Supporting Information

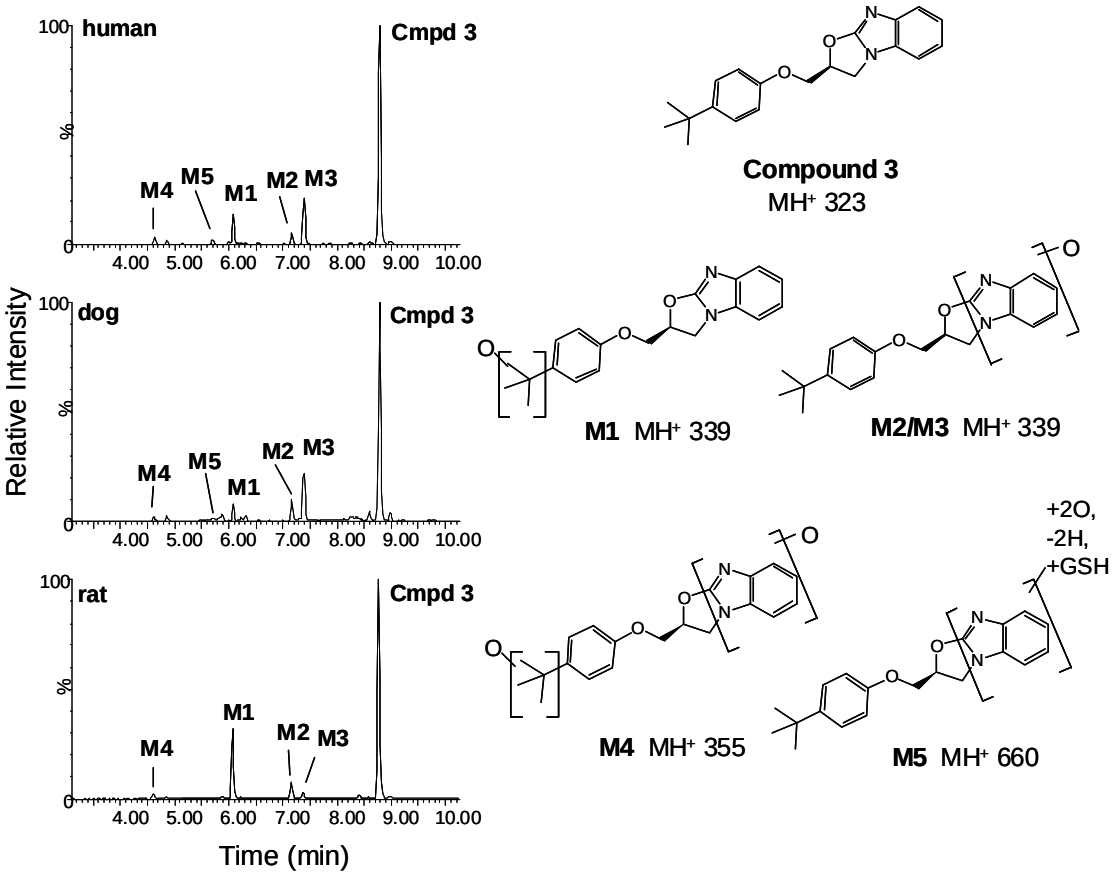

Figure S1. Metabolite identification for oxazolobenzimidazole **3**.

Experimental Section:

Biological Assays:

All animal studies were performed according to the NIH Guide for the Care and Use of Laboratory Animals, and experimental protocols were reviewed by the Merck Animal Care and Use Committee.

FLIPR Assay: CHOdhfr- cells co-expressing human mGluR2 receptors and the promiscuous G-protein Gα16 (see reference 18) were plated (40K cells per well) in clear-bottomed, poly-D-lysine–coated 384-well plates (BD Biosciences, Franklin Lakes, NJ) in glutamate/glutamine-free medium using a Multidrop384 cell dispenser (Thermo Electron Corporation, Waltham, MA). The plated cells were

grown overnight at 37 °C in the presence of 6% CO_2. The next day, the cells were washed with 3 x 100 µl of assay buffer [Hanks' balanced salt solution (Invitrogen) containing 20 mM HEPES (Invitrogen), 2.5 mM probenecid (Sigma Chemical Co., St. Louis, MO), and 0.1% bovine serum albumin (Sigma)] using an EMBLA cell washer (Molecular Devices Corp., Sunnyvale, CA). The cells were incubated with 2 µM Fluo-4AM and 0.02% Pluronic acid (Molecular Probes, Eugene, OR) for 1 h at 37 °C and 6% CO_2. The extracellular dye was removed by washing as described above. Ca^{2+} flux was measured using FLIPR384 fluorometric imaging plate reader (Molecular Devices Corp., Sunnyvale, CA). Compounds were serially diluted in 100% DMSO and then diluted in assay buffer to a 3x stock at 2% DMSO. This stock was then applied to the cells for a final DMSO concentration of 0.67%. For potency determination, the cells were preincubated with various concentrations of compound for 5 min and then stimulated for 3 min with an EC_{20} concentration of glutamate to measure potentiation. The peak of the calcium response was used to construct concentration response curves. For glutamate shift assays, concentrations of glutamate over a dose response range of (0.01- 10 µM) were employed.

Pharmacokinetic Studies. Male Wistar Hannover rats weighing approximately 200 to 300 g were obtained from Charles River (Raleigh, NC). Male beagle dogs weighing approximately 8 to 10 kg were obtained from Marshall Farms (North Rose, NY). All procedures were approved by the Merck Research Laboratories Institutional Animal Care and Use Committee. Rats and dogs were housed in temperature-controlled rooms with a 12-h light/dark cycle. Rats were surgically prepared with a cannula in the jugular vein for sample collection. For all studies the animals were deprived of food 14 to 18 h before dosing but were allowed free access to water. Food was provided to rats and dogs 6 to 8 h after dosing. Blood samples for the determination of test agent plasma concentration were collected in heparinized syringes at multiple time points up to 24 h after single dose administration and plasma was subsequently obtained by centrifugation. All samples were stored at -20 °C until analyzed. Finally, all biological samples were centrifuged before analysis to remove particulate matter.

Incubation with Human, Dog, and Rat Liver Microsomes. All incubations were performed in phosphate buffer (100 mM, pH 7.4) containing $MgCl_2$ (10 mM). Compound **3** (10 μM) was incubated with liver microsomes (0.5 mg/mL) for 30 to 60 min in the presence of both NADPH (1 mM) and GSH (5 mM). Reactions were terminated by adding one-half reaction volume of acetonitrile to precipitate proteins. After brief vortexing and centrifugation (10 min at 3800 × g), the supernatant was subjected to vacuum centrifugation for 10 minutes to remove excess acetonitrile and the resulting solution was submitted for LC-HRMS analysis.

Sample Analysis. For metabolite identification, separation of metabolites and parent compound was achieved on a C18 Synergi MAX-RP 100A column (2.0 x 50 mm, 2.5 μm, Phenomenex, Torrance, CA) using a Waters Acquity UPLC system (Waters, Milford, MA) with a flow rate of 0.5 mL/min. Solvent A consisted of 0.1% formic acid in water and solvent B consisted of acetonitrile containing 0.1% formic acid. The initial mobile phase of 5% solvent B and was increased linearly to 15% B in 0.5 min followed by a linear increase to 50% B over 11.5 minutes. The gradient was then increased linearly to 90% solvent B and held at that value for an additional 1.5 minutes. The gradient was returned to 5% solvent B in 0.5 min and the column was re-equilibrated prior to the next injection. Mass spectrometric analysis was performed on a Waters Q-Tof Premier mass spectrometer equipped with an electrospray ionization source (Waters, Milford, MA) as described previously. (Reference: Tiller PR, Yu S, Castro-Perez J, Fillgrove KL, Baillie TA. Rapid Commun Mass Spectrom. 2008 Apr;22(7):1053-61.)

Synthesis Methods

(2S)-2-[(4-tert-butylphenoxy)methyl]oxirane (**6**)

To (R)-(-)-epichlorohydrin (**5**) (25 mL, 320 mmol, 2.0 equiv) at 64 ^{o}C was added a warm solution of 4-tert-butylphenol (**4**) (24 grams, 160 mmol, 1.0 equiv) and sodium hydroxide (6.7 g, 170 mmol, 1.1 equiv) in water (50 mL) over 1 hour with vigorous stirring. The mixture was stirred at 64 ^{o}C for 7 hours and cooled to room temperature. The aqueous solution was extracted with diethyl ether and the combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to yield (2S)-2-[(4-tert-butylphenoxy)methyl]oxirane (**6**) (16 g, 47%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.17 (m, 1H), 3.98 (m, 1H), 3.35 (m, 1H), 2.88 (m, 1H), 2.75 (m, 1H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.4, 144.1, 126.5, 114.3, 69.0, 50.4, 45.0, 34.3, 31.7. HRMS calcd for $C_{13}H_{18}O_2$ (M + H): 207.1380. Found: 207.1376.

(2S)-2-[(4-tert-butylphenoxy)methyl]-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole (**3**)

A mixture of (2S)-2-[(4-tert-butylphenoxy)methyl]oxirane (**6**) (4.3 g, 21 mmol, 1.6 equiv), 2-chlorobenzimidazole (**7**, 2.0 g, 13 mmol, 1.0 equiv) and cesium carbonate (7.3 g, 22 mmol, 1.7 equiv) in ethanol (50 mL) was stirred at 23 ^{o}C for 72 hours. The mixture was concentrated under reduced pressure and the resulting residue was suspended in water (150 mL) and stirred vigorously for 1 hour. The solid product was filtered and recrystallized from isopropanol to yield (2S)-2-[(4-tert-butylphenoxy)methyl]-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole (**3**) (2.3 g, 54%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, J = 7.7 Hz), 7.32-7.27 (m, 2H), 7.21-7.12 (m, 3H), 6.87-6.79 (m, 2H), 5.66 (m, 1H), 4.43-4.26 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 155.8, 146.8, 144.9, 131.2, 126.6, 122.2, 121.4, 119.1, 114.4, 108.7, 84.8, 67.8, 44.1, 34.3, 31.7. HRMS calcd for $C_{20}H_{22}N_2O_2$ (M + H): 323.1754. Found: 323.1741. $[\alpha]_D$ = +98.4 (c = 1.0, chloroform).

(6-bromo-3-pyridyl)oxy-triisopropyl-silane (**8**)

To a solution of 2-bromo-5-hydroxypyridine (500 g, 2870 mmol) and imidazole (235 g, 3450 mmol, 1.20 equiv) in DMF (3000 mL) at 0 ^{o}C under nitrogen was added triisopropylchlorosilane (736 mL, 3450 mmol, 1.20 equiv) slowly. The resulting reaction was stirred at 23 ^{o}C for 16 h. The solvent was removed by evaporation under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated to yield (6-bromo-3-pyridyl)oxy-triisopropyl-silane (**8**) (949 g, 100%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, J = 3.1, 0.6 Hz, 1 H); 7.32 (dd, J = 8.6, 0.6 Hz, 1 H); 7.07 (dd, J = 8.6, 3.1 Hz, 1 H); 1.31-1.21 (m, 3 H); 1.10 (d, J = 7.3 Hz, 18 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6, 142.3, 132.4, 130.0, 128.4, 18.0, 12.7. HRMS calcd for $C_{14}H_{24}BrNOSi$ (M + H): 330.0883. Found: 330.0874.

(6-tert-butyl-3-pyridyl)oxy-triisopropyl-silane (**10**)

To a mixture of copper(I) cyanide (333 g, 3720 mmol, 2.04 equiv) in THF (8000 mL) at -78 ^{o}C under nitrogen was added dropwise 2 M tert-butyl magnesium chloride in THF (3630 mL, 7260 mmol, 3.99 equiv). The resulting reaction was stirred at -78 ^{o}C for 30 min and a solution of (6-bromo-3-pyridyl)oxy-triisopropyl-silane (**8**) (600 g, 1820 mmol, 1.00 equiv) in THF (1000 mL) was added dropwise. The resulting reaction was stirred an additional 30 min at -78 ^{o}C and 16 h at 23 ^{o}C. The reaction mixture was cooled to 0 ^{o}C and quenched with the slow addition of 1:1 NH_4OH/H_2O (3000 mL) followed by saturated aqueous ammonium chloride solution (2000 mL). The mixture was diluted with heptane (4000 mL) and ethyl acetate (4000 mL) and the thick mixture was filtered through celite. The organic layer was separated, washed with a 1:1 mixture of saturated ammonium chloride solution and concentrated ammonium hydroxide solution (2 x 2500 mL) followed by a 3:1 mixture of brine and concentrated ammonium hydroxide solution. The organic layer was dried over sodium sulfate and

concentrated to give (6-tert-butyl-3-pyridyl)oxy-triisopropyl-silane (**10**) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, J = 2.9, 0.7 Hz, 1 H); 7.19 (dd, J = 8.6, 0.7 Hz, 1 H); 7.10 (dd, J = 8.6, 2.9 Hz, 1 H); 1.33 (s, 8 H); 1.30-1.21 (m, 3H); 1.10 (d, J = 7.3 Hz, 19 H); 1.05 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7, 150.3, 140.6, 126.9, 119.4, 36.9, 30.6, 18.0, 12.8. HRMS calcd for $C_{18}H_{33}NOSi$ (M + H): 308.2404. Found: 308.2392.

6-tert-butylpyridin-3-ol (**11**)

To a solution of crude (6-tert-butyl-3-pyridyl)oxy-triisopropyl-silane (**10**) (559 g, 1820 mmol) in THF (8000 mL) under nitrogen was added dropwise 1 M tetrabutylammonium fluoride in THF (2180 mL, 2880 mmol, 1.58 equiv) and the reaction was stirred at 23 ^{o}C for 1.5 h. The reaction mixture was diluted with ethyl acetate (3000 mL) and water (2000 mL) was slowly added. The organic solvent was removed by evaporation under reduced pressure and the resulting mixture was diluted with ethyl acetate. The organic phase was separated, washed with water, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0-65% ethyl acetate/dichloromethane) to yield 6-tert-butylpyridin-3-ol (**11**) (74.7 g, 27.2% over two steps) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 2.9 Hz, 1 H); 7.24 (d, J = 8.7 Hz, 1 H); 7.16 (dd, J = 8.7, 2.9 Hz, 1 H); 1.34 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.2, 152.1, 135.9, 124.9, 120.6, 36.8, 30.5. HRMS calcd for $C_9H_{13}NO$ (M + H): 152.1070. Found: 152.1067.

1-(5-methoxypyridin-2-yl)ethanone (**12**)

To a solution of 2-bromo-5-methoxypyridine (**9,** 238 g, 1270 mmol) in anhydrous methyl tert-butyl ether (2000 mL) at -40 ^{o}C was added dropwise 2.5 M ^{n}butyl lithium in hexanes (510 mL, 1270 mmol,

1.00 equiv) over 45 minutes while maintaining the temperature at -40 ^{o}C. The reaction mixture was stirred an additional 20 minutes at -40 ^{o}C followed by the dropwise addition of dimethyl acetamide (130 mL, 1390 mmol, 1.09 equiv) over 30 minutes. The reaction mixture was warmed to 20 ^{o}C and after 20 minutes was added 6 M aqueous HCl solution (430 mL, 2550 mmol, 2.01 equiv) followed by 6 M aqueous NaOH solution (232 mL, 1400 mmol, 1.10 equiv). The organic layer was separated and the aqueous layer was extracted with methyl tert-butyl ether. The combined organic layers were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0-30% ethyl acetate/heptane) to yield 1-(5-methoxypyridin-2-yl)ethanone (**12**, 37.3 g, 19.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J = 2.9 Hz, 1 H), 8.05 (d, J = 8.7 Hz, 1 H), 7.29-7.23 (m, 1 H), 3.93 (s, 3 H), 2.69 (s, 3 H). LRMS m/z (M+H) 152.1 found, 152.1 required.

1,1,1-trifluoro-2-(5-methoxypyridin-2-yl)propan-2-ol (**13**)

To a solution of 1-(5-methoxypyridin-2-yl)ethanone (**12**, 37.3 g, 247 mmol) in DMF (300 mL) was added (trifluoromethyl)trimethyl silane (50 mL, 320 mmol, 1.29 equiv) followed by lithium acetate (1.65 g, 25.0 mmol, 0.101 equiv) and the reaction mixture was stirred at 23 ^{o}C for 16 hours. To the reaction mixture was added 1 M aqueous HCl solution (370 mL, 370 mmol, 1.50 equiv) and the resulting reaction was stirred at 23 ^{o}C for 1.5 h. The reaction mixture was diluted with water (600 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with water (2 x 200 mL), followed by brine (1 x 200 mL) and dried over sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (0-40% ethyl acetate/heptane) to yield 1,1,1-trifluoro-2-(5-methoxypyridin-2-yl)propan-2-ol (**13**, 47.3 g, 86.6%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J = 2.8 Hz, 1 H), 7.43 (d, J = 8.7 Hz, 1 H), 7.31 (dd, J = 8.7, 2.8 Hz, 1 H), 3.90 (s, 3 H), 2.97 (s, 1 H), 1.71 (d, J = 1.3 Hz, 3 H). LRMS m/z (M+H) 222.1 found, 222.1 required.

1,1,1-trifluoro-2-(5-methoxypyridin-2-yl)propan-2-yl methanesulfonate (**14**)

To a solution of 1,1,1-trifluoro-2-(5-methoxypyridin-2-yl)propan-2-ol (**13**, 46.9 g, 212 mmol) in THF (350 mL) was added 60% sodium hydride in mineral oil (17.0 g, 424 mmol, 2.00 equiv) portion wise. The resulting reaction was stirred at 23 ^{o}C for 1 h and then heated at 40 ^{o}C for 2 h. The reaction mixture was cooled to 23 ^{o}C and methanesulfonyl chloride (33.0 mL, 424 mmol, 2.00 equiv) was added dropwise. The reaction mixture was stirred at 23 ^{o}C for 1 h and quenched with the addition of water (800 mL) and saturated aqueous sodium bicarbonate solution (800 mL). The mixture was extracted with ethyl acetate (3 x 500 mL) and the combined organic layers were dried over sodium sulfate and concentrated to give 1,1,1-trifluoro-2-(5-methoxypyridin-2-yl)propan-2-yl methanesulfonate (**14**) (59.6 g, 93.8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 3.0 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 1 H), 7.27 (dd, J = 8.8, 3.1 Hz, 1 H), 3.89 (s, 3 H), 3.18 (s, 3 H), 2.31 (s, 3 H). LRMS m/z (M+H) 300.1 found, 300.0 required.

5-methoxy-2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridine (**15**)

To a solution of 1,1,1-trifluoro-2-(5-methoxypyridin-2-yl)propan-2-yl methanesulfonate (**14**, 59.6 g, 200 mmol) in dichloromethane (600 mL) under nitrogen at 0 ^{o}C was added trimethylaluminum (200 mL, 400 mmol, 2.00 equiv) dropwise maintaining a reaction temperature below 15 ^{o}C. The reaction mixture was warmed to 23 ^{o}C and stirred for 48 h and then poured into a saturated aqueous solution of sodium bicarbonate (1000 mL) and brine (500 mL). The mixture was filtered through a pad of celite and the resulting aluminum salts were washed and filtered with dichloromethane. The combined filtrates were separated and the organic layer was dried over sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (0-40% ethyl acetate/heptane) to yield 5-methoxy-2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridine (**15**) (16.2 g, 36.9%). ^{1}H NMR (300

MHz, $CDCl_3$): δ 8.31 (d, J = 3.0 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 1 H), 7.18 (dd, J = 8.8, 3.0 Hz, 1 H), 3.86 (s, 3 H), 1.60 (s, 6 H). LRMS m/z (M+H) 220.2 found, 220.1 required.

6-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-3-ol (**16**)

A solution of 5-methoxy-2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridine (**14,** 16.2 g, 73.9 mmol) and sodium ethanethiolate (31.1 g, 370 mmol, 5.01 equiv) in DMF (300 mL) was heated at 150 ^oC for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, washed with brine, dried over sodium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography (0-40% ethyl acetate/heptane) to yield 6-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-3-ol (**16**) (15.1 g, 64.0%) as a white solid . ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 3.0 Hz, 1 H), 7.40 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 3.0 Hz, 1 H), 1.59 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.1, 150.1, 136.3, 128.2 (q, J = 283.0 Hz), 124.2, 123.6, 46.1 (q, J = 25.2 Hz), 22.2. HRMS calcd for $C_9H_{10}F_3NO$ (M + H): 206.0787. Found: 206.0779.

(2S)-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile

A mixture of 2-chloro-1H-benzimidazole-5-carbonitrile (**18**, 3.0 g, 17 mmol, 1.0 equiv), tert-butyl(dimethyl)[(2S)-oxiran-2-ylmethoxy]silane (**17**) (3.5 g, 19 mmol, 1.1 equiv) and cesium carbonate (0.10 g, 0.31 mmol, 0.020 equiv) were heated under microwave irradiation at 130 ^oC for 45 minutes. Ethyl acetate was added (200 mL) and the organic layer was washed with water (50 mL) and dried over sodium sulfate. The residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) followed by purification by super critical fluid chromatography (ChiralPak AS-H, 21x250mm, 90/10 CO_2/Methanol, 70 mL/min) to separate regioisomers and yield (2S)-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (2.0 g,

36%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.42 (d, 1H, J = 8.2 Hz), 7.19 (d, 1H, J = 8.2 Hz), 5.51-5.44 (m, 1H), 4.35-4.26 (m, 2H), 4.10 (dd, 1H, J = 11.8, 3.8 Hz), 3.95 (d, 1H, J = 3.1 Hz), 0.76 (s, 9 H), 0.00 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 146.6, 134.1, 125.5, 123.1, 120.2, 109.2, 105.3, 88.0, 63.4, 43.2, 25.8, 18.3, 2.1. HRMS calcd for $C_{17}H_{23}N_3O_2Si$ (M + H): 330.1632. Found: 330.1626.

(2S)-2-(hydroxymethyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**19**)

To a solution of (2S)-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (2.2 g, 6.8 mmol, 1.0 equiv) in acetonitrile (50 mL) was added triethylamine trihydrofluoride (2.2 mL, 13 mmol, 2.0 equiv) and the solution was stirred at 37 ^{o}C for 16 hours. The reaction mixture was cooled to 0 ^{o}C and the precipitate was collected by filtration and washed with cold acetonitrile to give (2S)-2-(hydroxymethyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**19**) (1.1 g, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.51 (s, 2H), 5.59-5.54 (m, 1H), 5.33 (t, 1H, J = 5.6 Hz), 4.44 (t, 1H, J = 9.1 Hz), 4.19 (dd, 1H, J = 9.4, 6.4 Hz), 3.90-3.83 (m 1H), 3.72 (dt, 1H, J = 12.7, 4.8 Hz); ^{13}C NMR (101 MHz, DMSO): δ 165.9, 146.6, 134.9, 125.3, 122.0, 120.7, 111.0, 103.7, 90.1, 62.0, 43.4. HRMS calcd for $C_{11}H_9N_3O_2$ (M + H): 216.0768. Found: 216.0761.

(2S)-2-{[(6-tert-butylpyridin-3-yl)oxy]methyl}-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**20**)

To a mixture of (2S)-2-(hydroxymethyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**19**) (370 mg, 1.7 mmol, 1.0 equiv), 6-tert-butylpyridin-3-ol (**11**) (2.1 g, 9.8 mmol, 1.0 equiv) and PS-triphenyl phosphine (2.63 mmol/gram) (9.3 g, 24 mmol, 2.5 equiv) in dichloromethane (75 mL) was added DIAD (2.1 mL, 11 mmol, 1.5 equiv) and the mixture was stirred at 23 ^{o}C for 16 hours. The

resulting mixture was filtered and the filtrate was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to yield (2S)-2-{[(6-tert-butylpyridin-3-yl)oxy]methyl}-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**20**) (2.2 g, 65%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 3.0 Hz), 7.76 (s, 1H), 7.37 (d, 1H, J = 8.2 Hz), 7.25-7.14 (m, 2H), 7.09 (dd, 1H, J = 8.7, 3.1 Hz), 5.76-5.70 (m, 1H), 4.51-4.31 (m, 4H), 1.28 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 163.5, 151.9, 146.6, 136.2, 134.1, 125.7, 123.2, 122.4, 120.0, 119.7, 109.5, 105.5, 85.4, 68.1, 43.7, 37.1, 30.5. HRMS calcd for $C_{20}H_{20}N_4O_2$ (M + H): 349.1659. Found: 349.1645. $[\alpha]_D$ = +89.6 (c = 1.0, chloroform).

A procedure analogous to that used to prepare (2S)-2-{[(6-tert-butylpyridin-3-yl)oxy]methyl}-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**20**) was employed using 6-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-3-ol (**16**) (230 mg, 1.1 mmol, 1.2 equiv) to provide (2S)-2-({[6-(2,2,2-trifluoro-1,1-dimethylethyl)pyridin-3-yl]oxy}methyl)-2,3-dihydro[1,3]oxazolo[3,2-a]benzimidazole-7-carbonitrile (**21**) (320 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 3.0 Hz, 1 H); 7.83 (d, J = 1.4 Hz, 1 H); 7.46-7.42 (m, 2 H); 7.26-7.16 (m, 2 H); 5.79 (ddt, J = 8.5, 6.3, 4.1 Hz, 1 H); 4.57-4.37 (m, 4 H); 1.59 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.8, 153.2, 152.9, 146.6, 136.4, 134.0, 128.4 (q, J = 248.8 Hz), 125.8, 123.3, 122.8, 122.3, 120.0, 109.5, 105.7, 85.2, 68.0, 46.4 (q, J = 24.2 Hz), 43.7, 22.2. HRMS calcd for $C_{20}H_{17}F_3N_4O_2$ (M + H): 403.1376. Found: 403.1363. $[\alpha]_D$ = +79.4 (c = 1.0, chloroform).

(27) Tiller, P. R.; Yu, S.; Castro-Perez, J.; Fillgrove, K. L.; Baillie, T. A. High-throughput, accurate mass liquid chromatography/tandem mass spectrometry on a quadrupole time-of-flight system as a 'first-line' approach for metabolite identification studies. *Rapid Commun. Mass Spectrom.* **2008**, *22* (7), 1053-1061.