Supporting Information

Synthesis and Structure-activity Relationships of Anti-tubercular 2-Nitroimidazooxazines Bearing Heterocyclic Side Chains

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Contents:

4-[5-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)-2-thienyl]benzonitrile (10) (Scheme 1). Reaction of (6*S*)-6-[(5-bromo-2-thienyl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**63**) and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure B gave **10** (60%) as a white solid: mp 170-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.87-7.79 (m, 4 H), 7.61 (d, *J* = 3.7 Hz, 1 H), 7.16 (d, *J* = 13.8 Hz, 1 H), 4.88 (d, *J* = 13.8 Hz, 1 H), 4.85 (d, *J* = 13.8 Hz, 1 H), 4.64 (dt, *J* = 12.0, 1.3 Hz, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 4.28-4.21 (m, 3 H). Anal. ($C_{18}H_{14}N_4O_4S$) C, H, N.

(6*S*)-6-{[5-(4-Fluorophenyl)-2-thienyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (11). Reaction of **63** and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure B gave **11** (61%) as a white solid: mp 190-193 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.69-7.63 (m, 2 H), 7.35 (d, *J* = 3.6 Hz, 1 H), 7.28-7.21 (m, 2 H), 7.09 (d, *J* = 3.6 Hz, 1 H), 4.84 (d, *J* = 13.2 Hz, 1 H), 4.81 (d, *J* = 13.2 Hz, 1 H), 4.63 (dt, *J* = 12.0, 1.4 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.28-4.21 (m, 3 H). Anal. ($C_{17}H_{14}FN_3O_4S$) C, H, N.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethoxy)phenyl]-2-thienyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (12). Reaction of **63** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure B gave **12** (37%) as a white solid: mp 190-191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.74 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 3.6 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.12 (d, *J* = 3.6 Hz, 1 H), 4.86 (d, *J* = 13.5 Hz, 1 H), 4.82 (d, *J* = 13.5 Hz, 1 H), 4.63 (br d, *J* = 12.0 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.28-4.21 (m, 3 H). Anal. ($C_{18}H_{14}F_3N_3O_5S$) C, H, N.

(6*S*)-6-{[5-(3-Fluoro-4-methoxyphenyl)-2-thienyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (13). Reaction of **63** and 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure B gave **13** (48%) as a white

solid: mp 191-192 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.51 (dd, *J* = 12.7, 2.2 Hz, 1 H), 7.36 (dq, *J* = 8.5, 1.2 Hz, 1 H), 7.32 (d, *J* = 3.6 Hz, 1 H), 7.18 (t, *J* = 8.8. Hz, 1 H), 7.06 (d, *J* = 3.6 Hz, 1 H), 4.83 (d, *J* = 13.8 Hz, 1 H), 4.79 (d, *J* = 13.8 Hz, 1 H), 4.63 (dt, *J* = 12.0, 1.3 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.28-4.21 (m, 3 H), 3.86 (s, 3 H). Anal. ($C_{18}H_{16}FN_3O_5S$) C, H, N.

(6*S*)-6-({5-[4-(Difluoromethoxy)phenyl]-2-thienyl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (14). Reaction of **63** and 4-(difluoromethoxy)phenyl boronic acid under the Suzuki coupling conditions described in Procedure B gave **14** (95%) as a white solid: mp 170-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 3.6 Hz, 1 H), 7.25 (t, J_{H-F} = 74.0 Hz, 1 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 7.09 (d, *J* = 3.5 Hz, 1 H), 4.86 (d, *J* = 13.4 Hz, 1 H), 4.81 (d, *J* = 13.4 Hz, 1 H), 4.64 (dt, *J* = 12.0, 1.3 Hz, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 4.29-4.21 (m, 3 H). Anal. ($C_{18}H_{15}F_2N_3O_5S$) C, H, N.

(6*S*)-6-{[5-(6-Methoxy-3-pyridinyl)-2-thienyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (15). Reaction of **63** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure B gave **15** (61%) as a white solid: mp 171-174 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (dd, *J* = 2.5, 0.4 Hz, 1 H), 8.03 (s, 1 H), 7.94 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.34 (d, *J* = 3.6 Hz, 1 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 6.87 (dd, *J* = 8.7, 0.6 Hz, 1 H), 4.84 (d, *J* = 13.4 Hz, 1 H), 4.81 (d, *J* = 13.1 Hz, 1 H), 4.63 (dt, *J* = 12.0, 1.3 Hz, 1 H), 4.46 (d, *J* =12.0 Hz, 1 H), 4.28-4.21 (m, 3 H), 3.88 (s, 3 H). Anal. ($C_{17}H_{16}N_4O_5S$) C, H, N.

(6*S*)-2-Nitro-6-({5-[4-(trifluoromethyl)-2-pyridinyl]-2-thienyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (16). Reaction of **63** and 4-(trifluoromethyl)-2-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure B gave **16** (33%) as a cream solid: mp 158-160 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.72 (d, *J* = 5.2 Hz, 1 H), 8.07 (d, *J* = 1.0 Hz, 1 H), 8.03 (s, 1 H), 7.92-7.85 (m, 2 H), 7.21 (d, *J* =3.7 Hz, 1 H), 4.92 (d,

J = 13.8 Hz, 1 H), 4.88 (d, *J* = 13.8 Hz, 1 H), 4.66 (br d, *J* = 12.1 Hz, 1 H), 4.88 (d, *J* = 11.9 Hz, 1 H), 4.33-4.22 (m, 3 H). Anal. ($C_{17}H_{13}F_3N_4O_4S$) C, H, N.

(6*S*)-2-Nitro-6-({5-[6-(trifluoromethyl)-3-pyridinyl]-2-thienyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (17). Reaction of **63** and 6-(trifluoromethyl)-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure B gave **17** (22%) as a pale pink solid: mp 169-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.06 (d, *J* = 2.2 Hz, 1 H), 8.27 (dd, *J* = 8.2, 1.8 Hz, 1 H), 8.03 (s, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.70 (d, *J* = 3.7 Hz, 1 H), 7.20 (d, *J* = 3.7 Hz, 1 H), 4.90 (d, *J* = 13.6 Hz, 1 H), 4.86 (d, *J* = 13.6 Hz, 1 H), 4.65 (dt, *J* = 12.0, 1.1 Hz, 1 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.31-4.23 (m, 3 H). Anal. ($C_{17}H_{13}F_3N_4O_4S{\cdot}0.25H_2O$) C, H, N.

(6*S*)-6-{[5-(6-Fluoro-3-pyridinyl)-2-thienyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (18). Reaction of **63** and 6-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure B gave **18** (65%) as a tan solid: mp 171-172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.51 (dd, *J* = 2.6, 0.8 Hz, 1 H), 8.25-8.18 (m, 1 H), 8.02 (s, 1 H), 7.49 (d, *J* = 3.6 Hz, 1 H), 7.24 (ddd, *J* = 8.3, 2.9, 0.4 Hz, 1 H), 7.14 (d, *J* = 3.6 Hz, 1 H), 4.87 (d, *J* = 13.1 Hz, 1 H), 4.84 (d, *J* = 13.1 Hz, 1 H), 4.64 (dt, *J* = 12.0, 1.4 Hz, 1 H), 4.47 (d, *J* =12.0 Hz, 1 H), 4.30-4.23 (m, 3 H). Anal. ($C_{16}H_{13}FN_4O_4S$) C, H, N.

(6*S*)-6-{[5-(5-Fluoro-3-pyridinyl)-2-thienyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (19). Reaction of **63** and 5-fluoro-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure B gave **19** (68%) as a tan solid: mp 150-152 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.73 (t, *J* = 1.7 Hz, 1 H), 8.50 (d, *J* = 2.7 Hz, 1 H), 8.03 (s, 1 H), 8.00 (ddd, *J* = 10.2, 2.7, 2.0 Hz, 1 H), 7.62 (d, *J* = 3.7 Hz, 1 H), 7.17 (d, *J* = 3.7 Hz, 1 H), 4.89 (d, *J* = 13.4 Hz, 1 H), 4.85 (d, *J* = 13.4 Hz, 1 H), 4.65 (dt, *J* = 12.0, 1.1 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.30-4.22 (m, 3 H). Anal. ($C_{16}H_{13}FN_4O_4S$) 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)-1,3-thiazol-2-yl]benzonitrile (21) (Scheme 1). Reaction of (6*S*)-6-[(2-chloro-1,3-thiazol-4-yl)methoxy]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**65**) and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure B for 1 h gave **21** (41%) as a white solid: mp 170-172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (d, *J* = 8.6 Hz, 2 H), 8.03 (s, 1 H), 7.96 (d, *J* = 8.6 Hz, 2 H), 7.78 (s, 1 H), 4.84 (dd, *J* = 13.0, 0.6 Hz, 1 H), 4.80 (dd, *J* = 13.0, 0.6 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.50 (d, *J* =11.8 Hz, 1 H), 4.38-4.34 (m, 1 H), 4.31 (dd, *J* = 13.5, 2.1 Hz, 1 H), 4.25 (dd, *J* = 13.5, 3.2 Hz, 1 H). Anal. ($C_{17}H_{13}N_5O_4S$) C, H, N.

(6*S*)-6-{[2-(4-Fluorophenyl)-1,3-thiazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (22). Reaction of **65** and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure B for 1 h gave **22** (57%) as a cream solid: mp 149-150 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 8.00-7.94 (m, 2 H), 7.62 (s, 1 H), 7.35-7.29 (m, 2 H), 4.80 (dd, *J* = 12.8, 0.7 Hz, 1 H), 4.76 (dd, *J* = 12.8, 0.7 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.6 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.36-4.32 (m, 1 H), 4.30 (dt, *J* = 13.5, 2.0 Hz, 1 H), 4.25 (dd, *J* = 13.5, 3.3 Hz, 1 H). Anal. ($C_{16}H_{13}FN_4O_4S$) C, H, N.

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethoxy)phenyl]-1,3-thiazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (23). Reaction of **65** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure B for 1 h gave **23** (54%) as a white solid: mp 141-142 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (d, *J* = 8.9 Hz, 2 H), 8.03 (s, 1 H), 7.68 (s, 1 H), 7.49 (d, *J* = 8.9 Hz, 2 H), 4.82 (d, *J* = 13.2 Hz, 1 H), 4.78 (d, *J* = 13.2 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.37-4.34 (m, 1 H), 4.31 (dt, *J* = 13.5, 2.1 Hz, 1 H), 4.24 (dd, *J* = 13.5, 3.3 Hz, 1 H). Anal. ($C_{17}H_{13}F_3N_4O_5S$) C, H, N.

(6*S*)-6-{[2-(3-Fluoro-4-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (24). Reaction of **65** and 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure B for 1 h gave **24** (74%) as a white solid: mp 160-161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.75-7.68 (m, 2 H), 7.58 (s, 1 H), 7.27 (t, *J* = 8.6 Hz, 1 H), 4.78 (d, *J* = 13.3 Hz, 1 H), 4.75 (d, *J* = 13.3 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.48 (d, *J* = 12.5 Hz, 1 H), 4.36-4.21 (m, 3 H), 3.91 (s, 3 H). Anal. ($C_{17}H_{15}FN_4O_5S$) C, H, N.

(6*S*)-6-{[2-(6-Methoxy-3-pyridinyl)-1,3-thiazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (25). Reaction of **65** and 6-methoxy-3-pyridinylboronic acid under the Suzuki coupling conditions described in Procedure B for 1 h gave **25** (45%) as a cream solid: mp 159-161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.72 (dd, *J* = 2.5, 0.6 Hz, 1 H), 8.19 (dd, *J* = 8.7, 2.5 Hz, 1 H), 8.02 (s, 1 H), 7.61 (s, 1 H), 6.95 (dd, *J* = 8.7, 0.6 Hz, 1 H), 4.80 (dd, *J* =13.1, 0.6 Hz, 1 H), 4.77 (dd, *J* = 13.1, 0.6 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.5 Hz, 1 H), 4.49 (d, *J* = 12.7 Hz, 1 H), 4.38-4.34 (m, 1 H), 4.31 (dt, *J* = 13.6, 2.0 Hz, 1 H), 4.25 (dd, *J* = 13.5, 3.2 Hz, 1 H), 3.92 (s, 3 H). Anal. ($C_{16}H_{15}N_5O_5S\cdot H_2O$) C, H, N.

Methyl 2-(4-cyanophenyl)-1-methyl-1*H*-imidazole-5-carboxylate (67b) (Scheme 2). Reaction of methyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate[1] (**66**) and 4-cyanophenylboronic acid under the Suzuki coupling conditions described in Procedure B for 2 h gave **67b** (83%) as a white solid: mp 159-161 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.85-7.75 (m, 4 H), 3.99 (s, 3 H), 3.90 (s, 3 H). APCI MS *m/z* 242 $[M + H]^+$.

4-[5-(Hydroxymethyl)-1-methyl-1*H*-imidazol-2-yl]benzonitrile (68b). Lithium pyrrolidinoborohydride[2] (2 mL of 0.63M in THF, 1.26 mmol) was added to a solution of **67b** (0.200 g, 0.829 mmol) in THF (5 mL), and the solution was stirred at room temperature for 1.5 h. Further lithium pyrrolidinoborohydride (2 mL of 0.63M in THF, 1.26 mmol) was added and the solution was stirred for an additional 15 min. The resulting mixture was quenched

with MeOH and partitioned between EtOAc and water. The organic fraction was dried ($MgSO_4$) and evaporated, and then column chromatography of the residue (eluting with EtOAc) gave **68b** (0.104 g, 59%) as a white solid: mp 223-226 °C; ^{1}H NMR [$(CD_3)_2SO$] 7.99 (d, *J* = 8.6 Hz, 2 H), 7.87 (d, *J* = 8.6 Hz, 2 H), 6.99 (s, 1 H), 5.15 (t, *J* = 4.6 Hz, 1 H), 4.51 (d, *J* = 4.6 Hz, 2 H), 3.74 (s, 3 H). APCI MS *m/z* 214 $[M + H]^+$.

4-[5-(Chloromethyl)-1-methyl-1*H*-imidazol-2-yl]benzonitrile hydrochloride (69b). Chlorination of **68b** with $SOCl_2$, using Procedure D, gave crude **69b** (87%) as a white solid, which was used directly in the next step; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (d, *J* = 8.6 Hz, 2 H), 7.99 (d, *J* = 8.6 Hz, 2 H), 7.75 (s, 1 H), 5.08 (s, 2 H), 3.82 (s, 3 H).

4-[1-Methyl-5-({[(6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)-1*H*-imidazol-2-yl]benzonitrile (27). Reaction of (6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-ol[3] (**61**) with **69b** (1.0 equiv.) and NaH (3 equiv.) in DMF, using Procedure A, gave **27** (54%) as a white solid: mp 174-176 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.93 (d, *J* = 8.6 Hz, 2 H), 7.87 (d, *J* = 8.6 Hz, 2 H), 7.14 (s, 1 H), 4.77-4.64 (m, 3 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.29-4.20 (m, 3 H), 3.65 (s, 3 H). Anal. ($C_{18}H_{16}N_6O_4 \cdot 0.5H_2O$) C, H, N.

Methyl 2-(4-fluorophenyl)-1-methyl-1*H*-imidazole-5-carboxylate (67c). Reaction of **66** and 4-fluorophenylboronic acid under the Suzuki coupling conditions described in Procedure B for 2 h gave **67c** (59%) as a tan solid: mp 101-104 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1 H), 7.64-7.59 (m, 2 H), 7.22-7.16 (m, 2 H), 3.94 (s, 3 H), 3.88 (s, 3 H). APCI MS *m/z* 235 $[M + H]^+$.

[2-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl]methanol (68c). Reduction of **67c** with $LiAlH_4$ in THF, using Procedure C, gave **68c** (91%) as tan needles: mp 180-183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.70-7.64 (m, 2 H), 7.34-7.27 (m, 2 H), 6.90 (s, 1 H), 5.07 (t, *J* = 5.2 Hz, 1 H), 4.49 (d, *J* = 5.2 Hz, 2 H), 3.66 (s, 3 H). APCI MS *m/z* 207 $[M + H]^+$.

5-(Chloromethyl)-2-(4-fluorophenyl)-1-methyl-1*H*-imidazole hydrochloride (69c). Chlorination of **68c** with $SOCl_2$, using Procedure D, gave crude **69c** (80%) as a white solid, which was used directly in the next step; ^{1}H NMR [$(CD_3)_2SO$] δ 7.90-7.82 (m, 2 H), 7.85 (s, 1 H), 7.56-7.49 (m, 2 H), 5.09 (s, 2 H), 3.81 (s, 3 H).

(6*S*)-6-{[2-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (28). Reaction of alcohol **61** with **69c** (1.0 equiv.) and NaH (3 equiv.) in DMF, using Procedure A, gave **28** (50%) as a cream solid: mp 182-184 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.81-7.65 (m, 2 H), 7.34-7.27 (m, 2 H), 7.05 (s, 1 H), 4.74-4.64 (m, 3 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.29-4.20 (m, 3 H), 3.58 (s, 3 H). Anal. ($C_{17}H_{16}FN_5O_4 \cdot 0.75H_2O$) C, H, N.

Methyl 1-methyl-2-[4-(trifluoromethoxy)phenyl]-1*H*-imidazole-5-carboxylate (67d). Reaction of **66** and 4-(trifluoromethoxy)phenylboronic acid under the Suzuki coupling conditions described in Procedure B for 2 h gave **67d** (65%) as a white solid: mp 70-71 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 3.96 (s, 3 H), 3.89 (s, 3 H). APCI MS *m/z* 301 $[M + H]^+$.

{1-Methyl-2-[4-(trifluoromethoxy)phenyl]-1*H*-imidazol-5-yl}methanol (68d). Reduction of **67d** with $LiAlH_4$ in THF, using Procedure C, gave **68d** (90%) as cream flakes: mp 143-146 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.78 (d, *J* = 8.9 Hz, 2 H), 7.47 (d, *J* = 8.9 Hz, 2 H), 6.93 (s, 1 H), 5.09 (t, *J* = 5.3 Hz, 1 H), 4.50 (d, *J* = 5.3 Hz, 2 H), 3.69 (s, 3 H). APCI MS *m/z* 273 $[M + H]^+$.

5-(Chloromethyl)-1-methyl-2-[4-(trifluoromethoxy)phenyl]-1*H*-imidazole hydrochloride (69d). Chlorination of **68d** with $SOCl_2$, using Procedure D, gave crude **69d** (81%) as a white solid, which was used directly in the next step; ^{1}H NMR [$(CD_3)_2SO$] δ 7.95 (d, *J* = 8.9 Hz, 2 H), 7.83 (s, 1 H), 7.67 (d, *J* = 8.9 Hz, 2 H), 5.09 (s, 2 H), 3.82 (s, 3 H).

(6*S*)-6-({1-Methyl-2-[4-(trifluoromethoxy)phenyl]-1*H*-imidazol-5-yl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (29). Reaction of alcohol **61** with **69d** (1.0 equiv.) and NaH (3 equiv.) in DMF, using Procedure A, gave **29** (32%) as a white solid: mp 106-109 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.78 (d, *J* = 8.1 Hz, 2 H), 7.46 (d, *J* = 8.1 Hz, 2 H), 7.08 (s, 1 H), 4.75-4.63 (m, 3 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.29-4.20 (m, 3 H), 3.61 (s, 3 H). Anal. ($C_{18}H_{16}F_3N_5O_5 \cdot 0.5H_2O$) C, H, N.

Methyl 2-(3-fluoro-4-methoxyphenyl)-1-methyl-1*H*-imidazole-5-carboxylate (67e). Reaction of **66** and 3-fluoro-4-methoxyphenylboronic acid under the Suzuki coupling conditions described in Procedure B for 2 h gave **67e** (69%) as a tan solid: mp 154-156 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (s, 1 H), 7.41-7.35 (m, 2 H), 7.06 (t, *J* = 8.3 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.88 (s, 3 H). APCI MS *m/z* 265 $[M + H]^+$.

[2-(3-Fluoro-4-methoxyphenyl)-1-methyl-1*H*-imidazol-5-yl]methanol (68e). Reduction of **67e** with $LiAlH_4$ (2.3 equiv.) in THF, using Procedure C, gave **68e** (79%) as a tan solid: mp 139-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.47 (dd, *J* = 12.5, 2.1 Hz, 1 H), 7.42 (ddd, *J* = 8.5, 2.1, 1.2 Hz, 1 H), 7.26 (t, *J* = 8.8 Hz, 1 H), 6.88 (s, 1 H), 5.06 (t, *J* = 5.2 Hz, 1 H), 4.48 (d, *J* = 5.2 Hz, 2 H), 3.90 (s, 3 H), 3.67 (s, 3 H). APCI MS *m/z* 237 $[M + H]^+$.

5-(Chloromethyl)-2-(3-fluoro-4-methoxyphenyl)-1-methyl-1*H*-imidazole hydrochloride (69e). Chlorination of **68e** with $SOCl_2$, using Procedure D, gave crude **69e** (93%) as a white solid, which was used directly in the next step; ^{1}H NMR [$(CD_3)_2SO$] δ 7.85 (s, 1 H), 7.76 (dd, *J* = 12.0, 2.2 Hz, 1 H), 7.63 (ddd, *J* = 8.6, 2.2, 1.2 Hz, 1 H), 7.45 (t, *J* = 8.6 Hz, 1 H), 5.08 (s, 2 H), 3.96 (s, 3 H), 3.83 (s, 3 H).

(6*S*)-6-{[2-(3-Fluoro-4-methoxyphenyl)-1-methyl-1*H*-imidazol-5-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (30). Reaction of alcohol **61** with **69e** (1.0 equiv.) and NaH (3 equiv.) in DMF, using Procedure A, gave **30** (41%) as a cream solid: mp 105-108 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.48 (dd, *J* = 12.5, 2.1 Hz, 1 H), 7.42 (ddd,

J = 8.5, 2.0, 1.1 Hz, 1 H), 7.26 (t, *J* = 8.5 Hz, 1 H), 7.04 (s, 1 H), 4.73-4.63 (m, 3 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.28-4.19 (m, 3 H), 3.89 (s, 3 H), 3.59 (s, 3 H). Anal. ($C_{18}H_{18}FN_5O_5 \cdot 0.5H_2O$) C, H. N: calcd, 16.98; found, 16.42. HPLC purity 97.5%.

3-(4-Fluorophenyl)-1-methyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-1*H*-pyrazole (72b) (Scheme 3). Reaction of 2-(2-propynyloxy)tetrahydro-2*H*-pyran[4] (**70**) with 1-fluoro-4-iodobenzene (**71b**), methylhydrazine and CO, using Procedure E, gave **72b** (54%) as a brown solid: mp 40-41 °C; ^{1}H NMR ($CDCl_3$) δ 7.75-7.70 (m, 2 H), 7.09-7.02 (m, 2 H), 6.48 (s, 1 H), 4.75 (d, *J* = 12.8 Hz, 1 H), 4.69 (t, *J* = 3.3 Hz, 1 H), 4.56 (d, *J* = 12.8 Hz, 1 H), 3.93 (s, 3 H), 3.91-3.85 (m, 1 H), 3.60-3.54 (m, 1 H), 1.87-1.78 (m, 1 H), 1.76-1.69 (m, 1 H), 1.66-1.51 (m, 4 H). APCI MS *m/z* 291 $[M + H]^+$.

[3-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methanol (73b). Hydrolysis of THP ether **72b** with 4M HCl, using Procedure F, gave **73b** (64%) as a white solid: mp 113-115 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.80-7.74 (m, 2 H), 7.23-7.16 (m, 2 H), 6.58 (s, 1 H), 5.28 (t, *J* = 5.5 Hz, 1 H), 4.51 (d, *J* = 5.5 Hz, 2 H), 3.82 (s, 3 H). APCI MS *m/z* 207 $[M + H]^+$.

5-(Bromomethyl)-3-(4-fluorophenyl)-1-methyl-1*H*-pyrazole (74b). Bromination of **73b** with PBr_3, using Procedure G, gave **74b** (69%): mp 81-83 °C; ^{1}H NMR ($CDCl_3$) δ 7.74-7.68 (m, 2 H), 7.10-7.04 (m, 2 H), 6.52 (s, 1 H), 4.49 (s, 2 H), 3.93 (s, 3 H). APCI MS *m/z* 269, 271 $[M + H]^+$.

(6*S*)-6-{[3-(4-Fluorophenyl)-1-methyl-1*H*-pyrazol-5-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (32). Reaction of alcohol **61** with **74b** (1.0 equiv.) and NaH (2 equiv.) in DMF, using Procedure A, gave **32** (63%) as a white solid: mp 229-231 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (s, 1 H), 7.80-7.74 (m, 2 H), 7.23-7.17 (m, 2 H), 6.70 (s, 1 H), 4.76 (d, *J* = 12.6 Hz, 1 H), 4.71 (d, *J* = 12.6 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.30-4.20 (m, 3 H), 3.77 (s, 3 H). Anal. ($C_{17}H_{16}FN_5O_4$) C, H, N.

1-Methyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-3-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole (72c). Reaction of alkyne **70** with 1-iodo-4-(trifluoromethoxy)benzene (**71c**), methylhydrazine and CO, using Procedure E, gave **72c** (64%) as a brown solid: mp 40-42 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 6.51 (s, 1 H), 4.75 (d, *J* = 12.8 Hz, 1 H), 4.69 (t, *J* = 3.3 Hz, 1 H), 4.57 (d, *J* = 12.8 Hz, 1 H), 3.94 (s, 3 H), 3.91-3.84 (m, 1 H), 3.60-3.53 (m, 1 H), 1.88-1.68 (m, 2 H), 1.66-1.50 (m, 4 H). APCI MS *m/z* 357 $[M + H]^+$.

{1-Methyl-3-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazol-5-yl}methanol (73c). Hydrolysis of THP ether **72c** with 4M HCl, using Procedure F, gave **73c** (38%) as a white solid: mp 91-93 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.86 (d, *J* = 8.9 Hz, 2 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 6.64 (s, 1 H), 5.30 (t, *J* = 5.2 Hz, 1 H), 4.52 (d, *J* = 5.2 Hz, 2 H), 3.84 (s, 3 H). APCI MS *m/z* 273 $[M + H]^+$.

5-(Bromomethyl)-1-methyl-3-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole (74c). Bromination of **73c** with PBr_3, using Procedure G, gave **74c** (85%) as a white solid: mp 70-71 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 2 H), 7.22 (d, *J* = 8.9 Hz, 2 H), 6.55 (s, 1 H), 4.50 (s, 2 H), 3.94 (s, 3 H). APCI MS *m/z* 335, 337 $[M + H]^+$.

(6*S*)-6-({1-Methyl-3-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazol-5-yl}methoxy)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**33)**. Reaction of alcohol **61** with **74c** (1.0 equiv.) and NaH (2 equiv.) in DMF, using Procedure A, gave **33** (48%) as a white solid: mp 178-179 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (s, 1 H), 7.85 (d, *J* = 8.9 Hz, 2 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 6.76 (s, 1 H), 4.77 (d, *J* = 12.6 Hz, 1 H), 4.72 (d, *J* = 12.6 Hz, 1 H), 4.69 (dt, *J* = 12.1, 2.3 Hz, 1 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 4.32-4.21 (m, 3 H), 3.79 (s, 3 H). Anal. ($C_{18}H_{16}F_3N_5O_5$) C, H, N.

Ethyl 5-amino-1-(4-fluorophenyl)-1*H*-pyrazole-4-carboxylate (77b) (Scheme 4). Reaction of ethyl (2*E*)-2-cyano-3-ethoxy-2-propenoate (**75**) with 4-fluorophenylhydrazine

hydrochloride (**76b**) in aq AcOH, using Procedure H, gave **77b** (75%) as tan needles: mp 150-151 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.69 (s, 1 H), 7.59-7.53 (m, 2 H), 7.40-7.33 (m, 2 H), 6.29 (br s, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 250 $[M + H]^+$.

Ethyl 1-(4-fluorophenyl)-1*H*-pyrazole-4-carboxylate (78b). Deamination of **77b** with isoamyl nitrite, using Procedure I, gave **78b** (90%) as white needles: mp (EtOH) 120-122 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.06 (s, 1 H), 8.13 (s, 1 H), 7.99-7.94 (m, 2 H), 7.41-7.34 (m, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 235 $[M + H]^+$.

[1-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]methanol (79b). Reduction of **78b** with $LiAlH_4$ in Et_2O, using Procedure J, gave **79b** (62%) as a white solid: mp 84-86 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.33 (s, 1 H), 7.85-7.79 (m, 2 H), 7.66 (s, 1 H), 7.35-7.28 (m, 2 H), 4.95 (t, *J* = 5.3 Hz, 1 H), 4.44 (d, *J* = 5.3 Hz, 2 H). APCI MS *m/z* 193 $[M + H]^+$.

4-(Bromomethyl)-1-(4-fluorophenyl)-1*H*-pyrazole (80b). Bromination of **79b** with PBr_3 (0.5 equiv.) for 2 h, using Procedure G, gave crude **80b** (12%) as a white solid, which was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.72 (s, 1 H), 7.74-7.69 (m, 2 H), 7.18-7.12 (m, 2 H), 4.50 (s, 2 H). APCI MS *m/z* 255, 257 $[M + H]^+$.

(6*S*)-6-{[1-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (35). Reaction of alcohol **61** with **80b** (1.06 equiv.) and NaH (2 equiv.) in DMF, using Procedure A, gave **35** (51%) as a white solid: mp 145-148 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.46 (s, 1 H), 8.02 (s, 1 H), 7.85-7.78 (m, 2 H), 7.73 (s, 1 H), 7.33 (t, *J* = 8.8 Hz, 2 H), 4.66-4.55 (m, 3 H), 4.45 (d, *J* = 11.9 Hz, 1 H), 4.25-4.18 (m, 3 H). Anal. ($C_{16}H_{14}FN_5O_4$) C, H, N.

Ethyl 5-amino-1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole-4-carboxylate (77c). Reaction of **75** with 4-(trifluoromethoxy)phenylhydrazine hydrochloride (**76c**) in aq AcOH, using Procedure H, gave **77c** (94%) as tan flakes: mp 102-103 °C; ^{1}H NMR [$(CD_3)_2SO$] δ

7.73 (s, 1 H), 7.68 (d, *J* = 9.1 Hz, 2 H), 7.53 (d, *J* = 9.1 Hz, 2 H), 6.41 (br s, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 316 $[M + H]^+$.

Ethyl 1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole-4-carboxylate (78c). Deamination of **77c** with isoamyl nitrite, using Procedure I, gave **78c** (87%) as a white solid: mp 114-116 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, *J* = 0.5 Hz, 1 H), 8.10 (s, 1 H), 7.74 (d, *J* = 9.1 Hz, 2 H), 7.34 (d, *J* = 9.1 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 301 $[M + H]^+$.

{1-[4-(Trifluoromethoxy)phenyl]-1*H*-pyrazol-4-yl}methanol (79c). Reduction of **78c** with $LiAlH_4$ in Et_2O, using Procedure J, gave **79c** (83%) as a white solid: mp 73-74 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1 H), 7.73-7.67 (m, 3 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.69 (d, *J* = 5.5 Hz, 2 H), 1.57 (t, *J* = 5.5 Hz, 1 H). APCI MS *m/z* 259 $[M + H]^+$.

4-(Bromomethyl)-1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole (80c). Bromination of **79c** with PBr_3 (1.0 equiv.) for 2 h, using Procedure G, gave **80c** (81%) as a white solid: mp 50-51 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, *J* = 0.5 Hz, 1 H), 7.74 (s, 1 H), 7.69 (d, *J* = 9.1 Hz, 2 H), 7.31 (d, *J* = 9.1 Hz, 2 H), 4.50 (s, 2 H). APCI MS *m/z* 321, 323 $[M + H]^+$.

(6*S*)-2-Nitro-6-({1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (36). Reaction of alcohol **61** with **80c** (1.0 equiv.) and NaH (1.5 equiv.) in DMF, using Procedure A, gave **36** (71%) as a white solid: mp 150-151 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (s, 1 H), 8.02 (s, 1 H), 7.93 (d, *J* = 9.1 Hz, 2 H), 7.77 (s, 1 H), 7.50 (d, *J* = 9.1 Hz, 2 H), 4.66-4.56 (m, 3 H), 4.46 (d, *J* = 11.8 Hz, 1 H), 4.26-4.20 (m, 3 H). Anal. ($C_{17}H_{14}F_3N_5O_5$) C, H, N.

Ethyl 1-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate (84b) (Scheme 4). Cycloaddition of ethyl 2-chloro[(4-fluorophenyl)hydrazono]ethanoate[5] (**83b**) and bicyclo[2.2.1]hepta-2,5-diene in toluene, followed by retro Diels-Alder reaction in refluxing xylenes, using Procedure L, gave **84b** (67%) as a cream solid: mp 108-110 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J* = 2.5 Hz,

1 H), 7.74-7.68 (m, 2 H), 7.20-7.13 (m, 2 H), 6.99 (d, *J* = 2.5 Hz, 1 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 235 $[M + H]^+$.

[1-(4-Fluorophenyl)-1*H*-pyrazol-3-yl]methanol (85b). Reduction of **84b** with $LiAlH_4$ in Et_2O, using Procedure M, gave **85b** (67%) as white flakes: mp 71-72 °C; ^1H NMR ($CDCl_3$) δ 7.80 (d, *J* = 2.4 Hz, 1 H), 7.64-7.57 (m, 2 H), 7.17-7.08 (m, 2 H), 6.45 (d, *J* = 2.4 Hz, 1 H), 4.78 (d, *J* = 5.9 Hz, 2 H), 2.02 (t, *J* = 5.9 Hz, 1 H). APCI MS *m/z* 193 $[M + H]^+$.

3-(Bromomethyl)-1-(4-fluorophenyl)-1*H*-pyrazole (86b). Bromination of **85b** with PBr_3 (1.0 equiv.) for 17 h, using Procedure G, gave **86b** (78%) as a white solid: mp 71-73 °C; ^1H NMR ($CDCl_3$) δ 7.79 (d, *J* = 2.5 Hz, 1 H), 7.65-7.59 (m, 2 H), 7.18-7.11 (m, 2 H), 6.52 (d, *J* = 2.5 Hz, 1 H), 4.56 (s, 2 H). APCI MS *m/z* 255, 257 $[M + H]^+$.

(6*S*)-6-{[1-(4-Fluorophenyl)-1*H*-pyrazol-3-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (38). Reaction of alcohol **61** with **86b** (1.0 equiv.) and NaH (1.5 equiv.) in DMF, using Procedure A, gave **38** (89%) as a white solid: mp 161-163 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.42 (d, *J* = 2.5 Hz, 1 H), 8.02 (s, 1 H), 7.87-7.80 (m, 2 H), 7.37-7.30 (m, 2 H), 6.51 (d, *J* = 2.5 Hz, 1 H), 4.73-4.62 (m, 3 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.30-4.20 (m, 3 H). Anal. ($C_{16}H_{14}FN_5O_4$) C, H, N.

Ethyl 2-chloro{[4-(trifluoromethoxy)phenyl]hydrazono}ethanoate (83c). Reaction of 4-(trifluoromethoxy)benzenediazonium tetrafluoroborate[6] (**82c**) and ethyl 2-chloroacetoacetate (**81**) in aq. pyridine, using Procedure K, gave **83c** (82%) as pale orange needles: mp 128-130 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.68 (s, 1 H), 7.43 (d, *J* = 9.2 Hz, 2 H), 7.34 (d, *J* = 9.2 Hz, 2 H), 4.30 (t, *J* = 7.1 Hz, 2 H), 1.30 (q, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 309, 311 $[M - H]^-$.

Ethyl 1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole-3-carboxylate (84c). Cycloaddition of **83c** and bicyclo[2.2.1]hepta-2,5-diene in toluene, followed by retro Diels-Alder reaction in refluxing xylenes, using Procedure L, gave **84c** (79%) as a white solid: mp 76-78 °C; ^1H NMR ($CDCl_3$) δ 7.91 (d, *J* = 2.5 Hz, 1 H), 7.79 (d, *J* = 8.9 Hz, 2 H), 7.33 (d, *J* = 8.9 Hz, 2

H), 7.00 (d, *J* = 2.5 Hz, 1 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H). APCI MS *m/z* 301 $[M + H]^+$.

{1-[4-(Trifluoromethoxy)phenyl]-1*H*-pyrazol-3-yl}methanol (85c). Reduction of **84c** with $LiAlH_4$ in Et_2O, using Procedure M, gave **85c** (96%) as a white solid: mp 53-54 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.44 (d, *J* = 2.5 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 6.50 (d, *J* = 2.5 Hz, 1 H), 5.15 (t, *J* = 5.8 Hz, 1 H), 4.51 (d, *J* = 5.8 Hz, 2 H). APCI MS *m/z* 259 $[M + H]^+$.

3-(Bromomethyl)-1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazole (86c). Bromination of **85c** with PBr_3 (1.0 equiv.) for 17 h, using Procedure G, gave **86c** (89%) as a white solid: mp 71-73 °C; ^1H NMR ($CDCl_3$) δ 7.84 (d, *J* = 2.5 Hz, 1 H), 7.69 (d, *J* = 9.1 Hz, 2 H), 7.31 (d, *J* = 9.1 Hz, 2 H), 6.54 (d, *J* = 2.5 Hz, 1 H), 4.56 (s, 2 H). APCI MS *m/z* 321, 323 $[M + H]^+$.

(6*S*)-2-Nitro-6-({1-[4-(trifluoromethoxy)phenyl]-1*H*-pyrazol-3-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (39). Reaction of alcohol **61** with **86c** (1.1 equiv.) and NaH (1.5 equiv.) in DMF, using Procedure A, gave **39** (78%) as a white solid: mp 103-105 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.50 (d, *J* = 2.5 Hz, 1 H), 8.01 (s, 1 H), 7.93 (d, *J* = 9.1 Hz, 2 H), 7.49 (d, *J* = 9.1 Hz, 2 H), 6.54 (d, *J* = 2.5 Hz, 1 H), 4.74-4.68 (m, 2 H), 4.65 (dt, *J* = 12.3, 2.4 Hz, 1 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.31-4.20 (m, 3 H). Anal. ($C_{17}H_{14}F_3N_5O_5$) C, H, N.

4-[5-({[(6*S*)-2-Nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)-3-isoxazolyl]benzonitrile (41) (Scheme 5). Reaction of (6*S*)-2-nitro-6-(2-propynyloxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**88**) with 4-cyano-*N*-hydroxybenzenecarboximidoyl chloride[7] (**89b**) and Et_3N in THF, using Procedure N, gave **41** (67%) as a white solid: mp 237-239 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.07 (d, *J* = 8.6 Hz, 2 H), 8.04 (s, 1 H), 7.99 (d, *J* =8.6 Hz, 2 H), 7.19 (s, 1 H), 4.92 (d, *J* = 14.4 Hz, 1 H), 4.88 (d, *J* = 14.4 Hz, 1 H), 4.69 (dt, *J* =

12.1, 2.2 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.37-4.22 (m, 3 H). Anal ($C_{17}H_{13}N_5O_5$) C, H, N.

(6*S*)-6-{[3-(4-Fluorophenyl)-5-isoxazolyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (42). Reaction of alkyne **88** with 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride[8] (**89c**) and Et_3N in THF, using Procedure N, gave **42** (67%) as a white solid: mp 151-153 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.04 (s, 1 H), 7.96-7.89 (m, 2 H), 7.39-7.31 (m, 2 H), 7.06 (s, 1 H), 4.89 (d, *J* = 14.4 Hz, 1 H), 4.85 (d, *J* = 14.4 Hz, 1 H), 4.69 (dt, *J* = 12.1, 2.2 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.37-4.21 (m, 3 H). Anal ($C_{16}H_{13}FN_4O_5$) C, H, N.

(6*S*)-2-Nitro-6-({3-[4-(trifluoromethoxy)phenyl]-5-isoxazolyl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (43). Reaction of alkyne **88** with *N*-hydroxy-4-(trifluoromethoxy)benzenecarboximidoyl chloride[9] (**89d**) and Et_3N in THF, using Procedure N, gave **43** (48%) as a white solid: mp 161-163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.04 (s, 1 H), 8.00 (d, *J* = 8.9 Hz, 2 H), 7.52 (d, *J* = 8.9 Hz, 2 H), 7.10 (s, 1 H), 4.91 (d, *J* = 14.4 Hz, 1 H), 4.87 (d, *J* = 14.4 Hz, 1 H), 4.69 (dt, *J* = 12.1, 2.2 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.37-4.23 (m, 3 H). Anal. ($C_{17}H_{13}F_3N_4O_6$) C, H, N.

(6*S*)-6-{[3-(3-Fluoro-4-methoxyphenyl)-5-isoxazolyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (44). Reaction of alkyne **88** with 3-fluoro-*N*-hydroxy-4-methoxybenzenecarboximidoyl chloride[9] (**89e**) and Et_3N in THF, using Procedure N, gave **44** (33%) as a white solid: mp 160-161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 7.73-7.65 (m, 2 H), 7.30 (t, *J* = 8.7 Hz, 1 H), 7.04 (s, 1 H), 4.87 (d, *J* = 14.4 Hz, 1 H), 4.84 (d, *J* = 14.4 Hz, 1 H), 4.68 (dt, *J* = 12.1, 2.2 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.36-4.22 (m, 3 H), 3.90 (s, 3 H). Anal. ($C_{17}H_{15}FN_4O_6$) C, H, N.

(6*S*)-6-{[3-(6-Methoxy-3-pyridinyl)-5-isoxazolyl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (45). Reaction of alkyne **88** with *N*-hydroxy-6-methoxy-3-

pyridinecarboximidoyl chloride[10] (**89f**) and Et_3N in THF, using Procedure N, gave **45** (77%) as a white solid: mp 180-182 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.67 (dd, *J* = 2.4, 0.4 Hz, 1 H), 8.15 (dd, *J* = 8.7, 2.5 Hz, 1 H), 8.04 (s, 1 H), 7.07 (s, 1 H), 6.96 (dd, *J* = 8.7, 0.6 Hz, 1 H), 4.89 (d, *J* = 14.1 Hz, 1 H), 4.85 (d, *J* = 14.1 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.3 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.37-4.22 (m, 3 H), 3.92 (s, 3 H). Anal. ($C_{16}H_{15}N_5O_6$) 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)-1*H*-1,2,3-triazol-1-yl]benzonitrile (48) (Scheme 5). A mixture of alkyne **88** (0.100 g, 0.448 mmol), 4-azidobenzamide[11] (**93g**) (0.77 g, 4.75 mmol), CuI (5 mg, 0.026 mmol) and $Cu(OAc)_2$ (5 mg, 0.028 mmol) in THF (5 mL) was stirred in a sealed tube at 50 °C for 16 h. The resulting mixture was partitioned between EtOAc and water. The organic layer was dried and evaporated, and then column chromatography of the residue using gradient elution (1:1 hexanes:EtOAc to EtOAc) gave crude 4-[4-({[(6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)-1*H*-1,2,3-triazol-1-yl]benzamide. This benzamide was refluxed with trifluoroacetic anhydride (2 mL) in THF (20 mL) for 2 h, and then the solvent was removed. Column chromatography of the residue using gradient elution (1:1 hexanes:EtOAc to EtOAc) gave **48** (0.046 g, 28%) as a white solid: mp 233-235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.95 (s, 1 H), 8.14 (d, *J* = 9.2 Hz, 2 H), 8.10 (d, *J* = 9.2 Hz, 2 H), 8.03 (s, 1 H), 4.84 (d, *J* = 12.6 Hz, 1 H), 4.81 (d, *J* = 12.6 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.2 Hz, 1 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.35-4.21 (m, 3 H). Anal. ($C_{16}H_{13}N_7O_4$) C, H, N.

(6*S*)-6-{[1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (49). Reaction of alkyne **88** with 1-azido-4-fluorobenzene (**93c**) (1.05 equiv.) in THF, using Procedure O, gave **49** (31%) as a white solid: mp 200-202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.77 (s, 1 H), 8.02 (s, 1 H), 7.96-7.90 (m, 2 H), 7.48-7.42 (m, 2 H), 4.82 (d, *J* = 12.5 Hz, 1 H), 4.77 (d, *J* = 12.5 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.2 Hz, 1 H), 4.49 (dd, *J* = 11.9, 0.8 Hz, 1 H), 4.34-4.21 (m, 3 H). Anal. ($C_{15}H_{13}FN_6O_4$) C, H, N.

(6*S*)-2-Nitro-6-({1-[4-(trifluoromethoxy)phenyl]-1*H*-1,2,3-triazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (50). Reaction of alkyne **88** with 1-azido-4-(trifluoromethoxy)benzene[12] (**93d**) (1.2 equiv.) in THF, using Procedure O, gave **50** (71%) as a white solid: mp 143-146 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.84 (s, 1 H), 8.05-8.01 (m, 3 H), 7.62 (d, *J* = 8.3 Hz, 2 H), 4.83 (d, *J* = 12.5 Hz, 1 H), 4.79 (d, *J* = 12.5 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.2 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.35-4.22 (m, 3 H). Anal. ($C_{16}H_{13}F_3N_6O_5$) C, H, N.

(6*S*)-6-{[1-(3-Fluoro-4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (51). Reaction of alkyne **88** with 4-azido-2-fluoro-1-methoxybenzene[13] (**93e**) (1.2 equiv.) in THF, using Procedure O, gave **51** (73%) as a white solid: mp 190-191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.74 (s, 1 H), 8.03 (s, 1 H), 7.83 (dd, *J* = 12.1, 2.2 Hz, 1 H), 7.72-7.67 (m, 1 H), 7.37 (t, *J* = 9.1 Hz, 1 H), 4.81 (d, *J* = 12.6 Hz, 1 H), 4.77 (d, *J* = 12.6 Hz, 1 H), 4.67 (dt, *J* = 12.0, 2.1 Hz, 1 H), 4.48 (dd, *J* = 12.0, 0.8 Hz, 1 H), 4.34-4.21 (m, 3 H), 3.91 (s, 3 H). Anal. ($C_{16}H_{15}FN_6O_5$) C, H, N.

(6*S*)-6-{[1-(6-Methoxy-3-pyridinyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (52). Reaction of alkyne **88** with 5-azido-2-methoxypyridine[14] (**93f**) (2.0 equiv.) in THF, using Procedure O, gave **52** (72%) as a white solid: mp 182-184 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.74 (s, 1 H), 8.66 (d, *J* = 2.7 Hz, 1 H), 8.19 (dd, *J* = 8.9, 2.8 Hz, 1 H), 8.03 (s, 1 H), 7.04 (dd, *J* = 8.9, 0.4 Hz, 1 H), 4.83 (d, *J* = 12.5 Hz, 1 H), 4.79 (d, *J* = 12.5 Hz, 1 H), 4.68 (dt, *J* = 12.0, 2.2 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.35-4.22 (m, 3 H), 3.93 (s, 3 H). Anal. ($C_{15}H_{15}N_7O_5$) C, H, N.

2-[(4-Fluorophenyl)hydrazono]propanedial dioxime (96c) (Scheme 6). Condensation of 4-fluorophenylhydrazine hydrochloride (**95c**) and 2-oxopropanedial dioxime[15] (**94**) in EtOH, using Procedure P, gave **96c** (78%) as a yellow solid: mp 134-137 °C; ^{1}H NMR [$(CD_3)_2CO$) δ 12.03 (s, 1 H), 11.09 (s, 1 H), 10.27 (s, 1 H), 8.37 (s, 1 H), 7.83 (s, 1 H), 7.25-7.19 (m, 2 H), 7.12-7.06 (m, 2 H). APCI MS *m/z* 225 $[M + H]^+$.

2-(4-Fluorophenyl)-2*H*-1,2,3-triazole-4-carbaldehyde (97c). Acetylation of **96c** with Ac_2O, followed by reaction with Cs_2CO_3 in THF, and then with paraformaldehyde in 2M HCl, using Procedure Q, gave **97c** (67%) as a white solid: mp 81-83 °C; ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1 H), 8.25 (s, 1 H), 8.16-8.10 (m, 2 H), 7.26-7.19 (m, 2 H). APCI MS *m/z* 190 $[M - H]^-$.

[2-(4-Fluorophenyl)-2*H*-1,2,3-triazol-4-yl]methanol (98c). Reduction of **97c** with $NaBH_4$ in MeOH, using Procedure R, gave **98c** (97%) as white flakes: mp 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 8.05-7.99 (m, 2 H), 7.77 (s, 1 H), 7.20-7.14 (m, 2 H), 4.87 (d, *J* = 6.0 Hz, 2 H), 1.96 (t, *J* = 6.0 Hz, 1 H). APCI MS *m/z* 194 $[M + H]^+$.

4-(Bromomethyl)-2-(4-fluorophenyl)-2*H*-1,2,3-triazole (99c). Bromination of **98c** with PBr_3 for 15 h, using Procedure G, gave **99c** (67%) as a white solid, which was used directly in the next step: mp 52-53 °C; ^{1}H NMR ($CDCl_3$) δ 8.05-7.99 (m, 2 H), 7.80 (s, 1 H), 7.20-7.14 (m, 2 H), 4.59 (s, 2 H).

(6*S*)-6-{[2-(4-Fluorophenyl)-2*H*-1,2,3-triazol-4-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**55**)**.** Reaction of alcohol **61** with **99c** (1.0 equiv.) and NaH (2 equiv.) in DMF, using Procedure A, gave **55** (93%) as a white solid: mp 170-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.08 (s, 1 H), 8.05-7.99 (m, 3 H), 7.44-7.37 (m, 2 H), 4.86 (d, *J* = 12.7 Hz, 1 H), 4.82 (d, *J* = 12.7 Hz, 1 H), 4.69 (dt, *J* = 12.1, 2.4 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.36-4.22 (m, 3 H). Anal. ($C_{15}H_{13}FN_6O_4$) C, H, N.

2-{[4-(Trifluoromethoxy)phenyl]hydrazono}propanedial dioxime (96d). Condensation of 4-(trifluoromethoxy)phenylhydrazine (**95d**) and 2-oxopropanedial dioxime (**94**) in EtOH, using Procedure P, gave **96d** (76%) as bronze flakes: mp 132-135 °C; ^{1}H NMR [$(CD_3)_2CO$) δ 12.09 (s, 1 H), 11.17 (s, 1 H), 10.36 (s, 1 H), 8.38 (s, 1 H), 7.84 (s, 1 H), 7.32-7.26 (m, 4 H). APCI MS *m/z* 291 $[M + H]^+$.

2-[4-(Trifluoromethoxy)phenyl]-2*H*-1,2,3-triazole-4-carbaldehyde (97d). Acetylation of **96d** with Ac_2O, followed by reaction with Cs_2CO_3 in THF, and then with paraformaldehyde in 2M HCl, using Procedure Q, gave **97d** (46%) as a pale yellow solid: mp 49-50 °C; ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1 H), 8.27 (s, 1 H), 8.20 (d, *J* = 9.2 Hz, 2 H), 7.39 (d, *J* = 9.2 Hz, 2 H). APCI MS *m/z* 256 $[M - H]^-$.

{2-[4-(Trifluoromethoxy)phenyl]-2*H*-1,2,3-triazol-4-yl}methanol (98d). Reduction of **97d** with $NaBH_4$ in MeOH, using Procedure R, gave **98d** (90%) as a white solid: mp 43-45 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, *J* = 9.2 Hz, 2 H), 7.80 (s, 1 H), 7.32 (dd, *J* = 9.2, 0.8 Hz, 2 H), 4.88 (d, *J* = 6.0 Hz, 2 H), 1.93 (t, *J* = 6.0 Hz, 1 H). APCI MS *m/z* 258 $[M - H]^-$.

4-(Bromomethyl)-2-[4-(trifluoromethoxy)phenyl]-2*H*-1,2,3-triazole (99d). Bromination of **98d** with PBr_3 for 15 h, using Procedure G, gave **99d** (45%) as a white solid, which was used directly in the next step: mp 41-42 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, *J* = 9.1 Hz, 2 H), 7.83 (s, 1 H), 7.33 (d, *J* = 9.1 Hz, 2 H), 4.59 (s, 2 H).

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethoxy)phenyl]-2*H*-1,2,3-triazol-4-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (56). Reaction of alcohol **61** with **99d** (1.0 equiv.) and NaH (1.5 equiv.) in DMF, using Procedure A, gave **56** (79%) as a white solid: mp 157-159 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (s, 1 H), 8.10 (d, *J* = 9.1 Hz, 2 H), 8.02 (s, 1 H), 7.57 (d, *J* = 9.1 Hz, 2 H), 4.88 (d, *J* = 12.7 Hz, 1 H), 4.84 (d, *J* = 12.7 Hz, 1 H), 4.69 (dt, *J* = 12.0, 2.4 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.36-4.22 (m, 3 H). Anal. ($C_{16}H_{13}F_3N_6O_5$) C, H, N.

Methyl 2-(4-fluorophenyl)-2*H*-tetraazole-5-carboxylate (101c) (Scheme 6). Reaction of 2-[(4-fluorophenyl)hydrazono]ethanoic acid[16] (**100c**) with 2-azido-1,3,5-tribromobenzene[17] in NaOEt/EtOH, followed by esterification with diazomethane, using Procedure S, gave **101c** (40%) as a white solid: mp 119-120 °C; ^{1}H NMR ($CDCl_3$) δ 8.24-8.18 (m, 2 H), 7.37-7.26 (m, 2 H), 4.10 (s, 3 H). APCI MS *m/z* 223 $[M + H]^+$.

[2-(4-Fluorophenyl)-2*H*-tetraazol-5-yl]methanol (102c). Reduction of **101c** with $LiAlH_4$ (2.0 equiv.) in Et_2O at 0 °C for 1 h, using Procedure M, gave **102c** (77%) as a white solid: mp 100-102 °C; ^{1}H NMR ($CDCl_3$) δ 8.15-8.09 (m, 2 H), 7.29-7.22 (m, 2 H), 5.05 (d, *J* = 6.5 Hz, 2 H), 2.36 (t, *J* = 6.5 Hz, 1 H). APCI MS *m/z* 195 $[M + H]^+$.

5-(Bromomethyl)-2-(4-fluorophenyl)-2*H*-tetraazole (103c). Bromination of **102c** with PBr_3, using Procedure G, gave **103c** (28%) as a pale brown solid: mp 40-41 °C; ^{1}H NMR ($CDCl_3$) δ 8.14-8.09 (m, 2 H), 7.28-7.22 (m, 2 H), 4.70 (s, 2 H). APCI MS *m/z* 257, 259 $[M + H]^+$.

(6*S*)-6-{[2-(4-Fluorophenyl)-2*H*-tetraazol-5-yl]methoxy}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (59). Reaction of alcohol **61** with **103c** (1.0 equiv.) and NaH (1.5 equiv.) in DMF, using Procedure A, gave **59** (88%) as a white solid: mp 150-152 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.15-8.09 (m, 2 H), 8.03 (s, 1 H), 7.55-7.48 (m, 2 H), 5.08 (d, *J* = 13.2 Hz, 1 H), 5.04 (d, *J* = 13.2 Hz, 1 H), 4.71 (dt, *J* = 12.1, 2.5 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.44-4.41 (m, 1 H), 4.33 (dt, *J* = 13.7, 2.0 Hz, 1 H), 4.26 (dd, *J* = 13.6, 3.2 Hz, 1 H). Anal. ($C_{14}H_{12}FN_7O_4$) C, H, N.

Methyl 2-[4-(trifluoromethoxy)phenyl]-2*H*-tetraazole-5-carboxylate (101d). Reaction of 2-{[4-(trifluoromethoxy)phenyl]hydrazono}ethanoic acid[16] (**100d**) with 2-azido-1,3,5-tribromobenzene in NaOEt/EtOH, followed by esterification with diazomethane, using Procedure S, gave **101d** (70%) as white flakes: mp 83-85 °C; ^{1}H NMR ($CDCl_3$) δ 8.27 (d, *J* = 9.1 Hz, 2 H), 7.45 (d, *J* = 9.1 Hz, 2 H), 4.11 (s, 3 H). APCI MS *m/z* 289 $[M + H]^+$.

{2-[4-(Trifluoromethoxy)phenyl]-2*H*-tetraazol-5-yl}methanol (102d). Reduction of **101d** with $LiAlH_4$ (2.0 equiv.) in Et_2O at 0 °C for 1 h, using Procedure M, gave **102d** (69%) as a white solid: mp 71-72 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, *J* = 9.1 Hz, 2 H), 7.41 (d, *J* = 9.1 Hz, 2 H), 5.06 (d, *J* = 6.4 Hz, 2 H), 2.30 (t, *J* = 6.4 Hz, 1 H). APCI MS *m/z* 261 $[M + H]^+$.

5-(Bromomethyl)-2-[4-(trifluoromethoxy)phenyl]-2*H*-tetraazole (103d). Bromination of **102d** with PBr_3, using Procedure G, gave **103d** (80%) as a white solid: mp 43-45 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, *J* = 9.2 Hz, 2 H), 7.44 (d, *J* = 9.2 Hz, 2 H), 4.73 (s, 2 H). APCI MS *m/z* 323, 325 $[M + H]^+$.

(6*S*)-2-Nitro-6-({2-[4-(trifluoromethoxy)phenyl]-2*H*-tetraazol-5-yl}methoxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (60). Reaction of alcohol **61** with **103d** (1.0 equiv.) and NaH (1.5 equiv.) in DMF, using Procedure A, gave **60** (86%) as a white solid: mp 138-140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.21 (d, *J* = 9.1 Hz, 1 H), 8.03 (s, 1 H), 7.67 (d, *J* = 9.1 Hz, 2 H), 5.09 (d, *J* = 13.3 Hz, 1 H), 5.05 (d, *J* = 13.3 Hz, 1 H), 4.72 (dt, *J* = 12.1, 2.5 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.45-4.42 (m, 2 H), 4.33 (dt, *J* = 13.7, 2.0 Hz, 1 H), 4.26 (dd, *J* = 13.6, 3.2 Hz, 1 H). Anal. ($C_{15}H_{12}F_3N_7O_5$) C, H, N.

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Combustion analyses for the compounds of Table 1.

No	Formula	Calculated			Found		
		C	H	N	C	H	N
9	$C_{18}H_{14}F_3N_3O_4S$	50.82	3.32	9.88	50.97	3.26	9.98
10	$C_{18}H_{14}N_4O_4S$	56.54	3.69	14.65	56.62	3.54	14.63
11	$C_{17}H_{14}FN_3O_4S$	54.39	3.76	11.19	54.47	3.80	11.10
12	$C_{18}H_{14}F_3N_3O_5S$	48.98	3.20	9.52	49.38	3.20	9.62
13	$C_{18}H_{16}FN_3O_5S$	53.33	3.98	10.37	53.56	4.03	10.28
14	$C_{18}H_{15}F_2N_3O_5S$	51.06	3.57	9.92	51.19	3.58	10.03
15	$C_{17}H_{16}N_4O_5S$	52.57	4.15	14.43	52.84	4.17	14.31
16	$C_{17}H_{13}F_3N_4O_4S$	47.89	3.07	13.14	47.78	3.33	12.88
17	$C_{17}H_{13}F_3N_4O_4S{\cdot}0.25H_2O$	47.39	3.16	13.00	47.41	3.14	12.88
18	$C_{16}H_{13}FN_4O_4S$	51.06	3.48	14.89	51.24	3.73	14.90
19	$C_{16}H_{13}FN_4O_4S$	51.06	3.48	14.89	51.35	3.70	14.84
20	$C_{17}H_{13}F_3N_4O_4S$	47.89	3.07	13.14	47.96	3.05	13.17
21	$C_{17}H_{13}N_5O_4S$	53.26	3.42	18.27	52.97	3.56	18.21
22	$C_{16}H_{13}FN_4O_4S$	51.06	3.48	14.89	51.08	3.67	14.82
23	$C_{17}H_{13}F_3N_4O_5S$	46.16	2.96	12.67	46.39	3.15	12.64
24	$C_{17}H_{15}FN_4O_5S$	50.24	3.72	13.79	50.21	3.91	13.91
25	$C_{16}H_{15}N_5O_5S{\cdot}H_2O$	47.17	4.21	17.19	47.43	3.89	17.01
26	$C_{18}H_{16}F_3N_5O_4{\cdot}0.5H_2O$	50.00	3.96	16.20	50.09	3.90	16.16
27	$C_{18}H_{16}N_6O_4{\cdot}0.5H_2O$	55.52	4.40	21.58	55.78	4.45	21.58
28	$C_{17}H_{16}FN_5O_4{\cdot}0.75H_2O$	52.78	4.56	18.10	52.84	4.74	17.92
29	$C_{18}H_{16}F_3N_5O_5{\cdot}0.5H_2O$	48.22	3.82	15.62	48.44	3.92	15.71
30	$C_{18}H_{18}FN_5O_5{\cdot}0.5H_2O$	52.43	4.64	16.98	52.40	4.60	16.42
31	$C_{18}H_{16}F_3N_5O_4$	51.07	3.81	16.54	51.14	3.80	16.66
32	$C_{17}H_{16}FN_5O_4$	54.69	4.32	18.76	54.70	4.40	18.68

33	$C_{18}H_{16}F_3N_5O_5$	49.21	3.67	15.94	49.32	3.75	16.00
34	$C_{17}H_{14}F_3N_5O_4$	49.88	3.45	17.11	49.85	3.50	16.95
35	$C_{16}H_{14}FN_5O_4$	53.48	3.93	19.49	53.26	4.15	19.45
36	$C_{17}H_{14}F_3N_5O_5$	48.01	3.32	16.47	48.01	3.27	16.35
37	$C_{17}H_{14}F_3N_5O_4$	49.88	3.45	17.11	49.86	3.39	17.27
38	$C_{16}H_{14}FN_5O_4$	53.48	3.93	19.49	53.49	3.83	19.44
39	$C_{17}H_{14}F_3N_5O_5$	48.01	3.32	16.47	48.10	3.19	16.61
40	$C_{17}H_{13}F_3N_4O_5$	49.76	3.19	13.65	49.90	3.19	13.71
41	$C_{17}H_{13}N_5O_5$	55.59	3.57	19.07	55.77	3.63	18.78
42	$C_{16}H_{13}FN_4O_5$	53.34	3.64	15.55	53.57	3.56	15.64
43	$C_{17}H_{13}F_3N_4O_6$	47.90	3.07	13.14	48.19	3.16	13.13
44	$C_{17}H_{15}FN_4O_6$	52.31	3.87	14.35	52.46	4.07	14.28
45	$C_{16}H_{15}N_5O_6$	51.48	4.05	18.76	51.34	4.16	18.53
46	$C_{15}H_{12}FN_5O_5$	49.87	3.35	19.38	50.01	3.51	19.43
47	$C_{16}H_{13}F_3N_6O_4$	46.84	3.19	20.48	46.77	3.33	20.37
48	$C_{16}H_{13}N_7O_4$	52.32	3.57	26.69	52.02	3.64	26.31
49	$C_{15}H_{13}FN_6O_4$	50.00	3.64	23.33	50.06	3.80	23.19
50	$C_{16}H_{13}F_3N_6O_5$	45.08	3.07	19.71	45.23	3.18	19.77
51	$C_{16}H_{15}FN_6O_5$	49.23	3.87	21.53	49.29	4.04	21.67
52	$C_{15}H_{15}N_7O_5$	48.26	4.05	26.26	48.48	4.35	26.16
53	$C_{15}H_{14}N_6O_4$	52.63	4.12	24.55	52.86	4.14	24.75
54	$C_{16}H_{13}F_3N_6O_4$	46.84	3.19	20.48	47.07	3.31	20.68
55	$C_{15}H_{13}FN_6O_4$	50.00	3.64	23.33	50.26	3.85	23.45
56	$C_{16}H_{13}F_3N_6O_5$	45.08	3.07	19.71	45.16	3.24	19.93
57	$C_{14}H_{13}N_7O_4$	48.98	3.82	28.56	49.72	4.00	28.65
58	$C_{15}H_{12}F_3N_7O_4$	43.80	2.94	23.84	43.68	3.06	23.71
59	$C_{14}H_{12}FN_7O_4$	46.54	3.35	27.14	46.74	3.56	27.28
60	$C_{15}H_{12}F_3N_7O_5$	42.16	2.83	22.95	42.45	3.03	23.07

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

No	**Formula**	**Calculated**			**Found**		
		C	**H**	**N**	**C**	**H**	**N**
63	$C_{11}H_{10}BrN_3O_4S$	36.68	2.80	11.67	36.90	2.87	11.54
88	$C_9H_9N_3O_4$	48.43	4.06	18.83	48.63	4.13	18.94