} = 74.0 Hz, 1 H), 7.28 (br d, *J* = 8.8 Hz, 2 H), 4.75 (d, *J* = 12.2 Hz, 1 H), 4.71 (d, *J* = 12.2 Hz, 1 H), 4.70 (dt, *J* = 12.0, 2.4 Hz, 1 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. (C₁₉H₁₆F₂N₄O₅) C, H, N.

(6S)-6-([6-(3-Fluoro-4-methoxyphenyl)-3-pyridinyl]methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (95). Reaction of bromide **160** with 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **95** (69%) as a white solid: mp 193-195 °C; ¹H NMR [(CD₃)₂SO] δ 8.57 (d, *J* = 1.7 Hz, 1 H), 8.03 (s, 1 H), 7.95-7.87 (m, 3 H), 7.78 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.27 (t, *J* = 9.0 Hz, 1 H), 4.76-4.66 (m, 3 H), 4.49 (d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H), 3.90 (s, 3 H). Anal. (C₁₉H₁₇FN₄O₅) C, H, N, F.

(6S)-6-([6-[2-Chloro-4-(trifluoromethoxy)phenyl]-3-pyridinyl]methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (96). Reaction of bromide **160** and 2-chloro-4-(trifluoromethoxy)phenylboronic acid (**167**) (1.5 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-1% MeOH/CH₂Cl₂ (foreruns) and then with 1% MeOH/CH₂Cl₂, gave impure product, which was further chromatographed on silica gel. Elution with 0-0.5% MeOH/CH₂Cl₂ gave foreruns, and then further elution with 0.5% MeOH/CH₂Cl₂ gave the crude product, which was further chromatographed on silica gel. Elution with 0-20% EtOAc/CH₂Cl₂ and EtOAc firstly gave foreruns, and then further elution with EtOAc gave the crude product, which was recolumned using the second elution system (0-

0.5% MeOH/CH₂Cl₂) to give **96** (48%) as a cream solid: mp (CH₂Cl₂/pentane) 103-106 °C; ¹H NMR (CDCl₃) δ 8.66 (br d, *J* = 1.6 Hz, 1 H), 7.75 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.68 (dd, *J* = 8.1, 0.6 Hz, 1 H), 7.64 (d, *J* = 8.6 Hz, 1 H), 7.42 (s, 1 H), 7.38 (m, 1 H), 7.24 (m, 1 H), 4.83 (d, *J* = 11.9 Hz, 1 H), 4.71 (d, *J* = 11.9 Hz, 1 H), 4.70 (ddd, *J* = 12.2, 3.3, 2.4 Hz, 1 H), 4.41 (br d, *J* = 12.3 Hz, 1 H), 4.30-4.17 (m, 3 H). Anal. (C₁₉H₁₄ClF₃N₄O₅) C, H, N.

(6*S*)-6-({6-[3-Chloro-4-(trifluoromethoxy)phenyl]-3-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (97). Reaction of bromide **160** and 3-chloro-4-(trifluoromethoxy)phenylboronic acid (**168**) (1.5 equiv.) under the Suzuki coupling conditions described in Procedure H (0.15 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/CH₂Cl₂ (foreruns) and then with 0.5% MeOH/CH₂Cl₂, gave **97** (89%) as a cream solid: mp (CH₂Cl₂/pentane) 169-171 °C; ¹H NMR (CDCl₃) δ 8.63 (br d, *J* = 1.3 Hz, 1 H), 8.15 (d, *J* = 2.2 Hz, 1 H), 7.91 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.75 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.71 (dd, *J* = 8.2, 0.8 Hz, 1 H), 7.44-7.39 (m, 2 H), 4.80 (d, *J* = 12.0 Hz, 1 H), 4.70 (d, *J* = 11.8 Hz, 1 H), 4.68 (ddd, *J* = 12.3, 3.5, 2.2 Hz, 1 H), 4.39 (dd, *J* = 12.2, 1.2 Hz, 1 H), 4.25 (dd, *J* = 13.3, 4.5 Hz, 1 H), 4.22-4.15 (m, 2 H). Anal. (C₁₉H₁₄ClF₃N₄O₅) C, H, N.

(6*S*)-6-({6-[2-Fluoro-4-(trifluoromethoxy)phenyl]-3-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (98). Reaction of bromide **160** and 2-fluoro-4-(trifluoromethoxy)phenylboronic acid (**169**) (1.5 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/CH₂Cl₂ (foreruns) and then with 0.5% MeOH/CH₂Cl₂, gave **98** (80%) as a cream solid: mp (CH₂Cl₂/pentane) 181-182 °C; ¹H NMR (CDCl₃) δ 8.66 (br d, *J* = 1.8 Hz, 1 H), 8.06 (t, *J* = 8.7 Hz, 1 H), 7.80 (br dd, *J* = 8.2, 1.4 Hz, 1 H), 7.74 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.41 (s, 1 H), 7.15 (m, 1 H), 7.07 (m, 1 H), 4.81 (d, *J* = 12.0 Hz, 1 H), 4.70 (d, *J* = 12.0 Hz, 1 H), 4.68 (ddd, *J* = 12.2, 3.6, 2.2

Hz, 1 H), 4.40 (br d, $J = 12.0$ Hz, 1 H), 4.25 (dd, $J = 13.3, 4.6$ Hz, 1 H), 4.22-4.15 (m, 2 H).

Anal. ($C_{19}H_{14}F_4N_4O_5$) C, H, N.

(6*S*)-6-({6-[3-Fluoro-4-(trifluoromethoxy)phenyl]-3-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (99). Reaction of bromide **160** and 3-fluoro-4-(trifluoromethoxy)phenylboronic acid (**170**) (1.4 equiv.) under the Suzuki coupling conditions described in Procedure H (0.13 equiv. catalyst) for 2 h, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/ CH_2Cl_2 (foreruns) and then with 0.5% MeOH/ CH_2Cl_2 , gave **99** (89%) as a cream solid: mp (CH_2Cl_2 /pentane) 187-189 °C; 1H NMR ($CDCl_3$) δ 8.62 (br d, $J = 1.5$ Hz, 1 H), 7.90 (dd, $J = 11.3, 2.1$ Hz, 1 H), 7.78 (ddd, $J = 8.6, 2.0, 1.3$ Hz, 1 H), 7.75 (dd, $J = 8.2, 2.2$ Hz, 1 H), 7.71 (dd, $J = 8.2, 0.8$ Hz, 1 H), 7.41 (s, 1 H), 7.40 (ddq, 8.7, 7.6, 1.2 Hz, 1 H), 4.80 (d, $J = 12.0$ Hz, 1 H), 4.70 (d, $J = 11.8$ Hz, 1 H), 4.68 (ddd, $J = 12.2, 3.5, 2.3$ Hz, 1 H), 4.40 (dd, $J = 12.2, 1.1$ Hz, 1 H), 4.25 (dd, $J = 13.3, 4.5$ Hz, 1 H), 4.22-4.15 (m, 2 H). Anal. ($C_{19}H_{14}F_4N_4O_5$) C, H, N.

(6*S*)-6-({6-[4-Chloro-3-(trifluoromethoxy)phenyl]-3-pyridinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (100). Reaction of bromide **160** and 4-chloro-3-(trifluoromethoxy)phenylboronic acid (**171**) (1.5 equiv.) under the Suzuki coupling conditions described in Procedure H (0.16 equiv. catalyst) for 80 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/ CH_2Cl_2 (foreruns) and then with 0.5% MeOH/ CH_2Cl_2 , gave **100** (83%) as a cream solid: mp (CH_2Cl_2 /pentane) 151-153 °C; 1H NMR ($CDCl_3$) δ 8.63 (br d, $J = 1.2$ Hz, 1 H), 8.03 (quintet, $J = 1.6$ Hz, 1 H), 7.87 (dd, $J = 8.4, 2.0$ Hz, 1 H), 7.75 (dd, $J = 8.2, 2.1$ Hz, 1 H), 7.71 (dd, $J = 8.2, 0.8$ Hz, 1 H), 7.57 (d, $J = 8.4$ Hz, 1 H), 7.41 (s, 1 H), 4.80 (d, $J = 12.0$ Hz, 1 H), 4.70 (d, $J = 11.8$ Hz, 1 H), 4.67 (ddd, $J = 12.3, 3.4, 2.3$ Hz, 1 H), 4.39 (br d, $J = 12.2$ Hz, 1 H), 4.25 (dd, $J = 13.3, 4.5$ Hz, 1 H), 4.21-4.14 (m, 2 H). Anal. ($C_{19}H_{14}ClF_3N_4O_5$) C, H, N.

(6*S*)-2-Nitro-6-[[6'-(trifluoromethyl)[2,3'-bipyridin]-5-yl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (101). Reaction of bromide **160** and 6-(trifluoromethyl)-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 90 min, followed by chromatography of the product on silica gel, eluting with 0-2% MeOH/CH₂Cl₂, gave **101** (74%) as a white solid: mp 252-255 °C; ¹H NMR [(CD₃)₂SO] δ 9.43 (br d, *J* = 2.0 Hz, 1 H), 8.73-8.67 (m, 2 H) 8.17 (br d, *J* = 8.2 Hz, 1 H), 8.03 (s, 1 H), 8.03 (d, *J* = 7.8 Hz, 1 H), 7.92 (dd, *J* = 8.1, 2.2 Hz, 1 H), 4.81 (d, *J* = 12.4 Hz, 1 H), 4.77 (d, *J* = 12.5 Hz, 1 H), 4.71 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.50 (br d, *J* = 11.7 Hz, 1 H), 4.34-4.23 (m, 3 H); HRFABMS calcd for C₁₈H₁₅F₃N₅O₄ *m/z* [M + H]⁺ 422.1076, found 422.1079. HPLC purity: 99.5%.

(6*S*)-6-[(6'-Fluoro[2,3'-bipyridin]-5-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (102). Reaction of bromide **160** and 6-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A, followed by chromatography of the product on silica gel, eluting with 5% MeOH/EtOAc, gave **102** (51%) as a yellow solid: mp 188-191 °C; ¹H NMR [(CD₃)₂SO] δ 8.92 (d, *J* = 2.5 Hz, 1 H), 8.64 (dd, *J* = 2.3, 1.3 Hz, 1 H), 8.61 (dd, *J* = 8.2, 2.5 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 8.03 (s, 1 H), 7.86 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.31 (dd, *J* = 8.6, 2.8 Hz, 1 H), 4.77 (d, *J* = 12.3 Hz, 1 H), 4.75-4.67 (m, 2 H), 4.49 (br d, *J* = 11.8 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. (C₁₇H₁₄FN₅O₄) C, H, N.

(6*S*)-6-[(6'-Methoxy[2,3'-bipyridin]-5-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (103). Reaction of bromide **160** with 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure A for 20 min, followed by chromatography of the product on silica gel, eluting with EtOAc, gave **103** (88%) as a light yellow solid: mp 177-179 °C; ¹H NMR [(CD₃)₂SO] δ 8.87 (dd, *J* = 2.5, 0.6 Hz, 1 H), 8.60 (d, *J* = 1.7 Hz, 1 H), 8.36 (dd, *J* = 8.7, 2.5 Hz, 1 H), 8.03 (s, 1 H), 7.95 (dd, *J* = 8.1, 0.5 Hz, 1 H), 7.80 (dd, *J* = 8.2, 2.3 Hz, 1 H), 6.93 (dd, *J* = 8.7, 0.6 Hz, 1 H), 4.76-4.66

(m, 3 H), 4.49 (br d, $J = 11.8$ Hz, 1 H), 4.32-4.21 (m, 3 H), 3.91 (s, 3 H). Anal. ($C_{18}H_{17}N_5O_5$) C, H, N.

4-[6-([(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy)methyl)-3-pyridazinyl]benzonitrile (105) (Scheme 4A). Reaction of (6*S*)-6-[(6-chloro-3-pyridazinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**178**) and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **105** (40%) as a white solid: mp 181-185 °C; 1H NMR [$(CD_3)_2SO$] δ 8.37-8.32 (m, 3 H), 8.04 (br d, $J = 8.6$ Hz, 2 H), 8.03 (s, 1 H), 7.80 (d, $J = 8.8$ Hz, 1 H), 5.06 (d, $J = 13.2$ Hz, 1 H), 5.02 (d, $J = 13.2$ Hz, 1 H), 4.74 (dt, $J = 12.1, 2.6$ Hz, 1 H), 4.52 (br d, $J = 12.0$ Hz, 1 H), 4.44-4.33 (m, 2 H), 4.28 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{18}H_{14}N_6O_4$) C, H, N: calcd, 22.21; found, 21.64. HPLC purity: 98.0%.

(6*S*)-6-[[6-(4-Fluorophenyl)-3-pyridazinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (106). Reaction of chloride **178** and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **106** (86%) as a white solid: mp 183 °C (dec.); 1H NMR [$(CD_3)_2SO$] δ 8.24 (d, $J = 8.8$ Hz, 1 H), 8.23-8.18 (m, 2 H), 8.03 (s, 1 H), 7.73 (d, $J = 8.8$ Hz, 1 H), 7.43-7.37 (m, 2 H), 5.02 (d, $J = 13.2$ Hz, 1 H), 4.99 (d, $J = 13.2$ Hz, 1 H), 4.73 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.52 (br d, $J = 12.0$ Hz, 1 H), 4.44-4.34 (m, 2 H), 4.28 (dd, $J = 13.5, 3.2$ Hz, 1 H). Anal. ($C_{17}H_{14}FN_5O_4$) C, H, N.

(6*S*)-2-Nitro-6-([6-[4-(trifluoromethoxy)phenyl]-3-pyridazinyl]methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (107). Reaction of chloride **178** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **107** (66%) as a white solid: mp 194 °C (dec.); 1H NMR [$(CD_3)_2SO$] δ 8.30-8.25 (m, 3 H), 8.03 (s, 1 H), 7.76 (d, $J = 8.9$ Hz, 1 H), 7.55 (br dd, $J = 8.9, 0.9$ Hz, 2 H), 5.04 (d, $J = 13.2$ Hz, 1 H), 5.00 (d, $J = 13.2$ Hz, 1 H), 4.74 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.52 (br d,

$J = 11.9$ Hz, 1 H), 4.43-4.33 (m, 2 H), 4.28 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

(6S)-6-({6-[4-(Difluoromethoxy)phenyl]-3-pyridazinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (108). Reaction of chloride **178** and 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **108** (60%) as a white solid: mp 191 °C (dec.); 1H NMR [$(CD_3)_2SO$] δ 8.24 (d, $J = 8.8$ Hz, 1 H), 8.21 (br d, $J = 8.9$ Hz, 2 H), 8.03 (s, 1 H), 7.73 (d, $J = 8.8$ Hz, 1 H), 7.36 (br d, $J = 8.9$ Hz, 2 H), 7.35 (t, $J_{H-F} = 73.8$ Hz, 1 H), 5.02 (d, $J = 13.2$ Hz, 1 H), 4.99 (d, $J = 13.2$ Hz, 1 H), 4.74 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.52 (br d, $J = 11.8$ Hz, 1 H), 4.42-4.33 (m, 2 H), 4.27 (dd, $J = 13.5, 3.2$ Hz, 1 H). Anal. ($C_{18}H_{15}F_2N_5O_5$) C, H, N.

(6S)-6-{{6-[3-Fluoro-4-methoxyphenyl]-3-pyridazinyl}methoxy}-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (109). Reaction of chloride **178** and 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **109** (27%) as a white solid: mp 193 °C (dec.); 1H NMR [$(CD_3)_2SO$] δ 8.23 (d, $J = 8.9$ Hz, 1 H), 8.05-7.94 (m, 3 H), 7.70 (d, $J = 8.8$ Hz, 1 H), 7.34 (t, $J = 8.8$ Hz, 1 H), 5.00 (d, $J = 13.2$ Hz, 1 H), 4.97 (d, $J = 13.2$ Hz, 1 H), 4.72 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.41-4.32 (m, 2 H), 4.27 (dd, $J = 13.5, 3.2$ Hz, 1 H), 3.93 (s, 3 H). Anal. ($C_{18}H_{16}FN_5O_5 \cdot 0.25H_2O$) C, H, N: calcd, 17.26; found, 16.62. HPLC purity: 98.8%.

(6S)-2-Nitro-6-({6-[6-(trifluoromethyl)-3-pyridinyl]-3-pyridazinyl}methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (110). Reaction of chloride **178** and 6-(trifluoromethyl)-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure I gave **110** (60%) as a white solid: mp 220-224 °C; 1H NMR [$(CD_3)_2SO$] δ 9.48 (d, $J = 2.0$ Hz, 1 H), 8.79 (dd, $J = 8.1, 1.7$ Hz, 1 H), 8.45 (d, $J = 8.8$ Hz, 1 H), 8.11 (dd, $J = 8.3, 0.4$ Hz, 1 H), 8.03 (s, 1 H), 7.85 (d, $J = 8.8$ Hz, 1 H), 5.07 (d, $J = 13.2$ Hz, 1 H), 5.04 (d, $J =$

13.2 Hz, 1 H), 4.74 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.52 (br d, $J = 12.0$ Hz, 1 H), 4.45-4.35 (m, 2 H), 4.28 (dd, $J = 13.5, 3.2$ Hz, 1 H). Anal. ($C_{17}H_{13}F_3N_6O_4$) C, H, N.

(6*S*)-6-[[6-(6-Methoxy-3-pyridinyl)-3-pyridazinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (111). Reaction of chloride **178** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure I gave **111** (69%) as a white solid: mp 186-190 °C; ^1H NMR [$(\text{CD}_3)_2\text{SO}$] δ 8.93 (dd, $J = 2.4, 0.6$ Hz, 1 H), 8.45 (dd, $J = 8.7, 2.5$ Hz, 1 H), 8.25 (d, $J = 8.9$ Hz, 1 H), 8.03 (s, 1 H), 7.73 (d, $J = 8.9$ Hz, 1 H), 7.00 (dd, $J = 8.7, 0.6$ Hz, 1 H), 5.01 (d, $J = 13.2$ Hz, 1 H), 4.98 (d, $J = 13.2$ Hz, 1 H), 4.73 (dt, $J = 12.1, 2.5$ Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.42-4.32 (m, 2 H), 4.27 (dd, $J = 13.5, 3.2$ Hz, 1 H), 3.94 (s, 3 H). Anal. ($C_{17}H_{16}N_6O_5$) C, H, N: calcd, 21.87; found, 21.46. HPLC purity: 98.5%.

(6*S*)-6-[[5-(4-Fluorophenyl)-2-pyrazinyl]methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (113) (Scheme 4B). Reaction of (6*S*)-6-[(5-chloro-2-pyrazinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**182**) and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **113** (72%) as a white solid: mp 201-203 °C; ^1H NMR [$(\text{CD}_3)_2\text{SO}$] δ 9.19 (d, $J = 1.4$ Hz, 1 H), 8.69 (d, $J = 1.4$ Hz, 1 H), 8.22-8.15 (m, 2 H), 8.03 (s, 1 H), 7.41-7.33 (m, 2 H), 4.88 (d, $J = 13.2$ Hz, 1 H), 4.84 (d, $J = 13.2$ Hz, 1 H), 4.73 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.51 (br d, $J = 12.0$ Hz, 1 H), 4.41-4.32 (m, 2 H), 4.26 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{17}H_{14}FN_5O_4$) C, H, N.

(6*S*)-2-Nitro-6-([5-[4-(trifluoromethoxy)phenyl]-2-pyrazinyl]methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (114). Reaction of chloride **182** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **114** (82%) as a white solid: mp 182-184 °C; ^1H NMR [$(\text{CD}_3)_2\text{SO}$] δ 9.23 (d, $J = 1.4$ Hz, 1 H), 8.72 (d, $J = 1.4$ Hz, 1 H), 8.25 (br d, $J = 8.9$ Hz, 2 H), 8.03 (s, 1 H), 7.53

(br d, $J = 8.9$ Hz, 2 H), 4.89 (d, $J = 13.3$ Hz, 1 H), 4.85 (d, $J = 13.3$ Hz, 1 H), 4.74 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.52 (br d, $J = 11.9$ Hz, 1 H), 4.43-4.33 (m, 2 H), 4.27 (dd, $J = 13.5, 3.2$ Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

(6*S*)-6-({5-[4-(Difluoromethoxy)phenyl]-2-pyrazinyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (115). Reaction of chloride **182** and 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **115** (91%) as a white solid: mp 175-178 °C; 1H NMR [$(CD_3)_2SO$] δ 9.20 (d, $J = 1.4$ Hz, 1 H), 8.69 (d, $J = 1.4$ Hz, 1 H), 8.20 (br d, $J = 8.9$ Hz, 2 H), 8.03 (s, 1 H), 7.34 (t, $J_{H-F} = 73.8$ Hz, 1 H), 7.33 (br d, $J = 8.9$ Hz, 2 H), 4.88 (d, $J = 13.2$ Hz, 1 H), 4.84 (d, $J = 13.2$ Hz, 1 H), 4.73 (dt, $J = 12.0, 2.6$ Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.41-4.32 (m, 2 H), 4.27 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{18}H_{15}F_2N_5O_5$) C, H, N.

(6*S*)-2-Nitro-6-({5-[6-(trifluoromethyl)-3-pyridinyl]-2-pyrazinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (116). Reaction of chloride **182** and 6-(trifluoromethyl)-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure I gave **116** (92%) as a white solid: mp 221-223 °C; 1H NMR [$(CD_3)_2SO$] δ 9.48 (d, $J = 1.9$ Hz, 1 H), 9.38 (d, $J = 1.4$ Hz, 1 H), 8.80 (d, $J = 1.4$ Hz, 1 H), 8.76 (dd, $J = 8.1, 1.7$ Hz, 1 H), 8.08 (d, $J = 8.1$ Hz, 1 H), 8.03 (s, 1 H), 4.93 (d, $J = 13.2$ Hz, 1 H), 4.90 (d, $J = 13.2$ Hz, 1 H), 4.75 (dt, $J = 12.1, 2.6$ Hz, 1 H), 4.52 (br d, $J = 12.1$ Hz, 1 H), 4.44-4.33 (m, 2 H), 4.28 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{17}H_{13}F_3N_6O_4$) C, H, N.

(6*S*)-6-{{5-[4-Fluorophenyl]-2-pyrimidinyl}methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (118) (Scheme 4C). Reaction of (6*S*)-6-[(5-bromo-2-pyrimidinyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**185**) and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **118** (78%) as a white solid: mp 183-185 °C; 1H NMR [$(CD_3)_2SO$] δ 9.11 (s, 2 H), 8.05 (s, 1 H), 7.88-7.81 (m, 2 H), 7.41-7.35 (m, 2 H), 4.90 (d, $J = 14.5$ Hz, 1 H), 4.86 (d, $J = 14.5$ Hz, 1

H), 4.72 (dt, $J = 11.9, 2.6$ Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.45-4.41 (m, 1 H), 4.35 (dt, $J = 13.5, 2.1$ Hz, 1 H), 4.27 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{17}H_{14}FN_5O_4$) C, H, N.

(6S)-2-Nitro-6-({5-[4-(trifluoromethoxy)phenyl]-2-pyrimidinyl}methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (119). Reaction of bromide **185** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **119** (89%) as a white solid: mp 223-226 °C; 1H NMR [$(CD_3)_2SO$] δ 9.14 (s, 2 H), 8.05 (s, 1 H), 7.93 (br d, $J = 8.8$ Hz, 2 H), 7.53 (br d, $J = 8.8$ Hz, 2 H), 4.91 (d, $J = 14.5$ Hz, 1 H), 4.87 (d, $J = 14.5$ Hz, 1 H), 4.72 (dt, $J = 11.9, 2.6$ Hz, 1 H), 4.51 (br d, $J = 12.0$ Hz, 1 H), 4.45-4.42 (m, 1 H), 4.35 (dt, $J = 13.5, 2.1$ Hz, 1 H), 4.27 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

(6S)-6-({5-[4-(Difluoromethoxy)phenyl]-2-pyrimidinyl}methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (120). Reaction of bromide **185** and 4-(difluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure I gave **120** (62%) as a white solid: mp 201-203 °C; 1H NMR [$(CD_3)_2SO$] δ 9.12 (s, 2 H), 8.05 (s, 1 H), 7.87 (br d, $J = 8.8$ Hz, 2 H), 7.34 (br d, $J = 8.8$ Hz, 2 H), 7.32 (t, $J_{H-F} = 73.9$ Hz, 1 H), 4.90 (d, $J = 14.5$ Hz, 1 H), 4.86 (d, $J = 14.5$ Hz, 1 H), 4.72 (dt, $J = 11.9, 2.6$ Hz, 1 H), 4.51 (br d, $J = 11.9$ Hz, 1 H), 4.45-4.41 (m, 1 H), 4.35 (dt, $J = 13.5, 2.1$ Hz, 1 H), 4.27 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{18}H_{15}F_2N_5O_5$) C, H, N.

(6S)-2-Nitro-6-({5-[6-(trifluoromethyl)-3-pyridinyl]-2-pyrimidinyl}methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (121). Reaction of bromide **185** and 6-(trifluoromethyl)-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure I gave **121** (80%) as a white solid: mp 215-217 °C; 1H NMR [$(CD_3)_2SO$] δ 9.27 (s, 2 H), 9.22 (d, $J = 2.0$ Hz, 1 H), 8.53 (dd, $J = 8.2, 2.0$ Hz, 1 H), 8.08 (d, $J = 8.2$ Hz, 1 H), 8.05 (s, 1 H), 4.95 (d, $J = 14.5$ Hz, 1 H), 4.90 (d, $J = 14.5$ Hz, 1 H), 4.73 (dt, $J = 11.9, 2.6$ Hz, 1

H), 4.52 (br d, $J = 11.9$ Hz, 1 H), 4.47-4.43 (m, 1 H), 4.37 (dt, $J = 13.5, 2.1$ Hz, 1 H), 4.27 (dd, $J = 13.5, 3.3$ Hz, 1 H). Anal. ($C_{17}H_{13}F_3N_6O_4$) C, H, N.

(6S)-6-([2-(4-Fluorophenyl)-5-pyrimidinyl]methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (123) (Scheme 4D). Reaction of (6S)-6-{[2-(methylsulfanyl)-5-pyrimidinyl]methoxy}-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (**189**) and 4-fluorophenylboronic acid under the Leibeskind-Srogl cross-coupling conditions described in Procedure K gave **123** (37%) as a pale yellow solid: mp (MeOH) 210-211 °C; 1H NMR [$(CD_3)_2SO$] δ 8.85 (s, 2 H), 8.46-8.40 (m, 2 H), 8.03 (s, 1 H), 7.38-7.32 (m, 2 H), 4.78 (d, $J = 12.6$ Hz, 1 H), 4.73 (d, $J = 12.6$ Hz, 1 H), 4.70 (dt, $J = 12.1, 2.6$ Hz, 1 H), 4.49 (br d, $J = 12.1$ Hz, 1 H), 4.35-4.22 (m, 3 H); HRESIMS calcd for $C_{17}H_{15}FN_5O_4$ m/z $[M + H]^+$ 372.1103, found 372.1093. HPLC purity: 98.5%.

(6S)-2-Nitro-6-([2-[4-(trifluoromethoxy)phenyl]-5-pyrimidinyl]methoxy)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (124) (alternative method). Reaction of methyl sulfide **189** and 4-(trifluoromethoxy)phenylboronic acid under the Leibeskind-Srogl cross-coupling conditions described in Procedure K gave **124** (42%) as a cream solid: mp (MeOH) 227-230 °C; 1H NMR [$(CD_3)_2SO$] δ 8.88 (s, 2 H), 8.49 (br d, $J = 8.9$ Hz, 2 H), 8.03 (s, 1 H), 7.51 (br dd, $J = 8.9, 0.8$ Hz, 2 H), 4.79 (d, $J = 12.6$ Hz, 1 H), 4.76 (d, $J = 12.6$ Hz, 1 H), 4.70 (dt, $J = 12.0, 2.5$ Hz, 1 H), 4.49 (br d, $J = 12.0$ Hz, 1 H), 4.35-4.29 (m, 2 H), 4.25 (dd, $J = 13.3, 3.1$ Hz, 1 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

(6S)-6-([2-[4-(Difluoromethoxy)phenyl]-5-pyrimidinyl]methoxy)-2-nitro-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]oxazine (125). Reaction of methyl sulfide **189** and 4-(difluoromethoxy)phenylboronic acid under the Leibeskind-Srogl cross-coupling conditions described in Procedure K gave **125** (37%) as pale yellow crystals: mp (MeOH) 209-211 °C; 1H NMR [$(CD_3)_2SO$] δ 8.85 (s, 2 H), 8.43 (br d, $J = 8.9$ Hz, 2 H), 8.03 (s, 1 H), 7.35 (t, $J_{H-F} = 73.8$ Hz, 1 H), 7.31 (br d, $J = 8.9$ Hz, 2 H), 4.78 (d, $J = 12.6$ Hz, 1 H), 4.74 (d, $J = 12.6$

Hz, 1 H), 4.70 (dt, $J = 12.0, 2.5$ Hz, 1 H), 4.49 (br d, $J = 12.0$ Hz, 1 H), 4.34-4.22 (m, 3 H).

Anal. ($C_{18}H_{15}F_2N_5O_5$) C, H, N.

(6*S*)-2-Nitro-6-({2-[6-(trifluoromethyl)-3-pyridinyl]-5-pyrimidinyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (126). Reaction of methyl sulfide **189** and 6-(trifluoromethyl)-3-pyridinylboronic acid under the Leibeskind-Srogl cross-coupling conditions described in Procedure K gave **126** (53%) as pale yellow flakes: mp (MeOH) 280-283 °C; ^1H NMR [$(\text{CD}_3)_2\text{SO}$] δ 9.64 (d, $J = 1.9$ Hz, 1 H), 8.97 (s, 2 H), 8.92 (dd, $J = 8.3, 1.5$ Hz, 1 H), 8.08 (dd, $J = 8.3, 0.6$ Hz, 1 H), 8.03 (s, 1 H), 4.84 (d, $J = 12.8$ Hz, 1 H), 4.80 (d, $J = 12.8$ Hz, 1 H), 4.72 (dt, $J = 12.1, 2.5$ Hz, 1 H), 4.50 (br d, $J = 11.4$ Hz, 1 H), 4.37-4.23 (m, 3 H); HRESIMS calcd for $C_{17}H_{14}F_3N_6O_4$ m/z $[\text{M} + \text{H}]^+$ 423.1023, found 423.1001. HPLC purity: 96.3%.

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Table S1. Combustion analyses for the new compounds of Table 1

| No | Calculated | | | | Found | | | |
|----|------------|------|-------|------|-------|------|-------|------|
| | C | H | N | F | C | H | N | F |
| 9 | 61.36 | 4.58 | 15.90 | | 61.47 | 4.83 | 15.53 | |
| 10 | 58.38 | 4.08 | 15.13 | 5.13 | 58.22 | 4.02 | 14.98 | 5.26 |
| 11 | 58.31 | 4.89 | 14.32 | | 57.96 | 4.65 | 14.14 | |
| 12 | 64.86 | 4.90 | 12.10 | | 65.09 | 5.14 | 11.65 | |
| 15 | 54.29 | 3.60 | 13.33 | | 54.53 | 3.65 | 13.54 | |
| 16 | 54.55 | 3.85 | 13.39 | | 54.28 | 3.91 | 13.33 | |
| 18 | 54.29 | 3.60 | 13.33 | | 54.53 | 3.66 | 13.37 | |
| 19 | 55.03 | 4.49 | 14.26 | 4.84 | 55.16 | 4.01 | 14.16 | 5.07 |
| 21 | 64.86 | 4.90 | 12.10 | | 64.55 | 4.85 | 11.98 | |
| 23 | 61.36 | 4.58 | 15.90 | | 61.06 | 4.62 | 15.74 | |
| 24 | 54.29 | 3.60 | 13.33 | | 54.16 | 3.60 | 13.36 | |
| 25 | 50.18 | 3.10 | 12.32 | | 50.43 | 3.07 | 12.29 | |
| 26 | 60.47 | 4.01 | 18.56 | | 60.24 | 4.01 | 18.48 | |
| 27 | 58.38 | 4.08 | 15.13 | | 58.16 | 4.25 | 15.04 | |
| 28 | 58.38 | 4.08 | 15.13 | | 58.65 | 4.24 | 15.14 | |
| 29 | 54.55 | 3.85 | 13.39 | | 54.21 | 3.89 | 13.38 | |
| 30 | 59.68 | 4.74 | 14.65 | | 59.76 | 4.49 | 14.78 | |
| 31 | 61.36 | 4.58 | 15.90 | | 61.49 | 4.71 | 15.76 | |
| 32 | 54.29 | 3.60 | 13.33 | | 54.33 | 3.69 | 13.22 | |
| 33 | 59.06 | 4.17 | 18.13 | | 58.91 | 3.99 | 18.06 | |
| 34 | 58.38 | 4.08 | 15.13 | | 58.55 | 4.31 | 15.04 | |
| 35 | 57.68 | 4.17 | 14.95 | | 57.89 | 4.51 | 14.53 | |
| 36 | 58.14 | 4.74 | 18.83 | | 58.44 | 4.83 | 18.28 | |
| 37 | 54.55 | 3.85 | 13.39 | | 54.64 | 3.87 | 13.10 | |
| 38 | 59.68 | 4.74 | 14.65 | | 59.95 | 4.86 | 14.36 | |
| 39 | 64.86 | 4.90 | 12.10 | | 64.80 | 4.96 | 11.94 | |
| 40 | 61.36 | 4.58 | 15.90 | | 61.23 | 4.68 | 15.61 | |
| 41 | 57.68 | 4.17 | 14.95 | | 57.77 | 4.08 | 15.01 | |
| 42 | 57.68 | 4.17 | 14.95 | | 57.55 | 4.08 | 14.84 | |

Table S2. Combustion analyses for the new compounds of Table 2

| No | Calculated | | | | Found | | | |
|----|------------|------|-------|-------|-------|------|-------|-------|
| | C | H | N | F | C | H | N | F |
| 43 | 53.71 | 3.68 | 13.19 | | 53.79 | 3.61 | 13.20 | |
| 45 | 56.99 | 4.25 | 14.77 | | 56.87 | 3.95 | 14.60 | |
| 46 | 52.30 | 3.46 | 12.84 | 13.06 | 52.98 | 3.58 | 12.47 | 12.93 |
| 47 | 54.55 | 3.85 | 13.39 | | 54.80 | 3.99 | 13.21 | |
| 48 | 57.00 | 4.28 | 13.99 | | 57.06 | 4.38 | 13.45 | |
| 49 | 56.39 | 4.47 | 18.27 | | 56.25 | 4.46 | 17.99 | |
| 50 | 53.71 | 3.68 | 13.19 | | 53.75 | 3.48 | 13.07 | |
| 51 | 59.06 | 4.17 | 18.13 | | 58.76 | 3.98 | 17.79 | |
| 52 | 56.32 | 4.33 | 14.60 | | 56.25 | 3.93 | 14.63 | |
| 53 | 51.76 | 3.54 | 12.71 | | 51.89 | 3.57 | 12.60 | |
| 54 | 54.55 | 3.85 | 13.39 | | 54.34 | 3.75 | 13.11 | |
| 55 | 56.37 | 4.36 | 13.84 | | 56.53 | 4.15 | 13.79 | |
| 56 | 55.10 | 4.62 | 17.85 | | 54.99 | 4.58 | 16.75 | |
| 57 | 53.71 | 3.68 | 13.19 | 13.42 | 53.60 | 3.59 | 13.03 | 13.26 |
| 58 | 59.06 | 4.17 | 18.13 | | 59.08 | 4.06 | 17.73 | |
| 59 | 58.38 | 4.08 | 15.13 | 5.13 | 58.31 | 4.15 | 14.45 | 5.19 |
| 60 | 51.76 | 3.54 | 12.71 | 12.93 | 51.58 | 3.38 | 12.56 | 12.83 |
| 61 | 54.55 | 3.85 | 13.39 | | 54.59 | 3.82 | 13.24 | |
| 62 | 54.55 | 4.58 | 13.39 | 4.54 | 54.59 | 4.42 | 13.03 | 4.68 |
| 63 | 54.47 | 4.70 | 17.65 | | 54.30 | 4.41 | 17.30 | |
| 64 | 52.06 | 3.91 | 12.78 | | 52.12 | 3.67 | 12.54 | |
| 65 | 58.38 | 4.25 | 17.92 | | 58.77 | 4.16 | 17.47 | |
| 66 | 57.68 | 4.17 | 14.95 | 5.07 | 57.95 | 4.10 | 14.78 | 5.08 |
| 69 | 57.00 | 4.28 | 13.99 | | 57.05 | 4.39 | 13.68 | |
| 70 | 55.74 | 4.55 | 18.06 | | 55.48 | 4.49 | 17.98 | |
| 71 | 54.29 | 3.60 | 13.33 | 13.56 | 54.45 | 3.69 | 13.10 | 13.58 |
| 72 | 59.06 | 4.17 | 18.13 | | 59.43 | 4.34 | 17.98 | |

| | | | | | | | | |
|------------|-------|------|-------|-------|-------|------|-------|-------|
| 73 | 56.99 | 4.25 | 14.77 | 5.01 | 56.97 | 4.04 | 14.51 | 4.81 |
| 74 | 52.30 | 3.46 | 12.84 | 13.06 | 52.06 | 3.45 | 12.66 | 13.10 |
| 75 | 54.55 | 3.85 | 13.39 | | 54.72 | 3.84 | 13.37 | |
| 76 | 53.40 | 4.72 | 13.11 | | 53.13 | 4.42 | 12.81 | |
| 77 | 48.47 | 3.00 | 11.90 | | 48.63 | 3.19 | 11.74 | |
| 78 | 48.47 | 3.00 | 11.90 | | 48.65 | 3.21 | 11.81 | |
| 79 | 50.23 | 3.11 | 12.33 | | 50.20 | 3.03 | 12.41 | |
| 80 | 50.23 | 3.11 | 12.33 | | 50.22 | 3.05 | 12.43 | |
| 81 | 48.47 | 3.00 | 11.90 | | 48.74 | 2.94 | 11.97 | |
| 82 | 54.99 | 3.80 | 18.86 | | 54.92 | 3.82 | 18.90 | |
| 83 | 51.31 | 3.35 | 16.62 | | 51.42 | 3.52 | 16.68 | |
| 86 | 54.33 | 3.89 | 18.63 | | 54.66 | 4.19 | 18.15 | |
| 87 | 56.39 | 4.47 | 18.27 | | 56.41 | 4.59 | 18.00 | |
| 90 | 53.71 | 3.68 | 13.19 | 13.42 | 53.84 | 3.55 | 12.94 | 13.30 |
| 91 | 60.47 | 4.01 | 18.56 | | 60.60 | 4.13 | 18.40 | |
| 92 | 54.41 | 4.57 | 14.10 | 4.78 | 54.37 | 3.87 | 13.72 | 5.03 |
| 93 | 52.30 | 3.46 | 12.84 | | 51.94 | 3.43 | 12.59 | |
| 94 | 54.55 | 3.85 | 13.39 | | 54.51 | 3.86 | 13.32 | |
| 95 | 57.00 | 4.28 | 13.99 | 4.75 | 56.77 | 4.26 | 13.68 | 4.81 |
| 96 | 48.47 | 3.00 | 11.90 | | 48.73 | 2.99 | 11.91 | |
| 97 | 48.47 | 3.00 | 11.90 | | 48.65 | 3.24 | 11.86 | |
| 98 | 50.23 | 3.11 | 12.33 | | 50.59 | 3.22 | 12.36 | |
| 99 | 50.23 | 3.11 | 12.33 | | 50.29 | 3.06 | 12.54 | |
| 100 | 48.47 | 3.00 | 11.90 | | 48.62 | 2.95 | 11.97 | |
| 102 | 54.99 | 3.80 | 18.86 | | 54.92 | 3.82 | 18.68 | |
| 103 | 56.39 | 4.47 | 18.27 | | 56.11 | 4.54 | 18.00 | |

Table S3. Combustion analyses for the new compounds of Table 3

| No | Calculated | | | | Found | | | |
|------------|------------|------|-------|-------|-------|------|-------|-------|
| | C | H | N | other | C | H | N | other |
| 104 | 51.31 | 3.35 | 16.62 | | 51.70 | 3.36 | 16.76 | |
| 105 | 57.14 | 3.73 | 22.21 | | 57.10 | 3.82 | 21.64 | |
| 106 | 54.99 | 3.80 | 18.86 | | 55.20 | 3.97 | 18.49 | |
| 107 | 49.43 | 3.23 | 16.01 | | 49.67 | 3.37 | 16.04 | |
| 108 | 51.56 | 3.61 | 16.70 | | 51.69 | 3.62 | 16.46 | |
| 109 | 53.27 | 4.10 | 17.26 | | 53.55 | 4.03 | 16.62 | |
| 110 | 48.35 | 3.10 | 19.90 | | 48.25 | 3.02 | 19.98 | |
| 111 | 53.12 | 4.20 | 21.87 | | 53.51 | 4.27 | 21.46 | |
| 112 | 51.31 | 3.35 | 16.62 | | 51.33 | 3.32 | 16.65 | |
| 113 | 54.99 | 3.80 | 18.86 | | 55.16 | 3.81 | 18.79 | |
| 114 | 49.43 | 3.23 | 16.01 | | 49.45 | 3.23 | 16.00 | |
| 115 | 51.56 | 3.61 | 16.70 | | 51.43 | 3.63 | 16.52 | |
| 116 | 48.35 | 3.10 | 19.90 | | 48.44 | 3.24 | 19.89 | |
| 117 | 51.31 | 3.35 | 16.62 | | 51.03 | 3.35 | 16.44 | |
| 118 | 54.99 | 3.80 | 18.86 | | 55.24 | 3.75 | 18.90 | |
| 119 | 49.43 | 3.23 | 16.01 | | 49.60 | 3.21 | 15.79 | |
| 120 | 51.56 | 3.61 | 16.70 | | 51.74 | 3.60 | 16.51 | |
| 121 | 48.35 | 3.10 | 19.90 | | 48.56 | 3.16 | 19.89 | |
| 124 | 49.43 | 3.23 | 16.01 | | 49.15 | 3.24 | 15.79 | |
| 125 | 51.56 | 3.61 | 16.70 | | 51.40 | 3.64 | 16.57 | |

Table S4. Combustion analyses for new intermediates, in order of their appearance in the Experimental Section

| No | Calculated | | | | Found | | | |
|------------|------------|------|-------|-------|-------|------|-------|-------|
| | C | H | N | Br | C | H | N | Br |
| 148 | 40.58 | 3.12 | 15.78 | 22.50 | 40.80 | 3.28 | 15.56 | 22.51 |
| 152 | 40.07 | 3.22 | 15.58 | 22.22 | 40.09 | 3.15 | 15.26 | 21.97 |
| 156 | 40.58 | 3.12 | 15.78 | | 40.76 | 3.18 | 15.64 | |
| 160 | 40.58 | 3.12 | 15.78 | | 40.62 | 3.12 | 15.79 | |
| 178 | 42.39 | 3.23 | 22.47 | | 42.46 | 3.31 | 22.20 | |
| 182 | 42.39 | 3.23 | 22.47 | | 42.68 | 3.19 | 22.51 | |
| 184 | 23.84 | 1.60 | 11.12 | | 24.11 | 1.57 | 11.02 | |
| 185 | 37.10 | 2.83 | 19.67 | | 37.28 | 2.77 | 19.17 | |
| 189 | 44.58 | 4.05 | 21.66 | | 44.68 | 4.15 | 21.65 | |