Supporting Information

α-Ketoheterocycle Inhibitors of Fatty Acid Amide Hydrolase: Exploration of Conformational Constraints in the Acyl Side Chain

Katharine K. Duncan, Katerina Otrubova and Dale L. Boger

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

General Procedures. All commercial reagents were used without further purification unless otherwise noted. THF was distilled prior to use. All reactions were performed in oven-dried (200 °C) glassware and under an inert atmosphere of anhydrous Ar unless otherwise noted. Column chromatography was performed with silica gel 60. TLC was performed on Whatman silica gel (250 μm) F_{254} glass plates and spots were visualized by UV. PTLC was performed on Whatman silica gel (250 and 500 μm) F_{254} glass plates. ^{1}H NMR was recorded on a Bruker 500 MHz spectrometer. Chemical shifts are reported in ppm from an internal standard of residual $CHCl_3$ (δ 7.26 for ^{1}H). Proton chemical data are reported as follows: chemical shift (δ), multiplicity (ovlp = overlapping, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, and integration. High resolution mass spectra was obtained on an Agilent ESI-TOF/MS using Agilent ESI-L low concentration tuning mix as internal high resolution calibration standards.
General Procedure A. The alcohol (1 equiv), TBSCl (2.5 equiv) and imidazole (5 equiv) were dissolved in anhydrous DMF (0.16 M) and the mixture was stirred at room temperature for 16 h before it was diluted with EtOAc, washed with H_2O, and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (SiO_2).
General Procedure B. The stannane intermediate (1 equiv), $(Ph_3P)_4Pd$ (0.3 equiv), and aryl halide (2 equiv) were dissolved in anhydrous 1,4-dioxane (8 mL / 0.150 mmol of stannane) and the mixture was warmed at reflux for 16 h under Ar. The mixture was diluted with EtOAc, washed with saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation in vacuo yielded the crude coupling product that was purified by flash chromatography (SiO_2).
General Procedure C. Dess–Martin periodinane (2 equiv) was added to a stirred solution of the alcohol (1 equiv) in CH_2Cl_2 (0.05 M). The reaction mixture was stirred at room temperature for 2 h, at which point it was diluted with EtOAc and $Na_2S_2O_3$ (saturated aqueous) and $NaHCO_3$ (saturated aqueous) were added. Once the reaction mixture had clarified (ca. 5 min), the organic layer was extracted twice, washed with saturated aqueous NaCl, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give the crude product that was further purified by flash chromatography (SiO_2) or preparative TLC.
General Procedure D. The TBS ether (1 equiv) was dissolved in THF (3 mL/0.163 mmol of TBS ether), treated with Bu_4NF (1 M in THF, 1.2 equiv) and the mixture was stirred at room temperature for 2 h under Ar. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation in vacuo yielded the crude alcohol that was purified by flash chromatography (SiO_2).
***N*-Methoxy-*N*-methyl-6-phenoxychroman-2-carboxamide (5).** 6-Phenoxychroman-2-carboxylic acid (**4**, 237 mg, 0.876 mmol) was dissolved in anhydrous THF (2.8 mL) and stirred under an Ar atmosphere. CDMT (200 mg, 1.14 mmol, 1.3 equiv) and NMM (290 μL, 2.63 mmol,

3 equiv) were added and the reaction mixture was stirred at room temperature. After 1 h, MeO(Me)NH•HCl (104 mg, 1.07 mmol, 1.2 equiv) was added and the reaction mixture stirred for an additional 18 h. The reaction mixture was then diluted with EtOAc, washed with H_2O, saturated aqueous $NaHCO_3$, 1 N aqueous HCl and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated. Flash chromatography (SiO_2, 18–32% EtOAc/hexanes gradient elution) yielded **5** as a white solid (183 mg, 67%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.05–7.02 (m, 1H), 6.95 (d, 2H, *J* = 7.8 Hz), 6.88–6.87 (m, 1H), 6.80 (dd, 1H, *J* = 2.7, 8.7 Hz), 6.74 (s, 1H), 4.99 (s, 1H), 3.78 (s, 3H), 3.26 (s, 3H), 2.87–2.78 (m, 2H), 2.18–2.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 600 MHz) δ 170.8, 158.4, 150.3, 149.9, 129.5 (2C), 122.7, 122.4, 120.2, 119.0, 117.7 (3C), 72.3, 61.7, 32.3, 23.8 (2C).

6-Phenoxychroman-2-carboxaldehyde (6). $LiAlH_4$ (520 μL, 1 M in THF, 2 equiv) was added dropwise to a room temperature solution of **5** (80.6 mg, 0.257 mmol) in anhydrous THF (4 mL). The reaction mixture was stirred for 15 min at room temperature, at which point it was cooled to 0 °C and quenched with the addition of 1 N aqueous $KHSO_4$. The product was extracted twice with EtOAc and the combined organic layers washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified with flash chromatography (SiO_2, 10–24% EtOAc/hexanes gradient elution) to give **6** as a white solid (62.8 mg, 96%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.83 (s, 1H), 7.30 (t, 2H, *J* = 9.3 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 6.95 (d, 2H, *J* = 7.8 Hz), 6.92 (d, 1H, *J* = 8.4 Hz), 6.84 (dd, 1H, *J* = 3.0, 9.0 Hz), 6.73 (d, 1H, *J* = 3.0 Hz), 4.48 (dd, 1H, *J* = 3.3, 8.7 Hz), 2.86–2.80 (m, 1H), 2.76–2.71 (m, 1H), 2.24–2.20 (m, 1H), 2.08–2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.4, 158.2, 150.4, 149.5, 129.6 (2C), 122.6 (2C), 120.2, 119.3, 117.9, 117.8 (2C), 79.4, 23.5, 22.3.

Oxazol-2-yl(6-phenoxychroman-2-yl)methanol (7). Oxazole (0.150 mL, 2.28 mmol) in anhydrous THF (5 mL) was treated with BH_3•THF (2.12 mL, 1 M in THF, 2.12 mmol) under Ar. The reaction mixture was stirred for 1 h at room temperature before being cooled to –78 °C. The reaction mixture was then treated dropwise with *n*-BuLi (2.45 M in hexanes, 0.86 mL, 2.11 mmol) and stirred for an additional 1 h. A solution of **6** (250.6 mg, 0.986 mmol) in THF (5 mL) was added to the reaction mixture and stirring was continued for 2 h. The reaction mixture was allowed to warm to room temperature and 5% AcOH/EtOH (20 mL) was added. After 18 h, the solvent was removed in vacuo. The residue was redissolved in EtOAc and the organic layer was washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product that was purified by flash chromatography (SiO_2, 10–50% EtOAc/hexanes gradient elution) to afford **7** as a white solid (225 mg, 70%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.72–7.70 (m, 2H), 7.31–7.28 (m, 4H), 7.18–7.17 (m, 2H), 7.05–7.03 (m, 2H), 6.94–6.93 (m, 4H), 6.79–6.77 (m, 4H), 6.75–6.74 (m, 2H), 5.10 (d, 1H, *J* = 4.8 Hz), 4.97 (d, 1H, *J* = 4.8 Hz), 4.44–4.42 (m, 2H), 2.89–2.84 (m, 2H), 2.78–2.74 (m, 2H), 2.56–2.53 (bs, 2H), 2.10–2.08 (m, 1H), 1.98–1.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.8, 162.5, 158.3 (2C), 150.2, 150.0, 149.9, 139.5, 139.3, 129.6 (4C), 127.0, 126.5, 122.9, 122.8, 122.4 (2C), 120.3, 119.0 (2C), 117.7 (2C), 117.6 (2C), 70.3, 69.7, 24.4, 24.3, 23.2, 22.1.

2-(((*tert*-Butyldimethylsilyl)oxy)(6-phenoxychroman-2-yl)methyl)oxazole (8). Compound **8** was prepared from **7** (101 mg, 0.313 mmol) following general procedure A. Flash chromatography (SiO_2, 5–15% EtOAc/hexanes gradient elution) yielded **8** (131 mg, 95%) as a thick colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67 (s, 2H), 7.30–7.26 (m, 4H), 7.14–7.13 (m, 2H), 7.04–7.02 (m, 2H), 6.94–6.92 (m, 4H), 6.82–6.79 (m, 2H), 6.76–6.73 (m, 3H), 6.67 (d, 1H, *J* = 8.4 Hz), 5.03 (d, 1H, *J* = 6.6 Hz), 4.99 (d, 1H, *J* = 6.0 Hz), 4.44–4.41 (m, 1H), 4.35–4.32 (m, 1H), 2.84–2.69 (m, 4H), 2.23–2.20 (m, 1H), 1.97–1.94 (m, 1H), 1.86–1.83 (m, 1H), 1.73–1.67 (m, 1H), 0.89–0.88 (m,

18H), 0.14 (s, 3H), 0.11 (s, 3H), 0.02 (s, 3H), –0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 600 MHz) δ 163.1, 162.6, 158.5 (2C), 150.5 (2C), 149.6 (2C), 139.0, 138.8, 129.5 (4C), 127.0 (2C), 123.0, 122.9, 122.3 (2C), 120.3, 120.2, 119.0, 118.9, 117.8, 117.6 (2C), 117.5 (3C), 77.8, 77.3, 70.9, 70.3, 25.6 (6C), 24.3, 24.2, 22.7, 22.4, 18.3, 18.2, –5.0, –5.1, –5.3 (2C).

2-(((*tert*-Butyldimethylsilyl)oxy)(6-phenoxychroman-2-yl)methyl)-5-(tributylstannyl)-oxazole (9). A solution of 2-(((*tert*-butyldimethylsilyl)oxy)(6-phenoxychroman-2-yl)methyl) oxazole (**8**, 84.9 mg, 0.194 mmol) in anhydrous THF (1.9 mL) was cooled to –78 °C. *n*-BuLi (81 μL of 2.4 M solution, 0.194 mmol, 1 equiv) was added dropwise and the reaction mixture was stirred at that temperature for 2 h. At this point, Bu_3SnCl (105 μL, 0.388 mmol, 2 equiv) was added slowly and the reaction mixture was allowed to stir for 5 min. The reaction mixture was then allowed to warm to room temperature before it was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and evaporated. Flash chromatography (SiO_2, 0–20% EtOAc/hexanes gradient elution) yielded **9** (101 mg, 72%) as a thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30–7.27 (m, 4H), 7.13–7.12 (m, 2H), 7.04–7.01 (m, 2H), 6.94–6.92 (m, 4H), 6.81–6.77 (m, 2H), 6.76–6.72 (m, 3H), 6.68–6.66 (m, 1H), 5.05–5.03 (m, 2H), 4.45–4.41 (m, 1H), 4.37–4.33 (m, 1H), 2.86–2.67 (m, 4H), 2.20–2.16 (m, 2H), 2.00–1.96 (m, 1H), 1.83–1.78 (m, 1H), 1.55–1.53 (m, 12H), 1.35–1.31 (m, 12H), 1.13–1.10 (m, 12H), 0.90 (m, 36H), 0.11 (s, 3H), 0.09 (s, 3H), –0.01 (s, 3H), –0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 166.5, 158.6 (2C), 155.6, 155.3, 150.9, 150.7, 149.5, 149.4, 137.4 (2C), 129.5 (4C), 123.1, 123.0, 122.2 (2C), 120.3, 120.2, 119.0, 118.9, 117.8, 117.6 (5C), 117.5 (1C), 78.0, 77.6, 71.0, 70.5, 29.0, 28.9 (6C), 27.1 (7C), 25.7 (6C), 24.3, 22.7, 22.1, 18.3, 18.2, 13.6 (6C), 10.2 (6C), –5.0, –5.1, –5.3, –5.5.

2-(((*tert*-Butyldimethylsilyl)oxy)(6-phenoxychroman-2-yl)methyl)-5-(pyridin-2-yl)oxazole (10). Compound **10** was prepared from compound **9 (**107 mg, 0.148 mmol) and 2-bromopyridine following general procedure B. Compound **10** was isolated an opaque oil (57.4 mg, 76%) after flash chromatography (SiO_2, 0–24% EtOAc/hexanes gradient elution): **Less polar diastereomer (10a)**: ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.64 (d, 1H, J = 4.2 Hz), 7.95–7.92 (m, 1H), 7.78 (d, 1H, J = 7.8 Hz), 7.73 (s, 1H), 7.37 (dd, 1H, J = 4.8, 7.2 Hz), 7.34–7.31 (m, 2H), 7.05 (t, 1H, J = 7.2 Hz), 6.92 (d, 2H, J = 7.8 Hz), 6.79 (d, 1H, J = 2.4 Hz), 6.76–6.74 (m, 1H), 6.69–6.68 (m, 1H), 5.11 (d, 1H, J = 6.0 Hz), 4.59–4.56 (m, 1H), 2.95–2.83 (m, 2H), 2.35–2.32 (m, 1H), 2.02–1.99 (m, 1H), 0.91 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 164.8, 160.4, 153.1, 152.4, 151.8, 151.5, 148.9, 139.1, 131.5 (2C), 127.1, 125.3, 125.0, 124.2, 122.2, 120.8, 120.6, 119.3 (3C), 79.1, 72.2, 27.0 (3C), 25.6, 24.1, 19.7, –3.9, –4.0. **More polar diastereomer (10b):** ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.64 (d, 1H, J = 4.8 Hz), 7.94–7.91 (m, 1H), 7.77 (d, 1H, J = 7.8 Hz), 7.70 (s, 1H), 7.38–7.36 (m, 1H), 7.33–7.31 (m, 2H), 7.04 (t, 1H, J = 7.5 Hz), 6.91 (d, 2H, J = 8.4 Hz), 6.82–6.78 (m, 3H), 5.13 (d, 1H, J = 6.6 Hz), 4.49–4.46 (m, 1H), 2.88–2.85 (m, 1H), 2.82–2.79 (m, 1H), 2.05–2.02 (m, 1H), 1.86–1.82 (m, 1H), 0.93 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 164.4, 160.5, 153.3, 152.5, 151.9, 151.5, 149.0, 139.0, 131.5 (2C), 127.0, 125.3, 124.2, 122.3, 120.8, 120.7, 119.4, 119.1 (2C), 79.5, 72.8, 27.0, 25.8, 24.6, 19.8, –3.8, –4.0.

The enantiomers of both diastereomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 5% *i*-PrOH–hexanes, 7 mL/min, α = 1.10 for **10a** and α = 1.29 for **10b)**.

10a-Enant 1: $[\alpha]^{23}_D$ –13 (*c* 0.47, THF).

10a-Enant 2: $[\alpha]^{23}_D$ +14 (*c* 0.43, THF).

10b-Enant 1: $[\alpha]^{23}_D$ –29 (*c* 0.35, THF).

10b-Enant 2: $[\alpha]^{23}_D$ +31 (*c* 0.37, THF).

Methyl 6-(2-(((*tert*-Butyldimethylsilyl)oxy)(6-phenoxychroman-2-yl)methyl)oxazol-5-yl)picolinate (11). Compound **11** was prepared from **9** (105 mg, 0.145 mmol and methyl 6-bromopicolinate following general procedure B. Compound **11** was isolated a thick oil (66.8 mg, 80%) after flash chromatography (SiO_2, 0–50% EtOAc/hexanes gradient elution): **Less polar diastereomer (11a):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (d, 1H, *J* = 8.0 Hz), 7.92 (t, 1H, *J* = 7.75 Hz), 7.85–7.82 (m, 2H), 7.30–7.27 (m, 2H), 7.03 (t, 1H, *J* = 7.5 Hz), 6.93 (d, 2H, *J* = 7.5 Hz), 6.76–6.74 (m, 2H), 6.68–6.66 (m, 1H), 5.06 (d, 1H, *J* = 6.0 Hz), 4.53–4.50 (m, 1H), 4.03 (s, 3H), 2.90–2.83 (m, 1H), 2.80–2.75 (m, 1H), 2.27–2.22 (m, 1H), 2.04–1.95 (m, 1H), 0.90 (s, 9H), 0.14 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.4, 163.6, 158.5, 150.5, 150.3, 149.7, 148.3, 147.6, 138.0, 129.5 (2C), 126.7, 124.0, 123.0, 122.3, 120.2, 118.9, 117.7 (3C), 77.2, 70.6, 53.0, 25.7, 24.2, 22.4, 18.2, –5.0, –5.1. **More polar diastereomer (11b)**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05 (d, 1H, *J* = 7.2 Hz), 7.93 (t, 1H, *J* = 7.8 Hz), 7.85–7.84 (m, 2H), 7.28 (t, 2H, *J* = 7.8 Hz), 7.03 (t, 1H, *J* = 7.5 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.82–6.78 (m, 2H), 6.73 (s, 1H), 5.09 (d, 1H, *J* = 6.6 Hz), 4.41–4.38 (m, 1H), 4.02 (s, 3H), 2.84–2.78 (m, 1H), 2.76–2.71 (m, 1H), 1.98–1.95 (m, 1H), 1.81–1.77 (m, 1H), 0.91 (s, 9H), 0.16 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.4, 163.1, 158.5, 150.5, 150.4, 149.7, 148.3, 147.6, 138.1, 129.5 (2C), 126.5, 124.1, 122.9, 122.3, 122.2, 120.3, 119.1, 117.8, 117.5 (2C), 77.7, 71.1, 53.0, 25.7 (3C), 24.3, 22.8, 18.3, –5.0, –5.1.

The enantiomers of both diastereomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 10% *i*-PrOH/hexanes, 7 mL/min, α = 1.12 for **11a** and α = 1.08 for **11b)**.

11a-Enant 1: $[\alpha]^{23}_D$ –25 (*c* 0.41, THF).
11a-Enant 2: $[\alpha]^{23}_D$ +27 (*c* 0.26, THF).
11b-Enant 1: $[\alpha]^{23}_D$ –21 (*c* 0.36, THF).
11b-Enant 2: $[\alpha]^{23}_D$ +23 (*c* 0.30, THF).

(6-Phenoxychroman-2-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (12). Compound **12** was prepared from **10** (57.4 mg, 0.112 mmol) according to general procedure D. The crude product was purified by flash chromatography (SiO_2, 30–70% EtOAc/hexanes gradient elution) to give **12** (as a mixture of diastereomers) as a white solid (39.1 mg, 87%). **Less polar diastereomer (12a):** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (d, 1H, *J* = 4.8 Hz), 7.77 (td, 1H, *J* = 1.8, 7.8 Hz), 7.70 (s, 1H), 7.67 (d, 1H, *J* = 7.8 Hz), 7.30–7.24 (m, 3H), 7.03 (t, 1H, *J* = 7.5 Hz), 6.93 (d, 2H, *J* = 7.8 Hz), 6.81–6.77 (m, 2H), 6.74 (s, 1H), 5.14 (t, 1H, *J* = 5.4 Hz), 4.94–4.67 (m, 1H), 3.08 (t, 1H, *J* = 6.6 Hz), 2.88–2.85 (m, 1H), 2.80–2.76 (m, 1H), 2.18–2.15 (m, 1H), 2.03–2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.6, 158.3, 151.6, 150.1 (2C), 150.0, 147.0, 136.9, 129.6 (2C), 125.3, 123.1, 122.8, 122.4, 120.2, 119.4, 119.0, 117.8, 117.7 (2C), 70.4, 24.4, 23.4. **More polar diastereomer (12b):** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.65 (d, 1H, *J* = 4.8 Hz), 7.78 (td, 1H, *J* = 1.2, 7.5), 7.70 (s, 1H), 7.67 (d, 1H, *J* = 7.8 Hz), 7.29 (t, 2H, *J* = 7.8 Hz), 7.25–7.24 (m, 3H), 7.04 (t, 1H, *J* = 7.5 Hz), 6.93 (d, 2H, *J* = 8.4 Hz), 6.81–6.79 (m, 2H), 6.77–6.75 (m, 1H), 5.03 (t, 1H, *J* = 6.0 Hz), 4.52 (q, 1H, *J* = 4.5 Hz), 3.32 (d, 1H, *J* = 6.6 Hz), 2.90–2.86 (m, 1H), 2.80–2.77 (m, 1H), 2.05–2.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.6, 158.3, 151.6, 150.1 (2C), 150.0, 147.0, 136.9, 129.6 (2C), 125.3, 123.1, 122.8, 122.4, 120.2, 119.4, 119.0, 117.8, 117.7 (2C), 70.4, 24.4, 23.4.

12a-Enant 1: $[\alpha]^{23}_D$ –13 (*c* 0.023, THF).
12a-Enant 2: $[\alpha]^{23}_D$ +14 (*c* 0.14, THF).
12b-Enant 1: $[\alpha]^{23}_D$ –30 (*c* 0.14, THF).
12b-Enant 2: $[\alpha]^{23}_D$ +33 (*c* 0.069, THF).

Methyl 6-(2-(Hydroxy(6-phenoxychroman-2-yl)methyl)oxazol-5-yl)picolinate (13). Compound **13** was prepared from compound **11** (104 mg, 0.181 mmol) according to general procedure D. The crude product was purified by flash chromatography (SiO_2, 30–80% EtOAc/hexanes gradient elution) to give **13** as a white solid (79.0 mg, 0.172 mmol, 95%). **Less polar diastereomer (13a)**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05 (d, 1H, *J* = 7.8 Hz), 7.92 (t, 1H, *J* = 7.8 Hz), 7.83–7.82 (m, 2H), 7.28 (t, 2H, *J* = 8.1 Hz), 7.03 (t, 1H, *J* = 7.5 Hz), 6.93 (d, 2H, *J* = 7.8 Hz), 6.77 (s, 2H), 6.74 (s, 1H), 5.13 (s, 1H), 4.50–4.47 (m, 1H), 4.02 (s, 3H), 3.50 (bs, 1H), 2.90–2.85 (m, 1H), 2.79–2.75 (m, 1H), 2.20–2.16 (m, 1H), 2.03–1.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ165.3, 163.2, 158.4, 150.6, 150.3, 150.0, 148.2, 147.3, 138.0, 129.6 (2C) 126.4, 124.2, 122.4 (2C), 120.3, 119.0, 117.7 (3C), 69.8, 53.0, 24.3, 22.3. **More polar diastereomer (13b)**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06 (d, 1H, *J* = 7.8 Hz), 7.92 (t, 1H, *J* = 7.8 Hz), 7.85–7.83 (m, 2H), 7.29 (t, 2H, *J* = 8.1 Hz), 7.04 (t, 1H, *J* = 7.8 Hz), 6.93 (d, 2H, *J* = 7.8 Hz), 6.79 (s, 2H), 6.75 (s, 1H), 5.03 (d, 1H, *J* = 4.8 Hz), 4.54–4.51 (m, 1H), 4.03 (s, 3H), 3.30 (bs, 1H), 2.92–2.87 (m, 1H), 2.81–2.76 (m, 1H), 2.06–2.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.3, 163.0, 158.3, 150.8, 150.2, 150.0, 148.3, 147.3, 138.0, 129.6 (2C), 126.5, 124.2, 122.8, 122.5, 122.4, 120.2, 119.0, 117.7 (3C), 76.9, 70.4, 53.0, 24.4, 23.4.
13a-Enant 1: $[\alpha]^{23}_D$ –30 (*c* 0.24, THF).
13a-Enant 2: $[\alpha]^{23}_D$ +28 (*c* 0.16, THF).
13b-Enant 1: $[\alpha]^{23}_D$ –8 (*c* 0.18, THF).
13b-Enant 2: $[\alpha]^{23}_D$ +8 (*c* 0.18, THF).
6-Phenoxychroman-2-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanone (14). Compound **14** was prepared from (6-phenoxychroman-2-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (**12**, 39.1 mg, 0.0976 mmol) according to general procedure C. Flash chromatography (SiO_2, 20–40% EtOAc/hexanes gradient elution) yielded **14** as a bright yellow solid (33.2 mg, 85%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.69 (d, 1H, *J* = 4.8 Hz), 7.94 (s, 1H), 7.91 (d, 1H, *J* = 7.8 Hz), 7.85 (td, 1H, *J* = 1.2, 8.0 Hz), 7.36 (dd, 1H, *J* = 4.8, 6.6 Hz), 7.31 (t, 2H, *J* = 8.1 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.96 (dd, 3H, *J* = 2.4, 8.4 Hz), 6.85 (dd, 1H, *J* = 2.7, 8.7 Hz), 6.76 (d, 1H, *J* = 2.4 Hz), 5.71 (dd, 1H, *J* = 3.6, 8.4 Hz), 2.99–2.94 (m, 1H), 2.79–2.74 (m, 1H), 2.57–2.52 (m, 1H), 2.32–2.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 184.4, 158.3, 155.3, 153.8, 150.1, 150.0, 149.9, 145.9, 137.3, 129.6 (2C), 127.1, 124.5, 122.4, 122.2, 120.7, 120.1, 119.3, 117.9, 117.7 (2C), 76.9, 24.7, 23.7; HRMS-ESI-TOF *m/z* 399.1346 ($M + H^+$, $C_{24}H_{18}N_2O_4$ requires 399.1339).
The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralCel OD, 10 μm, 2 × 25 cm, 50% *i*-PrOH/hexanes, 7 mL/min, α = 1.80).
14-Enant 1: $[\alpha]^{23}_D$ +30 (*c* 0.087, THF).
14-Enant 2: $[\alpha]^{23}_D$ –31 (*c* 0.042, THF).
Methyl 6-(2-(6-Phenoxychroman-2-carbonyl)oxazol-5-yl)picolinate (15). Compound **15** was prepared from methyl 6-(2-(hydroxy(6-phenoxychroman-2-yl)methyl)oxazol-5-yl)picolinate (**13**, 79.0 mg, 0.172 mmol) according to general procedure C. Flash chromatography (SiO_2, 20–50% EtOAc/hexanes gradient elution) yielded **15** as a white solid (58.3 mg, 74%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.14 (d, 1H, *J* = 7.8 Hz), 8.07–8.06 (m, 2H), 8.00 (t, 1H, *J* = 7.8 Hz), 7.31 (t, 2H, *J* = 8.1 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.97–6.95 (m, 3H), 6.85 (dd, 1H, *J* = 3.0, 9.0 Hz), 6.76 (d, 1H, *J* = 3 Hz), 5.71 (dd, 1H, *J* = 2.4, 3.6 Hz), 4.04 (s, 3H), 2.99–2.93 (m, 1H), 2.79–2.75 (m, 1H), 2.57–2.52 (m, 1H), 2.32–2.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 184.4, 165.0, 158.3, 155.6, 152.9, 150.2, 149.9, 148.6, 146.3, 138.4, 129.6 (2C), 128.1, 125.4, 123.5, 122.5, 122.2, 120.1, 119.3, 117.9, 117.8 (2C), 76.9, 53.1, 24.8, 23.7; HRMS-ESI-TOF *m/z* 457.1394 ($M + H^+$, $C_{26}H_{22}N_2O_6$ requires 457.1394).

The enantiomers can be separated using a semipreparative chiral phase HPLC column (Diacel ChiralCel OD, 10 μm, 2 × 25 cm, 80% *i*-PrOH/hexanes, 7 mL/min, α = 1.40).
15-Enant 1: $[\alpha]^{23}_{D}$ +30 (*c* 0.044, THF).
15-Enant 2: $[\alpha]^{23}_{D}$ –34 (*c* 0.16, THF).
Oxazol-2-yl(6-phenoxychroman-2-yl)methanone (16). Compound **16** was prepared from **7** (29.9 mg, 0.0927 mmol) according to general procedure C. After purification on two 250 μm PTLC plates, 2 × 40% EtOAc/hexanes (R_f = 0.57), **16** was isolated as a white solid (21.3 mg, 71%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.39 (s, 1H), 7.30 (t, 2H, *J* = 8.1 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.96 (d, 2H, *J* = 7.8 Hz), 6.94 (s, 1H) 6.84 (dd, 1H, *J* = 3.0, 9.0 Hz), 6.75 (d, 1H, *J* = 2.4 Hz), 5.66 (dd, 1H, *J* = 3.6, 8.4 Hz), 2.96–2.90 (m, 1H), 2.74 (td, 1H, *J* = 5.7, 16.2 Hz), 2.53–2.49 (m, 1H), 2.30–2.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 184.4, 158.3, 156.1, 150.2, 149.9, 142.2, 129.6 (2C), 129.3, 122.5, 122.2, 120.1, 119.2, 117.8 (3C), 76.9, 24.7, 23.6; HRMS-ESI-TOF *m/z* 322.1081 ($M + H^+$, $C_{19}H_{15}NO_4$ requires 322.1074).
The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 40% *i*-PrOH–hexanes, 7 mL/min, α = 1.21).
16-Enant 1: $[\alpha]^{23}_{D}$ +11 (*c* 0.25, THF).
16-Enant 2: $[\alpha]^{23}_{D}$ –10 (*c* 0.30, THF).
***tert*-Butyl 7-(((Trifluoromethyl)sulfonyl)oxy)chroman-3-carboxylate (18).** A sample of *tert*-butyl 7-hydroxychroman-3-carboxylate (**17**, 204 mg, 0.813 mmol) was dissolved in anhydrous pyridine (3.35 mL) and cooled to 0 °C. Triflic anhydride (200 μL, 1.22 mmol, 1.5 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred under Ar for 2 h. The mixture was then diluted with CH_2Cl_2, washed with H_2O, saturated aqueous NaCl and dried over Na_2SO_4. The crude reaction mixture was purified by column chromatography (SiO_2, 2.5–10% EtOAc/hexanes gradient elution) to yield **18** as a white solid (283 mg, 91%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.13 (d, 1H, *J* = 8.4 Hz), 6.78 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.75 (d, 1H, *J* = 2.4 Hz), 4.41 (dd, 1H, *J* = 2.4, 10.8 Hz), 4.12 (dd, 1H, *J* = 8.7, 10.5 Hz), 3.04–2.89 (m, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.8, 155.0, 148.2, 130.8, 121.3, 118.7 (q, CF_3, *J* = 319 Hz), 113.3, 109.8, 81.7, 67.0, 38.7, 27.9 (3C), 27.2.
***tert*-Butyl 7-Phenylchroman-3-carboxylate (19).** A mixture of *tert*-butyl 7-(((trifluoromethyl)sulfonyl)oxy)chroman-3-carboxylate (**18**, 92.5 mg, 0.249 mmol), $(Ph_3P)_4Pd$ (7.3 mg, 6.3 μmol, 3 mol %), phenylboronic acid (38.0 mg, 0.312 mmol, 1.3 equiv), and powdered K_3PO_4 (82.0 mg, 0.386 mmol, 1.5 equiv) were dissolved in anhydrous dioxanes (3.5 mL) and the mixture was heated at 80 °C for 16 h. The mixture was diluted with EtOAc, washed with saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo gave the crude product that was purified by column chromatography (SiO_2, 0–5% EtOAc/hexanes gradient elution) to give **19** (68.2 mg, 88%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.56 (d, 2H, *J* = 7.2 Hz), 7.41 (t, 2H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.5 Hz), 7.15 (d, 1H, *J* = 7.8 Hz), 7.12 (dd, 1H, *J* = 1.2, 7.8 Hz), 7.07 (d, 1H, *J* = 1.2 Hz), 4.46–4.44 (m, 1H), 4.10 (dd, 1H, *J* = 9.6, 10.8 Hz), 3.08–2.93 (m, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 154.4, 140.7 (2C), 130.1, 128.7 (2C), 127.2, 126.9 (2C), 119.7, 119.5, 115.1, 81.4, 66.9, 39.4, 28.0 (3C), 27.5.
***tert*-Butyl 7-(Benzyloxy)chroman-3-carboxylate (20).** Compound **17** (25.9 mg, 0.091 mmol) was dissolved in DMF (0.6 mL) and K_2CO_3 (25.2 mg, 0.182 mmol, 2 equiv) and Bu_4NI (1.35 mg, 0.004 mmol, 0.04 equiv) were added. After 5 min, BnBr (13 uL, 0.109 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature for 18 h at which point saturated aqueous NaCl and EtOAc were added to quench the reaction. The organic layer was washed with saturated aqueous NaCl three times, dried over Na_2SO_4, filtered, and evaporated in vacuo. The

crude product was purified by flash chromatography (SiO_2, 5–20% EtOAc/hexanes gradient elution) to provide **20** (31.9 mg, 93%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42–7.41 (m, 2H), 7.39–7.36 (m, 2H), 7.33–7.30 (m, 1H), 6.96 (d, 1H, *J* = 8.4 Hz), 6.53 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.45 (d, 1H, *J* = 3 Hz), 5.01 (s, 2H), 4.40–4.38 (m, 1H), 4.03 (t, 1H, *J* = 9.9 Hz), 2.96–2.86 (m, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 158.3, 154.8, 137.0, 130.1, 128.5 (2C), 127.9, 127.4 (2C), 113.0, 108.4, 102.4, 81.3, 70.0, 66.8, 39.4, 28.0 (3C), 27.1.

***tert*-Butyl 7-Phenoxychroman-3-carboxylate (21).** *tert*-Butyl 7-hydroxychroman-3-carboxylate (**17**, 564 mg, 2.25 mmol), phenyl boronic acid (563 mg, 4.62 mmol, 2 equiv), and $Cu(OAc)_2$ (412 mg, 2.27 mmol, 1 equiv) were dissolved in anhydrous CH_2Cl_2 (28 mL) and 4Å MS (10 mg) were added. The reaction mixture was stirred at room temperature for 15 min before Et_3N (0.630 mL, 4.49 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 18 h under an ambient atmosphere. The mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl, saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product which was purified by flash chromatography (SiO_2, 1–5% EtOAc/hexanes gradient elution) to provide **21** (462 mg, 63%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, 2H, *J* = 7.8 Hz), 7.11–7.07 (m, 1H), 7.03–7.00 (m, 3H), 6.55 (dd, 1H, *J* = 2.3, 8.3 Hz), 6.47 (d, 1H, *J* = 2.5 Hz), 4.39 (dd, 1H, *J* = 3.4, 11.1 Hz), 4.05 (t, 1H, *J* = 9.8 Hz), 2.99–2.92 (m, 2H), 2.91–2.88 (m, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.4, 157.0, 156.6, 154.9, 130.4, 129.7 (2C), 123.2, 119.0 (2C), 115.5, 111.5, 106.8, 81.4, 66.8, 39.3, 28.0 (3C), 27.2.

(7-Phenylchroman-3-yl)methanol (22). A stirred solution of *tert*-butyl 7-phenylchroman-3-carboxylate (**19**, 107 mg, 0.344 mmol) in anhydrous THF (1.3 mL) at 0 °C was treated with $LiAlH_4$ (0.69 mL, 1 M solution in THF, 0.69 mmol, 2 equiv) over approximately 5 min. The suspension was stirred at 0 °C for 30 min and then brought to room temperature for an additional 30 min. The reaction mixture was then cooled to 0 °C and quenched with the addition of 1 M aqueous $KHSO_4$. The resulting slurry was extracted twice with EtOAc and the organic layer washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2, 20–40% EtOAc/hexanes gradient elution) to yield **22** as a white solid (75.7 mg, 92%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.56 (d, 2H, *J* = 7.2 Hz), 7.42 (t, 2H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.2 Hz), 7.13–7.10 (m, 2H), 7.06 (s, 1H), 4.35 (dd, 1H, *J* = 2.1, 10.5 Hz), 4.06 (dd, 1H, *J* = 7.8, 10.2 Hz), 3.77–3.74 (m, 1H), 3.72–3.68 (m, 1H), 2.92 (dd, 1H, *J* = 5.7, 16.5 Hz), 2.64 (dd, 1H, *J* = 7.8, 16.2 Hz), 2.35–2.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.8, 140.7, 140.6, 130.3, 128.7 (2C), 127.2, 126.9 (2C), 120.0, 119.4, 115.1, 67.7, 63.4, 34.8, 27.1.

(7-(Benzyloxy)chroman-3-yl)methanol (23). A stirred solution of *tert*-butyl 7-(benzyloxy)chroman-3-carboxylate (**20**, 38.7 mg, 0.114 mmol) in anhydrous THF (480 µL) at 0 °C was treated with $LiAlH_4$ (280 µL, 1 M solution in THF, 0.280 mmol, 2.4 equiv) over approximately 5 min. The suspension was stirred at 0 °C for 30 min and then brought to room temperature for an additional 30 min. The reaction mixture was then cooled to 0 °C and quenched with the addition of 1 M aqueous $KHSO_4$. The resulting slurry was extracted twice with EtOAc and the organic layer washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2, 20–40% EtOAc/hexanes gradient elution) to yield **23** as a white solid (27.0 mg, 88%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42–7.41 (m, 2H), 7.39–7.36 (m, 2H), 7.33–7.30 (m, 1H), 6.94 (d, 1H, *J* = 8.4 Hz), 6.53 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.45 (d, 1H, *J* = 2.4 Hz), 5.01 (s, 2H), 4.28 (dd, 1H, *J* = 2.1, 10.5 Hz), 3.98 (dd, 1H, *J* = 7.8, 10.2 Hz), 3.71 (dd, 1H, *J* = 6.0, 10.2 Hz), 3.65 (dd, 1H, *J* = 7.5, 10.5 Hz), 2.81 (dd, 1H, *J* = 5.7, 16.5 Hz), 2.52 (dd, 1H, *J* = 7.8, 15.6 Hz), 2.27–2.23 (m, 1H),

1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 155.2, 137.0, 130.4, 128.5 (2C), 127.9, 127.4 (2C), 113.3, 108.2, 102.4, 70.0, 67.7, 63.4, 34.9, 26.7.

(7-Phenoxychroman-3-yl)methanol (24). A stirred solution of **21** (150 mg, 0.460 mmol) in anhydrous THF (1.8 mL) at 0 °C was treated with $LiAlH_4$ (1 mL, 1 M solution in THF, 1 mmol, 2.2 equiv) over approximately 5 min. The suspension was stirred at 0 °C for 30 min and then brought to room temperature for an additional 30 min. The reaction mixture was then cooled to 0 °C and quenched with the addition of 1 M aqueous $KHSO_4$. The resulting slurry was extracted twice with EtOAc and the organic layer washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2, 20–30% EtOAc/hexanes gradient elution) to yield **24** as an off-white solid (112 mg, 95%):^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, 2H, *J* = 7.7 Hz), 7.09 (t, 1H, *J* = 7.5 Hz) 7.02–6.98 (m, 3H), 6.54 (dd, 1H, *J* = 2.2, 8.2 Hz), 6.47 (d, 1H, *J* = 2.5 Hz), 4.29 (dd, 1H, *J* = 3.0, 10.5 Hz), 3.99 (dd, 1H, *J* = 7.7, 10.7 Hz), 3.73 (dd, 1H, *J* = 6.0, 10.5 Hz), 3.68–3.64 (m, 1H), 2.85 (dd, 1H, *J* = 5.7, 16.2 Hz), 2.56 (dd, 1H, *J* = 8.0, 16.5 Hz), 2.29–2.25 (m, 1H). 1.49 (bs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 157.1, 156.5, 155.3, 130.6, 129.7, 123.2, 118.9, 115.8, 111.4, 106.9, 67.7, 63.4, 34.8, 26.9.

7-Phenylchroman-3-carboxaldehyde (25). Compound **25** was prepared from (7-phenylchroman-3-yl)methanol (**22**, 62.7 mg, 0.261 mmol) according to general method C. The crude reaction mixture was purified by flash chromatography (SiO_2, 0–20% EtOAc/hexanes gradient elution) and **25** was isolated as an off-white solid (58.9 mg, 95%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.52 (d, 2H, *J* = 7.8 Hz), 7.42 (t, 2H, *J* = 7.8 Hz), 7.33 (t, 1H, *J* = 7.5 Hz), 7.19 (d, 1H, *J* = 7.8 Hz), 7.14 (dd, 1H, *J* = 1.8, 7.8 Hz), 7.06 (d, 1H, *J* = 0.6 Hz), 4.45 (dd, 1H, *J* = 2.7, 11.1 Hz), 4.40 (dd, 1H, *J* = 6.3, 11.1 Hz), 3.17 (dd, 1H, *J* = 6.9, 16.5 Hz), 3.07 (dd, 1H, *J* = 6.0, 16.2 Hz), 3.02–2.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.9, 154.5, 141, 140.5, 130.2, 128.7 (2C), 127.3, 126.9 (2C), 119.9, 118.6, 115.4, 64.5, 45.2, 24.2.

7-(Benzyloxy)chroman-3-carboxaldehyde (26). Compound **23** (51.1 mg, 0.189 mmol) was dissolved in CH_2Cl_2 (3.9 mL) and Dess–Martin periodinane (140 mg, 1.8 equiv) was added. The mixture was stirred at room temperature for 2 h before the reaction mixture was reduced to half volume and then was directly loaded onto silica gel and purified by flash chromatography (SiO_2, 10–40% EtOAc/hexanes gradient elution) yielding **26** (44.7 mg, 88%) as an off-white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.82 (s, 1H), 7.42–7.36 (m, 4H), 7.32–7.30 (m, 1H), 7.00 (d, 1H, *J* = 8.4 Hz), 6.56 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.45 (d, 1H, *J* = 2.4 Hz), 5.01 (s, 2H), 4.38 (dd, 1H, *J* = 2.7, 11.1 Hz), 4.33 (dd, 1H, *J* = 6.3, 11.1 Hz), 3.05–2.92 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1, 158.4, 154.9, 136.9, 130.4, 128.6 (2C), 127.9, 127.4 (2C), 111.9, 108.8, 102.7, 70.0, 64.7, 45.2, 23.9.

7-Phenoxychroman-3-carboxaldehyde (27). A solution of oxalyl chloride (0.136 mL, 1.56 mmol, 2 equiv) in anhydrous CH_2Cl_2 (7.3 mL) was cooled to –78 °C before anhydrous DMSO (0.241 mL, 3.12 mmol, 4 equiv) was added slowly. This solution was stirred for 10 min before a solution of **(**7-phenoxychroman-3-yl)methanol (**24**, 175 mg, 0.682 mmol) in CH_2Cl_2 (2.0 mL) was added. After 15 min, Et_3N (0.438 mL, 3.12 mmol, 4 equiv) was added and stirring was continued for an additional 15 min. The flask was then removed from the ice bath and allowed to warm to room temperature. H_2O was added to the reaction mixture and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product. The pure aldehyde **27** (152 mg, 87%) was obtained as clear resin by flash chromatography (SiO_2, 10–30% EtOAc/hexanes gradient elution): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.83 (s, 1H), 7.34–7.31 (m,

2H), 7.10–7.00 (m, 4H), 6.58 (dd, 1H, *J* = 1.8, 8.4 Hz), 6.46 (d, 1H, *J* = 1.8 Hz), 4.40–4.33 (m, 2H), 3.11–3.07 (m, 1H), 3.02–2.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.9, 156.9 (2C), 155.0, 130.6, 129.7, 123.4, 119.0, 114.3, 111.9, 107.0, 64.6, 45.1, 24.0.

Oxazol-2-yl(7-phenylchroman-3-yl)methanol (28). Oxazole (0.045 mL, 0.682 mmol) in anhydrous THF (1.0 mL) was treated with BH_3•THF (1 M in THF, 0.60 mL, 0.60 mmol) under Ar. The reaction mixture was stirred for 1 h at room temperature before being cooled to –78 °C. The reaction mixture was then treated dropwise with *n*-BuLi (2.45 M in hexanes, 0.256 mL, 0.628 mmol) and stirred for an additional 1 h. The 7-phenylchroman-3-carboxaldehyde (**25**, 81.8 mg, 0.343 mmol) dissolved in THF (1.0 mL) was added to the reaction mixture and stirring was continued for 2 h. The reaction mixture was allowed to warm to room temperature and 5% AcOH/EtOH (4 mL) was added to quench the reaction. Stirring was continued overnight at room temperature after which the solvent was removed in vacuo. The crude product was dissolved in EtOAc and the organic layer was washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product that was purified by flash chromatography (SiO_2, 20–50% EtOAc/hexanes gradient elution) to afford **28** as a white solid (82.4 mg, 78%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.69 (s, 2H), 7.56 (d, 4H, *J* = 7.8 Hz), 7.41 (t, 4H, *J* = 7.5 Hz), 7.32 (t, 2H, *J* = 7.5 Hz), 7.14–7.05 (m, 8H), 4.94–4.92 (m, 1H), 4.82–4.80 (m, 1H), 4.42 (d, 1H, *J* = 10.2 Hz), 4.32–4.30 (m, 1H), 4.23 (dd, 1H, *J* = 8.4, 10.2 Hz), 4.01 (dd, 1H, *J* = 8.4, 10.8 Hz), 3.12–3.01 (bm, 3H), 2.81–2.77 (m, 2H), 2.70–2.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2 (2C), 154.7, 154.6, 140.7 (4C), 139.4, 139.3, 130.4, 130.3, 128.7 (4C), 127.2 (2C), 127.0 (2C), 126.9 (4C), 119.9, 119.5 (3C), 115.1 (2C), 68.0, 67.8, 67.4, 66.8, 37.6, 37.5, 27.0, 25.6.

(7-(Benzyloxy)chroman-3-yl)(oxazol-2-yl)methanol (29). Oxazole (0.092 mL, 1.40 mmol) in anhydrous THF (2.8 mL) was treated with BH_3•THF (1 M in THF, 1.23 mL, 1.23 mmol) under Ar. The reaction mixture was stirred for 1 h at room temperature before being cooled to –78 °C. The reaction mixture was then treated dropwise with *n*-BuLi (2.50 M in hexanes, 0.500 mL,1.23 mmol) and stirred for an additional 1 h. Compound **26** (155 mg, 0.576 mmol) dissolved in THF (2.8 mL) was added to the reaction mixture and stirring was continued for 2 h. The reaction mixture was allowed to warm to room temperature and 5% AcOH/EtOH (16 mL) was added to quench the reaction. Stirring was continued overnight at room temperature after which the solvent was removed in vacuo. The crude product was dissolved in EtOAc and the organic layer was washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product which was purified by flash chromatography (SiO_2, 30–60% EtOAc/hexanes gradient elution) to afford **29** as a white solid (164 mg, 84%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.66 (d, 2H, *J* = 3.0 Hz), 7.42–7.36 (m, 8H), 7.32–7.31 (m, 2H), 7.11 (d, 2H, *J* = 2.4 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 6.54–6.51 (m, 2H), 6.46 (dd, 2H, *J* = 2.4, 6.6 Hz), 5.01 (s, 4H), 4.87 (t, 1H, *J* = 5.7 Hz), 4.75 (dd, 1H, *J* = 6.0, 7.8 Hz), 4.38–4.36 (m, 1H), 4.24–4.22 (m, 1H), 4.16 (dd, 1H, *J* = 7.8, 10.8 Hz), 3.92 (dd, 1H, *J* = 8.4, 10.8 Hz), 3.59–3.35 (bs, 2H), 2.91 (dd, 1H, *J* = 9.0, 16.2 Hz), 2.71–2.59 (m, 4H), 2.52 (dd, 1H, *J* = 7.8, 15.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.4, 164.3, 158.2 (2C), 155.1, 155.0, 139.3, 139.2, 137.0 (2C), 130.5, 130.3, 128.5 (4C), 127.9 (2C), 127.4 (2C), 126.9 (2C), 113.1, 112.8, 108.4 (2C), 102.5 (2C), 70.0 (2C), 67.9, 67.7, 67.3, 66.8, 37.7, 37.5, 26.6, 25.2.

Oxazol-2-yl(7-phenoxychroman-3-yl)methanol (30). Oxazole (0.071 mL, 1.08 mmol) in anhydrous THF (3.5 mL) was treated with BH_3•THF (1 M in THF, 0.996 mL, 0.996 mmol) under Ar. The reaction mixture was stirred for 1 h at room temperature before being cooled to –78 °C. The reaction mixture was then treated dropwise with *n*-BuLi (2.50 M in hexanes, 0.400 mL, 0.996

mmol) and stirred for an additional 1 h. Compound **27** (112 mg, 0.440 mmol) dissolved in THF (2.5 mL) was added to the reaction mixture and stirring was continued for 2 h. The reaction mixture was allowed to warm to room temperature and 5% AcOH/EtOH (8 mL) was added. Stirring was continued overnight at room temperature after which the solvent was removed in vacuo. The crude product was dissolved in EtOAc and the organic layer was washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product that was purified by flash chromatography (SiO_2, 10–60% EtOAc/hexanes gradient elution) to afford **30** as a white solid (105.6 mg, 74%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68 (s, 2H), 7.33–7.30 (m, 4H), 7.13 (s, 2H), 7.10–7.07 (m, 2H), 7.01–6.99 (m, 5H), 6.93 (d, 1H, *J* = 8.4 Hz), 6.55–6.52 (m, 1H), 6.47 (dd, 1H, *J* = 2.4, 6.6 Hz), 4.90 (t, 1H, *J* = 6.0 Hz), 4.78 (dd, 0.5 H, *J* = 6.0, 7.8 Hz), 4.37–4.36 (m, 1H), 4.26–4.24 (m, 1H), 4.17 (dd, 1H, *J* = 7.8, 10.8 Hz), 3.95 (dd, 1H, *J* = 9.0, 10.8 Hz), 3.08 (bs, 2H), 2.95 (dd, 1H, *J* = 9.0, 16.2 Hz), 2.73–2.70 (m, 1H), 2.65–2.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.2, 164.1, 157.1 (2C), 156.6, 156.5, 155.3, 155.1, 139.4, 139.3, 130.7, 130.6, 129.7 (4C), 127.0 (2C), 123.2, 118.9 (4C), 115.6, 115.2, 111.5 (2C), 106.9 (2C), 67.9, 67.7, 67.3, 66.7, 37.5, 37.4, 26.7, 25.3.

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenylchroman-3-yl)methyl)oxazole (31). Compound **31** was prepared from oxazol-2-yl(7-phenylchroman-3-yl)methanol (**28**, 89.7 mg, 0.291 mmol) according to general procedure A. Flash chromatography (SiO_2, 0–20% EtOAc/hexanes gradient elution) yielded **31** (112.2 mg, 91%) as an opaque resin: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (s, 2H), 7.56 (m, 4H), 7.41 (m, 4H), 7.32 (t, 2H, *J* = 7.5 Hz), 7.14–7.03 (m, 8H), 4.91 (d, 1H, *J* = 6.6 Hz), 4.76 (d, 1H, *J* = 8.4 Hz), 4.45 (d, 1H, *J* = 10.8 Hz), 4.23–4.19 (m, 1H), 4.18 (dd, 1H, *J* = 7.8, 10.2 Hz), 3.89 (dd, *J* = 8.4, 10.8 Hz), 2.99–2.88 (m, 2H), 2.67–2.61 (m, 3H), 2.53–2.47 (m, 1H), 0.88 (s, 18H), 0.09 (s, 3H), 0.03 (s, 3H), –0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.7 (2C), 154.8, 154.6, 140.8, 140.6, 140.5 (2C), 138.9, 138.8, 130.4, 130.3, 128.7 (4C), 127.2 (2C), 127.1 (2C), 126.9 (4C), 120.1 (2C), 119.6, 119.4 (3C), 115.0 (2C), 68.9, 68.6, 67.4, 67.0, 38.4, 37.9, 26.8, 26.3, 25.6 (6C), 18.1 (2C), –5.4, –5.5 (3C).

2-((7-(Benzyloxy)chroman-3-yl)((*tert*-butyldimethylsilyl)oxy)methyl)oxazole (32). Compound **32** was prepared from (7-(benzyloxy)chroman-3-yl)(oxazol-2-yl)methanol (**29**, 29.9 mg, 0.089 mmol) according to general procedure A. Flash chromatography (SiO_2, 5–15% EtOAc/hexanes gradient elution) on the crude reaction mixture yielded **32** (37.0 mg, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (s, 2H), 7.42–7.41 (m, 4H), 7.38–7.36 (m, 4H), 7.32–7.30 (m, 2H), 7.11 (s, 2H), 6.94 (d, 1H, *J* = 8.4 Hz), 6.85 (d, 1H, *J* = 8.4 Hz), 6.53–6.49 (m, 2H), 6.45 (dd, 2H, *J* = 2.4, 9.0 Hz), 5.01 (s, 4H), 4.86 (d, 1H, *J* = 7.2 Hz), 4.71 (d, 1H, *J* = 9.0 Hz), 4.40–4.38 (m, 1H), 4.16–4.08 (m, 2H), 3.81 (dd, 1H, *J* = 8.4, 10.8 Hz), 2.86–2.78 (m, 2H), 2.63–2.51 (m, 3H), 2.38 (dd, 1H, *J* = 8.4, 16.2 Hz), 0.86 (s, 18H), 0.07 (s, 3H), 0.00 (s, 3H), –0.14 to –0.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.7 (2C), 158.2 (2C), 155.2, 155.0, 138.8 (2C), 137.0 (2C), 130.5, 130.4, 128.5 (4C), 127.9 (2C), 127.4 (4C), 127.1, 127.0, 113.3, 112.9, 108.3, 108.2, 102.4 (2C), 70.0 (2C), 68.9, 68.6, 67.2, 67.0, 38.4, 38.0, 26.3, 25.9, 25.6 (6C), 18.1 (2C), –5.4 (2C), –5.5 (2C).

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)oxazole (33). Compound **33** was prepared from oxazol-2-yl(7-phenoxychroman-3-yl)methanol (**30**, 106 mg, 0.327 mmol) following general procedure A. Flash chromatography (SiO_2, 5–15% EtOAc/hexanes gradient elution) yielded **33** (136 mg, 95%) as an opaque oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67–7.66 (m, 2H), 7.33–7.30 (m, 4H), 7.11 (s, 2H), 7.09–7.06 (m, 2H), 7.01–6.99 (m, 5H), 6.90 (d, 1H, *J* = 7.8 Hz), 6.55–6.49 (m, 4H), 4.88 (d, 1H, *J* = 6.6 Hz), 4.73 (d, 1H, *J* = 9.0 Hz), 4.40–4.38 (m, 1H), 4.17–4.10 (m, 2H), 3.83 (dd, 1H, *J* = 8.4, 10.8 Hz), 2.90–2.82 (m, 2H), 2.64–2.56 (m, 3H), 2.44–

2.40 (m, 1H), 0.86 (s, 18H), 0.07 (s, 3H), 0.01 (s, 3H), –0.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.7 (2C), 157.2, 157.1, 156.5, 156.4, 155.4, 155.1, 138.9, 138.8, 130.7, 130.6, 129.6 (4C), 127.1, 127.0, 123.1 (2C), 118.9 (2C), 118.8 (2C), 115.8, 115.4, 111.5, 111.4, 107.0, 106.9, 68.9, 68.5, 67.3, 66.9, 38.3, 37.9, 28.6, 26.5, 26.0, 25.6 (6C), 18.1 (2C), –5.4 (2C), –5.5 (2C).

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenylchroman-3-yl)methyl)-5-(tributylstannyl)oxazole (34). A solution of the 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenylchroman-3-yl)methyl)oxazole (**31**, 41.6 mg, 0.099 mmol) in anhydrous THF (1.0 mL) was cooled to –78 °C. *n*-BuLi (51 μL of ~2.3 M solution, 0.118 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred at that temperature for 2 h. At this point, Bu_3SnCl (54 μL, 0.197 mmol, 2 equiv) was added slowly and the reaction mixture was allowed to stir for 5 min. The reaction mixture was then allowed to warm to room temperature before it was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and evaporated. Flash chromatography (SiO_2, 0–20% EtOAc/hexanes gradient elution) yielded **34** as an opaque resin (50.9 mg, 73%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (m, 4H), 7.41 (m, 4H), 7.33–7.30 (m, 2H), 7.12–7.01 (m, 8H), 4.94 (d, 1H, *J* = 6.5 Hz), 4.76 (d, 1H, *J* = 8.5 Hz), 4.49–4.46 (m, 1H) 4.24–4.21 (m, 1H), 4.14 (dd, 1H, *J* = 8.5, 10.5 Hz), 3.87 (dd, 1H, *J* = 9.0, 10.5 Hz), 2.97–2.86 (m, 2H), 2.69–2.53 (m, 3H), 2.53–2.47 (m, 1H), 1.58–1.55 (m, 12H), 1.36–1.32 (m, 12H), 1.14–1.10 (m, 12H), 0.92–0.87 (36H), 0.07 (s, 3H), 0.02 (s, 3H), –0.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.5 (2C), 155.6, 155.5, 154.9, 154.7, 140.8 (2C), 140.6, 140.4, 137.3 (2C), 130.4, 130.3, 128.6 (4C), 127.1, 126.9 (5C), 120.4, 119.9, 119.3 (2C), 115.0 (2C), 69.0, 68.9, 67.6, 67.2, 38.5, 38.1, 28.9 (6C), 27.1 (7C), 26.4, 25.6 (6C), 18.1, 17.5, 13.6 (6C), 10.2 (6C), –5.4 (2C), –5.5 (2C).

2-((7-(Benzyloxy)chroman-3-yl)((*tert*-butyldimethylsilyl)oxy)methyl)-5-(tributylstannyl)-oxazole (35). A solution of **32** (82.5 mg, 0.183 mmol) in anhydrous THF (1.8 mL) was cooled to –78 °C. *n*-BuLi (85 μL of 2.3 M solution, 0.196 mmol, 1.1 equiv) was added dropwise and the reaction was stirred at that temperature for 2 h. At this point, Bu_3SnCl (96 μL, 0.354 mmol, 1.9 equiv) was added slowly and the reaction mixture was allowed to stir for 5 min. The reaction mixture was then allowed to warm to room temperature before it was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and evaporated. Flash chromatography (SiO_2, 0–15% EtOAc/hexanes gradient elution) yielded **35** as a pale yellow resin (99.8 mg, 74%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42–7.38 (m, 4H), 7.37–7.36 (m, 4H), 7.32–7.30 (m, 2H), 7.11–7.10 (m, 2H), 6.93 (d, 1H, *J* = 8.4 Hz), 6.84 (d, 1H, *J* = 8.4 Hz), 6.52–6.48 (m, 2H), 6.46–6.44 (m, 2H), 5.00 (s, 4H), 4.89 (d, 1H, *J* = 7.2 Hz), 4.73 (d, 1H, *J* = 8.4 Hz), 4.42 (dd, 1H, *J* = 1.8, 10.8 Hz), 4.16 (dd, 1H, *J* = 8.4, 10.2 Hz), 4.07 (dd, 1H, *J* = 8.4, 10.2 Hz), 3.80 (dd, 1H, *J* = 9.0, 10.2 Hz), 2.84–2.76 (m, 2H), 2.63–2.53 (m, 2H), 2.48 (dd, 1H, *J* = 5.4, 16.2 Hz), 2.39 (dd, 1H, *J* = 8.7, 15.9 Hz), 1.57–1.53 (m, 12H), 1.35–1.30 (m, 12H), 1.13–1.10 (m, 12H), 0.90–0.87 (m, 18H), 0.84 (m, 18H), 0.05 (s, 3H), –0.00 (s, 3H), –0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.6, 167.5, 158.2, 158.1, 155.5, 155.4, 155.3, 155.1, 137.3 (2C), 137.1 (2C), 130.3, 130.3, 128.5 (4C), 127.8 (2C), 127.4 (4C), 113.6, 113.2, 108.2, 108.1, 102.4 (2C), 70.0 (2C), 69.1, 68.8, 67.4, 67.2, 38.6, 38.2, 28.9 (6C), 27.1 (6C), 26.4, 26.0, 25.6 (6C), 18.1 (2C), 13.6 (6C), 10.2 (6C), –5.4 (2C), –5.5 (2C).

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)-5-(tributylstannyl)-oxazole (36). A solution of 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)oxazole (**33**, 136 mg, 0.311 mmol) in anhydrous THF (3.2 mL) was cooled to –78 °C. *n*-BuLi (125 μL of 2.5 M solution, 0.312 mmol, 1 equiv) was added dropwise and the reaction mixture was stirred at that temperature for 2 h. At this point, Bu_3SnCl (169 μL, 0.622 mmol, 2 equiv) was added slowly and the reaction mixture was allowed to stir for 5 min. The reaction

mixture was then allowed to warm to room temperature before it was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and evaporated. Flash chromatography (SiO_2, 0–8% EtOAc/hexanes gradient elution) yielded **36** as a thick oil (161 mg, 71%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33–7.30 (m, 4H), 7.11–7.06 (m, 4H), 7.01–6.98 (m, 4H), 6.90 (d, 1H, *J* = 8.4 Hz), 6.54–6.45 (m, 4H), 4.91 (d, 1H, *J* = 6.6 Hz), 4.54 (d, 1H, *J* = 8.4 Hz), 4.43–4.41 (m, 1H), 4.17–4.16 (m, 1H), 4.08 (dd, 1H, *J* = 8.4, 10.2 Hz), 3.82 (dd, 1H, *J* = 9.6, 10.2 Hz), 2.88–2.80 (m, 2H), 2.64–2.50 (m, 3H), 2.43 (dd, 1H, *J* = 8.4, 16.2 Hz), 1.56–1.54 (m, 12H), 1.35–1.30 (m, 12H), 1.17–1.06 (m, 12H), 0.90–0.85 (m, 36H), 0.05 (s, 3H), 0.01 (s, 3H), –0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.5 (2C), 157.3, 157.2, 156.4, 156.3, 155.6, 155.5 (2C), 155.2, 137.3 (2C), 130.7, 130.6, 129.7 (4C), 123.1, 123.0, 118.8 (4C), 116.2, 115.7, 111.4, 111.3, 107.0, 106.9, 69.0, 68.7, 67.5, 67.2, 38.5, 38.0, 28.9 (6C), 27.1 (6C), 26.8, 26.6, 25.6 (6C), 18.1 (2C), 13.6 (6C), 10.2 (6C), –5.4 (2C), –5.5 (2C).

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenylchroman-3-yl)methyl)-5-(pyridin-2-yl)oxazole (37). Compound **37** was prepared from 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenylchroman-3-yl)methyl)-5-(tributylstannyl)oxazole (**34**, 97.1 mg, 0.137 mmol) and 2-bromopyridine as described in general procedure B. The crude reaction mixture was purified by flash chromatography (SiO_2, 0–30% EtOAc/hexanes gradient elution) to give **37** as a mixture of diastereomers and as a colorless resin (45.2 mg, 66%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (d, 2H, *J* = 4.8 Hz), 7.81–7.76 (m, 2H), 7.69–7.66 (m, 4H), 7.56–7.55 (m, 4H), 7.43–7.40 (m, 4H), 7.34–7.31 (m, 2H), 7.26–7.24 (m, 2H), 7.15–7.03 (m, 6H), 4.97 (d, 1H, *J* = 6.6 Hz), 4.80 (d, 1H, *J* = 8.4 Hz), 4.49–4.47 (m, 1H), 4.23 (dd, 1H, *J* = 7.5, 10.5 Hz), 3.98 (dd, 1H, *J* = 8.4, 10.8 Hz), 3.01 (dd, 1H, *J* = 9.0, 16.2 Hz), 2.94 (dd, 1H, *J* = 4.8, 16.2 Hz), 2.76–2.70 (m, 3H), 2.60–2.56 (m, 1H), 0.90 (s, 18H), 0.12 (s, 3H), 0.05 (s, 3H), –0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8 (2C), 154.8, 154.6, 151.1, 150.0, 147.2 (2C), 140.7 (2C), 140.5 (2C), 137.0 (2C), 130.4, 130.3, 128.7 (4C), 127.1, 127.0, 126.9 (4C), 125.3, 125.2, 123.0 (2C), 120.0, 119.5 (2C), 119.4, 119.2, 119.1, 115.0 (2C), 69.0, 68.7, 67.4, 66.9, 38.4, 37.9, 26.9, 26.2, 25.7 (6C), 18.2 (2C), –5.1, –5.2, –5.4 (2C).

The enantiomers of each diastereomer were separated using a semipreparative chiral phase HPLC column (Daicel ChiralPak AD, 10 μm, 2 × 25 cm, 5% *i*-PrOH–hexanes, 7 mL/min, α = 1.58 for the faster eluting diastereomer (**37a**) and α = 1.30 for the more slowly eluting diastereomer (**37b**)).

37a-Enant 1: $[\alpha]^{23}_D$ +37 (*c* 0.15, THF).

37a-Enant 2: $[\alpha]^{23}_D$ –37 (*c* 0.34, THF).

37b-Enant 1: $[\alpha]^{23}_D$ –16 (*c* 0.31, THF).

37b-Enant 2: $[\alpha]^{23}_D$ +19 (*c* 0.25, THF).

2-((7-(Benzyloxy)chroman-3-yl)((*tert*-butyldimethylsilyl)oxy)methyl)-5-(pyridin-2-yl)oxazole (38). Compound **38** was prepared from 2-((7-(benzyloxy)chroman-3-yl)((*tert*-butyldimethylsilyl)oxy)methyl)-5-(tributylstannyl)oxazole (**35**, 133 mg, 0.180 mmol) and 2-bromopyridine (35 μL, 0.366 mmol, 2.0 equiv) according to general procedure B. Compound **38** was isolated as a mixture of diastereomers as a colorless resin (60.7 mg, 64%) after flash chromatography (SiO_2, 0–30% EtOAc/hexanes gradient elution): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (d, 2H, *J* = 2.4 Hz), 7.79–7.77 (m, 2H), 7.68–7.64 (m, 4H), 7.42–7.36 (m, 8H), 7.32–7.30 (m, 2H), 7.26–7.24 (m, 2H), 6.95 (d, 1H, *J* = 8.4 Hz), 6.86 (d, 1H, *J* = 8.4 Hz), 6.51 (dd, 2H, *J* = 8.4, 14.4 Hz), 6.46 (d, 2H, *J* = 10.2 Hz), 5.01 (s, 4H), 4.92 (d, 1H, *J* = 6.6 Hz), 4.76 (d, 1H, *J* = 8.4 Hz), 4.43 (d, 1H, *J* = 10.8 Hz), 4.21 (d, 1H, *J* = 10.8 Hz), 4.15 (t, 1H, *J* = 9.0 Hz), 3.91 (t, 1H, *J* = 9.6 Hz), 2.89 (dd, 1H, *J* = 8.7, 15.9 Hz), 2.83 (dd, 1H, *J* = 4.5, 15.9 Hz), 2.69–2.59 (m, 3H), 2.47 (dd, 1H, *J* = 7.8, 16.2 Hz), 0.88 (s, 18H), 0.10 (s, 3H), 0.04 (s, 3H), –0.08 (s, 6H); ^{13}C NMR

($CDCl_3$, 150 MHz) δ 163.8 (2C), 158.2 (2C), 155.2, 155.0, 151.1, 151.0, 149.9 (2C), 147.2 (2C), 137.0 (4C), 130.5, 130.4, 128.5 (4C), 127.9 (2C), 127.4 (4C), 125.3, 125.2, 123.0 (2C), 119.2, 119.1, 113.2, 112.8, 108.3, 108.2, 102.5, 102.4, 70.0 (2C), 69.1, 68.7, 67.3, 66.9, 38.4, 38.0, 26.5, 25.8, 25.6 (6C), 18.1 (2C), –5.2 (2C), –5.4 (2C).

The enantiomers of both diastereomers were separated using a semipreparative chiral phase HPLC column (Daicel ChiralPak AD, 10 μm, 2 × 25 cm, 5% *i*-PrOH–hexanes, 7 mL/min, α = 1.78 for the faster eluting diastereomer (**38a**) and α = 1.33 for the slower eluting diastereomer (**38b**)).

38a-Enant 1: $[\alpha]^{23}_D$ +19 (*c* 0.25, THF).

38a-Enant 2: $[\alpha]^{23}_D$ –21 (*c* 0.25, THF).

38b-Enant 1: $[\alpha]^{23}_D$ –17 (*c* 0.23, THF).

38b-Enant 2: $[\alpha]^{23}_D$ +15 (*c* 0.11, THF).

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)-5-(pyridin-2-yl)oxazole (39). Compound **39** was prepared from 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)-5-(tributylstannyl)oxazole (**36**, 66.1 mg, 0.091 mmol) and 2-bromopyridine following general procedure B. Compound **39** was isolated as a yellow oil (39.8 mg, 85%) after flash chromatography (SiO_2, 0–20% EtOAc/hexanes gradient elution): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (d, 2H, *J* = 4.2 Hz), 7.79–7.61 (m, 2H), 7.70–7.65 (m, 4H), 7.33–7.30 (m, 4H), 7.25–7.23 (m, 2H), 7.09–7.06 (m, 2H), 7.00 (t, 5H, *J* = 8.4 Hz), 6.91 (d, 1H, *J* = 7.8 Hz), 6.55–6.47 (m, 4H), 4.94 (d, 1H, *J* = 6.6 Hz), 4.77 (d, 1H, *J* = 8.4 Hz), 4.43 (dd, 1H, *J* = 1.5, 10.5 Hz), 4.23 (dd, 1H, *J* = 1.5, 11.1 Hz), 4.16 (dd, 1H, *J* = 7.8, 10.8 Hz), 3.93 (dd, 1H, *J* = 9.0, 10.8 Hz), 2.94 (dd, 1H, *J* = 9.0, 16.2 Hz), 2.87 (dd, 1H, *J* = 4.8, 16.2 Hz), 2.72–2.64 (m, 3H), 2.52 (dd, 1H, *J* = 7.8, 16.2 Hz), 0.89–0.88 (m, 18H), 0.10 (s, 3H), 0.05 (s, 3H), –0.07 to –0.08 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.8 (2C), 157.2, 157.1, 156.5, 156.4, 155.4, 155.1, 151.2, 151.1, 150.0 (2C), 147.2 (2C), 136.7 (2C), 130.8, 130.6, 129.6 (4C), 125.3, 125.2, 123.1 (2C), 123.0, 119.2, 119.1, 118.9 (2C), 118.8 (2C), 115.8, 115.3, 111.6, 111.5, 107.0, 106.9, 69.0, 68.6, 67.3, 66.9, 38.3, 37.9, 26.6, 25.9, 25.6 (6C), 18.1 (2C), –5.2 (2C), –5.4 (2C).

Methyl 6-(2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)oxazol-5-yl)picolinate (40). Compound **40** was prepared from 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)-5-(tributylstannyl)oxazole (**36**, 161 mg, 0.222 mmol) and methyl-6-bromopicolinate according to general procedure B. Flash chromatography (SiO_2, 0–20% EtOAc/hexanes gradient elution) provided **40** as a thick yellow oil (117 mg, 92%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05 (d, 2H, *J* = 7.8 Hz), 7.93 (td, 2H, *J* = 2.4, 7.8 Hz), 7.83–7.81 (m, 4H) 7.33–7.30 (m, 4H), 7.09–7.06 (m, 2H), 7.01–6.98 (m, 5H), 6.90 (d, 1H, *J* = 8.4 Hz), 6.55–6.47 (m, 4H), 4.94 (d, 1H, *J* = 6.6 Hz), 4.78 (d, 1H, *J* = 9.0 Hz), 4.43–4.41 (m, 1H), 4.23–4.18 (m, 1H), 4.17 (dd, 1H, *J* = 7.5, 10.5 Hz), 4.02 (s, 6H), 3.93 (dd, 1H, *J* = 8.4, 10.8 Hz), 2.94 (dd, 1H, *J* = 8.4, 16.2 Hz), 2.87 (dd, 1H, *J* = 5.4, 16.2 Hz), 2.71–2.63 (m, 3H), 2.51 (dd, 1H, *J* = 7.8, 16.2 Hz), 0.89–0.88 (m, 18H), 0.10 (s, 3H), 0.04 (s, 3H), –0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.3, 164.1, 157.2, 157.1, 156.5, 156.4, 155.4, 155.1, 150.4, 150.3, 148.3, 147.4, 138.1 (2C), 130.8, 130.6, 129.6 (4C), 126.5, 126.4, 124.1 (2C), 123.2, 123.1, 122.1 (2C), 118.9 (4C), 118.8 (4C), 115.7, 115.2, 111.6, 111.5, 106.9 (2C), 69.0, 68.6, 67.2, 66.8, 53.0 (2C), 38.3, 37.9, 26.6, 25.9, 25.6 (6C), 18.1 (2C), –5.2, –5.3, –5.4 (2C).

The enantiomers of each diastereomer were separated using a semipreparative chiral phase HPLC column (Daicel ChiralCel OD, 10 μm, 2 × 25 cm, 20% *i*-PrOH–hexanes, 7 mL/min, α = 1.55 for the less polar diastereomer (**40a**) and α = 1.48 for the more polar diastereomer (**40b**)).

40a-Enant 1: $[\alpha]^{23}_D$ +17 (*c* 0.47, THF).

40a-Enant 2: $[\alpha]^{23}_D$ –16 (*c* 0.53, THF).

40b-Enant 1: $[\alpha]^{23}_D$ +14 (*c* 0.57, THF).
40b-Enant 2: $[\alpha]^{23}_D$ –15 (*c* 0.57, THF).
(7-Phenylchroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (41). Compound **41** was prepared from 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenylchroman-3-yl)methyl)-5-(pyridin-2-yl)oxazole (**37**, 45.2 mg, 0.091 mmol) according to general procedure D. The crude product was purified by flash chromatography (SiO_2, 20–80% EtOAc/hexanes gradient elution) to give **41** as a white crystalline solid (27.2 mg, 78%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (d, 2H, *J* = 4.2 Hz), 7.78–7.77 (m, 2H), 7.71 (s, 2H), 7.67–7.63 (m, 2H), 7.55–7.54 (m, 4H), 7.42–7.39 (m, 4H), 7.33–7.31 (m, 2H), 7.26–7.24 (m, 2H), 7.14–7.06 (m, 6H), 5.02 (d, 1H, *J* = 6.0 Hz), 4.89 (d, 1H, *J* = 8.4 Hz), 4.48 (d, 1H, *J* = 10.8 Hz), 4.36 (d, 1H, *J* = 10.8 Hz), 4.29 (dd, 1H, *J* = 6.9, 11.1 Hz), 4.09 (dd, 1H, *J* = 8.4, 10.8 Hz), 3.08 (dd, 1H, *J* = 9.0, 16.2 Hz), 2.87–2.84 (m, 2H), 2.79–2.70 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4 (2C), 154.7, 154.6, 151.2, 149.5, 146.5 (2C), 140.7 (2C), 140.6 (2C), 137.4 (2C), 130.4, 130.3, 128.7 (4C), 127.2 (2C), 127.0 (4C), 125.5, 125.4, 123.3 (2C), 119.9, 119.5 (5C), 115.1 (2C), 68.1, 67.8, 67.4, 66.8, 37.5, 37.4, 27.1, 25.6.
The enantiopure alcohols were prepared from the corresponding enantiopure TBS ethers according to general procedure C.
41a-Enant 1: $[\alpha]^{23}_D$ +78 (*c* 0.082, THF).
41a-Enant 2: $[\alpha]^{23}_D$ –71 (*c* 0.20, THF).
41b-Enant 1: $[\alpha]^{23}_D$ –7 (*c* 0.23, THF).
41b-Enant 2: $[\alpha]^{23}_D$ +8 (*c* 0.14, THF).
(7-(Benzyloxy)chroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (42). Compound **42** was prepared from 2-((7-(benzyloxy)chroman-3-yl)((*tert*-butyldimethylsilyl)oxy)methyl)-5-(pyridin-2-yl)oxazole (**38**, 6.78 mg, 0.013 mmol) according to general procedure D. Purification by preparative TLC (SiO_2, 50% EtOAc/hexanes) gave **42** as a white solid (4.11 mg, 77%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.64 (bs, 2H), 7.76 (t, 2H, *J* = 7.5 Hz), 7.67 (s, 2H), 7.63 (t, 2H, *J* = 8.1 Hz), 7.42–7.36 (m, 8H), 7.32–7.31 (m, 2H), 7.26–7.24 (m, 2H), 6.95 (d, 1H, *J* = 8.4 Hz), 6.88 (d, 1H, *J* = 7.8 Hz), 6.53–6.51 (m, 2H), 6.46 (d, 2H, *J* = 10.8 Hz), 5.00–4.96 (m, 5H), 4.84 (d, 1H, *J* = 7.8 Hz), 4.41 (d, 1H, *J* = 10.8 Hz), 4.30 (d, 1H, *J* = 10.8 Hz), 4.23–4.20 (m, 1H), 4.03 (t, 1H, *J* = 9.6 Hz), 3.06 (bs, 2H), 2.96 (dd, 2H, *J* = 8.4, 15.6 Hz), 2.74–2.70 (m, 3H), 2.61 (dd, 1H, *J* = 6.9, 14.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.2 (2C), 158.3, 158.2, 155.2, 155.0, 151.6, 151.4, 150.0 (2C), 146.9 (2C), 137.0 (4C), 130.5, 130.4, 128.5 (4C), 127.9 (2C), 127.4 (4C), 125.1, 125.0, 123.2 (2C), 119.4 (2C), 113.1, 112.7, 108.4 (2C), 102.5 (2C), 70.0 (2C), 68.1, 67.9, 67.4, 66.7, 37.6, 37.5, 26.7, 25.1.
The enantiopure alcohols were prepared from the corresponding enantiopure TBS ethers according to general procedure C.
42a-Enant 1: $[\alpha]^{23}_D$ +38 (*c* 0.18, THF).
42a-Enant 2: $[\alpha]^{23}_D$ –40 (*c* 0.13, THF).
42b-Enant 1: $[\alpha]^{23}_D$ –7 (*c* 0.15, THF).
42b-Enant 2: $[\alpha]^{23}_D$ +8 (*c* 0.065, THF).
(7-Phenoxychroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (43). Compound **43** was prepared from **39** (39.8 mg, 0.077 mmol) according to general procedure D. The crude reaction mixture was purified by flash chromatography (SiO_2, 50–100% EtOAc/hexanes gradient elution) to give **43** as a white solid (25.6 mg, 83%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.63 (s, 2H), 7.78–7.76 (m, 2H), 7.67–7.64 (m, 4H), 7.31–7.30 (m, 4H), 7.25–7.23 (m, 2H), 7.09–7.07 (m, 2H), 7.00–6.99 (m, 5H), 6.94–6.92 (m, 1H), 6.54–6.52 (m, 2H), 6.48–6.46 (m, 2H), 5.00 (d, 1H, *J* = 4.2 Hz), 4.87 (d, 1H, *J* = 6.6 Hz), 4.43 (d, 1H, *J* = 10.8 Hz), 4.31 (d, 1H, *J* = 10.8 Hz), 4.22–4.20 (m, 1H), 4.05–

4.02 (m, 1H), 3.51 (bs, 2H), 3.02–2.98 (m, 1H), 2.79–2.73 (m, 5H), 2.67–2.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.3 (2C), 157.1 (2C), 156.5 (2C), 155.2 (2C), 151.5 (2C), 149.9 (2C), 146.8 (2C), 137.0 (2C), 130.7, 130.6, 129.6 (4C), 125.1, 125.0, 123.2 (4C), 119.5, 119.4, 118.9 (4C), 115.8, 115.4, 111.5 (2C), 106.9 (2C), 68.0, 67.7, 67.4, 66.8, 37.5, 37.4, 27.9, 26.9.

Methyl 6-(2-(Hydroxy(7-phenoxychroman-3-yl)methyl)oxazol-5-yl)picolinate (44). Compound **44** was prepared from methyl 6-(2-(((*tert*-butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)oxazol-5-yl)picolinate (**40**, 110 mg, 0.191 mmol) according to general procedure D. The crude product was purified by flash chromatography (SiO_2, 50–100% EtOAc/hexanes gradient elution) to give **44** as a white solid (51.4 mg, 59%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.07–8.05 (m, 2H), 7.92 (td, 2H, *J* = 3.0, 7.8 Hz), 7.81–7.78 (m, 4H), 7.33–7.30 (m, 4H), 7.09–7.07 (m, 2H), 7.01–6.98 (m, 5H), 6.92 (d, 1H, *J* = 8.4 Hz), 6.55–6.52 (m, 2H), 6.48 (dd, 2H, *J* = 2.4, 11.4 Hz), 5.00 (t, 1H, *J* = 5.7 Hz), 4.87 (dd, 1H, *J* = 6.0, 7.8 Hz), 4.41–4.39 (m, 1H), 4.32–4.30 (m, 1H), 4.24 (dd, 1H, *J* = 7.8, 10.8 Hz), 4.06–4.02 (m, 7H), 3.02–2.98 (m, 3H), 2.80–2.63 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.3 (2C), 164.5 (2C), 157.1 (2C), 156.6 (2C), 155.3, 155.1, 150.9, 150.7, 148.3 (2C), 147.2, 147.1, 138.1 (2C), 130.8, 130.6, 129.7 (4C), 126.3, 126.2, 124.3 (2C), 123.2 (2C), 122.4 (2C), 118.9 (4C), 115.5, 115.1, 111.6 (2C), 106.9 (2C), 68.0, 67.8, 67.3, 66.7, 53.0 (2C), 37.4, 37.3, 26.8, 25.2.

The enantiopure alcohols were prepared from the corresponding enantiopure TBS ethers according to general procedure C.

44a-Enant 1: $[\alpha]^{23}_D$ +40 (*c* 0.16, THF).

44a-Enant 2: $[\alpha]^{23}_D$ –40 (*c* 0.16, THF).

44b-Enant 1: $[\alpha]^{23}_D$ +23 (*c* 0.15, THF).

44b-Enant 2: $[\alpha]^{23}_D$ –21 (*c* 0.016, THF).

(7-Phenylchroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanone (45). Compound **45** was prepared from (7-phenylchroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (**41**, 20.6 mg, 0.054 mmol) according to general method C. Recrystallization of the crude product from hot EtOAc yielded **45** as a white solid (18.2 mg, 89% yield): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.69 (d, 1H, *J* = 4.2 Hz), 7.96 (s, 1H), 7.86 (d, 1H, *J* = 7.8 Hz), 7.85–7.82 (m, 1H), 7.58 (d, 2H, *J* = 7.2 Hz), 7.42 (t, 2H, *J* = 6.9 Hz), 7.35–7.32 (m, 2H), 7.20 (d, 1H, *J* = 7.8 Hz), 7.15 (d, 1H, *J* = 7.8 Hz), 7.11 (s, 1H), 4.64 (d, 1H, *J* = 10.8 Hz), 4.34 (t, 1H, *J* = 9.6 Hz), 4.22–4.20 (m, 1H), 3.27 (dd, 1H, *J* = 9.6, 16.2 Hz), 3.18 (dd, 1H, *J* = 5.1, 16.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.3, 156.5, 154.2, 153.7, 150.1, 146.0, 140.8, 140.6, 137.2, 130.1, 128.7 (2C), 127.3, 127.2, 127.0 (2C), 124.3, 120.6, 119.8, 119.5, 115.2, 66.8, 42.0, 27.3; HRMS-ESI-TOF *m/z* 383.1393 (M + H^+, $C_{24}H_{18}N_2O_3$ requires 383.1390).

The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 50% *i*-PrOH/hexanes, 7 mL/min, α = 1.19).

(*R*)-**45**: $[\alpha]^{23}_D$ +5.4 (*c* 0.10, THF).

(*S*)-**45**: $[\alpha]^{23}_D$ –5.4 (*c* 0.10, THF).

(7-(Benzyloxy)chroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanone (46). Compound **46** was prepared from **42** (4.1 mg, 0.010 mmol) according to general procedure C. Preparative TLC (SiO_2, 3 × 30% EtOAc/hexanes) yielded **46** as a white solid (2.08 mg, 51%; 92% BRSM): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.68 (d, 1H, *J* = 4.8 Hz), 7.93 (s, 1H), 7.87 (d, 1H, *J* = 7.8 Hz), 7.83 (td, H, *J* = 1.2, 7.8 Hz), 7.43–7.31 (m, 6H), 7.01 (d, 1H, *J* = 8.4 Hz), 6.58 (dd, 1H, *J* = 3.0, 8.4 Hz), 6.50 (d, 1H, *J* = 1.8 Hz), 5.03 (s, 2H), 4.60–4.57 (m, 1H), 4.28–4.24 (m, 1H), 4.16–4.11 (m, 1H), 3.15 (dd, 1H, *J* = 9.9, 15.9 Hz), 3.08 (dd, 1H, *J* = 5.4, 15.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 187.5, 158.4, 156.5, 154.7, 153.8, 150.2, 146.1, 137.2, 137.0, 130.2, 128.6 (2C), 127.9, 127.5 (2C), 127.2,

124.3, 120.5, 112.7, 108.7, 102.6, 70.0, 66.7, 42.1, 27.1. HRMS- ESI-TOF *m/z* 413.1499 ($M + H^+$, $C_{25}H_{20}N_2O_4$ requires 413.1496).

The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 50% *i*-PrOH/hexanes, 7 mL/min, α = 1.07). Enantiopure samples were prepared from the corresponding enantiopure alcohol according to the procedure described above:

(*R*)-**46**: $[\alpha]^{23}_D$ –5.6 (*c* 0.16, THF).

(*S*)-**46**: $[\alpha]^{23}_D$ +5.5 (*c* 0.22, THF).

(7-Phenoxychroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanone (47). Compound **47** was prepared from (7-phenoxychroman-3-yl)(5-(pyridin-2-yl)oxazol-2-yl)methanol (**43**, 13.7 mg, 0.034 mmol) according to general method C. Preparative TLC (SiO_2, 3 × 30% EtOAc/hexanes) on the crude reaction mixture yielded **47** as a pale yellow solid (10.2 mg, 75%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.69 (d, 1H, *J* = 4.2 Hz), 7.93 (s, 1H), 7.88 (d, 1H, *J* = 7.8 Hz), 7.83 (td, H, *J* = 1.8, 7.8 Hz), 7.35–7.32 (m, 3H), 7.11–7.06 (m, 2H), 7.02 (d, 2H, *J* = 7.8 Hz), 6.59 (dd, 1H, *J* = 2.4, 7.8 Hz), 6.51 (d, 1H, *J* = 2.4 Hz), 4.60–4.57 (m, 1H), 4.30–4.27 (m, 1H), 4.18–4.13 (m, 1H), 3.19 (dd, 1H, *J* = 9.6, 16.2 Hz), 3.12 (dd, 1H, *J* = 5.4, 15.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 187.3, 157.0, 156.7, 156.5, 154.8, 153.8, 150.2, 146.1, 137.2, 130.4, 129.7 (2C), 127.2, 124.3, 123.3, 120.5, 119.0 (2C), 115.2, 111.8, 107.0, 66.7, 42.0, 27.1; HRMS-ESI-TOF *m/z* 399.1340 ($M + H^+$, $C_{24}H_{18}N_2O_6$ requires 399.1390).

The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 50% *i*-PrOH/hexanes, 7 mL/min, α = 1.21).

(*R*)-**47**: $[\alpha]^{23}_D$ +5.5 (*c* 0.044, THF).

(*S*)-**47**: $[\alpha]^{23}_D$ –4.2 (*c* 0.063, THF).

Methyl 6-(2-(7-Phenoxychroman-3-carbonyl)oxazol-5-yl)picolinate (48). A stirred solution of **44** (43.6 mg, 0.0952 mmol) in CH_2Cl_2 (1.9 mL) was treated with Dess–Martin periodinane (80.7 mg, 0.190 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 2 h at which point it was diluted with EtOAc and saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ were added. Once the reaction mixture had clarified (~5 min), the organic layer was extracted twice, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and evaporated to give the crude product. Flash chromatography (SiO_2, 30–40% EtOAc/hexanes gradient elution) yielded **48** as a yellow solid (35.1 mg, 81%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.13 (d, 1H, *J* = 7.8 Hz), 8.07 (s, 1H), 8.03 (d, 1H, *J* = 7.2 Hz), 7.99 (t, 1H, *J* = 7.8 Hz), 7.33 (dd, 2H, *J* = 7.2, 8.4 Hz), 7.11–7.06 (m, 2H), 7.02 (d, 2H, *J* = 7.2 Hz), 6.59 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.51 (d, 1H, *J* = 2.4, Hz), 4.58–4.56 (m, 1H), 4.31–4.28 (m, 1H), 4.18–4.14 (m, 1H), 4.04 (s, 3H), 3.19 (dd, 1H, *J* = 9.6, 16.2 Hz), 3.12 (dd, 1H, *J* = 5.4, 15.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 187.3, 165.1, 157.0, 156.7, 156.6, 154.8, 152.8, 148.6, 146.4, 138.4, 130.4, 129.7 (2C), 128.2, 125.3, 123.4, 123.3, 119.0 (2C), 115.1, 111.8, 107.0, 66.7, 53.1, 42.0, 27.1; HRMS-ESI-TOF *m/z* 457.1384 ($M + H^+$, $C_{26}H_{20}N_2O_6$ requires 457.1394).

The two enantiomers were prepared from the corresponding enantiopure alcohols as described above.

(*R*)-**48**: $[\alpha]^{23}_D$ +13 (*c* 0.088, THF).

(*S*)-**48**: $[\alpha]^{23}_D$ –13 (*c* 0.035, THF).

Oxazol-2-yl(7-phenylchroman-3-yl)methanone (49). Compound **49** was prepared from oxazol-2-yl(7-phenylchroman-3-yl)methanol (**28**, 22.7 mg, 0.074 mmol) according to general method C. The crude mixture was purified by flash chromatography (SiO_2, 10–40% EtOAc/hexanes gradient elution) and the product was isolated as a white solid (13.5 mg, 60%; 90% BRSM): ^{1}H NMR

($CDCl_3$, 600 MHz) δ 7.88 (s, 1H), 7.57 (d, 1H, *J* = 7.8 Hz), 7.44–7.40 (m, 3H), 7.35–7.32 (m, 1H), 7.19 (d, 1H, *J* = 7.8 Hz), 7.15 (d, 1H, *J* = 7.8 Hz), 7.10 (s, 1H), 4.62 (d, 1H, *J* = 10.8 Hz), 4.31 (t, 1H, *J* = 9.9 Hz), 4.17–4.15 (m, 1H), 3.24 (dd, 1H, *J* = 10.2, 16.2 Hz), 3.15 (dd, 1H, *J* = 4.8, 16.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.4, 157.2, 154.2, 142.1, 140.8, 140.6, 130.0, 129.4, 128.7 (2C), 127.3, 127.0 (2C), 119.8, 119.4, 115.2, 66.7, 42.1, 27.2; HRMS-ESI-TOF *m/z* 306.1125 (M + H^+, $C_{19}H_{15}NO_3$ requires 306.1124).

The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 10% *i*-PrOH/hexanes, 7 mL/min, α = 1.14).

(*R*)-**49**: $[\alpha]^{23}_D$ +5.5 (*c* 0.063, THF).

(*S*)-**49**: $[\alpha]^{23}_D$ –5.1 (*c* 0.063, THF).

(7-(Benzyloxy)chroman-3-yl)(oxazol-2-yl)methanone (50). Compound **50** was prepared from **29** (22.1 mg, 0.066 mmol) according to general method C. The crude mixture was purified by flash chromatography (SiO_2, 10–20% EtOAc/hexanes gradient elution) and **50** was isolated as a yellow solid (19.2 mg, 87%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.87 (s, 1H), 7.43–7.37 (m, 5H), 7.33–7.31 (m, 1H), 7.00 (d, 1H, *J* = 8.4 Hz), 6.57 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.49 (d, 1H, *J* = 2.4 Hz), 5.02 (s, 2H), 4.57–4.53 (m, 1H), 4.24–4.21 (m, 1H), 4.11–4.08 (m, 1H), 3.12 (dd, 1H, *J* = 9.6, 15.6 Hz), 3.06 (dd, 1H, *J* = 4.8, 16.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 187.5, 158.3, 157.2, 154.6, 142.0, 137.0, 130.1, 129.3, 128.6 (2C), 127.9, 127.5 (2C), 112.7, 108.7, 102.5, 70.0, 66.6, 42.2, 26.9. HRMS-ESI-TOF *m/z* 336.1235 (M + H^+, $C_{20}H_{17}NO_4$ requires 336.1230).

The enantiomers were separated using an analytical chiral phase HPLC column (Diacel ChiralPak AS, 10 μm, 0.46 × 25 cm, 5% *i*-PrOH/hexanes, 1 mL/min, α = 1.32).

(*R*)-**50**: $[\alpha]^{23}_D$ +19 (*c* 0.036, THF).

(*S*)-**50**: $[\alpha]^{23}_D$ –19 (*c* 0.037, THF).

Oxazol-2-yl(7-phenoxychroman-3-yl)methanone (51). Compound **51** was prepared from oxazol-2-yl(7-phenoxychroman-3-yl)methanol (**30**, 16.5 mg, 0.051 mmol) according to general method C. The crude mixture was purified by flash chromatography (SiO_2, 20–50% EtOAc/hexanes gradient elution) and **51** was isolated as a white solid (15.2 mg, 92%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.87 (s, 1H), 7.39 (s, 1H), 7.33 (t, 2H, *J* = 7.2 Hz), 7.09 (t, 1H, *J* = 7.2 Hz), 7.07 (d, 1H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 7.8 Hz), 6.58 (d, 1H, *J* = 7.8 Hz), 6.50 (s, 1H), 4.55 (d, 1H, *J* = 10.8 Hz), 4.25 (t, 1H, *J* = 9.9 Hz), 4.10 (d, 1H, *J* = 3.6 Hz), 3.18–3.14 (m, 1H), 3.11–3.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 187.3, 157.2, 157.1, 156.7, 154.8, 142.1, 130.4, 129.7 (2C), 129.4, 123.3, 119.0 (2C), 115.1, 111.8, 106.9, 66.6, 42.0, 27.0; HRMS-ESI-TOF *m/z* 322.1076 (M + H^+, $C_{19}H_{15}NO_4$ requires 322.1074).

2-(((*tert*-Butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)-5-iodooxazole (52). A solution of **33** (56.8 mg, 0.130 mmol) in anhydrous THF (2.0 mL) was cooled to –78 °C. *n*-BuLi (51 μL, 2.45 M solution in THF, 0.125 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred at that temperature for 1 h. The reaction mixture was then treated with a solution of I_2 (35.5 mg, 0.145 mmol, 1.1 equiv) in anhydrous THF (1 mL) that was added slowly and the reaction mixture was allowed to stir for 5 min. The reaction mixture was then allowed to warm to room temperature before it was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and evaporated. Flash chromatography (SiO_2, 2–10% EtOAc/hexanes gradient elution) yielded **52** as a clear resin (59.2 mg, 81%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33–7.30 (m, 4H), 7.12 (s, 2H), 7.09–7.07 (m, 5H), 6.91 (d, 1H, *J* = 7.8 Hz), 6.55–6.51 (m, 2H), 6.48–6.46 (m, 2H), 4.84 (d, 1H, *J* = 6.6 Hz), 4.70 (d, 1H, *J* = 8.4 Hz), 4.36–4.34 (m, 1H), 4.18–4.11 (m, 2H), 3.89–3.84 (m, 1H), 2.91–2.81 (m, 2H), 2.65–2.58 (m, 3H), 2.45–2.42 (m, 1H), 0.87 (s, 18H), 0.07 (s, 3H), 0.01 (s, 3H), –0.11 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.4 (2C), 157.2

(2C), 156.4 (2C), 155.4, 155.1, 135.6, 135.5, 130.8, 130.6, 129.6 (4C), 123.2, 123.1,118.9 (2C), 118.8 (2C), 115.7, 115.2, 111.6, 111.5, 107.0, 106.9, 87.1, 87.0, 68.8, 68.4, 67.2, 66.7, 38.1, 37.6, 26.5, 25.8, 25.6 (6C), 18.1 (2C), –5.2,–5.3, –5.5 (2C).

(5-Iodooxazol-2-yl)(7-phenoxychroman-3-yl)methanol (53). Compound **53** was prepared from 2-(((*tert*-butyldimethylsilyl)oxy)(7-phenoxychroman-3-yl)methyl)-5-iodooxazole (**52**, 36.3 mg, 0.064 mmol) following general procedure D. The crude reaction mixture was purified by flash chromatography (SiO_2, 5–50% EtOAc/hexanes gradient elution) to give **53** as a white solid (23.6 mg, 82%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33–7.31 (m, 4H), 7.14 (s, 2H), 7.10–7.07 (m, 2H), 7.01–7.00 (m, 3H), 6.94 (d, 1H, *J* = 8.4 Hz), 6.54 (td, 2H, *J* = 2.4, 8.7 Hz), 6.47 (dd, 2H, *J* = 2.4, 7.8 Hz), 4.90–4.89 (m, 1H), 4.36–4.34 (m, 1H), 4.26–4.24 (m, 1H), 4.18 (dd, 1H, *J* = 7.5, 10.5 Hz), 3.98–3.95 (m, 1H), 2.95 (dd, 1H, *J* = 9.0, 16.2 Hz), 2.80–2.72 (m, 2H), 2.64–2.57 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5 (2C), 157.0 (2C), 156.6 (2C), 155.2, 155.0, 135.5, 135.4, 130.7, 130.6, 129.7 (2C), 123.2 (2C), 119.0 (2C), 118.9 (2C), 115.4, 115.0, 111.6, 106.9, 67.8, 67.6, 67.2, 66.6, 37.2, 37.1, 26.7, 25.2.

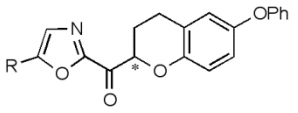
(5-Iodooxazol-2-yl)(7-phenoxychroman-3-yl)methanone (54). Compound **54** was prepared from (5-iodooxazol-2-yl)(7-phenoxychroman-3-yl)methanol (**53**, 23.6 mg, 0.053 mmol) according to general procedure C. The crude mixture was purified by flash chromatography (SiO_2, 5–30% EtOAc/hexanes gradient elution) and **54** was isolated as a pale yellow solid (16.3 mg, 69%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40 (s, 1H), 7.32 (t, 2H, *J* = 7.8 Hz), 7.09 (t, 1H, *J* = 7.2 Hz), 7.04 (d, 1H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 7.8 Hz), 6.58 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.49 (d, 1H, *J* = 2.4 Hz), 4.54–4.51 (m, 1H), 4.23–4.20 (m, 1H), 4.07–4.02 (m, 1H), 3.13 (dd, 1H, *J* = 9.6, 16.2 Hz), 3.05 (dd, 1H, *J* = 5.1, 15.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 186.0, 161.7, 157.0, 156.7, 154.7, 137.8, 130.4, 129.7 (2C), 123.3, 119.0 (2C), 115.0, 111.8, 106.9, 94.7, 66.6, 41.6, 27.0; HRMS-ESI-TOF *m/z* 448.0036 ($M + H^+$, $C_{19}H_{14}INO_4$ requires 448.0040).

The enantiomers were separated using a semipreparative chiral phase HPLC column (Diacel ChiralPak AD, 10 μm, 2 × 25 cm, 20% *i*-PrOH/hexanes, 7 mL/min, α = 1.18).

(*R*)-**54**: $[\alpha]^{23}_D$ +2.6 (*c* 0.18, THF).

(*S*)-**54**: $[\alpha]^{23}_D$ –2.9 (*c* 0.13, THF).

The structure and absolute stereochemistry of (*S*)-**54** (CCDC 975738) was confirmed with a single-crystal X-ray structure determination conducted on a colorless needle grown from EtOAc/CH_2Cl_2.



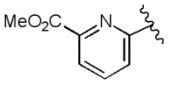
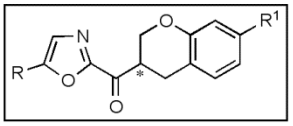
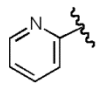
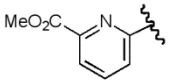
R	Enant 1	Enant 2	Compd
–H	17 ± 0.1	31 ± 1.2	**16**
	36 ± 2.5	120 ± 4.2	**14**
	94 ± 3.5	210 ± 6.8	**15**

Figure 3. FAAH inhibition, K_i (nM).



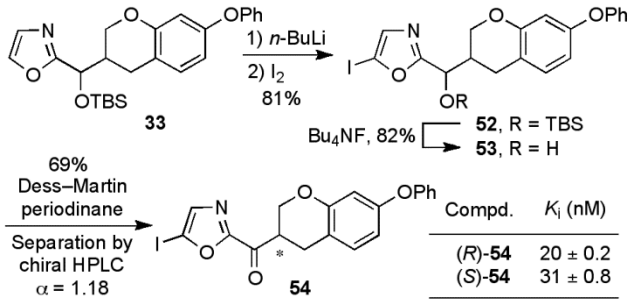
R	R^1 =	(*R*)	(*S*)	Compd	R^1 =	(*R*)	(*S*)	Compd	R^1 =	(*R*)	(*S*)	Compd
–H		20 ± 0.15	32 ± 1.6	**49**		20 ± 0.6	16 ± 1.6	**50**		33[a]		**51**
		23 ± 0.8	11 ± 0.5	**45**		18 ± 1.2	17 ± 2.0	**46**		18 ± 1.5	27 ± 3.3	**47**
										41 ± 2.6	333 ± 24	**48**

[a]Racemate. Enantiomers not separable

Figure 5. FAAH inhibition, K_i (nM).

Compd.	FAAH
(*R*)-**47**	90 ± 6.8
(*S*)-**47**	460 ± 24
14-enant 1	70 ± 8.2
14-enant 2	50 ± 5.0

Figure 7. ABPP screen, IC_{50} (nM)



Scheme 3

Inhibitor Purity Analysis[a]

Compd	Purity
14-enant 1	98
14-enant 2	98
15-enant 1	98
15-enant 2	98
16-enant 1	98
16-enant 2	98
(*R*)-**45**	98
(*S*)-**45**	98
(*R*)-**46**	99
(*S*)-**46**	99
(*R*)-**47**	98
(*S*)-**47**	98
(*R*)-**48**	98
(*S*)-**48**	98
(*R*)-**49**	99
(*S*)-**49**	98
(*R*)-**50**	98
(*S*)-**50**	98
51	98
(*R*)-**54**	98
(*S*)-**54**	98

[a]The purity of each inhibitor (>95%) was determined on an Agilent 1100 LC/MS instrument on a ZORBAX SB-C18, 3.5 mm × 50 mm, with a flow rate of 0.75 mL/min and detection at 220 and 254 nm, with a 10–98% acetonitrile/water/0.1% formic acid gradient and a 50–98% acetonitrile/water/0.1% formic acid gradient.