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EXPERIMENTAL PAPER

1,3,3-Trimethylindolin-5-amine and 4-Formylphenyl 4,4-Dimethylchroman-6-carboxylate Thiosemicarbazone (OHet72)

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A recent project required the development of efficient syntheses for structures that could be used to advance our anticancer studies. The first target was 1,3,3-trimethylindolin-5-amine (**1**, Figure 1), and the second was 4-formylphenyl 4,4-dimethylchroman-6-carboxylate thiosemicarbazone (**2**, OHet72). The nitrogen heterocycle **1** was sought as a building block for the synthesis of a library of anticancer drug analogs, while the second was a previously reported compound that has recently attracted renewed interest as an anticancer drug.[1,2]

Our current lead anticancer compound, SHetA2 (**3**),[3] incorporates a hydrophobic 2,2,4,4-tetramethylthiochroman unit linked *via* a thiourea to an aromatic ring substituted at C4 with a polar nitro group. It was anticipated that installation of a relatively hydrophobic nitrogen heterocycle in place of the thiochroman ring would lead to compounds having similar activity with increased water solubility. We also wished to replace the nitro group on the linked aromatic ring with other electron-withdrawing substituents such as trifluoromethyl, trifluoromethoxy and cyano. The chroman **2**, first reported in 1997,[4] is a compound we were contracted to prepare in multi-gram quantities. Since the original synthesis provided **2** in low yield and employed a number of hazardous reagents,[4,5] it was decided to seek a second-generation approach that would increase the efficiency and allow for safe scale-up. In both of these syntheses, we have developed approaches that feature an intramolecular reductive Mizoroki-Heck cyclization[6,7] under phase transfer conditions reported by Jeffery.[8] Target **1** requires closure of a side-chain terminal alkene to a 5-membered nitrogen heterocycle whereas target **2** requires closure of a 6-membered oxygen heterocycle.

The classic Mizoroki-Heck reaction[6,7] is characterized by the retention of the alkene in the cross-coupled product. The regeneration of the alkene results from a β-hydride elimination, which is considered the thermodynamically favored process.[9] In order to obtain the reduced product, several adjustments were made to the reaction.[8,10] Specifically, the addition of formate ion as a hydride source[10] and tetrabutylammonium chloride as a phase-transfer vehicle[8] and palladium nanoparticle stabilizing agent,[11] allowed a competing mechanism to prevail.[12] Using this protocol, β-hydride elimination competes with ligand exchange of a hydride for a halogen, leading to subsequent C-H bond formation upon reductive elimination of the catalyst.[13] The phase transfer reagent

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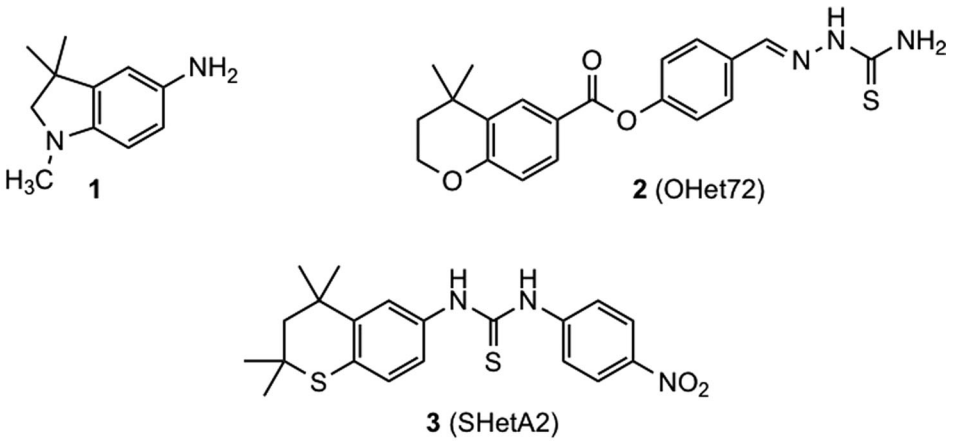
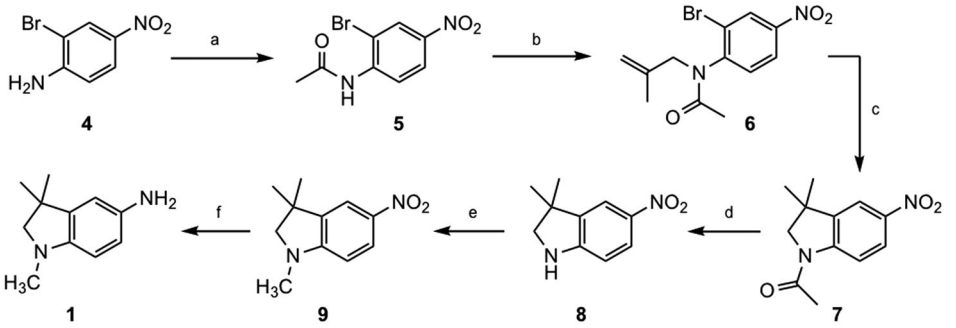


Figure 1. Target molecules **1**, **2** and lead compound **3**.

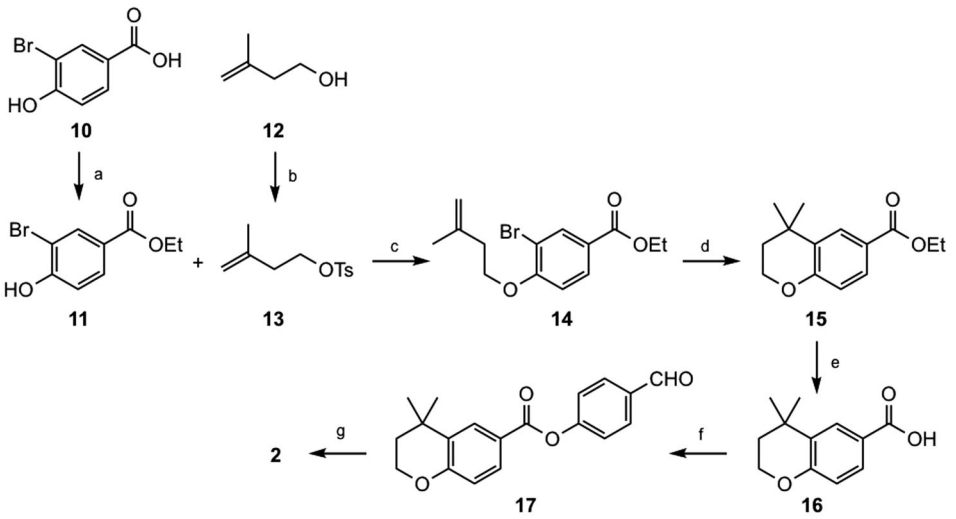


Scheme 1. The synthesis of 1,3,3-trimethylindolin-5-amine (**1**). Key: a) Ac_2O, AcOH, 84%; b) 3-iodo-2-methyl-1-propene, K_2CO_3, DMF, 60 °C, 99%; c) $Pd(OAc)_2$, CH_3CO_2Na, HCO_2Na, Et_4NCl, H_2O, DMF, 80 °C, 85%; d) 20% HCl, 94%; e) NaH, CH_3I, DMF, 98%; f) Fe powder, NH_4Cl, 4:1 EtOH-H_2O, 80%.

also permits the reaction to proceed at lower temperature (80-95 °C) and, in the current application, tetraethylammonium chloride gave superior results[14] compared to the tetrabutylammonium chloride used in the original disclosure.[8]

One positive feature of the Jeffery modification is the tolerance and requirement for the presence of water, thus avoiding the need for rigorously anhydrous reagents and reaction conditions.[14] A second attribute is the ability of the reaction to tolerate various functional groups.[14] This makes the method versatile and potentially very useful in the synthesis of SHetA2 (**3**) analogs. The Jeffery conditions are critical to the success of the required cyclizations. By using this procedure, heterocycles can be synthesized that include the geminal 3,3- and 4,4-dimethyl groups that are essential to anticancer activity in heteroarotinoid analogs of **3**.

The synthesis of the 1,3,3-trimethylindoline system required six steps (Scheme 1).[15] Initially, 2-bromo-4-nitroaniline (**4**) was treated with acetic anhydride in glacial acetic acid at room temperature to afford the acetamide product **5** in 84% yield. Subsequent alkylation of **5** with 3-iodo-2-methyl-1-propene using K_2CO_3 in *N*,*N*-



Scheme 2. Second generation synthesis of OHet72 (**2**). Key: a) EtOH, H_2SO_4, 86% b) *p*-TsCl, pyridine, DCM, 93%; c) K_2CO_3, DMF, 80 °C, 81%; d) $Pd(OAc)_2$, CH_3CO_2Na, HCO_2Na, Et_4NCl, H_2O, DMF, 95 °C, 94%; e) KOH, 2:1 EtOH-H_2O, 89%; f) 4-HO-C_6H_4-CHO, EDAC, DMAP, DCM, 90%; g) $H_2NNHC(S)NH_2$, 3:1 EtOH-H_2O, cat AcOH, 78%.

dimethylformamide (DMF) at 60 °C led to the formation of the tertiary amide **6** in nearly quantitative yield. Cyclization of **6** *via* a reductive Mizoroki-Heck reaction ($Pd(OAc)_2$, CH_3CO_2Na, HCO_2Na, Et_4NCl, H_2O, 80 °C) afforded the cyclic amide **7** in 85% yield.[9] Amide **7** was hydrolyzed with refluxing 20% aqueous HCl (94%), and the resulting indoline **8** was methylated by treatment with sodium hydride, followed by the dropwise addition of iodomethane to generate *N*-methylindoline **9** (98%). Finally, reduction of the aromatic nitro group in **9** with iron and ammonium chloride in refluxing ethanol–water (4:1) afforded 1,3,3-trimethylindolin-5-amine (**1**) in 80% yield.[16] The overall yield for the 6-step synthesis was 52%. Conversion of **1** to SHetA2 analogs and the associated biological studies will be reported in due course.

The previous synthesis[4,5] of compound **2** required 7 steps from 3-phenoxypropionic acid and proceeded in 7.1% overall yield. Our second-generation synthesis of OHet72 (**2**) also required 7 steps (Scheme 2), but the yield/step was considerably higher [6 linear steps from **10** (40.9%) or **12** (44.2%)]. Initially, 3-bromo-4-hydroxybenzoic acid (**10**) was converted to ester **11** (86%) by refluxing in ethanol containing H_2SO_4 as a catalyst. 3-Methyl-3-buten-1-ol (**12**) was converted to its *p*-toluenesulfonate **13** (93%) using *p*-toluenesulfonyl chloride and pyridine in dichloromethane (DCM). The hydroxy group in **11** was alkylated with **13** using K_2CO_3 in DMF at 80 °C to produce ether **14** in 81% yield. Subsequent cyclization of **14** using a reductive Mizoroki-Heck reaction under Jeffery conditions (as above, 95 °C) afforded chroman ester **15** in 94% yield. Ester **15** was then hydrolyzed to carboxylic acid **16** (89%) with KOH in ethanol–water (2:1). Coupling of acid **16** with 4-hydroxybenzaldehyde mediated by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) and 4-dimethylaminopyridine (DMAP) in DCM yielded the chroman ester-aldehyde **17** (90%). Finally, conversion of **17** to OHet72 (**2**, 78%) was accomplished by adding a warm aqueous solution of thiosemicarbazide and acetic acid to a warm solution of **17** in ethanol. The current

procedure utilized fewer corrosive reagents and afforded the desired compound in excellent overall yield. Since we needed OHet72 in batches larger than 10 g, this method proved to be a much more efficient process, and the cost was still reasonable.

The current article reports the synthesis of compounds **1** and **2** for use in our anticancer drug research program. The syntheses both utilize a Jeffrey modification of the Mizoroki-Heck reaction for heterocycle formation. The overall yields are good to excellent and will allow the efficient preparation of these materials in multi-gram quantities.

Experimental section

Commercial anhydrous *N,N*-dimethylformamide (DMF) was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates, and compound elution was followed using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks. The ^{1}H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 101 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz. Mass spectra (EI) were measured at 30 eV. Elemental analyses (±0.4%) were performed by Atlantic Microlabs, Norcross, GA.

N-(2-Bromo-4-nitrophenyl)acetamide (5)

2-Bromo-4-nitroaniline (**4**, 5.00 g, 1.0 equiv, 23.0 mmol) was dissolved in acetic acid (50 mL), and acetic anhydride (10.8 g, 10 mL, 4.6 equiv, 106 mmol) was added. The mixture was stirred at room temperature for 18 h, at which time TLC analysis (1:1 ether-hexane) indicated complete consumption of the starting material. The reaction mixture was poured into water (100 mL), at which time a yellow precipitate formed rapidly. The precipitate was collected by vacuum filtration and washed with copious amounts of water. The solid was dried under vacuum to yield **5** (5.01 g, 84%) as a yellow solid, mp 119-120 °C. IR: 3216, 1656, 1589, 1521, 1313 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, $J = 9.2$ Hz, 1H), 8.46 (d, $J = 2.5$ Hz, 1H), 8.26 (dd, $J = 9.2$, 2.5 Hz, 1H), 7.89 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 143.2, 141.3, 127.9, 124.2, 120.2, 11.8, 25.2; MS (EI): *m/z* 258, 260 (*ca* 1:1, $M^{+\cdot}$).

Anal. Calcd for $C_8H_7BrN_2O_3$: C, 37.09: H, 2.72: N, 10.81. Found: C, 37.17; H, 2.75; N, 10.79.

N-(2-Bromo-4-nitrophenyl)-N-(2-methyl-2-propenyl)acetamide (6)

N-(2-Bromo-4-nitrophenyl)acetamide (**5**, 5.00 g, 1.0 equiv, 19.3 mmol) was dissolved in DMF (60 mL), and anhydrous K_2CO_3 (10.6 g, 4.0 equiv, 77.2 mmol) was added. The mixture was stirred at room temperature under N_2 for 10 min, at which time 3-iodo-2-methyl-1-propene (7.00 g, 2.0 equiv, 38.6 mmol) was added in one portion. The mixture was heated to 60 °C for 18 h, after which TLC analysis (1:2 ether-hexane) indicated the

reaction was complete. The crude reaction mixture was poured into water (100 mL) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (2 × 75 mL) and aqueous NaCl (75 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **6** (6.02 g, 99%) as an orange oil. IR: 1652, 1583, 1513, 1317 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, $J = 2.5$ Hz, 1H), 8.24 (dd, $J = 8.6$, 2.5 Hz, 1H), 7.41 (d, $J = 8.6$ Hz, 1H), 4.96 (d, $J = 14.5$ Hz, 1H), 4.86 (s, 1H), 4.66 (s, 1H), 3.52 (d, $J = 14.5$ Hz, 1H), 1.87 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 147.5, 147.2, 140.0, 131.5, 129.2, 124.8, 123.5, 115.0, 52.7, 22.6, 20.6; MS (EI): *m/z* 312, 314 (*ca* 1:1, $M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{13}BrN_2O_3$: C, 46.03: H, 4.18: N, 8.95. Found: C, 46.08; H, 4.20; N, 8.90.

1-(3,3-Dimethyl-5-nitroindolin-1-yl)ethan-1-one (7)

N-(2-Bromo-4-nitrophenyl)-*N*-(2-methyl-2-propenyl)acetamide (**6**, 4.40 g, 1.0 equiv, 14.0 mmol) was dissolved in DMF (50 mL), and sodium acetate (2.84 g, 2.5 equiv, 35.0 mmol), sodium formate (1.19 g, 1.25 equiv, 17.5 mmol), and tetraethylammonium chloride (2.78 g, 1.2 equiv, 16.8 mmol) were added sequentially to form a slurry. Water (0.5 mL) and $Pd(OAc)_2$ (0.31 g, 0.1 equiv, 1.4 mmol, 10 mol%) were added, and the reaction mixture was heated to 80 °C under N_2 for 18 h. The reaction mixture was cooled, filtered through a 2 cm Celite pad and then partitioned between water (150 mL) and EtOAc (100 mL). The aqueous layer was washed with EtOAc (2 × 100 mL), and the combined organic layers were washed with water (2 × 50 mL), aqueous NaCl (75 mL), and then dried (Na_2SO_4). Concentration under vacuum afforded **7** (2.78 g, 85%) as a yellow solid, mp 183-184 °C. IR: 1674, 1571, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, $J = 9.0$ Hz, 1H), 8.15 (dd, $J = 9.0$, 2.4 Hz, 1H), 8.00 (d, $J = 2.4$ Hz, 1H), 3.91 (s, 2H), 2.28 (s, 3H), 1.42 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 146.9, 143.9, 141.7, 124.9, 118.0, 116.4, 64.1, 40.1, 28.7, 24.3; MS (EI): *m/z* 234 ($M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53: H, 6.02: N, 11.96. Found: C, 61.57; H, 6.04; N, 11.88.

3,3-Dimethyl-5-nitroindoline (8)

1-(3,3-Dimethyl-5-nitroindolin-1-yl)ethan-1-one (**7**, 2.70 g, 11.5 mmol) was added to 20% HCl (50 mL), and the mixture was heated to 100 °C. After 1 h, all of the solid had dissolved, indicating the reaction was complete. The mixture was poured into 1 M NaOH (150 mL). The aqueous mixture was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **8** (2.07 g, 94%) as a yellow solid, mp 74-76 °C. IR: 3388, 1558, 1363 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, $J = 8.7$, 2.3 Hz, 1H), 7.90 (d, $J = 2.3$ Hz, 1H), 6.49 (d, $J = 8.7$ Hz, 1H), 4.45 (br s, 1H), 3.49 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 139.2, 138.2, 126.1, 118.9, 106.6, 61.7, 41.1, 27.9; MS (EI): *m/z* 192 ($M^{+\cdot}$).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49: H, 6.29: N, 14.57. Found: C, 62.56; H, 6.31; N, 14.55.

1,3,3-Trimethyl-5-nitroindoline (9)

A suspension of oil-free NaH in DMF was prepared by washing a 60% mineral oil suspension of NaH (0.25 g, 1.15 equiv, 6.00 mmol) with hexane (3 × 5 mL) and then diluting with DMF (5 mL). 3,3-Dimethyl-5-nitroindoline (**8**, 1.0 g, 5.21 mmol), dissolved in DMF (10 mL), was added dropwise at room temperature to the NaH suspension over 5 min. After the base was consumed, a solution of iodomethane (0.81 g, 0.36 mL, 1.1 equiv, 5.70 mmol) in DMF (5 mL) was added dropwise. The reaction mixture was heated to 40 °C for 1 h, at which time TLC analysis (1:2 ether-hexane) indicated complete consumption of the starting material. The reaction was quenched slowly with aqueous NaCl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (3 × 30 mL), aqueous NaCl (30 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **9** (1.05 g, 98%) as a yellow oil. IR: 1551, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, $J = 8.8$, 2.3 Hz, 1H), 7.83 (d, $J = 2.3$ Hz, 1H), 6.29 (d, $J = 8.8$ Hz, 1H), 3.36 (s, 2H), 2.92 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 139.2, 138.2, 126.1, 118.9, 106.6, 61.7, 41.1, 37.4, 27.9; MS (EI): *m/z* 206 ($M^{+\cdot}$).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06: H, 6.84: N, 13.58. Found: C, 64.15; H, 6.82; N, 13.52.

1,3,3-Trimethylindolin-5-amine (1)

The general procedure of Zhao and coworkers[15] was followed. 1,3,3-Trimethyl-5-nitroindoline (**9**, 1.05 g, 1.0 equiv, 5.10 mmol) was placed in an EtOH-water mixture (4:1, 60 mL). Iron powder (1.15 g, 4.0 equiv, 20.5 mmol) and NH_4Cl (0.35 g, 1.3 equiv, 6.54 mmol) were added, and the mixture was heated at 85 °C for 2 h, after which time TLC analysis (1:1 ether-hexane) indicated complete consumption of the starting material. The reaction mixture was filtered through a 2 cm Celite pad, which was washed with additional EtOH (15 mL). The volume of the filtrate was reduced under vacuum, and then the mixture was diluted with saturated $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with an aqueous $NaHCO_3$ and NaCl mixture (1:1, 50 mL), and dried (Na_2SO_4). The solvent was removed under vacuum to afford **1** (0.72 g, 80%) as a purple oil. IR: 3421, 3347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (dd, $J = 7.5$ Hz, 1H), 6.47 (s, 1H), 6.36 (d, $J = 7.5$ Hz, 1H), 3.23 (br s, 2H), 2.96 (s, 2H), 2.67 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.5, 140.8, 138.5, 114.3, 110.4, 108.7, 71.1, 40.4, 37.4, 27.1; MS (EI): *m/z* 176 ($M^{+\cdot}$).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.01; H, 9.18; N, 15.83.

Ethyl 3-bromo-4-hydroxybenzoate (11)

Note: This is a commercial compound, but very expensive. 3-Bromo-4-hydroxybenzoic acid (**10**, 15.0 g, 69.1 mmol) was dissolved in EtOH (200 mL), and concentrated H_2SO_4 (1 mL) was added. The solution was heated at reflux for 3 days, and then the solvent was removed under vacuum. The residue was poured into water (200 mL), and the

aqueous layer was extracted with ether (3 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and aqueous NaCl (100 mL), and then dried (Na_2SO_4). Concentration under vacuum gave **11** (14.6 g, 86%) as a white solid, mp 102-104 °C (lit[17] mp 102-103 °C). IR: 3244, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, $J = 2.0$ Hz, 1H), 7.93 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.05 (d, $J = 8.5$ Hz, 1H), 5.92 (br s, 1H), 4.35 (q, $J = 7.1$ Hz, 2H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1, 156.0, 133.8, 131.0, 124.4, 115.7, 110.0, 61.1, 14.3; MS (EI): *m/z* 242, 244 (*ca* 1:1, $M^{+\cdot}$).

3-Methyl-3-buten-1-yl p-toluenesulfonate (13)

3-Methyl-3-buten-1-ol (**12**, 12.5 g, 14.4 mL, 1.0 equiv, 145.3 mmol) was dissolved in DCM (150 mL), and the solution was cooled to 0 °C. Pyridine (23.7 g, 24.2 mL, 2.05 equiv, 300.0 mmol) was added in one portion, followed by dropwise addition of a solution of *p*-toluenesulfonyl chloride (27.2 g, 0.98 equiv, 142.5 mmol) in DCM (50 mL) over 20 min. The mixture was allowed to slowly warm to room temperature with stirring overnight. The crude reaction mixture was washed with water (3 × 100 mL), aqueous NH_4Cl (150 mL), aqueous NaCl (100 mL), and then dried (Na_2SO_4). The solvent was removed under vacuum to afford **13** (31.7 g, 93%) as a pale yellow liquid. The spectra matched those reported previously.[18]

Ethyl 3-bromo-4-((3-methyl-3-buten-1-yl)oxy)benzoate (14)

Ethyl 3-bromo-4-hydroxybenzoate (**11**, 14.5 g, 1.0 equiv, 59.2 mmol) and 3-methyl-3-buten-1-yl *p*-toluenesulfonate (**13**, 14.2 g, 1.0 equiv, 59.2 mmol) were dissolved in DMF (50 mL), and K_2CO_3 (32.7 g, 4.0 equiv, 237.0 mmol) was added. The reaction mixture was stirred under N_2 at 80 °C for 18 h, at which time TLC analysis (1:2 ether-hexane) indicated complete consumption of the starting phenol. The reaction mixture was cooled to room temperature and then poured into water (200 mL). The aqueous layer was extracted with ether (3 × 100 mL), and the combined organic layers were washed with water (3 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), aqueous NaCl (100 mL), and then dried (Na_2SO_4). Removal of the solvent under vacuum gave **14** (15.0 g, 81%) as a colorless oil. IR: 1712, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, $J = 2.1$ Hz, 1H), 7.96 (dd, $J = 8.6$, 2.1 Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 1H), 4.88 (s, 1H), 4.82 (s, 1H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.19 (t, $J = 6.8$ Hz, 2H), 2.59 (t, $J = 7.1$ Hz, 2H), 1.85 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 158.8, 141.7, 134.8, 130.5, 124.0, 112.6, 111.8, 111.7, 68.1, 61.0, 36.9, 23.0, 14.3; MS (EI): *m/z* 312, 314 (*ca* 1:1, $M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47. Found: C, 53.73; H, 5.46.

Ethyl 4,4-dimethylchroman-6-carboxylate (15)

Ethyl 3-bromo-4-((3-methyl-3-buten-1-yl)oxy)benzoate (**14**, 14.8 g, 1.0 equiv, 47.3 mmol) was dissolved in DMF (30 mL), and sodium acetate (9.60 g, 2.5 equiv, 117 mmol), sodium formate (4.02 g, 1.25 equiv, 59.1 mmol), and tetraethylammonium chloride

(9.37 g, 1.2 equiv, 56.6 mmol) were added sequentially to form a slurry. Water (2 mL) and $Pd(OAc)_2$ (1.06 g, 0.1 equiv, 0.47 mmol, 10 mol%) were added, and the reaction mixture was heated at 95 °C under N_2 for 18 h. The mixture was cooled, filtered through a 2 cm Celite pad, and then partitioned between water (200 mL) and ether (100 mL). The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed with water (3 × 100 mL), aqueous NaCl (100 mL), and then dried (Na_2SO_4). The solvent was removed under vacuum to afford **15** (10.4 g, 94%) as a colorless oil. IR: 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, $J = 2.1$ Hz, 1H), 7.75 (dd, $J = 8.6$, 2.1 Hz, 1H), 6.79 (d, $J = 8.6$ Hz, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 4.24 (t, $J = 5.3$ Hz, 2H), 1.85 (t, $J = 5.4$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 1.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 157.7, 131.4, 129.1, 128.8, 122.5, 116.9, 63.4, 60.6, 37.1, 30.8, 30.6, 14.4; MS: *m/z* 234 ($M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.72; H, 7.74.

4,4-Dimethylchroman-6-carboxylic acid (16)

Ethyl 4,4-dimethylchroman-6-carboxylate (**15**, 10.0 g, 1.0 equiv, 42.7 mmol) was placed in an EtOH-water mixture (2:1, 150 mL), and KOH (4.8 g, 2.0 equiv, 85.7 mmol) was added. The reaction was stirred at 80 °C for 3 h, at which time TLC analysis (ether) indicated the reaction was complete. The volume was reduced under vacuum, the residue was acidified with 1 M HCl to pH 2, and then the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were washed with aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **16** (7.85 g, 89%) as a white solid, mp 226-228 °C (lit[4] mp 227.5-228.5). The spectral data matched those reported previously.[4]

4-Formylphenyl 4,4-dimethylchroman-6-carboxylate (17)

4,4-Dimethylchroman-6-carboxylic acid (**16**, 7.54 g, 1.0 equiv, 36.6 mmol) and 4-hydroxybenzaldehyde (4.46 g, 1 equiv, 36.6 mmol) were dissolved in DCM (200 mL). 4-Dimethylaminopyridine (11.2 g, 2.5 equiv, 91.8 mmol) was added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (7.02 g, 1.0 equiv, 36.6 mmol). The reaction mixture was stirred at 23 °C for 24 h and then washed with 1 M HCl (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and aqueous NaCl (100 mL), and then dried (Na_2SO_4). Concentration under vacuum afforded a tan, oily solid that was recrystallized from EtOH (15 mL) to afford **17** (10.2 g, 90%) as a cream-colored solid, mp 131-132 °C (lit[4] mp 132-133.5 °C). The spectral data matched those reported previously.[4]

4-Formylphenyl 4,4-Dimethylchroman-6-carboxylate Thiosemicarbazone (2)

4-Formylphenyl 4,4-dimethylchroman-6-carboxylate (**17**, 3.0 g, 1.0 equiv, 9.7 mmol) was suspended in ethanol (180 mL), and the mixture was heated to 70 °C until a clear solution was formed. To this warm solution was added a warm solution of thiosemicarbazide (0.97 g, 1.1 equiv, 10.6 mmol) in water (57 mL). Three drops of glacial acetic acid

were added, and the solution was allowed to cool to room temperature with stirring overnight. At this time, white crystals were noted in the flask, and the mixture was further cooled to –20 °C for 24 h. The mixture was warmed to room temperature for 1 h before collecting the crystals by vacuum filtration. The white solid was dried under vacuum overnight to afford **2** (2.88 g, 78%), mp 187-189 °C (lit[4] mp 185-186 °C). The spectra for this compound closely matched the previous report.[4] IR: 3436, 3402, 3263, 3166, 1729, 1601 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 8.22 (br s, 1H), 8.09 (superimposed d, $J = 1.8$ Hz, 1H and s, 1H), 8.06 (br s, 1H), 7.91 (d, $J = 8.6$ Hz, 2H), 7.85 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.31 (d, $J = 8.6$ Hz, 2H), 6.92 (d, $J = 8.6$ Hz, 1H), 4.28 (t, $J = 5.4$ Hz, 2H), 1.86 (t, $J = 5.4$ Hz, 2H), 1.35 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 178.5, 164.7, 158.7, 152.3, 141.8, 132.5, 132.4, 129.8, 129.7, 128.9, 122.8, 121.0, 117.7, 63.7, 36.6, 30.8, 30.7; MS: m/z 383 ($M^{+\cdot}$).

Anal. Calcd for $C_{20}H_{21}N_3O_3S$: C, 62.64; H, 5.52; N, 10.96. Found: C, 62.72; H, 5.54; N, 10.89.

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References

1. D. M. Benbrook, S. A. Kamelle, S. B. Guruswamy, S. A. Lightfoot, T. L. Rutledge, N. S. Gould, B. N. Hannafon, S. T. Dunn and K. D. Berlin, *Invest. New Drugs*, **23**, 417 (2005).
2. L. Garcia-Contreras, S. M. Hatipoglu and D. M. Benbrook, U.S. Patent US 20190133939 A1 20190509; *Chem. Abstr.*, **170**, 591029 (2019).
3. S. Liu, C. W. Brown, K. D. Berlin, A. Dhar, S Guruswamy, D. Brown, G. J. Gardner, M. J. Birrer and D. M. Benbrook, *J. Med. Chem.*, **47**, 999 (2004). doi:10.1021/jm030346v
4. D. M. Benbrook, M. M. Madler, L. W. Spruce, P. J. Birckbichler, E. C. Nelson, S. Subramanian, G. M. Weerasekare, J. B. Gale, M. K. Patterson, Jr., B. Wang, W. Wang, S. Lu, T. C. Rowland, P. DiSilvestro, C. Lindamood III, D. L. Hill and K. D. Berlin, *J. Med. Chem.*, **40**, 3567 (1997). doi:10.1021/jm970196m
5. K. M. Waugh, K. D. Berlin, W. T. Ford, E. M. Holt, J. P. Carrol, P. R. Schomber, M. D. Thompson and L. J. Schiff, *J. Med. Chem.*, **28**, 116 (1985). doi:10.1021/jm00379a021
6. T. Mizoroki, K. Mori and O. Atsumu, *Bull. Chem. Soc. Jpn.,* **44**, 581 (1971).
7. R. F. Heck and J. P. Nolley Jr., *J. Org. Chem.*, **37**, 2320 (1972).
8. T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1287 (1984).
9. J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; J. Wiley and Sons: Chichester, Sussex, England, 2004, pp 15-17, 115-119.
10. M. Catellani, G. P. Chiusoli, W. Giroldini and S. Giuseppi, *J. Organometal. Chem.*, **199**, C21 (1980).
11. M. T. Reetz, W. Helbig, S. A. Quaiser, U. Stimming, N. Breurer and R. Vogel, *Science*, **267**, 367 (1995).
12. S. Cacchi, *Pure Appl. Chem.,* **62**, 713 (1990).

13. A. Arcadi, F. Marinelli, E. Bernocchi, S. Cacchi and G. Ortar, *J. Organometal. Chem.,* 368, 249 (1989).
14. P. Liu, L. Huang, Y. Lu, M. Dilmeghani, J. Baum, T. Xiang, J. Adams, A. Tasker, R. Larsen and M. M. Faul, *Tetrahedron Lett.,* **48**, 2307 (2007). These authors also noted that Et_4NCl was better than Bu_4NCl.
15. R. Bakthavatchalam, C. A. Blum and B. L. Chenard, World Patent WO 2005023807 A2 20050317, 2005; *Chem Abstr.*, 142, 316855 (2005). Several of the compounds in this series were reported, but with no characterization data.
16. G. Zhao, A. J. Souers, M. Voorbach, H. D. Falls, B. Droz, S. Brodjian, Y. Y. Lai, R. R. Iyengar, J. Gao, A. S. Judd, S. H. Wagaw, M. M. Ravn, K. N. Engstrom, J. K. Lynch, M. M. Mulhern, J. Freeman, B. D. Dayton, X. Wang, N. Grihalde, D. Fry, D. W. A. Beno, K. C. Marsh, Z. Su, G. J. Diaz, C. A. Collins, H. Sham, R. M. Reilly, M. E. Brune and P. R. Kym, *J. Med. Chem.,* **51**, 380 (2008). doi:10.1021/jm7013887
17. A. S. Hussey and I. J. Wilk, *J. Am. Chem. Soc*., **72**, 830 (1950).
18. A. K. Ghosh and D. R. Nicponski, *Org. Lett*., **13**, 4328 (2011). doi:10.1021/ol2016675