Supporting information

Synthesis and biological evaluation of 3-nitro-4-chromanone derivatives as potential antiproliferative agents for castration-resistant prostate cancer

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Table of Contents

1. General experimental details ................................................................................................S2
2. General procedure and spectral data .....................................................................................S2
3. Biology materials and methods ..........................................................................................S18
4. NMR charts ........................................................................................................................S20
1. General experimental details

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates, visualized under UV. Flash column chromatography was performed using Qingdao Haiyang 200-300 mesh silica gel. Proton, carbon, and fluorine magnetic resonance spectra (\(^1\text{H} \text{NMR}, ~\text{\(^13\text{C} \text{NMR} \) and \(^{19}\text{F} \text{NMR}\)) were recorded on a Bruker Ascend or AVANCE III spectrometer (\(^1\text{H} \text{NMR at 400 MHz, 500 MHz or 600 MHz; \(^13\text{C} \text{NMR at 100 MHz, 125 MHz or 150 MHz; and \(^{19}\text{F} \text{NMR at 375 MHz or 565 MHz). Chemical shifts (\(\delta\)) are reported in ppm from the solvent resonance as the internal standard (\(^1\text{H} \text{NMR: CDCl}_3 \text{ at 7.26 ppm, DMSO-}
\text{\(\text{d}_6\text{ at 2.50 pm; \(^13\text{C} \text{NMR: CDCl}_3 \text{ at 77.0 ppm, DMSO-\(\text{d}_6\text{ at 39.5 pm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were performed using a Bruker microOTOF II high resolution mass spectrometer. Melting points were uncorrected and were recorded on a WRR melting point apparatus.

2. General procedure and spectral data

2.1 General Procedure

\[ \text{Scheme S1 General synthetic route of compound 3-43. Reagent and conditions: (a) 6N HCl/1,4-dioxane, 100 °C, 95% for 3a; (b) alcohols, SOCl}_2, 1,4-dioxane, 70 °C, 68-81%; (c) amines, HOBr, EDCI, DIPEA, DCM, rt, 64-88%.} \]

Compounds 2 were synthesized according to procedures which were previously described by our group\(^1\).

**General procedure for the synthesis of 3**

A solution of Compound 2 (2 mmol, 1 equiv.) in 10 mL of 1,4-dioxane and 10 mL of 6 N hydrochloric acid was heated to reflux at 100 °C for 12 h under nitrogen atmosphere. The reaction was monitored by means of TLC analysis. It was then cooled to room temperature. The reaction mixture was extracted with EtOAc. The combined organic phase was dried over Na\(_2\)SO\(_4\), reduced to a residue. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate/acetic acid = 100:20:1) to afford the title compound 3.
General procedure for the synthesis of 6 and 10

To a suspension of crude carboxylic acid 3a and alcohol substrate (2 mmol, 2 equiv.) in 1,4-dioxane (10 mL), thionyl chloride (3 mmol, 3 equiv.) was added and the resulting mixture was stirred at 70 °C for 4 h. The reaction mixture was cooled to 0 °C and water (2 mL) were added. The reaction mixture was concentrated and the residue was distributed between EtOAc (30 mL) and water (30 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (30 mL) and the combined organic layers were dried over Na₂SO₄, filtered and evaporated in vacuo to a residue. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate) to afford esters 6 and 10.

General procedure for the synthesis of 11-43

To the solution of carboxylic acid 3 (1 mmol, 1 equiv.) in DCM (10 mL) was added HOBt (162 mg, 1.2 mmol, 1.2 equiv.), EDCI (230 mg, 1.2 mmol, 1.2 equiv.), DIPEA (322 mg, 2.5 mmol, 2.5 equiv.) and amine substrate (1.2 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 18 h. It was then quenched with NH₄Cl solution, extracted with EtOAc. The combined organic phase was dried over Na₂SO₄, reduced to a residue. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate) to afford the product amide 11-43.

Reference
1 H. Q. Chen, J. Xie, D. Xing, J. P. Wang, J. Tang, Z. F. Yi, F. Xia, W. W. Qiu and F. Yang, *Org. Biomol. Chem.*, 2019, 17, 1062.

2.2 Spectral Data of Products

**2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3a)**

White solid, 95% yield. m.p. 132-135 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 12.81 (br, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.69 (dd, J = 8.0, 7.5 Hz, 1H), 7.23 (dd, J = 7.8, 7.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 5.26 (d, J = 10.2 Hz, 1H), 3.25 (d, J = 16.6 Hz, 1H), 2.53 (dd, J = 16.7, 10.2 Hz, 1H), 1.81 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 182.54, 170.57, 160.09, 137.18, 127.79, 122.96, 119.67, 117.88, 90.28, 79.01, 35.10, 15.81. HRMS (ESI): Calcd for C₁₂H₁₁NNaO₆ [M+Na]⁺: 288.0479. Found: 288.0496.

**prop-2-yn-1-yl 2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (6)**

Colorless oil, 68% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (dd, J = 7.9, 1.3 Hz, 1H), 7.61-7.57 (m, 1H), 7.17-7.14 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.61 (dd, J = 10.2, 2.3 Hz, 1H), 4.77 (d, J = 2.4 Hz, 2H), 2.93 (dd, J = 16.2, 10.2 Hz, 1H), 2.52-2.48 (m, 2H), 1.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 184.72, 167.67, 159.52, 137.54, 128.45, 123.22 (2C), 118.14, 92.01, 77.67, 76.88, 75.50, 52.83, 34.22, 14.28. HRMS (ESI): Calcd for C₁₅H₁₉NNaO₆ [M+Na]⁺: 326.0635. Found: 326.0643.

**benzyl 2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (10)**

Colorless oil, 77% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 7.2 Hz, 1H), 7.60-
7.56 (m, 1H), 7.37 (s, 5H), 7.15 (dd, J = 7.6, 7.4 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 5.63 (dd, J = 10.1, 1.9 Hz, 1H), 5.22-5.21 (m, 2H), 2.93 (dd, J = 16.0, 10.3 Hz, 1H), 2.50 (dd, J = 16.0, 1.9 Hz, 1H), 1.75 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 184.85, 168.24, 159.55, 137.49, 135.18, 128.64 (2C), 128.53, 128.46, 128.37 (2C), 123.17, 118.16, 118.11, 92.07, 77.90, 67.22, 34.50, 14.30. HRMS (ESI): Calcd for C15H12NNaO6 [M+Na]+: 378.0948. Found: 378.0933.

2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (11)
White solid, 87% yield. m.p. 179-181 °C. 1H NMR (400 MHz, DMSO-d6) δ 7.88 (d, J = 7.8 Hz, 1H), 7.73 (dd, J = 7.9, 7.6 Hz, 1H), 7.54 (s, 1H), 7.23 (dd, J = 7.6, 7.5 Hz, 1H), 7.16-7.12 (m, 2H), 5.53 (dd, J = 7.5, 2.2 Hz, 1H), 2.68 (dd, J = 15.5, 9.8 Hz, 1H), 2.35 (dd, J = 15.6, 2.5 Hz, 1H), 1.70 (s, 3H). 13C NMR (100 MHz, DMSO-d6) δ 184.71, 169.00, 159.17, 138.16, 127.71, 123.13, 118.34, 117.86, 92.22, 78.82, 34.28, 14.70. HRMS (ESI): Calcd for C13H13N2NaO5 [M+Na]+: 301.0795. Found: 301.0787.

N-methyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (12)
White solid, 83% yield. m.p. 128-130 °C. 1H NMR (400 MHz, CDCl3) δ 7.99 (dd, J = 7.9, 1.3 Hz, 1H), 7.57-7.53 (m, 1H), 7.15 (dd, J = 7.2, 7.2 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 5.83 (s, 1H), 4.97 (dd, J = 9.1, 2.7 Hz, 1H), 2.90 (d, J = 4.8 Hz, 3H), 2.88-2.86 (m, 1H), 2.68 (dd, J = 15.3, 9.2 Hz, 1H), 1.83 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 169.91, 167.64, 159.45, 137.47, 128.44, 123.14, 118.30, 118.17, 92.17, 78.45, 35.90, 26.66, 14.54. HRMS (ESI): Calcd for C13H13N2NaO5 [M+Na]+: 315.0951. Found: 315.0970.

N-ethyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (13)
White solid, 80% yield. m.p. 134-136 °C. 1H NMR (400 MHz, CDCl3) δ 7.96 (dd, J = 7.9, 1.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.15 (dd, J = 7.6, 7.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 5.64 (dd, J = 9.9, 2.3 Hz, 1H), 5.58 (s, 1H), 3.35 (dq, J = 7.2, 2.4 Hz, 2H), 2.62 (dd, J = 14.9, 9.9 Hz, 1H), 2.34 (dd, J = 15.0, 2.2 Hz, 1H), 1.75 (s, 3H), 1.17 (t, J = 7.3 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 185.00, 166.96, 159.50, 137.47, 128.31, 123.05, 118.21, 118.12, 92.22, 78.50, 35.92, 34.72, 14.64, 14.47. HRMS (ESI): Calcd for C14H14N2NaO5 [M+Na]+: 315.0970. Found: 315.0970.

2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)-N-(prop-2-yn-1-yl)acetamide (14)
White solid, 82% yield. m.p. 101-102 °C. 1H NMR (400 MHz, CDCl3) δ 7.91 (dd, J = 7.9, 1.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.13 (dd, J = 7.6, 7.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.39 (t, J = 4.8 Hz, 1H), 5.62 (dd, J = 10.0, 2.1 Hz, 1H), 4.07 (dd, J = 4.7, 1.9 Hz, 2H), 2.72 (dd, J = 15.1, 10.0 Hz, 1H), 2.36 (dd, J = 15.1, 2.0 Hz, 1H), 2.23 (t, J = 2.4 Hz, 1H), 1.72 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 184.93, 167.08, 159.43, 137.55, 128.36, 123.15, 118.19, 118.15, 92.19, 78.96, 78.24, 71.90, 35.66, 29.46, 14.42. HRMS (ESI): Calcd for C15H14N2NaO5 [M+Na]+: 325.0795. Found: 325.0785.

N-butyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (15)
White solid, 78% yield. m.p. 106-108 °C. 1H NMR (400 MHz, CDCl3) δ 7.95 (d, J = 7.8 Hz, 1H), 7.60-7.56 (m, 1H), 7.15 (dd, J = 7.6, 7.5 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.65-5.62
N-(tert-butyl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (16)
White solid, 78% yield. m.p. 192-193 °C. 1H NMR (400 MHz, CDCl3) δ 7.96 (d, J = 7.9 Hz, 1H), 7.60-7.57 (m, 1H), 7.15 (dd, J = 7.6, 7.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.61 (dd, J = 9.9, 2.4 Hz, 1H), 5.42 (s, 1H), 2.54 (dd, J = 14.8, 9.9 Hz, 1H), 2.28 (dd, J = 14.8, 2.4 Hz, 1H), 1.74 (s, 3H), 1.37 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 184.86, 166.16, 159.46, 137.41, 128.46, 123.10, 118.47, 118.07, 92.13, 78.84, 51.89, 36.90, 28.71 (3C), 14.68. HRMS (ESI): Calcd for C16H20N2NaO5 [M+Na]+: 343.1264. Found: 343.1257.

N-octyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (17)
White solid, 82% yield. m.p. 93-95 °C. 1H NMR (400 MHz, CDCl3) δ 7.95 (d, J = 7.8 Hz, 1H), 7.58 (dd, J = 7.6, 7.4 Hz, 1H), 7.14 (dd, J = 7.8, 7.3 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.67 (s, 1H), 5.63 (dd, J = 10.1, 2.4 Hz, 1H), 3.33-3.26 (m, 2H), 2.62 (dd, J = 14.8, 10.1 Hz, 1H), 2.33 (dd, J = 14.8, 2.4 Hz, 1H), 1.74 (s, 3H), 1.30-1.27 (m, 12H), 0.87 (t, J = 6.4 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 184.88, 166.91, 159.43, 137.43, 128.44, 123.12, 118.10, 92.15, 78.60, 39.91, 36.09, 31.75, 29.48, 29.20 (2C), 26.83, 22.61, 14.58, 14.07. HRMS (ESI): Calcd for C20H28N2NaO5 [M+Na]+: 399.1890. Found: 399.1902.

N-cyclohexyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (18)
White solid, 82% yield. m.p. 142-145 °C. 1H NMR (400 MHz, CDCl3) δ 7.96 (dd, J = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.62 (dd, J = 10.0, 1.0 Hz, 1H), 2.59 (dd, J = 14.8, 2.5 Hz, 1H), 1.98-1.90 (m, 2H), 1.75 (s, 3H), 1.72-1.70 (m, 2H), 1.41-1.34 (m, 2H), 1.22-1.11 (m, 4H). 13C NMR (100 MHz, CDCl3) δ 184.83, 165.97, 159.42, 137.43, 128.44, 123.11, 118.44, 118.09, 92.15, 78.72, 48.63, 36.25, 33.11, 32.96, 25.42, 24.76, 24.73, 14.64. HRMS (ESI): Calcd for C18H22N2NaO5 [M+Na]+: 369.1421. Found: 369.1439.

N-(adamantan-1-yl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (19)
White solid, 84% yield. m.p. 161-163 °C. 1H NMR (400 MHz, CDCl3) δ 7.95 (d, J = 7.7 Hz, 1H), 7.58 (dd, J = 7.5, 7.2 Hz, 1H), 7.14 (dd, J = 7.4, 7.4 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 5.59 (d, J = 9.3 Hz, 1H), 5.29 (s, 1H), 2.55 (dd, J = 14.5, 10.0 Hz, 1H), 2.28 (dd, J = 14.7, 2.5 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.74 (s, 3H), 1.68-1.68 (m, 6H). 13C NMR (100 MHz, CDCl3) δ 184.89, 165.90, 159.47, 137.39, 128.42, 123.06, 118.45, 118.11, 92.16, 78.85, 52.56, 41.54 (3C), 36.95, 36.22 (3C), 29.35 (3C), 14.68. HRMS (ESI): Calcd for C22H26N2NaO5 [M+Na]+: 421.1734. Found: 421.1748.

2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)-N-phenylacetamide (20)
White solid, 68% yield. m.p. 91-93 °C. 1H NMR (400 MHz, CDCl3) δ 7.96 (d, J = 7.8 Hz, 1H), 7.60-7.56 (m, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.33 (dd, J = 7.8, 7.5 Hz, 2H), 7.15 (dd,
**N-benzyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (21)**

White solid, 85% yield. m.p. 187-189 °C. **1H NMR** (400 MHz, DMSO-d6) δ 8.63 (dd, J = 5.3, 5.2 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.74 (dd, J = 8.2, 7.3 Hz, 1H), 7.35 (d, J = 7.4, 7.4 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 7.24 (dd, J = 7.6, 7.6 Hz, 2H), 7.08 (d, J = 8.4 Hz, 1H), 5.59 (d, J = 9.9 Hz, 1H), 4.38 (dd, J = 15.2, 6.0 Hz, 1H), 4.26 (dd, J = 15.2, 5.5 Hz, 1H), 2.79 (dd, J = 15.1, 10.2 Hz, 1H), 2.49 (dd, J = 15.1, 1.6 Hz, 1H), 1.72 (s, 3H). **13C NMR** (100 MHz, DMSO-d6) δ 184.57, 167.14, 159.05, 139.06, 138.19, 128.30 (2C), 127.76, 127.15 (2C), 126.86, 123.18, 118.23, 117.93, 92.18, 79.00, 42.24, 34.58, 14.74. HRMS (ESI): Calcd for C18H15N3O5S [M+Na]+: 377.1108. Found: 377.1112.

**2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)-N-(thiazol-2-yl)acetamide (22)**

Prepared according to the general procedure B to provide the title compound as a yellow solid, 73% yield. m.p. 182-183 °C. **1H NMR** (400 MHz, CDCl3) δ 12.29 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.58-7.54 (m, 1H), 7.37 (d, J = 3.5 Hz, 1H), 7.15 (dd, J = 7.6, 7.4 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.80 (dd, J = 9.9, 1.9 Hz, 1H), 3.05 (dd, J = 15.4, 10.0 Hz, 1H), 2.68 (dd, J = 15.4, 1.9 Hz, 1H), 1.82 (s, 3H). **13C NMR** (100 MHz, CDCl3) δ 184.52, 165.49, 159.68, 159.30, 137.59, 135.91, 128.47, 123.35, 118.27, 118.17, 114.52, 91.96, 77.84, 35.71, 14.72. HRMS (ESI): Calcd for C16H15N3O5S [M+Na]+: 370.0468. Found: 370.0474.

**2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)-N-(pyrimidin-2-yl)acetamide (23)**

Prepared according to the general procedure B to provide the title compound as a yellow solid, 72% yield. m.p. 217-219 °C. **1H NMR** (500 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.34 (s, 1H), 8.42 (dd, J = 2.5, 1.5 Hz, 1H), 8.39 (d, J = 2.5 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.73-7.70 (m, 1H), 7.24 (dd, J = 7.4, 7.3 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 5.67 (dd, J = 9.8, 2.7 Hz, 1H), 3.17 (dd, J = 15.9, 9.9 Hz, 1H), 2.81 (dd, J = 15.8, 2.7 Hz, 1H), 1.75 (s, 3H). **13C NMR** (125 MHz, DMSO-d6) δ 184.45, 167.34, 159.00, 148.35, 142.69, 140.09, 138.18, 136.22, 127.73, 123.24, 118.37, 117.88, 92.07, 78.36, 35.21, 14.74. HRMS (ESI): Calcd for C16H13N3O5S [M+Na]+: 365.0856. Found: 365.0864.

**N-(1H-indol-5-yl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (24)**

Prepared according to the general procedure B to provide the title compound as a yellow solid, 77% yield. m.p. 184-187 °C. **1H NMR** (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 9.94 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.85 (s, 1H), 7.72 (dd, J = 8.1, 7.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.31 (s, 1H), 7.24 (dd, J = 7.7, 7.4 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 6.38 (s, 1H), 5.66 (dd, J = 9.5, 2.3 Hz, 1H), 2.94 (dd, J = 15.4, 9.7 Hz, 1H), 2.67 (dd, J = 15.4, 2.2 Hz, 1H), 1.77 (s, 3H). **13C NMR** (100 MHz, DMSO-d6) δ 184.67, 165.25, 159.16, 138.20, 132.83, 130.75, 127.75, 127.43, 126.01, 123.20, 118.39, 117.94, 114.73, 111.23, 91.96, 77.84, 35.71, 14.72. HRMS (ESI): Calcd for C18H15N3O5S [M+Na]+: 377.1108. Found: 377.1112.
N-(benzo[d]thiazol-2-yl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (25)

White solid, 79% yield. m.p. 122-125 °C. ¹H NMR (500 MHz, CDCl₃) δ 12.41 (brs, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.54 (dd, J = 7.4, 7.4 Hz, 1H), 7.49 (dd, J = 7.7, 7.7 Hz, 1H), 7.38 (dd, J = 7.7, 7.5 Hz, 1H), 7.10 (dd, J = 7.7, 7.5 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.76 (d, J = 9.9 Hz, 1H), 2.95 (dd, J = 15.5, 10.2 Hz, 1H), 2.61 (d, J = 15.5 Hz, 1H), 1.45 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 184.51, 166.47, 159.93, 159.19, 147.18, 137.54, 131.81, 128.43, 126.82, 124.61, 123.33, 122.00, 120.10, 118.02, 117.93, 91.91, 77.63, 36.12, 14.16. HRMS (ESI): Calcd for C₁₀H₇N₃NaO₅ [M+Na]+: 420.1060. Found: 420.1071.

N′-(benzo[d]thiazol-2-yl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetohydrazide (26)

White solid, 72% yield. m.p. 208-210 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.97 (d, J = 7.7 Hz, 1H), 7.82 (dd, J = 11.9, 8.4 Hz, 2H), 7.58 (dd, J = 7.3, 7.3 Hz, 1H), 7.46 (dd, J = 7.6, 7.0 Hz, 1H), 7.34 (dd, J = 7.3, 7.3 Hz, 1H), 7.15 (dd, J = 7.5, 7.4 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 5.83 (d, J = 9.3 Hz, 1H), 4.86 (s, 2H), 3.73 (dd, J = 16.6, 9.8 Hz, 1H), 2.91 (d, J = 16.7 Hz, 1H), 1.86 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 185.07, 169.87, 159.87, 159.75, 147.64, 137.46, 133.74, 128.47, 126.30, 124.41, 123.10, 121.49, 121.39, 118.25, 118.22, 92.33, 77.49, 34.19, 14.57. HRMS (ESI): Calcd for C₁₉H₁₆N₄NaO₄S [M+Na]+: 435.0734. Found: 435.0739.

N-cyclohexyl-N-methyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (27)

White solid, 83% yield. m.p. 88-90 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 7.7 Hz, 1H), 7.58-7.54 (m, 1H), 7.15-7.11 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 5.78-5.75 (m, 1H), 4.48-4.44 (m, 0.6H), 3.43-3.38 (m, 0.4H), 2.96-2.88 (m, 1H), 2.86 (s, 1.2H), 2.82 (s, 1.8H), 2.35-2.29 (m, 1H), 1.86-1.81 (m, 2H), 1.78 (s, 3H), 1.68-1.63 (m, 4H), 1.40-1.08 (m, 4H), reflecting an amide conformer mixture in about 3:2 ratio. ¹³C NMR (100 MHz, CDCl₃) δ 185.28, 166.52, 159.90, 137.32, 128.36, 122.88, 118.25, 92.44, 78.43, 56.83, 52.90, 33.39, 32.72, 29.81, 29.74, 29.55, 27.66, 25.13, 14.73. HRMS (ESI): Calcd for C₁₉H₁₆N₄NaO₄S [M+Na]+: 383.1577. Found: 383.1589.

N,N-dimethyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (28)

White solid, 87% yield. m.p. 87-89 °C. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.00 (d, J = 7.9, 1.4 Hz, 1H), 7.57-7.52 (m, 1H), 7.14 (dd, J = 7.8, 7.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 5.13 (dd, J = 8.0, 2.7 Hz, 1H), 3.11 (s, 3H), 3.04 (s, 3H), 3.03 (dd, J = 16.3, 8.1 Hz, 1H), 2.89 (dd, J = 16.4, 2.6 Hz, 1H), 1.83 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 182.61, 168.10, 160.76, 136.79, 128.39, 122.89, 119.66, 118.07, 89.79, 80.20, 37.33, 35.90, 33.79, 16.59. HRMS (ESI): Calcd for C₁₄H₁₈N₂NaO₅ [M+Na]+: 315.0951. Found: 315.0970.

N-cyclopentyl-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (29)

White solid, 67% yield. m.p. 203-205 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (dd, J = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 7.01 (d, J = 8.3 Hz, 1H), 5.62 (dd, J = 8.3, 1.6 Hz, 1H), 3.46-3.38 (m, 1H), 3.37-3.03 (m, 1H), 2.98 (s, 1.2H), 2.91 (s, 1.8H), 2.51-2.43 (m, 1H), 2.07 (s, 3H), 1.86-1.81 (m, 2H), 1.78 (s, 3H), 1.68-1.63 (m, 4H), 1.40-1.08 (m, 4H), reflecting an amide conformer mixture in about 3:2 ratio. ¹³C NMR (100 MHz, CDCl₃) δ 185.28, 166.52, 159.90, 137.32, 128.36, 122.88, 118.25, 92.44, 78.43, 56.83, 52.90, 33.39, 32.72, 29.81, 29.74, 29.55, 27.66, 25.13, 14.73. HRMS (ESI): Calcd for C₁₄H₁₈N₂NaO₅ [M+Na]+: 315.0951. Found: 315.0970.
10.0, 2.4 Hz, 1H), 5.56-5.55 (m, 1H), 4.30-4.21 (m, 1H), 2.60 (dd, J = 14.9, 10.0 Hz, 1H), 2.32 (dd, J = 14.9, 2.4 Hz, 1H), 2.04-1.99 (m, 2H), 1.75 (s, 3H), 1.65-1.63 (m, 6H). \(^{13}C\) NMR (150 MHz, CDCl\(_3\)) \(\delta\) 184.84, 166.50, 159.41, 137.45, 128.46, 123.13, 118.42, 118.08, 92.14, 78.67, 51.59, 36.13, 33.15, 32.98, 23.66 (2C), 14.63. HRMS (ESI): Calcd for C\(_{17}\)H\(_{20}\)N\(_{2}\)NaO\(_{5}\) [M+Na]\(^+\): 355.1264. Found: 355.1266.

methyl (1R,4r)-4-(2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamido)cyclohexane-1-carboxylate (30)

White solid, 73% yield. m.p. 215-217 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96 (dd, J = 7.9, 1.6 Hz, 1H), 7.61-7.56 (m, 1H), 7.17-7.13 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.61 (dd, J = 10.0, 2.5 Hz, 1H), 5.43 (d, J = 8.1 Hz, 1H), 3.84-3.77 (m, 1H), 3.67 (s, 3H), 2.60 (dd, J = 14.9, 10.0 Hz, 1H), 2.33 (dd, J = 14.8, 2.4 Hz, 1H), 2.28-2.24 (m, 1H), 2.10-2.01 (m, 4H), 1.75 (s, 3H), 1.62-1.54 (m, 2H), 1.19-1.12 (m, 2H).

\(^{13}C\) NMR (150 MHz, CDCl\(_3\)) \(\delta\) 184.80, 175.58, 166.25, 159.39, 137.48, 128.49, 123.18, 118.38, 118.05, 92.13, 78.59, 51.72, 48.19, 42.25, 36.19, 32.11, 31.97, 27.63, 27.61, 14.59. HRMS (ESI): Calcd for C\(_{20}\)H\(_{24}\)N\(_{2}\)NaO\(_{7}\) [M+Na]\(^+\): 427.1476. Found: 427.1471.

N-(cyclohexylmethyl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (31)

White solid, 60% yield. m.p. 138-140 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96 (dd, J = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.67 (s, 1H), 5.63 (dd, J = 10.2, 2.3 Hz, 1H), 3.24-3.17 (m, 1H), 3.14-3.07 (m, 1H), 2.62 (dd, J = 14.8, 10.2 Hz, 1H), 2.35 (dd, J = 14.8, 2.2 Hz, 1H), 1.75 (s, 3H), 1.73-1.67 (m, 5H), 1.53-1.45 (m, 1H), 1.29-1.17 (m, 5H).

\(^{13}C\) NMR (150 MHz, CDCl\(_3\)) \(\delta\) 184.85, 167.00, 159.41, 137.44, 128.49, 123.15, 118.40, 118.05, 92.14, 78.70, 46.03, 37.88, 36.20, 30.71 (2C), 26.30, 25.74, 25.73, 14.60. HRMS (ESI): Calcd for C\(_{19}\)H\(_{24}\)N\(_{2}\)NaO\(_{5}\) [M+Na]\(^+\): 383.1577. Found: 383.1574.

N-(3,5-dimethyladamantan-1-yl)-2-((2R*,3R*)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (32)

White solid, 62% yield. m.p. 131-133 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96 (dd, J = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.67 (s, 1H), 5.63 (dd, J = 10.2, 2.3 Hz, 1H), 3.24-3.17 (m, 1H), 3.14-3.07 (m, 1H), 2.62 (dd, J = 14.8, 10.2 Hz, 1H), 2.35 (dd, J = 14.8, 2.2 Hz, 1H), 1.75 (s, 3H), 1.68-1.65 (m, 4H), 1.40-1.37 (m, 2H), 1.31-1.28 (m, 2H), 1.17-1.16 (m, 2H), 0.86 (s, 6H).

\(^{13}C\) NMR (150 MHz, CDCl\(_3\)) \(\delta\) 184.86, 165.99, 159.45, 137.41, 128.44, 123.08, 118.45, 118.12, 92.13, 78.82, 54.17, 50.46, 47.49, 47.47, 42.53 (2C), 40.09, 36.96, 32.40 (2C), 30.04, 30.00 (2C), 14.71. HRMS (ESI): Calcd for C\(_{24}\)H\(_{30}\)N\(_{2}\)NaO\(_{5}\) [M+Na]\(^+\): 449.2047. Found: 449.2054.

N-(adamantan-1-yl)-2-((2R*,3R*)-3-ethyl-3-nitro-4-oxochroman-2-yl)acetamide (33)

Hydrolysis of corresponding ester 2 (2 mmol, 1 equiv.) in 10 mL of 1,4-dioxane and 10 mL of 6 N hydrochloric acid gave the crude acid product according to general procedure for the synthesis of 3. Then it was used for next step directly to give title product following the general condensation procedure. White solid, 81% yield. m.p. 186-188 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.94 (d, J = 7.8 Hz, 1H), 7.57 (dd, J = 8.2, 7.3 Hz, 1H), 7.13 (dd, J = 7.7, 7.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 5.62 (dd, J = 9.9, 2.3 Hz, 1H), 5.23 (s, 1H), 2.51 (dd, J =
14.8, 10.1 Hz, 1H), 2.27 (dd, J = 14.9, 2.5 Hz, 1H), 2.18 (dd, J = 14.7, 7.3 Hz, 2H), 2.10-2.08 (m, 3H), 2.01-1.99 (m, 6H), 1.68-1.66 (m, 6H), 1.03 (t, J = 7.3 Hz, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 183.81, 165.94, 158.82, 137.21, 128.12, 122.87, 119.21, 118.11, 94.96, 79.26, 52.56, 41.52 (3C), 36.50, 36.21 (3C), 29.34 (3C), 21.93, 8.22. HRMS (ESI): Calcd for C\(_{23}\)H\(_{28}\)N\(_2\)O\(_5\) [M+Na]\(^+\): 435.1890. Found: 435.1866.

\(N\)-cyclohexyl-2-((2\(R^*,3R^*\))-3-ethyl-3-nitro-4-oxochroman-2-yl)acetamide (34)

Following the procedure for synthesis of 33. White solid, 78% yield. m.p. 156-158 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.94 (dd, J = 8.0, 1.6 Hz, 1H), 7.58-7.54 (m, 1H), 7.15-7.11 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.64 (dd, J = 10.4, 2.4 Hz, 1H), 3.84-3.76 (m, 1H), 2.56 (dd, J = 14.9, 10.2 Hz, 1H), 2.32 (dd, J = 14.8, 2.6 Hz, 1H), 2.21-2.16 (m, 2H), 1.96-1.88 (m, 2H), 1.73-1.68 (m, 2H), 1.60-1.59 (m, 1H), 1.42-1.31 (m, 2H), 1.18-1.09 (m, 3H), 1.03 (t, J = 7.4 Hz, 3H). \(^{13}C\) NMR (150 MHz, CDCl\(_3\)) \(\delta\) 183.79, 166.04, 158.78, 137.26, 128.11, 122.92, 119.17, 118.08, 94.98, 79.15, 48.62, 35.77, 33.08, 32.93, 25.38, 24.73, 24.72, 21.82, 8.22. HRMS (ESI): Calcd for C\(_{19}\)H\(_{24}\)N\(_2\)O\(_5\) [M+Na]\(^+\): 383.1577. Found: 383.1565.

\(N\)-(adamantan-1-yl)-2-((2\(R^*,3R^*\))-3-methyl-3-nitro-4-oxo-6-(trifluoromethyl)chroman-2-yl)acetamide (35)

Following the procedure for synthesis of 33. White solid, 64% yield. m.p. 115-117 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.29 (s, 1H), 7.78 (dd, J = 8.7, 1.8 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 5.37 (s, 1H), 4.98 (dd, J = 8.9, 2.9 Hz, 1H), 2.85 (dd, J = 15.2, 3.0 Hz, 1H), 2.62 (dd, J = 15.2, 9.0 Hz, 1H), 2.11-2.09 (m, 3H), 2.04-2.02 (m, 6H), 1.84 (s, 3H), 1.70-1.68 (m, 6H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 181.54, 166.40, 162.41, 133.07, 133.04, 126.25, 126.21, 119.45, 119.00, 89.39, 80.63, 52.72, 41.53 (3C), 38.13, 36.20 (3C), 29.34 (3C), 16.22. \(^{19}F\) NMR (375 MHz, CDCl\(_3\)) \(\delta\) -62.43. HRMS (ESI): Calcd for C\(_{23}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_5\) [M+Na]\(^+\): 489.1608. Found: 489.1633.

\(N\)-(adamantan-1-yl)-2-((2\(R^*,3R^*\))-6-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (36)

Following the procedure for synthesis of 33. White solid, 77% yield. m.p. 169-171 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.59 (dd, J = 7.8, 1.8 Hz, 1H), 7.33-7.28 (m, 1H), 7.02 (dd, J = 9.1, 4.0 Hz, 1H), 5.58 (dd, J = 9.6, 2.4 Hz, 1H), 5.25 (s, 1H), 2.53 (dd, J = 14.9, 9.7 Hz, 1H), 2.27 (dd, J = 14.9, 2.4 Hz, 1H), 2.08-2.6 (m, 3H), 2.01-1.99 (m, 6H), 1.73 (s, 3H), 1.68-1.65 (m, 6H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 184.19, 165.65, 157.99 (d, J = 243.3 Hz), 155.78, 125.06 (d, J = 24.5 Hz), 120.01 (d, J = 7.5 Hz), 119.19 (d, J = 7.0 Hz), 113.32 (d, J = 23.8 Hz), 91.93, 79.25, 52.65, 41.61 (3C), 36.80, 36.25 (3C), 29.40 (3C), 14.76. \(^{19}F\) NMR (375 MHz, CDCl\(_3\)) \(\delta\) -118.51. HRMS (ESI): Calcd for C\(_{25}\)H\(_{25}\)F\(_2\)N\(_2\)O\(_5\) [M+Na]\(^+\): 439.1640. Found: 439.1635.

\(N\)-(adamantan-1-yl)-2-((2\(R^*,3R^*\))-6-chloro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (37)

Following the procedure for synthesis of 33. White solid, 72% yield. m.p. 142-144 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.81 (d, J = 2.3 Hz, 1H), 7.44 (dd, J = 8.8, 2.4 Hz, 1H), 6.93
(d, J = 8.9 Hz, 1H), 5.46 (s, 1H), 4.65 (dd, J = 9.3, 2.0 Hz, 1H), 2.77 (dd, J = 15.0, 2.1 Hz, 1H), 2.55 (dd, J = 15.0, 9.5 Hz, 1H), 2.08-2.06 (m, 3H), 2.05-2.02 (m, 6H), 1.68-1.65 (m, 6H), 1.26 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 195.89, 168.14, 159.25, 136.44, 127.60, 127.00, 119.53, 118.85, 80.44, 72.30, 52.29, 41.62 (3C), 36.74, 36.28 (3C), 29.39 (3C), 18.15. HRMS (ESI): Calcd for C$_{22}$H$_{25}$ClN$_2$NaO$_5$ [M+Na]$^+$: 455.1344. Found: 455.1345.

$N$-(adamantan-1-yl)-2-((2$R^*$,3$R^*$)-6-bromo-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (38)

Following the procedure for synthesis of 33. White solid, 79% yield. m.p. 138-140 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.8, 2.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 5.59 (dd, J = 9.6, 2.4 Hz, 1H), 5.32 (s, 1H), 2.53 (dd, J = 14.9, 9.7 Hz, 1H), 2.28 (dd, J = 14.9, 2.4 Hz, 1H), 2.09-2.07 (m, 3H), 1.98- (s, 6H), 1.72 (s, 3H), 1.67-1.65 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 183.66, 165.59, 158.31, 140.01, 130.57, 119.81, 115.72, 91.70, 79.08, 52.61, 41.49 (3C), 36.89, 36.18 (3C), 29.32 (3C), 14.81. HRMS (ESI): Calcd for C$_{22}$H$_{25}$BrN$_2$NaO$_5$ [M+Na]$^+$: 499.0839. Found: 499.0817.

$N$-(adamantan-1-yl)-2-((2$R^*$,3$R^*$)-3,6-dimethyl-3-nitro-4-oxochroman-2-yl)acetamide (39)

Following the procedure for synthesis of 33. White solid, 82% yield. m.p. 119-121 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 5.54-5.52 (m, 1H), 5.41 (s, 1H), 2.57-2.51 (m, 1H), 2.32 (s, 3H), 2.24 (dd, J = 14.8, 2.5 Hz, 1H), 2.07-2.05 (m, 3H), 1.99-1.97 (m, 6H), 1.71 (s, 3H), 1.67-1.65 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 185.08, 166.04, 157.55, 138.52, 132.72, 127.78, 117.97, 117.85, 92.26, 78.78, 52.45, 41.46 (3C), 36.89, 36.19 (3C), 29.31 (3C), 20.39, 14.63. HRMS (ESI): Calcd for C$_{23}$H$_{28}$N$_2$NaO$_5$ [M+Na]$^+$: 435.1890. Found: 435.1903.

$N$-(adamantan-1-yl)-2-((2$R^*$,3$R^*$)-6-methoxy-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (40)

Following the procedure for synthesis of 33. White solid, 83% yield. m.p. 156-158 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (d, J = 2.9 Hz, 1H), 7.18 (dd, J = 2.9, 2.0 Hz, 1H), 6.59 (d, J = 9.0 Hz, 1H), 5.53 (dd, J = 9.9, 2.2 Hz, 1H), 5.26 (s, 1H), 3.82 (s, 3H), 2.53 (dd, J = 14.9, 9.9 Hz, 1H), 2.25 (dd, J = 14.9, 2.2 Hz, 1H), 2.09-2.07 (m, 3H), 2.04-2.00 (m, 6H), 1.74 (s, 3H), 1.68-1.65 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 185.01, 165.95, 155.19, 154.19, 126.83, 119.43, 118.42, 108.23, 92.30, 79.07, 55.88, 52.55, 41.57 (3C), 36.99, 36.24 (3C), 29.37 (3C), 14.72. HRMS (ESI): Calcd for C$_{23}$H$_{28}$N$_2$NaO$_6$ [M+Na]$^+$: 451.1840. Found: 451.1850.

$N$-(adamantan-1-yl)-2-((2$R^*$,3$R^*$)-5-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (41)

White solid, 54% yield. m.p. 76-78 °C. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.54-7.50 (m, 1H), 6.84-6.81 (m, 2H), 5.62 (dd, J = 9.7, 2.7 Hz, 1H), 5.24 (s, 1H), 2.52 (dd, J = 14.9, 9.6 Hz, 1H), 2.30 (dd, J = 14.9, 2.8 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.74 (s, 3H), 1.69-1.68 (m, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 181.89, 165.60, 162.29 (d, J = 267.9 Hz), 159.94 (d, J = 2.0 Hz), 137.50 (d, J = 11.6 Hz), 113.91 (d, J = 3.8 Hz), 110.47 (d, J = 20.4 Hz), 109.01
(d, J = 9.8 Hz), 92.11, 78.80, 52.65, 41.56 (3C), 36.72, 36.23 (3C), 29.37 (3C), 14.98. $^{19}$F NMR (565 MHz, CDCl$_3$) δ -107.97 (dd, d = 9.7, 6.0 Hz, 1F). HRMS (ESI): Calcd for C$_{22}$H$_{25}$FN$_2$NaO$_5$ [M+Na]$^+$: 439.1640. Found: 439.1637.

N-(adamantan-1-yl)-2-(((2$^R$,3$^R$)-7-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (42)

White solid, 75% yield. m.p. 126-128 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.98 (dd, d = 8.8, 6.3 Hz, 1H), 6.88-6.85 (m, 1H), 6.72 (dd, d = 9.3, 2.3 Hz, 1H), 5.63 (dd, J = 9.7, 2.6 Hz, 1H), 5.24 (s, 1H), 2.53 (dd, J = 14.9, 9.7 Hz, 1H), 2.29 (dd, J = 14.9, 2.6 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.73 (s, 3H), 1.69-1.68 (m, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 183.56, 168.20 (d, J = 258.6 Hz), 165.57, 161.27 (d, J = 13.8 Hz), 131.09 (d, J = 11.3 Hz), 115.38, 111.74 (d, J = 22.6 Hz), 105.20 (d, J = 24.6 Hz), 91.83, 79.37, 52.67, 41.59 (3C), 36.84, 36.23 (3C), 29.38 (3C), 14.79.

$^{19}$F NMR (565 MHz, CDCl$_3$) δ -96.93 (dd, J = 15.9, 8.2 Hz, 1F). HRMS (ESI): Calcd for C$_{22}$H$_{25}$FN$_2$NaO$_5$ [M+Na]$^+$: 439.1640. Found: 439.1652.

N-(adamantan-1-yl)-2-(((2$^R$,3$^R$)-8-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (43)

White solid, 65% yield. m.p. 90-92 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.74-7.73 (m, 1H), 7.40-7.37 (m, 1H), 7.11-7.08 (m, 1H), 5.62 (dd, d = 14.8, 10.0 Hz, 1H), 5.47 (s, 1H), 2.62 (dd, J = 14.8, 2.5 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.76 (s, 3H), 1.69-1.68 (m, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 184.02 (d, J = 3.0 Hz), 165.61, 151.31 (d, J = 249.5 Hz), 147.76 (d, J = 12.1 Hz), 123.46 (d, J = 3.9 Hz), 123.28 (d, J = 6.0 Hz), 120.57, 92.07, 79.79, 52.63, 41.43 (3C), 37.09, 36.25 (3C), 29.39 (3C), 14.64. $^{19}$F NMR (565 MHz, CDCl$_3$) δ -133.50 (d, d = 10.0, 3.8 Hz, 1F). HRMS (ESI): Calcd for C$_{22}$H$_{25}$FN$_2$NaO$_5$ [M+Na]$^+$: 439.1640. Found: 439.1627.

N-(adamantan-1-yl)-2-(((2$^R$,3$^R$)-6-fluoro-3-methyl-3-amino-4-oxochroman-2-yl)acetamide (44)

A suspension of 36 (83 mg, 0.2 mmol, 1.0 equiv) in ethanol (5 mL) was heated at reflux. Iron powder (110 mg, 2.0 mmol) and an aqueous solution of NH$_4$Cl (100 mg dissolved in 0.8 mL of water) were added. The reaction was stirred at reflux to completeness. The warm mixture was filtered through a Celite patch and the remaining solids were washed several times with warm EtOH. The filtrates were combined and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 50:1) on silica gel to afford compound 44. White solid, 79% yield. m.p. 93-95 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52-7.50 (m, 1H), 7.22-7.18 (m, 1H), 6.94-6.92 (m, 1H), 5.58 (s, 1H), 4.57 (d, J = 8.9 Hz, 1H), 2.82 (d, J = 14.9 Hz, 1H), 2.50 (dd, J = 14.5, 9.2 Hz, 1H), 2.08-2.07 (m, 3H), 2.03-2.02 (m, 6H), 1.86 (s, 3H), 1.69-1.68 (m, 6H), 1.18 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 196.98 (d, J = 0.9 Hz), 168.67, 157.51 (d, J = 241.0 Hz), 156.69 (d, J = 2.5 Hz), 123.64 (d, J = 24.5 Hz), 119.33 (d, J = 7.5 Hz), 119.22 (d, J = 6.6 Hz), 112.75 (d, J = 23.2 Hz), 81.54, 57.66, 52.19, 41.61 (3C), 37.44, 36.29 (3C), 29.38 (3C), 18.67. $^{19}$F NMR (375 MHz, CDCl$_3$) δ -120.69. HRMS (ESI): Calcd for C$_{22}$H$_{28}$FN$_2$O$_3$ [M+H]$^+$: 387.2078. Found: 387.2062.
Scheme S2 General synthetic route of compound 41-43. Reagent and conditions: (d) ethyl propiolate, 4-methylmorpholine, DCM, 0 °C - rt, 77-88%; (e) EtNO₂, 4-methylmorpholine, KF, iPrOH, 0 °C - rt, 80-98%;(f) DMP, DCM, 0 °C - rt, 85-91%;(g) tBuOK, THF, -40 °C, 75-94%; (a) 6N HCl/1,4-dioxane, 100 °C, 65-97%; (c) amines, HOBt, EDCI, DIPEA, DCM, rt, 54-75%.

Compounds s1, s2, s3, s4 and 2 were synthesized according to procedures which were previously described by our group¹.

General procedure for the synthesis of s2b-s2d

To a mixture of fluoro-substituted 2-hydroxybenzaldehyde s1 (560 mg, 4 mmol, 1 equiv.) and ethyl propiolate (440 mg, 4.4 mmol, 1.1 equiv.) in DCM (20 mL) at 0 °C was added 4-methylmorpholine (80 mg, 0.8 mmol, 0.2 equiv.) under N₂ atmosphere. The mixture was allowed to rise to room temperature and stirred for another 2 h. The mixture was quenched with 1N HCl and extracted 3 times with EtOAc. Combined organic phases were dried over sodium sulfate, filtered and purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford s2b-s2d.

General procedure for the synthesis of s3b-s3d

To a mixture of fluoro-substituted ethyl (E)-3-(2-formylphenoxy)acrylate derivatives s2b-s2d (830 mg, 3.5 mmol, 1 equiv.) and nitroethane (790 mg, 10.5 mmol, 3 equiv.) in iPrOH (20 mL) at 0 °C was added 4-methylmorpholine (35 mg, 0.35 mmol, 0.1 equiv.) and KF (20 mg, 0.35 mmol, 0.1 equiv.) under N₂ atmosphere. The mixture was allowed to rise to room temperature and stirred for another 18 h. The mixture was quenched with 1N HCl and extracted 3 times with EtOAc. Combined organic phases were dried over sodium sulfate, filtered and purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford s3b-s3d.

General procedure for the synthesis of s4b-s4d

To a solution of fluoro-substituted ethyl (E)-3-(2-(1-hydroxy-2-nitropropyl)phenoxy)-acrylate s3b-s3d (626 mg, 2 mmol, 1 equiv.) in DCM (20 mL) at 0 °C was added Dess-Martin periodinane (1020 mg, 2.4 mmol, 1.2 equiv.) under N₂ atmosphere. The mixture was allowed to rise to room temperature and stirred for another 18 h. The slurry was purified directly by column chromatography (dichloromethane/acetic acid = 100:1) on silica gel. The eluent fractions were collected and washed with water. Combined organic phases were dried over sodium sulfate and concentrated. Removal of the residual acetic acid in vacuo to afford
compound s4b-s4d.

**General procedure for the synthesis of 2b-2d**

A catalytic amount of tBuOK (11 mg, 0.1 mmol, 0.1 equiv.) was added to the corresponding α-nitro-acetophenone s4b-s4d (1 mmol, 1 equiv.) dissolved in THF (5 mL) at -40 °C. The reaction was monitored by TLC analysis and was completed in 4 h. To the crude reaction mixture was added 1N HCl (1 mL) and extracted with EtOAc. Combined organic phases were dried over sodium sulfate, filtered and purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford 2b-2d.

**ethyl (E)-3-(3-fluoro-2-formylphenoxy)acrylate (s2b)**

Column chromatography eluent petroleum ether/ethyl acetate = 5:1. Yellow oil, 88% yield. ¹H NMR (400 MHz, CDCl₃) δ 10.36 (s, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.61-7.56 (m, 1H), 7.05-7.00 (m, 1H), 6.96 (d, J = 8.7 Hz, 1H), 5.64 (d, J = 12.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 185.40 (d, J = 3.4 Hz), 166.31, 163.20 (d, J = 262.3 Hz), 157.42, 157.00 (d, J = 4.5 Hz), 136.07 (d, J = 11.2 Hz), 115.96 (d, J = 9.3 Hz), 114.16 (d, J = 3.5 Hz), 113.28 (d, J = 21.5 Hz), 104.49, 60.37, 14.19. ¹⁹F NMR (565 MHz, CDCl₃) δ -113.86 (dd, J = 15.4, 11.8 Hz, 1F). HRMS (ESI): Calcd for C₁₂H₁₁FNaO₄ [M+Na]⁺: 261.0534. Found: 261.0523.

**ethyl (E)-3-(5-fluoro-2-formylphenoxy)acrylate (s2c)**

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Colorless oil, 87% yield. ¹H NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H), 7.98-7.94 (m, 1H), 7.78 (d, J = 12.2 Hz, 1H), 7.03-6.99 (m, 1H), 6.88 (d, J = 9.2 Hz, 1H), 5.72 (d, J = 12.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 186.58, 167.00 (d, J = 261.7 Hz), 166.15, 158.98 (d, J = 10.8 Hz), 156.64, 131.27 (d, J = 10.9 Hz), 123.16 (d, J = 3.0 Hz), 112.80 (d, J = 21.7 Hz), 105.70 (d, J = 25.0 Hz), 105.45, 60.56, 14.24. ¹⁹F NMR (565 MHz, CDCl₃) δ -98.35 (dd, J = 15.1, 7.3 Hz, 1F). HRMS (ESI): Calcd for C₁₂H₁₁FNaO₄ [M+Na]⁺: 261.0534. Found: 261.0551.

**ethyl (E)-3-(6-fluoro-2-formylphenoxy)acrylate (s2d)**

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Colorless oil, 77% yield. ¹H NMR (400 MHz, CDCl₃) δ 10.23 (s, 1H), 7.81 (d, J = 12.3 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.48-7.44 (m, 1H), 7.37-7.32 (m, 1H), 5.35 (d, J = 12.3 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 186.93, 166.17, 160.10, 153.99 (d, J = 252.2 Hz), 144.08 (d, J = 12.5 Hz), 129.76, 126.89 (d, J = 6.9 Hz), 124.17 (d, J = 3.3 Hz), 122.98 (d, J = 18.6 Hz), 102.40, 60.40, 14.20. ¹⁹F NMR (565 MHz, CDCl₃) δ -129.23 (dd, J = 9.4, 3.1 Hz, 1F). HRMS (ESI): Calcd for C₁₂H₁₁FNaO₄ [M+Na]⁺: 261.0534. Found: 261.0546.

**ethyl (E)-3-(3-fluoro-2-(1-hydroxy-2-nitropropyl)phenoxy)acrylate (s3b)**

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 80% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, J = 8.1 Hz, 1H), 7.41-7.37 (m, 1H), 7.00-6.97 (m, 1H), 6.92 (d, J = 5.6 Hz, 1H), 5.70 (d, J = 8.1 Hz, 1H), 5.52 (d, J = 7.2 Hz, 1H), 5.13-5.10
ethyl (E)-3-(5-fluoro-2-(1-hydroxy-2-nitropropyl)phenoxy)acrylate (s3c)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 90% yield. 1H NMR (400 MHz, CDCl3) δ 7.70 (d, J = 8.1 Hz, 1H), 7.61-7.58 (m, 1H), 6.98-6.95 (m, 1H), 6.81 (d, J = 6.0 Hz, 1H), 5.66 (d, J = 8.1 Hz, 1H), 5.62 (s, 1H), 4.74-4.72 (m, 1H), 4.20 (q, J = 4.7 Hz, 2H), 3.12 (s, 1H), 1.44 (d, J = 4.6 Hz, 3H), 1.29 (t, J = 4.8 Hz, 3H).

13C NMR (150 MHz, CDCl3) δ 166.49, 163.01 (d, J = 248.5 Hz), 156.77, 152.49 (d, J = 9.8 Hz), 129.34 (d, J = 9.6 Hz), 124.55 (d, J = 3.4 Hz), 112.19 (d, J = 21.2 Hz), 105.05 (d, J = 25.1 Hz), 104.55, 84.96, 68.49, 60.55, 14.22, 11.67.

19F NMR (565 MHz, CDCl3) δ -109.57 (dd, J = 14.6, 7.4 Hz, 1F). HRMS (ESI): Calcd for C14H16FNaO6 [M+Na]+: 336.0854. Found: 336.0851.

ethyl (E)-3-(6-fluoro-2-(1-hydroxy-2-nitropropyl)phenoxy)acrylate (s3d)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 98% yield. 1H NMR (400 MHz, CDCl3) δ 7.72 (dd, J = 8.2, 1.0 Hz, 1H), 7.29-7.25 (m, 1H), 7.19-7.16 (m, 1H), 5.60 (s, 1H), 5.33 (d, J = 8.2 Hz, 1H), 4.76-4.72 (m, 1H), 4.16 (q, J = 4.8 Hz, 2H), 3.17 (d, J = 2.6 Hz, 1H), 1.44 (d, J = 4.6 Hz, 3H), 1.26 (t, J = 4.8 Hz, 3H).

13C NMR (150 MHz, CDCl3) δ 166.56, 159.53, 154.48 (d, J = 250.8 Hz), 138.50 (d, J = 12.9 Hz), 132.96, 126.94 (d, J = 7.6 Hz), 123.02, 117.17 (d, J = 17.9 Hz), 101.59, 84.89, 68.59, 60.45, 14.18, 11.54.

19F NMR (565 MHz, CDCl3) δ -129.45 (m, 1F). HRMS (ESI): Calcd for C14H16FNaO6 [M+Na]+: 336.0854. Found: 336.0835.

ethyl (E)-3-(3-fluoro-2-(2-nitropropanoyl)phenoxy)acrylate (s4b)

Column chromatography eluent dichloromethane/acetic acid = 100:1. Yellow oil, 88% yield. 1H NMR (600 MHz, CDCl3) δ 7.69 (d, J = 12.2 Hz, 1H), 7.54-7.50 (m, 1H), 7.04-7.02 (m, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 5.75 (q, J = 7.0 Hz, 1H), 5.70 (d, J = 12.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.80 (d, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

13C NMR (150 MHz, CDCl3) δ 187.97, 166.16, 160.11 (d, J = 253.3 Hz), 156.33, 153.95 (d, J = 5.8 Hz), 134.00 (d, J = 10.2 Hz), 116.65 (d, J = 17.8 Hz), 113.25 (d, J = 3.3 Hz), 112.77 (d, J = 21.6 Hz), 105.49, 89.13, 60.52, 14.86, 14.22.

19F NMR (565 MHz, CDCl3) δ -98.91 (m, 1F). HRMS (ESI): Calcd for C14H14FNaO6 [M+Na]+: 334.0697. Found: 334.0716.

ethyl (E)-3-(5-fluoro-2-(2-nitropropanoyl)phenoxy)acrylate (s4c)

Column chromatography eluent dichloromethane/acetic acid = 100:1. Yellow oil, 91% yield. 1H NMR (600 MHz, CDCl3) δ 7.99 (dd, J = 8.8, 6.4 Hz, 1H), 7.68 (d, J = 12.1 Hz, 1H), 7.04-7.01 (m, 1H), 6.87 (dd, J = 9.1, 2.3 Hz, 1H), 5.94 (q, J = 7.0 Hz, 1H), 5.84 (d, J = 12.2 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.81 (d, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H).

19F NMR (565 MHz, CDCl3) δ -98.91 (m, 1H). HRMS (ESI): Calcd for C14H14FNaO6 [M+Na]+: 334.0697. Found: 334.0716.
ethyl (E)-3-(6-fluoro-2-(2-nitropropanoyl)phenoxy)acrylate (s4d)

Column chromatography eluent dichloromethane/acetic acid = 100:1. Yellow oil, 85% yield. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 7.68 (d, J = 12.3, 2.9\) Hz, 1H), 7.64-7.62 (m, 1H), 7.47-7.44 (m, 1H), 7.36-7.33 (m, 1H), 5.88 (q, \(J = 7.0\) Hz, 1H), 5.50 (d, \(J = 12.2\) Hz, 1H), 4.19 (q, \(J = 7.1\) Hz, 2H), 1.80 (d, \(J = 7.1\) Hz, 3H), 1.28 (t, \(J = 7.1\) Hz, 3H). \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta 188.57 (d, J = 2.9\) Hz), 165.94, 158.83 (d, \(J = 3.2\) Hz), 153.92 (d, \(J = 252.0\) Hz), 141.44 (d, \(J = 12.7\) Hz), 129.48, 127.03 (d, \(J = 7.4\) Hz), 126.27 (d, \(J = 3.6\) Hz), 122.51 (d, \(J = 18.7\) Hz), 103.38, 87.58, 60.57, 15.50, 14.18.

\(^{19}\)F NMR (565 MHz, CDCl\(_3\)) \(\delta -127.61\). HRMS (ESI): Calcd for C\(_{14}\)H\(_{14}\)FNaO\(_6\) [M+Na\(^+\)]: 334.0697. Found: 334.0671.

ethyl 2-((2\(R^*,3R^*\))-5-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (2b)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 94% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.55-7.50 (m, 1H), 6.85-6.81 (m, 2H), 5.61 (d, \(J = 9.8\) Hz, 1H), 4.22 (q, \(J = 7.0\) Hz, 2H), 2.83 (dd, \(J = 16.0, 10.1\) Hz, 1H), 2.46 (d, \(J = 16.1\) Hz, 1H), 1.75 (s, 3H), 1.28 (t, \(J = 7.1\) Hz, 3H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 181.95, 168.18, 162.29 (d, J = 267.9 Hz), 160.01 (d, \(J = 2.5\) Hz), 137.67 (d, \(J = 11.5\) Hz), 113.87 (d, \(J = 4.0\) Hz), 110.57 (d, \(J = 20.3\) Hz), 108.68 (d, \(J = 9.6\) Hz), 92.07, 77.88, 61.58, 34.30, 14.51, 14.07. \(^{19}\)F NMR (375 MHz, CDCl\(_3\)) \(\delta -107.86\). HRMS (ESI): Calcd for C\(_{14}\)H\(_{14}\)FNaO\(_6\) [M+Na\(^+\)]: 334.0697. Found: 334.0697.

ethyl 2-((2\(R^*,3R^*\))-7-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (2c)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 75% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.00-7.97 (m, 1H), 6.90-6.86 (m, 1H), 6.73 (d, \(J = 9.2\) Hz, 1H), 5.63 (d, \(J = 10.0\) Hz, 1H), 4.23 (q, \(J = 7.0\) Hz, 2H), 2.85 (dd, \(J = 15.9, 10.2\) Hz, 1H), 2.45 (d, \(J = 16.0\) Hz, 1H), 1.74 (s, 3H), 1.29 (t, \(J = 7.0\) Hz, 3H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 183.55, 168.26 (d, J = 258.4 Hz), 168.18, 161.32 (d, J = 13.7 Hz), 131.14 (d, \(J = 11.4\) Hz), 115.13 (d, \(J = 2.4\) Hz), 111.89 (d, \(J = 22.8\) Hz), 105.21 (d, \(J = 24.9\) Hz), 91.75, 78.51, 61.62, 34.38, 14.43, 14.10. \(^{19}\)F NMR (375 MHz, CDCl\(_3\)) \(\delta -96.67\). HRMS (ESI): Calcd for C\(_{14}\)H\(_{14}\)FNaO\(_6\) [M+Na\(^+\)]: 334.0697. Found: 334.0697.

ethyl 2-((2\(R^*,3R^*\))-8-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (2d)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 89% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.74 (d, J = 7.9\) Hz, 1H), 7.41-7.36 (m, 1H), 7.12-7.10 (m, 1H), 5.66 (d, \(J = 9.9\) Hz, 1H), 4.23 (q, \(J = 7.0\) Hz, 2H), 2.91 (dd, \(J = 15.7, 10.0\) Hz, 1H), 2.49 (d, \(J = 16.0\) Hz, 1H), 1.77 (s, 3H), 1.29 (t, \(J = 7.0\) Hz, 3H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 184.00 (d, J = 3.3\) Hz), 168.03, 151.27 (d, \(J = 250.0\) Hz), 148.95 (d, \(J = 12.2\) Hz), 123.49 (d, \(J = 7.3\) Hz), 123.38 (d, \(J = 6.0\) Hz), 122.82 (d, \(J = 6.3\) Hz), 120.33, 91.93, 78.85, 61.68, 34.39, 14.44, 14.04. \(^{19}\)F NMR (375 MHz, CDCl\(_3\)) \(\delta -133.36\). HRMS (ESI): Calcd for C\(_{14}\)H\(_{14}\)FNaO\(_6\) [M+Na\(^+\)]: 334.0697. Found: 334.0701.

2-((2\(R^*,3R^*\))-5-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3b)

Column chromatography eluent petroleum ether/ethyl acetate/acetic acid = 100:20:1.
Yellow solid, 85% yield. m.p. 157-160 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.84 (s, 1H), 7.75-7.70 (m, 1H), 7.07-7.02 (m, 1H), 7.99 (d, $J$ = 8.4 Hz, 1H), 5.55 (d, $J$ = 9.8 Hz, 1H), 2.79 (dd, $J$ = 16.6, 10.0 Hz, 1H), 2.66 (d, $J$ = 16.5 Hz, 1H), 1.72 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 182.02, 170.08, 161.36 (d, $J$ = 264.1 Hz), 159.64 (d, $J$ = 2.4 Hz), 138.73 (d, $J$ = 11.8 Hz), 114.26 (d, $J$ = 3.6 Hz), 110.33 (d, $J$ = 20.0 Hz), 108.06 (d, $J$ = 9.7 Hz), 92.30, 78.13, 33.83, 14.47. $^{19}$F NMR (375 MHz, DMSO-$d_6$) δ -109.89. HRMS (ESI): Calcd for C$_{12}$H$_{10}$FNaO$_6$ [M+Na]$^+$: 306.0384. Found: 306.0377.

2-((2$^R$,3$^R$)-7-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3c)

Column chromatography eluent petroleum ether/ethyl acetate/acetic acid = 100:20:1. Yellow solid, 97% yield. m.p. 146-147 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02-7.98 (m, 1H), 6.92-6.88 (m, 1H), 6.77 (d, $J$ = 9.1 Hz, 1H), 5.63 (d, $J$ = 10.0 Hz, 1H), 2.93 (dd, $J$ = 16.3, 10.4 Hz, 1H), 2.53 (d, $J$ = 16.6 Hz, 1H), 1.76 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 183.42, 173.80, 168.31 (d, $J$ = 258.7 Hz), 161.22 (d, $J$ = 13.7 Hz), 131.24 (d, $J$ = 11.5 Hz), 115.02 (d, $J$ = 2.4 Hz), 112.08 (d, $J$ = 22.8 Hz), 105.28 (d, $J$ = 25.1 Hz), 91.66, 78.07, 34.11, 14.37. $^{19}$F NMR (375 MHz, DMSO-$d_6$) δ -97.71. HRMS (ESI): Calcd for C$_{12}$H$_{10}$FNaO$_6$ [M+Na]$^+$: 306.0384. Found: 306.0364.

2-((2$^R$,3$^R$)-8-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3d)

Column chromatography eluent petroleum ether/ethyl acetate/acetic acid = 100:20:1. Yellow solid, 65% yield. m.p. 142-144 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.89 (s, 1H), 7.74-7.69 (m, 2H), 7.25-7.20 (m, 1H), 5.62 (d, $J$ = 9.6 Hz, 1H), 2.84 (dd, $J$ = 16.5, 10.1 Hz, 1H), 2.70 (d, $J$ = 16.4 Hz, 1H), 1.75 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 184.01 (d, $J$ = 3.3 Hz), 169.98, 150.65 (d, $J$ = 246.4 Hz), 147.33 (d, $J$ = 12.2 Hz), 124.94 (d, $J$ = 17.3 Hz), 123.24 (d, $J$ = 3.8 Hz), 123.16 (d, $J$ = 6.8 Hz), 119.93, 92.08, 79.13, 33.92, 14.41. $^{19}$F NMR (375 MHz, DMSO-$d_6$) δ -134.32. HRMS (ESI): Calcd for C$_{12}$H$_{10}$FNaO$_6$ [M+Na]$^+$: 306.0384. Found: 306.0384.
3. Biology materials and methods

3.1 Cell lines and culture conditions

Human fibroblast cell line HAF and human prostate cancer cell lines PC3M, DU145, PC3, LNCaP and 22RV1 were obtained from the American Type Culture Collection (ATCC). DU145, PC3, LNCaP and 22RV1 cell lines were cultured in RPMI 1640 medium (Gibco), and PC3M cell lines were maintained in Dulbecco’s modified Eagle’s medium (Gibco, Cleveland, OH). Both media were supplemented with 10% FBS (Wisent, St. Bruno, QC, Canada). Moreover, the human fibroblast cell line HAF was cultured in DMEM medium with 10% FBS and an additional final concentration of 2 mM L-glutamine. All cells were incubated at 37 °C and 5% CO₂ incubator.

3.2 Cell viability assay

The cell viability of cell lines in the presence of this series of compounds was determined by Sulforhodamine B (SRB) assay (Sigma Aldrich) which was described previously. Cells were seeded in 96-well plates (3000 cells/well) after 24 h and incubated with compounds of which 8 concentrations were set at 100, 33, 11, 3.7, 1.2, 0.41, 0.14 and 0.05 μM. After incubation for 96 h, the cells were then fixed with 25 μl cold 50% trichloroacetic acid for 1 h at 4°C, stained with 50 μl 0.4% SRB (Sigma Aldrich, Argentina, Cat# S1402) for 10-20 min at room temperature, and OD value was measured by a microplate spectrophotometer at 515nm. The IC₅₀ (half maximal inhibitory concentration) value was calculated using GraphPad software.

3.3 Transwell migration assay

Transwell migration assay was performed as previously reported. The inhibition of tumor cell migration was assessed by the Boyden chamber (Corning Falcon) migration assay in 24-well cell culture plate with 8.0 μm pore. Briefly, the top chambers were seeded with 8×10⁴ DU145 cells in 200 μl of serum-free medium containing different dose of compound. The bottom chambers were filled with 500 μl of complete medium supplemented with different dose of compound. After 24 h incubation, non-migrated cells were removed with cotton swabs, and migrated cells were fixed with cold 4% paraformaldehyde for 20 min and stained with 0.2% crystal violet for 3 min. Then the chambers were washed using water, and the membrane was left to dry. Images were taken with an inverted microscope (Olympus) and cells from three random areas per filter were counted. The percentage of migrated cells was normalized to untreated control cells.

3.4 Wound healing migration assay

DU145 cells were seeded in a 6-well plate at a density that after 24 h of growth, and they were allowed to reach 95% confluence in complete medium. A single scratch wound was created on the confluent monolayers using a micropipette tip across the center of the well and a straight line was scratched in one direction. Then, wounded monolayers were washed with phosphate buffer saline (PBS) to remove the detached cells, and each assay was carried out
three times. After washing, fresh media with FBS was added, 10 μM of 36 were added to their respective wells, and then they were incubated for 24 h. The medium in each well was discarded and washed several times with PBS. Cells migrated to the wound surface and the average distance of migrating cells was determined under an inverted microscope at designated time points. Pictures of three different regions of each wound were taken. The experiment was performed three times.

3.5 Colony formation assay

Prostate cancer cells DU145, PC3 and PC3M were seeded 2000 per well in 6-well plate and allowed to grow for 24 hours. Then cells were treated with indicated concentrations of cisplatin or compound 36 for 7 days. Colonies were fixed with 4% paraformaldehyde for 30 min, stained with 0.1% crystal violet for 5 min. Colonies were visualized and all the fields were imaged and counted. Colony formation as a percentage of vehicle control for each cell line is presented.

3.6 Cell cycle analysis

Cell cycle analysis was conducted by propidium iodide (PI) staining as described previously. Briefly, cells were treated with different concentrations of compound 36 for 24h followed by PBS washing, then fixed with cold 70% ethanol at 4°C for at least 12h. After washing twice with PBS, cells were incubated in the dark with 50 mg/mL PI and 10 mg/L RNase for 30 min. Cell cycle distribution was analyzed by flow cytometry (FACS Calibur, BD biosciences).

3.7 Cell apoptosis assay

Apoptosis was measured using the apoptosis detection kit (BD Biosciences) with flow cytometry. DU145 cells (2.0×10⁵/well) were cultured in 6-well plate with concentrations of 0 μM, 2.5 μM, 5 μM and 10 μM of compound 36 or cisplatin for 48h. Cells were collected and washed with PBS, then resuspended in binding buffer and incubated with Annexin V-FITC and propidium iodide. About 15 min later, cells were analyzed immediately with flow cytometry (FACS Calibur, BD Biosciences).

3.8 Western Blot Analysis

Cells were lysed in cell lysis buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% Nonidet P-40, 0.5% sodium deoxycholate and 1% protease inhibitor cocktails) and boiled for 10 min with loading buffer (2% SDS, 10% glycerol, 10% β-Mercaptoethanol, Bromphenol Blue and Tris-HCl, pH 6.8). Lysates were fractionated on polyacrylamide gels and transferred to nitrocellulose. The blots were probed with specific antibodies followed by secondary antibody, then membranes were examined by the LI-COR Odyssey infrared imaging system (LI-COR Biotechnology, Lincoln NE). PARP antibody (Catalog #9542) was from Cell Signaling Technology and β-actin antibody (Catalog #A5441) was from Sigma. The secondary antibody was conjugated with IRDye 680/800 (Catalog #926-32221, #926-32210, Millennium Science).
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4. NMR charts

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