Application of the PMC Protecting Group in the Efficient Synthesis of 4,4-Disubstituted Piperidines

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Abstract: An efficient synthesis of the 4,4-disubstituted piperidine scaffold **1** was accomplished by treating the PMC N-protected α,β-unsaturated ethyl cyanoacetate **9** with various Grignard reagents (R_1MgX). Subsequent heating at 190°C in a strong base provided carboxylic acids **12–20b** in good yield. The PMC group was easily removed at room temperature with 33% HBr in acetic acid.

Keywords: 1,4-Addition, 4,4-disubstituted piperidines, PMC protecting group

INTRODUCTION

Substituted piperidines, well-known scaffolds in pharmaceutical research, are commonly found in tachykinin receptor antagonists.[1] In the course of our work to develop biologically active molecules, a method was needed to synthesize a wide variety of 4,4-disubstituted piperidines (**1**) (see Fig. 1). Ultimately, this procedure would allow us to vary R_1 and R_2 with a variety of functionality and be amenable to parallel solution phase synthesis. Although a literature search revealed very limited options in forming this quaternary center, one reported procedure from Schneider and colleagues looked promising.[2]
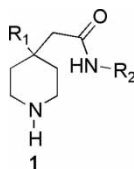
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Figure 1. 4,4-disubtituted piperidine.

They utilized the 1,4 addition of Grignard reagents to α,β-unsaturated ethyl cyanoacetates (Scheme 1). Tosylated piperidinone **2** was treated with ethyl cyanoacetate to provide the α,β-unsaturated ethyl cyanoacetate **3**. The substrate then reacted with Grignard reagents and the 4,4-disubstituted piperidines **4** were obtained in various yields. The substrates were heated at a high temperature with a strong base, causing hydrolysis of the cyano group and further decarboxylation to provide the carboxylic acid **5**. They subsequently used refluxing 33% HBr in acetic acid to remove the N-tosyl protecting group.

Although Schneider and colleagues' methodology looked attractive because it enabled us to take advantage of the large number of commercially available Grignard reagents, we found that removing the N-tosyl group with refluxing HBr in acetic acid as reported was not compatible with many of our target compounds. Removal of the N-tosyl group requires harsh conditions; common procedures for removal include not only refluxing HBr in acetic acid, which Schneider and coworkers used, but also lithium or sodium naphthalide.[3] Such harsh conditions are not compatible with many functional groups, including those of our target compounds. Reagents such as those listed previously are also unattractive for parallel solution phase synthesis. To utilize Schneider's methodology, a protecting group was required that would be stable in a strong base at high temperatures and that would be capable of being removed more conveniently.

We chose the 2,2,5,7,8-pentamethylchroman-6-sulphonyl (PMC) group, a protecting group reported by Ramage and Green and developed as an acid labile protecting group for the guanidine side chain functionality of arginine.[4] In addition, the PMC group has recently been used as a
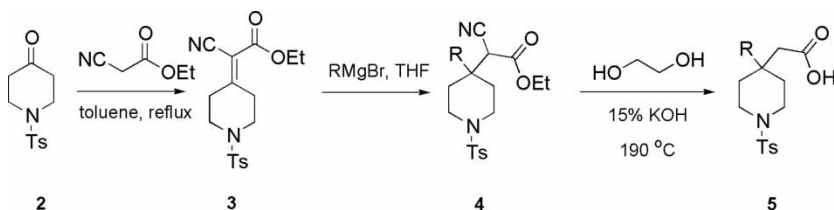
Scheme 1. Bochow and Schneider's synthesis.

replacement for the tosyl group in the Mitsunobu reaction of protected amines.[5] An advantage of the PMC group is that, like the tosyl group, it is robust enough to withstand many types of functional group transformations. But, unlike the tosyl group, the PMC group can be easily removed with HBr in acetic acid at room temperature. Utilization of the PMC protecting group afforded solutions to the liabilities of the tosyl moiety. The desired 4,4-disubstituted piperidine analogs could be formed in parallel, with fewer by-products, because of the less severe removal conditions.

RESULTS AND DISCUSSION
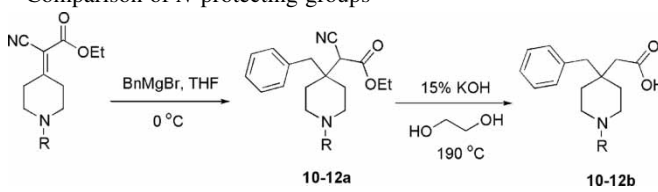
The starting PMC protected piperidine was easily synthesized in three steps (Scheme 2). The commercially available piperidine alcohol **6** was treated with PMC-Cl, triethylamine in methylene chloride, to yield **7**. The alcohol was oxidized to the ketone with TPAP (tetrapropylammonium perruthenate) and NMO (4-methylmorpholine-*N*-oxide) in methylene chloride. The crude material **8** then reacted with ethyl cyanoacetate, ammonium acetate, acetic acid, and trimethyl orthoformate in toluene at reflux to give **9** in 75% yield over three steps.

We compared the reactivity of the tosyl, PMC, and BOC protected piperidines upon addition of benzyl Grignard (Table 1). All compounds gave excellent yields of the cyanoacetate intermediate. Not surprisingly, upon heating with a strong base, the BOC group did not survive. The PMC and tosyl piperidines gave very good yields of the desired acid.

Table 2 summarizes the results from treating **9** with various commercially available Grignard reagents. Using two equivalents of the Grignard reagent was optimal and most of the additions afforded moderate to good yields. For example, the addition of benzyl magnesium bromide (**12a**) and pentyl magnesium bromide (**15a**) to **9** gave a 96% and 89% yield respectively. The methyl derivative **13a** was synthesized in 86% yield. However, the cyclopentyl Grignard (**16a**) and cyclopropyl Grignard (**17a**) produced
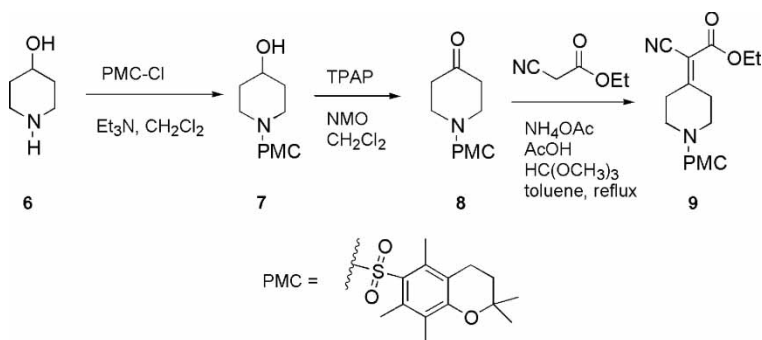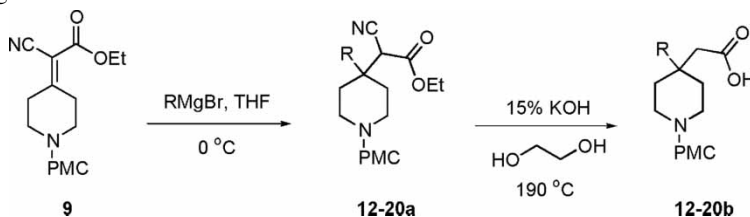
Scheme 2. Synthesis of PMC *N*-protected α,β-unsaturated ethyl cyanoacetate.

Table 1. Comparison of *N*-protecting groups

Entry	R	Yield (%)	Yield (%)
10	t-BOC	96	trace
11	tosyl	99	73
12	PMC	96	80

modest 33% and 39% yields respectively. In cases where remaining starting material was observed, adding additional Grignard reagent during the course of the reaction did not improve the yield. Example **14a**, an important intermediate because of the allyl group's potential to be further functionalized, proceeded in 53% yield. Hydrolysis of the cyano group followed by decarboxylation was achieved using 15% KOH in ethylene glycol at 190°C for 4 h. The reaction gave good yields with no major single impurity. All compounds were purified using the CombiFlash by Isco flash chromatography system.

To examine the utility of the methodology, aniline was coupled to the acid **12** using EDC, HOBt in methylene chloride to provide **21** in 75% yield

Table 2. Synthesis of 4,4-disubstituted piperidine scaffolds using various grignard reagents

Entry	R	Product	Yield (%)	Product	Yield (%)
12	benzyl	**12a**	96	**12b**	80
13	CH$_3$	**13a**	86	**13b**	74
14	allyl	**14a**	53	**14b**	94
15	*n*-C$_5$H$_{11}$	**15a**	89	**15b**	81
16	cyclopentyl	**16a**	33	**16b**	50
17	cyclopropyl	**17a**	39	**17b**	64
18	4-chlorophenyl	**18a**	48	**18b**	84
19	phenyl	**19a**	70	**19b**	78
20	4-methoxyphenyl	**20a**	70	**20b**	79
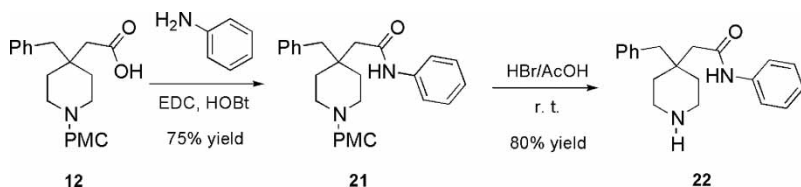
Scheme 3. Utilization of the resulting 4,4-disubstitued piperidine scaffold for further synthesis.

(Scheme 3). Removal of the PMC group was accomplished by treating **21** with 33% HBr in acetic acid for 2 h at room temperature. If the reaction went longer than 2 h, brominated by-products developed. (The allyl group in example **14** does not survive the conditions to remove the PMC group. It can only be used as a functional handle. The brominated by-products were not isolated but could be detected by LC/MS analysis of the crude reaction mixture.) After purification, the desired piperidine **22** was isolated in 80% yield. Subsequent reactions were run in parallel using a Radleys Carousal reaction station.

By utilizing the PMC protecting group, we were able to modify Schneider's procedure and develop an efficient synthesis of diverse 4,4-disubstituted piperidines. The relative ease of removal of the PMC protecting group afforded a parallel solution phase approach to the synthesis of the target compounds.

EXPERIMENTAL

All starting materials were commercially available and were not purified further before use. All NMR spectra were recorded on a Bruker Avance 300 (300 MHz, 75 MHz) spectrometer in the noted deuterated solvents. Chemical shifts (δ) are given in ppm downfield from TMS. HPLC purities were afforded by Hewlett-Packard 1050 using a 5% MeCN/H2O–95% MeCN/H2O gradient and a Supelco Supelcosil column. High-resolution mass spectra were collected using an Agilent 1100/Micromass LC-MS system.

***N*-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl)-piperidin-4-ol (7).** A solution of 4-hydroxypiperidine (2.0 g, 19.7 mmol) in dichloromethane (75 mL) was treated with triethylamine (3.29 mL, 23.6 mmol) and the reaction was allowed to stir at room temperature for 10 min. 2,2,5,7,8-Pentamethylchromane-6-sulfonyl chloride (PMC-Cl) (5.99 g, 19.7 mmol) was then added and the reaction was allowed to proceed at room temperature overnight. The reaction mixture was partitioned between saturated ammonium chloride (75 mL) and dichloromethane (3 × 75 mL). Combined organic extracts were dried over Na$_2$SO$_4$, filtered, and reduced. The crude product (**7**) was used directly in the next synthetic step without further purification.

N-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl)-piperidin-4-one (8). Crude product (**7**) (7.24 g, 19.7 mmol) was dissolved in dichloromethane (80 mL) and the solution was cooled to 0°C. The reaction mixture was treated with 4-methylmorpholine-N-oxide (4.62 g, 39.4 mmol) and tetrapropylammonium-perruthenate (TPAP) (346 mg, 0.985 mmol, 5 mol %) and the solution was allowed to stir overnight while gradually warming to room temperature. The reaction mixture was then poured over a plug of silica gel, which was repeatedly washed with dichloromethane (2 × 200 mL) and ethyl acetate (2 × 200 mL). The combined organic fractions were reduced to afford the crude product as a light yellow solid. Crude yield: 7.3 grams. Because of the purity of the crude product (∼90% by HPLC), further purification was not performed.

Cyano [N-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl)-piperidin-4-ylidene]-acetic acid ethyl ester (9). The crude **8** (7.24 g, 19.7 mmol) in anhydrous toluene (100 mL) was treated with cyanoacetic acid ethyl ester (2.71 mL, 23.9 mmol), ammonium acetate (365 mg, 4.74 mmol), acetic acid (0.717 mL, 11.9 mmol), and trimethylorthoformate (2.54 mL, 23.9 mmol). The reaction mixture was then heated to reflux until HPLC showed consumption of starting material. After 5 h of reaction, the mixture was allowed to cool and was reduced. The resulting oil was taken up in ethyl acetate (100 mL) and was washed with saturated sodium bicarbonate (100 mL). Combined organic layers were dried over sodium sulfate, filtered, and reduced. Pure product was isolated via Isco flash column chromatography using a heptanes/ethyl acetate solvent system (0% ethyl acetate to 40% ethyl acetate over 47 min). 6.93 g (75% for 3 steps) of **9** (98% by HPLC) was obtained as a fluffy white powder. HRMS m/z $(M + H)^+$ calculated: 461.2111, found: 461.2081. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.28 (q, 2H, $J = 7.14$ Hz), 3.41 (m, 4H), 3.23 (t, 2H, $J = 5.91$ Hz), 2.86 (t, 2H, $J = 6.0$ Hz), 2.66 (t, 2H, $J = 6.83$ Hz), 2.53 (s, 3H), 2.51 (s, 3H), 2.14 (s, 3H), 1.84 (t, 2H, $J = 6.80$ Hz), 1.37 t, 3H, $J = 7.14$ Hz), 1.33 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.3, 161.8, 155.7, 138.4, 126.2, 125.3, 118.9, 115.2, 104.7, 74.6, 62.5, 45.2, 44.9, 35.6, 33.0, 30.9, 27.1, 21.9, 18.6, 17.6, 14.4, 12.6.

Example Procedure for the Grignard Addition

[4-Benzyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-cyanoacetic acid ethyl ester (12a). A solution of **9** (200 mg, 0.434 mmol) in THF (2 mL) under nitrogen was cooled to 0°C and was treated with benzyl magnesium bromide (0.868 mL, 0.868 mmol, 1 M solution in THF) via syringe. The reaction mixture was allowed to stir overnight while gradually warming to room temperature. Upon completion, the solution was poured over saturated NH$_4$Cl (15 mL) and organics were extracted with ethyl

acetate ($3 \times 10\,\text{mL}$). Combined organic extracts were dried over Na_2SO_4, filtered, and reduced. The product was obtained via Isco flash column chromatography using a heptanes/ethyl acetate solvent system (0% ethyl acetate to 40% ethyl acetate over 47 min). 230 mg (96%) of **12a** was isolated as a white solid (90% purity by HPLC). HRMS m/z (M + H)$^+$ calculated: 553.2737, found: 553.2723. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.16–7.37 (m, 5H), 4.24 (q, 2H, $J = 7.14\,\text{Hz}$), 3.60 (s, 1H), 3.38 (m, 4H), 3.03 (s, 1H), 2.94 (s, 1H), 2.63 (t, 2H, $J = 6.82\,\text{Hz}$), 2.48 (s, 6H), 2.11 (s, 3H), 1.83 (t, 2H, $J = 6.88\,\text{Hz}$), 1.72 (m, 4H), 1.32 (s, 6H), 1.28 (t, 3H, $J = 7.16\,\text{Hz}$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.2, 155.5, 138.6, 138.4, 135.5, 131.1, 129.0, 128.9, 128.0, 127.7, 127.4, 125.9, 125.2, 118.9, 115.7, 74.5, 63.2, 44.7, 40.2, 40.0, 39.0, 33.0, 31.1, 27.2, 21.8, 18.5, 17.6, 14.4, 12.6.

Example Procedure for Decarboxylation

[4-Benzyl-1-2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (12b). **12a** (240 mg, 0.446 mmol) was gradually dissolved in a 15% (w/w) solution of KOH in ethylene glycol (5 mL) upon heating. The solution was further heated to 190°C and was allowed to stir at that temperature until HPLC showed consumption of starting materials (4 h). The mixture was allowed to cool and was diluted with water (50 mL) and 1 N HCl (50 mL). Organics were extracted with dichloromethane ($3 \times 40\,\text{mL}$) and ethyl acetate ($3 \times 40\,\text{mL}$). The combined organic layers were dried over Na_2SO_4, filtered, and reduced in vacuo. Purification was achieved via Isco flash column chromatography using a heptanes/ethyl acetate solvent system (0% ethyl acetate to 50% ethyl acetate over 50 min). 175 mg (80%) of **12b** was isolated as a white solid (96% purity by HPLC). HRMS m/z (M + H)$^+$ calculated: 500.2471, found: 500.2641. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19–7.31 (m, 5H), 3.36 (m, 2H), 3.15 (m, 2H), 2.85 (s, 2H), 2.64 (t, 2H, $J = 6.76\,\text{Hz}$), 2.52 (s, 3H), 2.51 (s, 3H), 2.33 (s, 2H), 2.12 (s, 3H), 1.83 (t, 2H, $J = 6.73\,\text{Hz}$), 1.63 (t, 4H, $J = 5.09\,\text{Hz}$), 1.33 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 179.1, 155.1, 138.2, 138.0, 135.6, 130.4, 128.6, 127.1, 125.7, 124.8, 118.5, 117.6, 74.1, 42.9, 39.8, 35.4, 33.7, 32.7, 26.8, 24.9, 21.5, 18.2, 17.2, 12.2.

Representative Procedure for Alkylation

2-[4-Benzyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-N-phenyl-acetamide (21). A stirred solution of **12b** (140 mg, 0.28 mmol) in anhydrous THF (5 mL) was treated with aniline (0.28 mL, 0.3 mmol), 1-[(3-dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (57 mg, 0.3 mmol) and 1-hydroxybenzotriazole (41 mg, 0.3 mmol). The reaction was allowed to stir at room temperature overnight. The solution was partitioned between saturated sodium bicarbonate (25 mL) and ethyl acetate ($3 \times 15\,\text{mL}$). The combined organic extracts were dried over Na_2SO_4,

filtered, and reduced. Isolation of pure product was achieved via Isco flash column chromatography using a heptanes/ethyl acetate solvent system (0% ethyl acetate to 40% ethyl acetate over 42 min). 120 mg (75%) of **21** was isolated as a white solid (96% purity by HPLC). HRMS m/z $(M + H)^+$ calculated: 575.2944, found: 575.2983. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.10–7.51 (m, 10H), 3.35 (m, 2H), 3.19 (m, 2H), 2.97 (s, 2H), 2.64 (t, 2H, $J = 6.77$ Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.25 (s, 2H), 2.12 (s, 3H), 1.83 (t, 2H, $J = 6.77$ Hz), 1.65 (m, 4H), 1.33 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.1, 154.8, 138.0, 137.3, 130.9, 128.9, 127.9, 125.2, 124.4, 124.2, 119.8, 118.3, 73.8, 39.7, 35.5, 34.1, 33.6, 32.3, 30.3, 26.4, 21.2, 17.7, 16.8, 11.8.

Example Procedure for PMC Cleavage

2-(4-Benzyl-piperidin-4-yl)-*N*-phenyl-acetamide (22). Compound **21** (115 mg, 0.2 mmol) was treated with 33% HBr/AcOH (3 mL) and the reaction was allowed to stir at room temperature for 2 h. HPLC showed almost complete consumption of starting material, but allowing the reaction to run longer afforded a brominated product. The mixture was then quenched with saturated sodium bicarbonate (5 mL) and the product was extracted repeatedly with ethyl acetate (5 × 25 mL). Combined organic layers were dried over Na$_2$SO$_4$, filtered, and reduced. The resulting syrup was dissolved in ethyl acetate (2 mL) and upon treatment with ethereal hydrogen chloride (5 mL), the solution became cloudy. The solution was reduced under nitrogen and the product was recrystallized from ethyl acetate. 55 mg (80%) of the desired product **22** was isolated as an off-white solid (100% purity by HPLC). HRMS m/z $(M + H)^+$ calculated: 309.1968, found: 309.1964. ^{1}H NMR (300 MHz, DMSO) δ 8.50 (s, 1H), 7.68 (d, 2H, $J = 7.87$ Hz), 7.22–7.32 (m, 8H), 4.59 (s, 1H), 3.20 (m, 4H), 2.91 (s, 2H), 2.42 (s, 2H), 1.67 (m, 4H). ^{13}C NMR (75 MHz, DMSO) δ 169.8, 139.4, 137.5, 131.8, 131.2, 128.9, 128.3, 126.6, 123.6, 121.6, 119.7, 43.4, 34.8, 30.9.

Compound Data

4-Benzyl-4-(cyano-ethoxycarbonyl-methyl)-piperidine-1-carboxylic acid tert-butyl ester (10a). 90% purity as determined by HPLC. HRMS m/z $(M + H)^+$ calculated: 387.2285, found: 387.2342. ^{1}H NMR (300 MHz, DMSO) δ 7.26–7.42 (m, 3H), 7.18 (d, 2H, $J = 6.55$ Hz), 4.15 (q, 2H, $J = 7.14$ Hz), 3.70 (s, 1H), 3.32–3.54 (m, 4H), 2.84 (d, 2H, $J = 7.05$ Hz), 1.74 (m, 2H), 1.54 (m, 2H), 1.35 (s, 9H), 1.23 (t, 3H, $J = 7.07$ Hz). ^{13}C NMR (75 MHz, DMSO) δ 165.2, 153.9, 135.5, 130.9, 128.5, 128.4, 127.9, 127.8, 116.1, 79.2, 62.9, 43.3, 40.3, 40.0, 39.8, 31.9, 30.7, 27.9, 13.8.

[4-Benzyl-1-(toluene-4-sulfonyl)-piperidin-4-yl]-cyanoacetic acid ethyl ester (11a). 90% purity as determined by HPLC. HRMS m/z $(M + H)^+$

calculated: 441.1849, found: 441.1851. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 (d, 2H, J = 8.23 Hz), 7.20–7.36 (m, 5H), 7.09 (d, 2H, J = 6.80 Hz), 4.23 (q, 2H, J = 7.15 Hz), 3.45 (s, 1H), 3.14 (m, 4H), 2.80 (d, 2H, J = 7.26 Hz), 2.46 (s, 3H), 1.65 (m, 4H), 1.28 (t, 3H, J = 7.11 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.0, 144.2, 135.1, 133.5, 131.1, 130.2, 128.9, 128.0, 127.8, 115.5, 63.3, 44.3, 41.9, 39.9, 39.7, 31.2, 31.1, 21.9, 14.4. Values are comparable to literature values.[2]

[4-Benzyl-1-(toluene-4-sulfonyl)-piperidin-4-yl]-acetic acid (11b). 95% purity as determined by HPLC. Data was comparable to literature values.[2]

Cyano-[4-methyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid ethyl ester (13a). 90% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 477.2424, found: 477.2422. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.27 (q, 2H, J = 7.16 Hz), 2.44 (s, 1H), 3.08 (m, 4H), 2.66 (t, 2H, J = 6.73 Hz), 2.51 (s, 9H), 2.12 (s, 3H), 1.83 (t, 2H, J = 6.80 Hz), 1.75 (m, 4H), 1.32 (s, 6H), 1.29 (t, 3H, J = 7.19 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.9, 155.5, 138.5, 138.4, 126.1, 125.1, 115.4, 74.5, 63.1, 48.7, 40.2, 40.1, 36.5, 35.3, 34.6, 33.0, 29.4, 27.1, 21.9, 20.6, 18.6, 17.6, 14.5, 12.6.

[4-Methyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (13b). 95% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 424.2158, found: 242.2151. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.09–3.27 (m, 4H), 2.65 (t, 2H, J = 6.78 Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.31 (s, 2H), 2.12 (s, 3H), 1.83 (t, 2H, J = 6.78 Hz), 1.48–1.66 (m, 4H), 1.32 (s, 6H), 1.12 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ176.8, 155.3, 138.5, 138.3, 126.5, 125.0, 74.4, 45.2, 40.4, 36.6, 33.1, 32.0, 27.1, 24.1, 21.9, 18.6, 17.6, 12.6.

[4-Allyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-cyano-acetic acid ethyl ester (14a). 90% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 503.2580, found: 503.2576. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.71 (m, 1H), 5.24 (m, 2H), 4.24 (q, 2H, J = 7.12 Hz), 3.61 (s, 1H), 3.35 (m, 2H), 3.12 (m, 2H), 2.63 (t, 2H, J = 6.76 Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.41 (d, 2H, J = 5.89 Hz), 2.12 (s, 3H), 1.83 (t, 2H, J = 6.81 Hz), 1.73 (m, 4H), 1.33 (s, 6H), 1.32 (t, 3H, J = 7.26 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.1, 164.7, 155.1, 138.2, 138.0, 131.1, 125.6, 124.8, 120.9, 118.5, 115.2, 74.1, 62.8, 45.3, 39.5, 38.9, 36.9, 32.7, 26.8, 21.5, 21.0, 18.2, 17.2, 14.2. 14.0, 12.2.

[4-Allyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (14b). 97% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 450.2315, found: 450.2266. ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.74 (m, 1H), 5.13 (m, 2H), 3.21 (m, 4H), 2.65 (t, 2H, J = 6.77 Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.36 (s, 2H), 2.26 (d, 2H, J = 7.45 Hz), 2.12 (s, 3H),

1.83 (t, 2H, $J = 6.88$ Hz), 1.60 (m, 4H), 1.33 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.7, 155.3, 138.2, 138.3, 133.2, 126.5, 125.0, 119.6, 118.8, 74.4, 41.0, 40.4, 40.1, 34.9, 34.5, 33.0, 27.2, 21.8, 18.5, 17.5, 12.6.

Cyano-[1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-4-pentyl-piperidin-4-yl]-acetic acid ethyl ester (15a). 94% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 533.3050, found: 533.3065. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.24 (q, 2H, $J = 7.12$ Hz), 3.61 (s, 1H), 3.31 (m, 2H), 3.10 (m, 2H), 2.65 (t, 2H, $J = 6.74$ Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.13 (s, 3H), 1.81 (t, 2H, $J = 7.07$ Hz), 1.71 (m, 4H), 1.33 (s, 6H), 1.26–1.32 (m, 11H), 0.89 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.2, 155.5, 138.4, 126.0, 125.1, 118.9, 115.8, 74.5, 63.1, 45.9, 39.9, 39.2, 33.3, 33.1, 32.6, 32.3, 32.2, 27.2, 22.9, 22.8, 21.9, 18.6, 17.6, 14.4, 14.3, 12.6.

[1-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl)-4-pentyl-piperidin-4-yl]-acetic acid (15b). 95% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 480.2784, found: 480.2780. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.18 (m, 4H), 2.65 (t, 2H, $J = 6.72$ Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.35 (s, 2H), 2.12 (s, 3H), 1.83 (t, 2H, $J = 6.88$ Hz), 1.59 (m, 4H), 1.32 (s, 6H), 1.25–1.28 (m, 8H), 0.87 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.3, 155.3, 138.5, 138.3, 126.5, 125.0, 118.7, 74.4, 47.2, 40.7, 40.2, 36.8, 34.8, 34.7, 33.1, 32.7, 27.1, 22.9, 22.8, 21.8, 18.6, 17.6, 14.4, 12.6.

Cyano-[4-cyclopentyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid ethyl ester (16a). 91% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 531.2893, found: 531.2593. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.24 (q, 2H, $J = 7.09$ Hz), 3.92 (s, 1H), 3.38 (m, 4H), 2.65 (t, 2H, $J = 6.79$ Hz), 2.52 (s, 3H), 2.51 (s, 3H), 2.13 (s, 3H), 1.83 (t, 2H, $J = 6.61$ Hz), 1.77 (m, 4H), 1.60 (m, 9H), 1.32 (s, 6H), 1.29 (t, 3H, $J = 7.15$ Hz). ^{13}C NMR (75 MHz, DMSO) δ 165.4, 154.2, 137.4, 137.1, 126.4, 123.7, 118.7, 117.6, 74.1, 63.1, 42.9, 38.2, 38.7, 37.7, 37.3, 32.2, 31.8, 28.1, 26.4, 21.8, 20.7, 18.1, 18.0, 17.9, 16.9.

[4-Cyclopentyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (16b). 97% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 478.2628, found: 478.2620. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.39 (m, 2H), 3.06 (m, 2H), 2.65 (t, 2H, $J = 6.73$ Hz), 2.53 (s, 3H), 2.52 (s, 3H), 2.43 (s, 2H), 2.12 (s, 3H), 1.83 (t, 2H, $J = 6.86$ Hz), 1.53–1.62 (m, 13H), 1.32 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 178.3, 154.9, 138.1, 137.9, 126.2, 124.6, 118.4, 74.0, 46.1, 39.8, 37.0, 36.7, 32.7, 31.2, 26.8, 26.1, 25.6, 21.5, 18.2, 17.2, 12.2.

Cyano-[4-cyclopropyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid ethyl ester (17a). 90% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 503.2580, found: 503.2579.

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.26 (q, 2H, J = 7.11 Hz), 3.94 (d, 1H, J = 3.63 Hz), 3.45 (m, 4H), 2.65 (t, 2H, J = 6.70 Hz), 2.55 (s, 3H), 2.54 (s, 3H), 2.12 (s, 3H), 1.83 (t, 2H, J = 6.78 Hz), 1.57 (m, 4H), 1.32 (s, 6H), 1.26 (m, 3H), 0.28–0.45 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.3, 155.2, 137.2, 126.2, 124.0, 117.7, 73.3, 61.9, 42.4, 38.9, 38.8, 37.2, 31.9, 28.2, 27.5, 25.9, 20.7, 17.4, 17.3, 16.4, 13.3, 11.4, 0.0, −0.2.

[4-Cyclopropyl-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (17b). 95% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 450.2315, found: 450.2251. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.38 (m, 2H), 2.97 (t, 2H, J = 10.51 Hz), 2.65 (t, 2H, J = 6.75 Hz), 2.52 (s, 3H), 2.50 (s, 3H), 2.46 (s, 2H), 2.12 (s, 3H), 1.83 (t, 2H, J = 6.86 Hz), 1.53 (m, 4H), 1.32 (s, 6H), 0.37 (m, 4H), 0.35 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 177.5, 154.7, 137.9, 137.7, 125.9, 124.4, 118.1, 73.8, 40.2, 39.7, 33.2, 32.5, 31.6, 26.5, 22.4, 21.2, 20.0, 17.9, 16.9, 13.8, 11.9, 0.0.

[4-(4-Chlorophenyl)-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-cyanoacetic acid ethyl ester (18a). 90% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 573.2191, found: 573.2206. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37 (d, 2H, J = 8.68 Hz), 7.27 (d, 2H, J = 8.63 Hz), 3.98 (q, 2H, J = 7.15 Hz), 3.59 (s, 1H), 3.45 (m, 2H), 2.89 (t, 2H, J = 11.75 Hz), 2.64 (t, 2H, J = 6.62 Hz), 2.50 (s, 3H), 2.49 (s, 3H), 2.12 (s, 3H), 1.83 (t, 2H, J = 6.85 Hz), 1.32 (s, 6H), 1.03 (t, 3H, J = 7.15 Hz), 0.90 (m, 4H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.2, 155.6, 138.6, 138.4, 135.9, 134.7, 129.7, 129.4, 129.0, 125.9, 125.2, 118.9, 115.0, 74.5, 63.1, 50.5, 43.3, 40.7, 40.6, 33.3, 33.2, 33.0, 27.1, 17.6, 14.5, 14.0, 12.6, 11.7.

[4-(4-Chlorophenyl)-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (18b). 93% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 520.1925, found: 520.1922. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19–7.31 (m, 4H), 3.31 (m, 2H), 3.05 (t, 2H, J = 9.48 Hz), 2.64 (t, 2H, J = 6.76 Hz), 2.58 (s, 2H), 2.50 (s, 3H), 2.49 (s, 3H), 2.24 (m, 2H), 2.04 (m, 2H), 1.83 (t, 2H, J = 6.74 Hz), 1.32 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.2, 155.4, 141.6, 138.5, 138.3, 133.0, 129.2, 128.4, 126.3, 125.1, 118.8, 74.5, 46.4, 40.8, 39.1, 35.0, 33.1, 27.1, 21.9, 18.5, 17.5, 12.5.

Cyano-[1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-4-phenyl-piperidin-4-yl]-acetic acid ethyl ester (19a). 96% purity as determined by HPLC. HRMS m/z (M + H)$^+$ calculated: 539.2580, found: 539.2590. ^{1}H NMR (300 MHz, DMSO) δ 7.07–7.60 (m, 5H), 3.90 (q, 2H, J = 7.05 Hz), 3.36 (m, 4H), 3.33 (s, 1H), 2.63 (m, 2H), 2.41 (s, 6H), 2.08 (s, 3H), 1.95 (t, 4H, J = 11.90 Hz), 1.83 (t, 2H, J = 6.51 Hz), 1.29 (s, 6H), 0.94 (t, 3H, J = 7.11 Hz). ^{13}C NMR (75 MHz, DMSO) δ 164.3, 154.3, 137.5, 137.2,

137.1, 128.7, 127.5, 127.4, 125.9, 123.7, 118.7, 115.8, 74.2, 61.8, 49.4, 42.7, 39.2, 38.9, 38.7, 32.2, 31.7, 26.4, 20.7, 17.8, 16.8, 13.5, 11.9.

[1-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl)-4-phenyl-piperidin-4-yl]-acetic acid (19b). 95% purity as determined by HPLC. HRMS m/z $(M + H)^+$ calculated: 486.2315, found: 486.2309. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19–7.35 (m, 5H), 3.32 (m, 2H), 3.07 (m, 2H), 2.63 (t, 2H, $J = 6.77$ Hz), 2.58 (s, 2H), 2.50 (s, 3H), 2.49 (s, 3H), 2.30 (m, 2H), 2.11 (s, 3H), 2.01 (m, 2H), 1.82 (t, 2H, $J = 6.86$ Hz), 1.32 (s, 6H). ^{13}C NMR (75 MHz, DMSO) δ 171.8, 154.2, 143.6, 137.4, 137.2, 128.3, 126.7, 126.1, 123.6, 118.7, 74.1, 46.0, 40.3, 38.9, 38.7, 38.5, 33.8, 31.8, 26.4, 20.7, 17.8, 16.9, 11.9.

Cyano-[4-(4-methoxyphenyl)-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid ethyl ester (20a). 93% purity as determined by HPLC. HRMS m/z $(M + H)^+$ calculated: 569.2686, found: 569.2679. ^{1}H NMR (300 MHz, DMSO) δ 7.28 (d, 2H, $J = 8.85$ Hz), 6.95 (d, 2H, $J = 8.82$ Hz), 4.35 (s, 1H), 3.93 (q, 2H, $J = 7.07$ Hz), 3.76 (s, 3H), 3.33 (m, 4H), 2.63 (t, 2H, $J = 6.32$ Hz), 2.42 (s, 6H), 2.07 (s, 3H), 1.91 (m, 4H), 1.81 (t, 2H, $J = 6.68$ Hz), 1.28 (s, 6H), 0.98 (t, 3H). ^{13}C NMR (75 MHz, DMSO) δ 164.4, 158.4, 154.3, 137.5, 137.2, 128.7, 125.9, 123.7, 118.7, 115.8, 114.0, 74.2, 61.8, 55.0, 49.7, 42.3, 39.5, 39.2, 38.9, 38.7, 31.9, 26.4, 20.7, 17.8, 16.9, 13.5, 11.9.

[4-(4-Methoxyphenyl)-1-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)-piperidin-4-yl]-acetic acid (20b). 95% purity as determined by HPLC. HRMS m/z $(M + H)^+$ calculated: 516.2421, found: 516.2433. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21 (d, 2H, $J = 8.85$ Hz), 6.85 (d, 2H, $J = 8.81$ Hz), 3.79 (s, 3H), 3.32 (m, 2H), 3.06 (m, 2H), 2.63 (t, 2H, $J = 6.75$ Hz), 2.56 (s, 2H), 2.50 (s, 3H), 2.49 (s, 3H), 2.27 (m, 2H), 1.82 (t, 2H, $J = 6.87$ Hz), 1.32 (s, 6H). ^{13}C NMR (75 MHz, DMSO) δ 171.9, 157.3, 137.4, 137.2, 127.8, 126.1, 123.6, 118.7, 113.6, 74.1, 54.9, 44.5, 38.9, 38.7, 37.9, 33.9, 31.8, 26.4, 22.1, 17.8, 16.9, 11.9.

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