Practical synthesis of 5-amino-6-chlorochroman-8-carboxylic acid – a key intermediate for several potent 5-HT4 receptor agonists

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Synthetic routes for 5-amino-6-chlorochroman-8-carboxylic acid 1 a key intermediate for several potent 5-HT4 agonists have been explored. An efficient, high yielding, and a concise synthetic route has been established with significant modifications to the earlier reported synthetic protocols, where we have avoided the use of toxic and corrosive reagents and reduced the reaction temperature from reflux to room temperature wherever is possible. We have also reduced the number of steps to reach the target compound and avoided the use of silica gel column purifications.

Keywords: 5-amino-6-chlorochroman-8-carboxylic acid; 5-HT4 receptor agonists; Claisen reaction; toxic reagents; Alzheimer’s disease

1. Introduction

5-Amino-6-chlorochroman-8-carboxylic acid 1 is a key constituent of several potent 5-HT4 compounds reported by Janssen Pharmaceutica (1), GlaxoSmithKline (GSK) (1), Pfizer (1) and several others (1) (Figure 1). 5-HT4 receptor agonists have potential utility in the treatment of neurodegenerative disorders such as cognitive deficits in Alzheimer’s disease, gastrointestinal disorders such as constipation, irritable bowel syndrome, and functional dyspepsia (2). Many synthetic routes have been established to make this key intermediate 1 (3). Recently, scientists from GSK have explored various synthetic strategies to make bromo analog IV in multi-kilogram quantities (4). As part of our internal program, aimed at discovery, and development of new molecules, as 5-HT4 agonists for the treatment of cognitive deficits in Alzheimer’s disease, we were exploring various synthetic methods to have 5-amino-6-chlorochroman-8-carboxylic acid 1 on multi-gram scale to begin our research work.

2. Results and discussion

As we had to make this chloro analog 1 on multi-gram scale, we initially explored the available synthetic routes in the literature (3). Initially, we had opted for the synthetic route reported by Geracimos Rassias et al. (4) for the bromo analog IV as it looked to be simple and scalable. Based on this synthetic scheme, a modified synthetic route was developed for the chloro analog synthesis. The modified scheme is depicted in Figure 2. The modification in the original scheme included the replacement of methanol sulfuric acid combination in the hydrogenation step (Compound 6b to 7b) with ethanol alone. In the penultimate step, chlorination was done instead of bromination. All reactions went smoothly, and the pivaloyl derivative 8b was obtained with good-to-excellent yields.

However, subjecting compound 8b to drastic acid/base pivaloyl deprotection conditions such as use of NaOH, KOH, concentrated HCl, HBr, dry HCl, or TFA from room temperature to reflux temperatures for several hours did not yield the desired acid 1. In all the conditions that were explored, either the starting material was recovered or pivaloyl derivative 9b was recovered (Figure 3). We felt that the steric and bulky nature of pivaloyl might be the reason for the failure of pivaloyl deprotection. When we had explored some more published data, it is reported (3) that the acetyl group on acetamide derivative 8a could be easily deprotected using excess KOH (Figure 4). Keeping this information in the background, the acetamide derivative 8a was prepared starting from 4-acetamido-methylsalicylate 2a. However, the intramolecular Friedel Craft’s acylation reaction on compound 4a in presence of pivaloyl chloride and BF3.Et2O afforded product 5a in <30% yields (Figure 2) as against reported 83% yields for its pivaloyl analog (4). The efforts to optimize the reaction conditions proved...
Figure 1. 5-Amino-6-chlorochroman-8-carboxylic acid I a key component for several 5-HT$_4$ receptor ligands.

Figure 2. Synthesis of key intermediates 8a and 8b.
futile. Upon using the mixture of trifluoroacetic acid and acetic anhydride in the Friedel Craft’s reaction as reported by Luiz F. Silva (5), the product yields improved from 40% to 50%. However, as the reaction conditions and yields are not practical to scale up on a large scale, we looked at the alternative scheme by Andrew J. Walker (4), which they have reported for the bromo analog. This alternative synthetic scheme involves high-temperature Clainsen reaction as the key step. The modification in the scheme was necessitated as per the chloro derivative requirements, and the changes were brought in the scheme successfully to complete the synthesis of acid 1 in lesser number of steps with improved yields (Figure 4) avoiding all silica gel column purifications.

The synthesis started with commercially available and economical 4-aminosalicylic acid which was refluxed with concentrated sulfuric acid in methanol to obtain the ester 9. The ester 9 on treatment with acetic anhydride in dichloromethane in the absence of a base resulted in the clean conversion to the product 2a which was filtered as it has precipitated out from the reaction mixture. This modification facilitated easy isolation of the product 2a with high purity in quantitative yields, thus avoiding the tedious and exhaustive work-up procedures and column purifications to get rid of the organic bases. Deviating from the original reported chlorination reaction which was originally done on the compounds having phenolic group protected as either methyl ether or propargyl ether, the chlorination was done on phenolic compound 2a having no phenol protecting group. Thus the phenol 2a on treatment with N-chlorosuccinimide (NCS) in dichloroethane at reflux temperature, underwent ring chlorination successfully to yield chloro compound 10 in >90% yields. This modification has reduced the unwanted protection/deprotection steps and avoided the use of toxic and corrosive boron-trichloride required for methyl ether deprotection in the later steps. Contrary to the reported higher temperature reaction conditions required for propargylation of phenolic group, the propargylation

Figure 3. Pivaloyl group deprotection.

Figure 4. Synthesis of titled compound 1.
reaction on compound 10 went smoothly at room temperature with excellent yields. The reason for the reactivity at room temperature could be the increase in electron density on the phenolic hydroxy by mesomeric effect of chlorine at the para position. As the propargyl ether 11 was available in good quantities with reasonable purity, the stage was set for the key high temperature Claisen reaction (4). Though our efforts aimed at improving the yields in this reaction proved futile, we were able to make the reaction conditions easy to handle and more practical with consistent yields. With the set of experiments carried out at our end, we observed that the yields and purities were consistent when the propargyl ether 11 and Dowtherm heated together till the reaction temperature reaches 220°C as against the original reported procedure (4) where propargyl ether 11 was added to the preheated (220°C) Dowtherm. As reported (4), the high yields were obtained when the reaction mass was worked up between 1.5 to 2 hours. After stirring the reaction mixture at 220°C for 1.5–2.0 h, it was rapidly cooled to 70°C and was diluted with hexane to obtain a precipitate which was filtered and washed with 1:2 mixture of ethylacetate/hexane which yielded compound 12 with ~90% purity in 61% yield with no trace of starting material 11. The careful optimization of the reaction conditions for the double bond reduction in the chromene 12 with Pd/C in ethanol in presence of hydrogen, yielded chroman derivative 8a with less than 1% des-chloro derivative (see Supplementary data). This modification enabled us to avoid the use of costly platinum reagent as reported (3) earlier for the same reaction. The trans esterification product, i.e., the ethyl ester analog was also not observed under these reaction conditions. Finally, both ester and amide groups were hydrolyzed with aqueous sodium hydroxide solution under reflux conditions as these conditions have given better yields as compared to the original (4) KOH/H2O/Dioxan system. The key intermediate acid 1 was isolated after acid base work up with 96% purity in ~90% yield and in 27.5% overall yield starting from 4-aminoosalicylic acid.

3. Conclusion

We have optimized the synthetic route for the preparation of 5-amino-6-chlorochroman-8-carboxylic acid 1 in multi-gram quantities with easy isolation techniques in excellent yields and purity. We have avoided the use of toxic chemicals/reagents such as borontrichloride and silica gel. We have reduced the reaction temperatures and number of steps to reach the target compound. We also have shown the alternate route to make this material.

4. Experimental

4.1. Materials and methods

All the reagents used are purchased from Aldrich. Both proton nuclear magnetic resonance (1H-NMR) and carbon 13 nuclear magnetic resonance (13C-NMR) spectra were recorded at 400 MHz on a Bruker NMR spectrometer instrument (Fallanden, Switzerland). All mass spectra were recorded using electrospray ionization (ESI) technique on API 2000, ABS triple quadrupole instrument (MDS-SCIEX, Concord, Ontario, Canada). IR spectra were recorded on KBr disc and in solid state using IR Pristage 2 instrument from Shimadzu. Elemental analysis was performed on “Elementar” GmbH, Vario micro-cube instrument. Column chromatography was performed using 100–200 mesh silica gel. Analytical HPLC was done using Agilent systems (Model-1100 series). DSC was recorded on Waters DSC Q100 instrument.

4.2. Methyl 4-amino-2-hydroxybenzoate (9)

To the stirred solution of 4-Aminosalicylic acid (50 g, 0.3267 mol) in methanol (375 mL), cooled to 0°C, 99.7 mL of 99.7% concentrated sulfuric acid was added. After 10 minutes, the reaction mixture was gradually warmed to room temperature, and then it was heated to reflux for 6 h. The reaction mixture was cooled to 0°C, diluted with water (750 mL) and neutralized with aqueous NaOH solution (10 M, 214.5 mL). The precipitated product was filtered, and the wet cake was dissolved in EtOAc (500 mL). The organic layer was washed with aqueous saturated NaHCO3 solution (1 × 200 mL) followed by brine solution (1 × 100 mL). The volatiles were removed under reduced pressure to obtain methyl ester 9 (49.7 g) in 91% yield.

DSC: 121.8°C; IR (KBr) 3474, 3381, 3249, 2952, 2866, 1704, 1634, 1532, 1151, 981, 699 cm−1; 1H – NMR (CDCl3): δ 10.96 (s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 6.18 (s, 1H), 6.16 (dd, J = 8.2, 2.0 Hz, 1H), 4.12 (bs, 2H), 3.90 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 170.4, 163.4, 153.4, 131.5, 106.7, 102.8, 100.5, 51.6; Mass (m/z): 168.2 (M + H)+; Anal. Calcd. For C8H9NO3: C, 57.48, H, 5.43, N, 8.38; Found: C, 57.39, H, 5.47, N, 8.62; HPLC Purity: 99.56%.

4.3. Methyl 4-acetamido-2-hydroxybenzoate (2a)

To a stirred solution of compound 9 (48.7 g, 291.6 mmol) in dichloromethane (583 mL) cooled to 0°C, acetic anhydride (29.7 mL, 320.7 mmol) was added over a period of 30 minutes. The reaction mixture was gradually warmed to room temperature and stirred for 2 h. The volatiles were removed under reduced pressure, and the crude product was diluted with...
water, and the suspension was filtered. The product was dried under reduced pressure to obtain compound 2a (58.3 g) in 95.6% yield.

DSC: 153.35°C; IR (KBr) 3318, 3197, 3116, 1680, 1603, 1544, 1444, 1344, 1269, 1098, 778, 741, 701 cm⁻¹; ¹H - NMR (DMSO-d₆): δ 10.21 (s, 1H), 10.21 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 2.0 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 160.3, 1544, 1444, 1344, 1269, 1098, 778, 741, 701 cm⁻¹; ¹H - NMR (CDCl₃): δ 10.48 (bs, 1H), 10.21 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 169.4, 161.6, 146.0, 131.0 110.6, 107.5, 106.2, 52.5, 24.5; Mass (m/z): 210.2 (M + H)⁺; Anal. Calcd. For C₁₀H₁₁NO₄: C, 57.41, H, 4.38, N, 5.89; HPLC Purity: 99.95%.

4.4. Methyl 4-acetamido-5-chloro-2-hydroxybenzoate (10)

To a stirred solution of compound 2a (57.3 g, 274.1 mmols) in dichloroethane (1.09 L), N-chlorosuccinimide (47.6 g, 356.4 mmols) was added, and the reaction mixture was refluxed for 1 h. The volatiles were removed under reduced pressure, and the crude product was diluted with water. The solid precipitated was filtered, and the resulting wet cake was dissolved in 1:9 mixture of MeOH, DCM (450 mL) and washed with brine solution (1 × 100 mL). The organic layer was dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure to obtain compound 10 (64.9 g) in 97.2% yield.

DSC: 154.5°C; IR (KBr) 3318, 3197, 3116, 1680, 1603, 1544, 1444, 1344, 1269, 1098, 778, 741, 701 cm⁻¹; ¹H - NMR (CDCl₃): δ 10.48 (bs, 1H), 9.47 (s, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 3.83 (s, 3H), 2.15 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 169.7, 167.7, 159.3, 141.0, 130.4, 114.2, 111.4, 110.0, 52.7, 24.3; Mass (m/z): 244.1, 246.1 (M + H)⁺; Anal. Calcd. For C₁₀H₁₁NO₄: C, 57.41, H, 4.38, N, 5.89; HPLC Purity: 96.0%.

4.5. Methyl 4-acetamido-5-chloro-2-(prop-2-ynyloxy) benzoate (11)

Potassium carbonate (90.5 g, 656.0 mmol) was added to the stirred solution of compound 10 (63.9 g, 262.4 mmols) in DMF (525 mL). The reaction mixture was cooled to 0°C, and propargyl bromide (80% in toluene, 39.0 mL, 262.4 mmols) was added. The reaction mixture was gradually warmed to room temperature and stirred for 5 h. Upon completion of the reaction, the reaction mixture was poured into cold water (1.0 L). The solid precipitated was filtered and the resulting wet cake was dissolved in 1:9 mixture of MeOH/DCM (1.0 L), washed with water (1 × 200 mL), and brine solution (1 × 100 mL). The organic layer was dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure to obtain compound 11 (55.0 g) in 74.4% yield.

DSC: 145.8°C; IR (KBr) 3371, 3262, 2952, 2128, 1727, 1709, 1603, 1577, 1373, 1320, 1097, 853, 777, 726 cm⁻¹; ¹H - NMR (CDCl₃): δ 8.48 (s, 1H), 7.92 (s, 1H), 7.79 (s, 1H), 4.84 (s, 2H), 3.89 (s, 3H), 2.58 (s, 1H), 2.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 164.5, 156.8, 138.7, 131.9, 115.9, 113.6, 106.3, 77.4, 76.2, 52.0, 24.9; Mass (m/z): 282.0, 284.0 (M + H)⁺; Anal. Calcd. For C₁₃H₁₂ClNO₄: C, 55.43, H, 4.29, N, 4.97. Found: C, 55.39, H, 4.36, N, 5.03; HPLC Purity: 99.7%.

4.6. Methyl 5-acetamido-6-chloro-2H-chromene-8-carboxylate (12)

A stirred mixture of Dowtherm A (323 mL) and compound 11 (63.8 g, 226.6 mmol) was heated to 220°C. The reaction temperature was maintained at 220°C for a period of 90 minutes, rapidly cooled to 70°C, and hexane (2.26 L) was poured into it. This mixture was further allowed to cool to room temperature and stirred for 1 h at this temperature. The product that precipitated out was filtered, washed with 1:9 mixtures of EtOAc and hexane (500 mL) to obtain compound 12 (38.9 g) in 61% yield.

DSC: 188.0°C; IR (KBr) 3234, 2955, 1709, 1655, 1514, 1199, 1178, 1097, 1015, 836, 773, 682 cm⁻¹; ¹H - NMR (CDCl₃): δ 7.93 (s, 1H), 7.11 (s, 1H), 6.35 (d, J = 9.8 Hz, 1H), 5.96–5.92 (m, 1H), 4.93 (s, 2H), 3.90 (s, 3H), 2.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.8, 164.5, 156.4, 138.3, 132.4, 122.5, 121.7, 120.9, 117.7, 65.2, 52.1, 23.1; Mass (m/z): 282.1, 284.2 (M + H)⁺; Anal. Calcd. For C₁₃H₁₂ClNO₄: C, 55.43, H, 4.29, N, 4.97. Found: C, 55.53, H, 4.25, N, 4.83; HPLC Purity: 89.8%.

4.7. Methyl 5-acetamido-6-chlorochroman-8-carboxylate (8a)

Pd/C (10% Pd w/w, 15.5 g) was added to a stirred solution of compound 12 (31.0 g, 110.1 mmols) in EtOH (440.0 mL). The reaction mixture was purged with hydrogen gas with balloon and stirred for 6 h under hydrogen atmosphere. The reaction mixture was filtered through the celite, and the filtrate was evaporated under reduced pressure to obtain a crude product that was diluted with a 1:9 mixture of EtOAc/hexane (300 mL) and filtered. The volatiles were removed under reduced pressure to obtain compound 8a (25.0 g) in 80.0% yield.

DSC: 179.3°C; IR (KBr) 3216, 2953, 1728, 1657, 1584, 1417, 1248, 1158, 1101, 784, 757, 720 cm⁻¹; ¹H - NMR (DMSO-d₆): δ 9.65 (s, 1H), 7.55 (s, 1H), 4.15
(t, J = 5.0 Hz, 2H), 3.76 (s, 3H), 2.58 (t, J = 6.3 Hz, 2H), 2.05 (s, 3H), 1.90–1.83 (m, 2H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 168.3, 165.2, 153.4, 137.9, 128.1, 124.5, 122.1, 119.1, 66.4, 52.4, 22.8, 22.1, 20.7; Mass (\(m/z\)): 284.2, 286.2 (M + H)+; Anal. Calcd. For C\(_{13}\)H\(_{14}\)ClNO\(_4\): C, 55.04, H, 4.97, N, 4.85. Found: C, 55.10, H, 4.85, N, 4.88; HPLC Purity: 95.34%.

4.8. 5-Amino-6-chlorochroman-8-carboxylic acid (1)

To the compound \(8a\) (24.0 g, 84.6 mmol) aqueous solution of NaOH (1.7 N, 596.0 mL) was added, and the reaction mass was heated at reflux for 8 h. Reaction mixture was cooled to 0°C, acidified with 5N HCl (120 mL), and the product which precipitated out was filtered, dried under vacuum to obtain compound 1 (17.2 g) in 89.5% yield. DSC: 212.2°C; IR (KBr) 3471, 3370, 3217, 1709, 1629, 1592, 1386, 1250, 796, 774, 696 cm\(^{-1}\); \(^1\)H - NMR (DMSO-\(d_6\)): \(\delta\) 11.8 (bs, 1H), 7.48 (s, 1H), 5.75 (bs, 2H), 4.09 (t, \(J = 4.8\) Hz, 2H), 2.43 (t, \(J = 6.5\) Hz, 2H), 1.96–1.85 (m, 2H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 165.9, 155.1, 147.0, 130.0, 108.3, 107.7, 107.6, 65.8, 21.2, 20.9; Mass (\(m/z\)): 228.1, 230.1 (M + H)+; Anal. Calcd. For C\(_{10}\)H\(_{10}\)ClNO\(_3\): C, 52.76, H, 4.43, N, 6.15. Found: C, 52.63, H, 4.49, N, 6.33; HPLC Purity: 96.1%.

4.9. Methyl 4-acetamido-2-(2-benzyloxyvinyl) benzoate (3a)

To a stirred solution of methyl 4-acetamido-2-hydroxybenzoate \(2a\) (24 g, 114.8 mmols) in dichloromethane (456 mL) at room temperature, sequentially benzylpropionate \(4\) (20.2 g, 126.3 mmols) and DABCO (1.29 g, 11.4 mmols) were added. The reaction mixture was stirred for 16 h followed by the removal of volatiles under reduced pressure to obtain a crude product which was purified by silica gel column chromatography, which yielded compound \(3a\) (45.0 g) in quantitative yields.

\(^1\)H - NMR (CDCl\(_3\)): (9:1 mixture of cis/trans isomers); \(\delta\) 8.31 (bs, 0.1H), 8.12 (bs, 0.9H), 7.88 (d, \(J = 8.6\) Hz, 0.9H), 7.79 (d, \(J = 8.6\) Hz, 0.1H), 7.71 (d, \(J = 12.3\) Hz, 1H), 7.50 (s, 0.9H), 7.48 (s, 0.1H), 7.45–7.25 (m, 6.8H), 7.18 (d, \(J = 6.8\) Hz, 0.1H), 6.73 (d, \(J = 6.8\) Hz, 0.1H), 5.43 (d, \(J = 12.3\) Hz, 0.9H), 5.23 (d, \(J = 7.0\) Hz, 0.1H), 5.21 (s, 0.2H), 5.16 (s, 1.8H), 3.85 (s, 2.7H), 3.79 (s, 0.3H), 2.17 (s, 2.7H), 2.13 (s, 0.3H).

\[\text{Mass (}m/z\text{): 370.3 (M + H)+.}\]

4.10. Methyl 4-acetamido-2-(2-carboxyethoxy) benzoate (4a)

To a stirred solution of compound \(3a\) as obtained above (20.0 g, 54.2 mmols) in dry THF (400 mL) in an autoclave, at room temperature, Pd/C (10% w/w, 8.0 g) was added. The reaction mixture was purged with nitrogen, and a hydrogen pressure (80 psi) was applied for 2 h. The reaction mixture was filtered through a pad of celite, and the filtrate was evaporated under reduced pressure to obtain crude mass which contained both desired product \(4a\) and the undesired compound \(2a\). The crude mass was triturated with a mixture of 3:7 EtOAc and hexane (2 × 100 mL) to remove the undesired compound \(2a\). The pure product \(4a\) (10.54 g) was obtained in 69.3% yield.

\(^1\)H - NMR (DMSO-\(d_6\)): \(\delta\) 12.36 (bs, 1H), 10.21 (s, 1H), 7.64 (d, \(J = 8.5\) Hz, 1H), 7.47 (s, 1H), 7.19 (d, \(J = 8.5\) Hz, 1H), 4.14 (t, \(J = 5.6\) Hz, 2H), 3.70 (s, 3H), 2.70 (t, \(J = 5.6\) Hz, 2H), 2.06 (s, 3H).

\[\text{Mass (}m/z\text{): 282.2 (M + H)+.}\]

4.11. Methyl 5-acetamido-4-oxo chroman-8-carboxylate (5a)

To a stirred solution of compound \(4a\) (2.58 g, 9.1 mmols) in dry THF (20 mL) at room temperature sequentially triethylamine (1.3 mL, 10.0 mmols) and a solution of pivaloyl chloride (3.2 mL, 26.75 mmols) in toluene (27 mL) were added. The precipitated triethylamine hydrochloride salt was filtered, and the filtrate was evaporated under reduced pressure. The crude mass was azeotroped with toluene to remove the excess pivaloyl chloride. The crude intermediate, thus obtained, was dissolved in toluene (30 mL), and the temperature was raised to 100°C. At this temperature, catalytic amount of BF\(_3\)Et\(_2\)O (0.103 g, 0.73 mmol) was added, and the reaction mixture was stirred at this temperature for another 6 h before it was cooled to 60°C. The reaction mixture was quenched with saturated sodium bicarbonate solution (15 mL). The aqueous phase was discarded, and the organic phase was washed with 2 N HCl (15 mL) and with water (15 mL). The toluene solution was concentrated to approximately 10 mL and cooled to ambient temperature and hexane (20 mL) was added. The resulting slurry was filtered, washed with hexane (20 mL) and dried to obtain desired compound \(5a\) (0.71 g) in 30% yield.

\(^1\)H - NMR (CDCl\(_3\)): \(\delta\) 12.13 (s, 1H), 8.37 (d, \(J = 9.0\) Hz, 1H), 8.0 (d, \(J = 9.0\) Hz, 1H), 4.62 (t, \(J = 6.3\) Hz, 2H), 3.89 (s, 3H), 2.91 (t, \(J = 6.3\) Hz, 2H), 2.27 (s, 3H).

\[\text{Mass (}m/z\text{): 262.6 (M - H)+.}\]
4.12. Alternative cyclization procedure (5a)

Compound 4a (0.5 g, 1.78 mmol) was added to a stirred mixture of trifluoroacetic acid (0.14 mL) and trifluoroacetic anhydride (0.92 mL) cooled at 0°C. The reaction mixture was gradually warmed to room temperature and stirred for 16 h before it was cooled to 0°C. The reaction was quenched by the addition of aqueous NaHCO₃ solution. The crude mass was extracted with EtOAc (3 × 50 mL), the organic layer was dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure. The crude product, thus obtained, was purified by silica gel column chromatography to obtain product 5a (0.201 g) in 43% yield.

4.13. Methyl 5-acetamido-4-hydroxychroman-8-carboxylate (6a)

To a stirred solution of compound 5a (0.1 g, 0.38 mmol) in MeOH (2 mL) cooled at 0°C, NaBH₄ (7.0 mg, 0.21 mmol) was added. The reaction mixture was gradually warmed to room temperature and stirred for 2h before it was quenched by adding cold aqueous NH₄Cl solution (1.0 mL). The crude mass was extracted with EtOAc (3 × 20 mL), and the combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure which yielded compound 6a (89 mg) in 87% yield.

\[ ^1H - NMR \ (CDCl_3): \delta \ 8.49 \ (bs, \ 1H), \ 7.83 \ (d, \ J = 8.6 \ Hz, \ 1H), \ 7.71 \ (d, \ J = 8.6 \ Hz, \ 1H), \ 4.90-4.80 \ (m, \ 1H), \ 4.50-4.43 \ (m, \ 1H), \ 4.20-4.18 \ (m, \ 1H), \ 3.87 \ (s, \ 3H), \ 2.33 \ (bs, \ 1H), \ 2.23 \ (s, \ 3H), \ 2.30-2.10 \ (m, \ 2H). \]

Mass (m/z): 266.1 (M + H)+.

4.14. Methyl 5-acetamidochroman-8-carboxylate (7a)

To a stirred solution of compound 6a (40.8 mg, 0.15 mmol) in MeOH (2 mL), NaBH₄ (7.0 mg, 0.21 mmol) was added. The reaction mixture was gradually warmed to room temperature and stirred for 16 h at room temperature before it was cooled to 0°C. The reaction mixture was gradually warmed to room temperature and stirred for 16 h before it was cooled to 0°C. The reaction was quenched by the addition of aqueous NaHCO₃ solution. The crude product was triturated with water and stirred mixture of trifluoroacetic acid (0.14 mL) and triethylamine (0.15 mL). The crude mass was filtered through a pad of celite, and the filtrate was evaporated under reduced pressure to obtain compound 7a (35.6 mg) in 93% yield.

\[ ^1H - NMR \ (CDCl_3): \delta \ 7.70 \ (d, \ J = 8.5 \ Hz, \ 1H), \ 7.55 \ (bs, \ 1H), \ 6.94 \ (bs, \ 1H), \ 4.26 \ (t, \ J = 4.9 \ Hz, \ 2H), \ 3.86 \ (s, \ 3H), \ 2.64 \ (t, \ J = 6.5 \ Hz, \ 2H), \ 2.22 \ (s, \ 3H), \ 2.13-2.05 \ (m, \ 2H). \]

Mass (m/z): 250.2 (M + H)+.

4.15. Methyl 5-acetamido-6-chlorochroman-8-carboxylate (8a)

To a stirred solution of compound 7a (60 mg, 0.24 mmol) in dichloroethane (2.4 mL), N-chlorosuccinimide (35 mg, 0.52 mmol) was added. The reaction mixture was stirred at room temperature for 16 h before the solvent was removed under reduced pressure. The crude product was triturated with water and washed with water (10 mL), brine solution (10 mL), dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure to obtain compound 8a (49.2 mg) in 73% yield. The characterization data of this compound exactly matches with the above reported data for the same compound obtained from Claisen cyclization route.

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Supplementary material

All Supplementary Material is available alongside this article on www.tandfonline.com - go to http://dx.doi.org/10.1080/17518253.2014.904010.

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