

Synthesis of 5-aryl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitriles

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Abstract

4-Chloro-2-aryl-2H-3-chromenecarbaldehydes **3a-g** on reaction with malononitrile in ethanol in the presence of piperidine gave 5-aryl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitriles **4a-g** in good yields.

Keywords: 4-Chloro-2-aryl-2H-3-chromenecarbaldehydes, malononitrile, piperidine

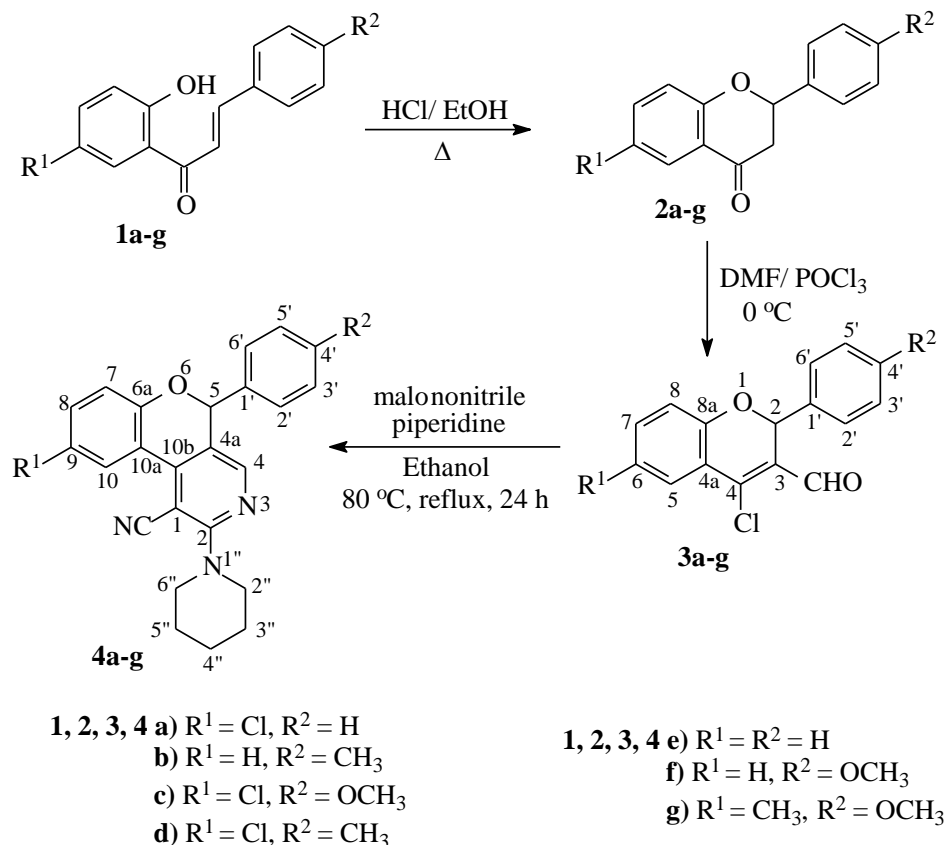
Introduction

Several chromanones, substituted chromenes and flavanones show a variety of biological activities, such as dopamine agonist¹, antihypertensive², ATP sensitive potassium channel opener³, antitumor⁴, gastroprotective⁵, coronary vasodilator⁶ and adrenergic receptor antagonist⁷. In the present study, new chromenopyridines **4a-g** were synthesized starting from 4-chloro-2-aryl-2H-3-chromenecarbaldehydes **3a-g**.

Several methods have been reported for the synthesis of substituted pyridones and piperidones.⁸⁻¹⁰ We developed a synthesis of ethyl 2-methyl-5-oxo-5H-[1]benzopyrano[3,4-c]pyridine-1-carboxylates and ethyl 2-methyl-5H-chromeno[3,4-c]pyridine-1-carboxylates in a modified Hantzsch reaction by the reaction of 4-chloro-3-formylcoumarins and 4-chloro-2H-3-chromenecarbaldehydes with ethyl 3-aminocrotonate.¹¹⁻¹³ We also reported the synthesis of 9-amino-6H-benzo[*c*]chromene-8,10-dicarbonitriles by the reaction of 2H-3-chromenecarbaldehydes with malononitrile and piperidine.¹⁴ In this present paper we report the results of the reaction of 4-chloro-2-aryl-2H-3-chromenecarbaldehydes **3a-g** with malononitrile in ethanol-piperidine wherein there is formation of pyridine ring fused to chromene with the participation of piperidine as a nucleophile during the pyridine ring formation.

Results and Discussion

4-Chloro-2-aryl-2*H*-3-chromenecarbaldehydes **3a-g** were prepared by the reaction of flavan-4-ones **2a-g** with dry DMF/ POCl_3 by the Vilsmeier-Haack reaction.¹⁵ 4-Chloro-2-aryl-2*H*-3-chromenecarbaldehydes **3a-g**, malononitrile and piperidine in dry ethanol were heated at 80 °C for 24 h. The crude product was purified using column chromatography to give 5-aryl-2-piperidino-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitriles **4a-g** in good yields (Scheme 1).



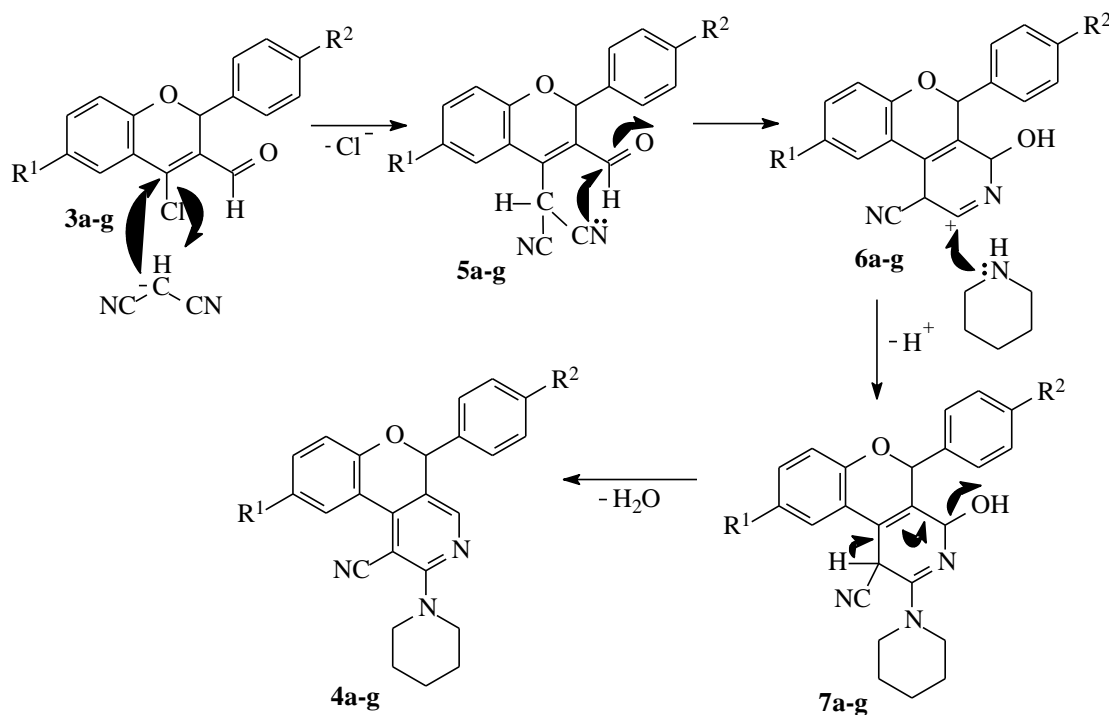
Scheme 1. Synthesis of 5-aryl-2-piperidino-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitriles **4a-g**.

Compound **4a** is characterized as 9-chloro-5-phenyl-2-piperidino-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitrile. In the IR spectrum **4a** showed a peak due to the nitrile group at 2205 cm^{-1} . The UV spectrum of **4a** showed bands at 218 nm ($\log \epsilon$ 4.5), 280 nm ($\log \epsilon$ 4.3) and 344 nm ($\log \epsilon$ 3.7). ^1H NMR of **4a** showed that a piperidine moiety is incorporated in the newly formed pyridine ring. The piperidine 3'', 5'' and 4'' methylene protons appeared as a multiplet at δ 1.75 and 2'',6'' methylene protons appeared as a multiplet at δ 3.65. H-4 of the pyridine appeared as a singlet δ 7.75, H-5 as a singlet at δ 5.95 and H-10 as a doublet at δ 8.40 ($J = 2.0$ Hz). The other aromatic H-2',3',4',5',6',7,8 appeared as a multiplet at δ 7.05-7.40. In the ^{13}C NMR of **4a** the piperidine ring carbons resonated at δ 24.4 (C-4''), 25.8 (C-3'',5'') and 50.6 (C-

2'',6''), the pyridine ring carbons at δ 89.1 (C-1), 154.2 (C-2), 148.6 (C-4), 137.3 (C-4a), 142.0 (C-10b) and 120.8 (C \equiv N). The other carbons resonated at δ 77.4 (C-5), 118.1 (C-10a), 119.8 (C-7), 126.9 (C-10), 127.3 (C-1'), 127.3 (C-9), 127.6 (C-2',6'), 128.7 (C-3',5'), 128.9 (C-4'), 132.7 (C-8), 164.3 (C-6a). In the MS of **4a** the molecular ion M^+ appeared at m/z 401 (70). The base peak appeared at m/z 400 (100) is due to loss of H radical from C-5 to give a resonance stabilized chromenyl cation.

The mechanism of the formation of 5-aryl-2-piperidino-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitriles **4a-g** is shown in Scheme 2. The first step is the nucleophilic substitution of the labile Cl by the malononitrile. A facile intramolecular nucleophilic attack by the nitrogen of CN on the CHO group leads to cyclic intermediate **6a-g**. Its reaction with nucleophile piperidine, followed by loss of H₂O results in pyridine ring derivatives **6a-g**. In several literature methods of pyridine synthesis, piperidine is used the solvent and acts as a base.^{16,17} However, in the present reaction the piperidine is incorporated into the product structure. The structure of **4a** is confirmed from single crystal X-ray analyses (Figure 1).

This work reports a new synthesis of pyridine fused to chromene, starting from the β -chloroacrolein moiety in the chromene and malononitrile in piperidine.



Scheme 2. Mechanism of the formation of 5-aryl-2-piperidino-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitriles **4a-g**.

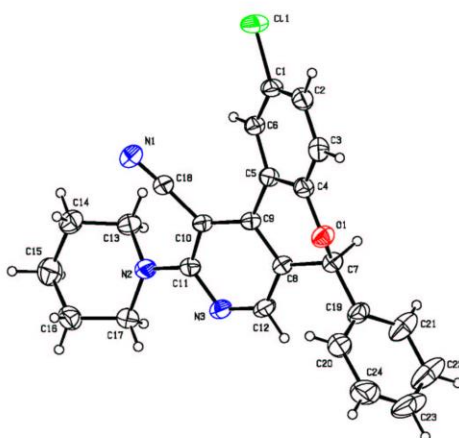


Figure 1. Single crystal X-ray structure of **4a**.

Experimental Section

General. All melting points were determined on a Polmon digital melting point apparatus (Model No. MP-96). IR spectra were recorded on a FT-IR Perkin-Elmer 1605 spectrophotometer using KBr discs and UV spectra were recorded on a Shimadzu UV-VIS 1601 spectrophotometer. The ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Varian Gemini Unity Spectrometer in CDCl_3 using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on a VG micromass 7070H instrument. Elemental analyses were performed on an Elemental Vario El instrument. XRD were recorded on a Bruker Smart Apex CCD area detector on a D8 goniometer.

General procedure for the synthesis of 4-chloro-2-aryl-2H-3-chromenecarbaldehydes **3a-g**

To a solution of flavan-4-ones **2a-g** (10 mmoles) in dry dimethylformamide (50 mmoles) freshly distilled dry phosphorus oxychloride (10 mmoles) was added with constant stirring at 0°C . The reaction mixture was kept overnight and then poured onto crushed ice. The yellow compound which separated out was filtered and washed with water. The solid product which was purified by column chromatography over silica gel by eluting with petroleum ether gave 4-chloro-2-aryl-2H-3-chromenecarbaldehydes **3a-g** in 70-85 % yields. Compounds **3a-g** were recrystallised from methanol to give pale yellow needles.

4,6-Dichloro-2-phenyl-2H-3-chromenecarbaldehyde (3a). M.p. 114°C ; IR (KBr): 1606 cm^{-1} ($\text{C}=\text{C}$), 1662 cm^{-1} (CHO); UV (MeOH): 207 nm ($\log \epsilon$ 4.8), 297 nm ($\log \epsilon$ 4.4), 367 nm ($\log \epsilon$ 3.9); ^1H NMR (200 MHz, CDCl_3): δ 6.45 (s, H-2), 6.83 (d, $J = 10.0$ Hz, H-8), 7.25 (m, H-7, H-2',3',4',5',6'), 7.68 (d, $J = 2.0$ Hz, H-5), 10.26 (s, CHO); ^{13}C NMR (50.3 MHz, CDCl_3): δ 75.3 (C-2), 118.5 (C-8), 121.5 (C-4a), 126.0 (C-7), 126.5 (C-2',6'), 127.0 (C-3), 127.5 (C-6), 128.5 (C-3',5'), 129.0 (C-4'), 134.0 (C-5), 137.8 (C-1'), 142.0 (C-4), 153.8 (C-8a), 188.5 (3-CHO); MS:

m/z 305 M^+ (40), 307 (26), 274 (100), 276 (66), 238 (10), 227 (5) and 176 (20); Anal. Calcd. for $C_{16}H_{10}Cl_2O_2$: C, 62.98, H, 3.30. Found C, 62.82, H, 3.39 %.

4-Chloro-2-(4'-methylphenyl)-2H-3-chromenecarbaldehyde (3b). M.p. 98 °C; IR (KBr): 1603 cm^{-1} (C=C), 1667 cm^{-1} (CHO); UV (MeOH): 210 nm (log ϵ 4.2), 292 nm (log ϵ 4.0), 307 nm (log ϵ 4.0); 1H NMR (200 MHz, $CDCl_3$): δ 2.22 (4'-CH₃), 6.25 (s, H-2), 6.68 (bd, J = 10.0 Hz, H-8), 6.95 (m, H-7), 7.00 (d, J = 10.0 Hz, H-3',5'), 7.10 (d, J = 10.0 Hz, H-2',6'), 7.30 (m, H-6), 7.65 (bd, J = 10.0 Hz, H-5), 10.22 (s, 3-CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 21.0 (C-4'-CH₃), 74.9 (C-2), 117.5 (C-8), 120.0 (C-4a), 122.0 (C-6), 126.2 (C-3, 7) 126.5 (C-2', 6'), 129.2 (C-3', 5'), 134.0 (C-5), 135.0 (C-4'), 138.5 (C-1'), 143.5 (C-4), 155.0 (C-8a), 188.0 (3-CHO); MS: m/z 284 M^+ (25), 286 (8), 270 (24), 256 (100), 220 (20) and 206 (20); Anal. Calcd. for $C_{17}H_{13}ClO_2$: C, 71.72, H, 4.60. Found C, 71.78, H, 4.67 %.

4,6-Dichloro-2-(4'-methoxyphenyl)-2H-3-chromenecarbaldehyde (3c). M.p. 126 °C; IR (KBr): 1601 cm^{-1} (C=C), 1660 cm^{-1} (CHO); UV (MeOH): 204 nm (log ϵ 4.2), 296 nm (log ϵ 4.6), 374 nm (log ϵ 4.2); 1H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 4'-OCH₃), 6.30 (s, H-2), 6.80 (d, J = 10.0 Hz, H-8), 6.75 (d, J = 10.0 Hz, H-3',5'), 7.20 (d, J = 10.0 Hz, H-2',6'), 7.30 (dd, J = 10.0, 2.0 Hz, H-7), 7.70 (d, J = 2.0 Hz, H-8), 10.28 (s, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 55.2 (4'-OCH₃), 75.0 (C-2), 114.0 (C-3',5'), 118.7 (C-8), 121.5 (C-4a), 126.0 (C-7), 127.0 (C-3), 127.5 (C-6), 128.5 (C-2',6'), 130.0 (C-1'), 134.1 (C-5), 142.0 (C-4), 153.8 (C-8a), 160.3 (C-4'), 188.0 (3-CHO); MS: m/z 335 M^+ (10), 337 (6), 304 (100), 306 (66), 298 (20), 227 (10) and 163 (10); Anal. Calcd. for $C_{17}H_{12}Cl_2O_3$: C, 60.92, H, 3.61. Found C, 61.08, H, 3.66 %.

4,6-Dichloro-2-(4'-methylphenyl)-2H-3-chromenecarbaldehyde (3d). M.p. 113 °C; IR (KBr): 1600 cm^{-1} (C=C), 1658 cm^{-1} (CHO); UV (MeOH): 206 nm (log ϵ 4.8), 297 nm (log ϵ 4.4), 375 nm (log ϵ 4.0); 1H NMR (200 MHz, $CDCl_3$): δ 6.25 (s, H-2), 6.82 (d, J = 10.0 Hz, H-8), 7.08 (m, H-4, H-3',5',2',6'), 7.30 (dd, J = 10.0, 2.0 Hz, H-7), 7.68 (d, J = 2.0 Hz, H-5), 10.25 (s, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.9 (CH₃), 75.0 (C-2), 118.6 (C-8), 121.0 (C-4a), 126.0 (C-7), 126.5 (C-2',6'), 127.0 (C-3), 127.5 (C-6), 129.0 (C-3',5'), 134.0 (C-5), 134.3 (C-4'), 138.6 (C-1'), 142.0 (C-4), 153.8 (C-8a), 187.9 (3-CHO); MS: m/z 319 M^+ (21), 321 (14), 288 (100), 290 (66), 238 (5) and 189 (10); Anal. Calcd. for $C_{17}H_{12}Cl_2O_2$: C, 63.97, H, 3.79. Found C, 63.75, H, 3.86%.

4-Chloro-2-phenyl-2H-3-chromenecarbaldehyde (3e). M.p. 105 °C; IR (KBr): 1601 cm^{-1} (C=C), 1661 cm^{-1} (CHO); UV (MeOH): 243 nm (log ϵ 4.5), 304 nm (log ϵ 4.5), 366 nm (log ϵ 4.1); 1H NMR (200 MHz, $CDCl_3$): δ 6.30 (s, H-2), 6.70 (m, H-8, 6), 7.20 (m, H-2',3',4',5',6', H-7), 7.48 (dd, J = 9.0, 2.0 Hz, H-5), 10.27 (s, 3-CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 74.8 (C-2), 117.2 (C-8), 119.7 (C-4a), 121.7 (C-6), 126.3 (C-5), 126.6 (C-3',5'), 126.6 (C-4'), 128.5 (C-7), 128.3 (C-2',6'), 134.3 (C-1'), 137.9 (C-3), 143.5 (C-4), 154.8 (C-8a), 187.8 (3-CHO); MS: m/z 270 M^+ (45), 172 (15), 243 (35), 241 (100), 235 (10), 205 (30), 193 (20), 178 (25) and 165 (10); Anal. Calcd. for $C_{17}H_{13}ClO_3$: C, 70.99, H, 4.10. Found C, 70.80, H, 4.21 %.

4-Chloro-2-(4'-methoxyphenyl)-2H-3-chromenecarbaldehyde (3f). M.p. 85 °C; IR (KBr): 1600 cm^{-1} (C=C), 1660 cm^{-1} (CHO); UV (MeOH): 226 nm (log ϵ 4.2), 302 nm (log ϵ 4.0), 366 nm (log ϵ 3.7); 1H NMR (200 MHz, $CDCl_3$): δ 3.75 (s, 4'-OCH₃), 6.30 (s, H-2), 6.75 (m, H-3',5',

H-8), 7.25 (m, H-2',6', H-7), 7.70 (dd, $J = 10.0, 2.0$ Hz, H-5), 10.30 (s, 3-CHO); ^{13}C NMR (50.3 MHz, CDCl_3): δ 54.9 (4'-OCH₃), 74.7 (C-2), 113.7 (C-3',5'), 117.3 (C-8), 119.8 (C-4a), 121.7 (C-6), 126.2 (C-5), 126.8 (C-1'), 128.2 (C-2',6'), 130.0 (C-7), 134.2 (C-3), 143.3 (C-4), 154.8 (C-8a), 159.8 (C-4'), 187.8 (3-CHO); MS: m/z 300 M⁺ (30), 302 (10), 273 (50), 271 (100), 265 (40), 221 (10), 193 (20) and 165 (25); Anal. Calcd. for C₁₇H₁₃ClO₃: C, 67.89, H, 4.36. Found C, 67.95, H, 4.43 %.

4-Chloro-2-(4'-methoxyphenyl)-6-methyl-2H-3-chromenecarbaldehyde (3g). M.p. 98 °C; IR (KBr): 1607 cm⁻¹ (C=C), 1666 cm⁻¹ (CHO); UV (MeOH): 230 nm (log ϵ 4.3), 304 nm (log ϵ 4.1), 381 nm (log ϵ 3.7); ^1H NMR (200 MHz, CDCl_3): δ 2.35 (s, 6-CH₃), 3.70 (s, 4'-OCH₃), 6.32 (s, H-2), 6.75 (m, H-3',5', H-8), 7.20 (m, H-2',6', H-7), 7.50 (d, $J = 2.0$ Hz, H-5), 10.28 (s, 3-CHO); ^{13}C NMR (50.3 MHz, CDCl_3): δ 20.5 (6-CH₃), 55.0 (4'-OCH₃), 74.6 (C-2), 113.7 (C-3',5'), 117.2 (C-8), 119.7 (C-4a), 126.3 (C-5), 126.9 (C-1'), 128.2 (C-2',6'), 130.1 (C-6), 131.2 (C-7), 135.1 (C-3), 143.6 (C-4), 152.8 (C-8a), 159.7 (C-4'), 187.9 (C-3-CHO); MS: m/z 314 M⁺ (25), 316 (10), 287 (50), 285 (100), 279 (35), 251 (5), 207 (10) and 178 (5); Anal. Calcd. for C₁₈H₁₅ClO₃: C, 68.69, H, 4.80. Found C, 68.82, H, 4.67 %.

General procedure for the synthesis of 5-aryl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitriles 4a-g

4-Chloro-2-aryl-2H-3-chromenecarbaldehydes **3a-g** (4 mmoles) and malononitrile (4 mmoles) were dissolved in ethanol (20 mL) and the piperidine (5 mL) was added and heated at 80 °C for 24 h. The ethanol was distilled off and the reaction mixture was poured into crushed ice. The light yellow solid which separated out was filtered and washed with water. The crude product was chromatographed over silica gel by eluting with petroleum ether: ethyl acetate (8 : 2) to give 5-aryl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitriles **4a-g** in 55-65 % yield, which were recrystallised from acetone as a yellowish needles.

9-Chloro-5-phenyl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile (4a). M.p. 169 °C; IR (KBr): 2205 cm⁻¹ (CN); UV (MeOH): 218 nm (log ϵ 4.5), 280 nm (log ϵ 4.3), 344 nm (log ϵ 3.7); ^1H NMR (200 MHz) (CDCl_3): δ 1.75 (m, CH₂-N-3'',4'',5''), 3.65 (m, CH₂-N-2'',6''), 5.95 (s, H-5), 7.05 (d, $J = 9.0$ Hz, H-7), 7.40 (m, H-2',3',4',5',6', H-8), 7.75 (s, H-4), 8.40 (d, $J = 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, CDCl_3): δ 24.4 (C-4''), 25.8 (C-3'',5''), 50.6 (C-2'',6''), 77.4 (C-5), 89.1 (C-1), 118.1 (C-10a), 119.8 (C-7), 120.8 (CN), 126.6 (C-10), 127.3 (C-9), 127.3 (C-1'), 127.6 (C-2',6'), 128.7 (C-3',5'), 128.9 (C-4'), 132.7 (C-8), 137.3 (C-4a), 142.0 (C-10b), 148.6 (C-4), 154.2 (C-2), 164.3 (C-6a); MS: m/z 401 M⁺ (70), 400 (100), 372 (30), 366 (50), 345 (15), 324 (25), 268 (10), 256 (10) and 84 (35); Anal. Calcd. for C₂₄H₂₀ClN₃O: C, 71.73, H, 5.02, N, 10.46. Found C, 71.61, H, 5.15, N, 10.59 %.

5-(4'-Methylphenyl)-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile (4b). M.p. 164 °C; IR (KBr): 2203 cm⁻¹ (CN); UV (MeOH): 221 nm (log ϵ 4.6), 275 nm (log ϵ 4.6), 334 nm (log ϵ 3.9); ^1H NMR (200 MHz, CDCl_3): δ 1.72 (m, 6H, CH₂-N-4'',3'',5''), 2.35 (s, 4'-CH₃), 3.60 (m, CH₂-N-2'',6''), 5.90 (s, H-5), 7.00-7.40 (m, H-1',3',5',6',7,8,9), 7.65 (s, H-4), 8.45 (dd, $J = 9.0, 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, CDCl_3): δ 21.1 (4'-CH₃), 25.8 (C-3'',5''), 50.6 (C-

2'',6''), 77.1 (C-5), 89.2 (C-1), 118.4 (C-7), 118.5 (C-10a), 119.7 (CN), 121.6 (C-1') 122.1 (C-9), 126.9 (C-8), 127.6 (C-2',6'), 129.3 (C-3',5'), 132.9 (C-10), 134.7 (C-4a), 138.6 (C-4'), 143.2 (C-10b), 148.3 (C-4), 155.7 (C-2), 164.5 (C-6a); MS: m/z 381 M^+ (75), 380 (100), 352 (20), 325 (15), 298 (10), 290 (15), 234 (5) and 84 (20); Anal. Calcd. for $C_{25}H_{23}N_3O$: C, 78.71, H, 6.08, N, 11.02. Found C, 78.85, H, 6.01, N, 11.13 %.

9-Chloro-5-(4'-methoxyphenyl)-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile

(4c). M.p. 167 °C; IR (KBr): 2206 cm^{-1} (CN); UV (MeOH): 222 nm (log ϵ 4.5), 279 nm (log ϵ 4.4), 347 nm (log ϵ 3.8); 1H NMR (200 MHz, $CDCl_3$): δ 1.70 (m, $CH_2-N-3'',4'',5''$), 3.60 (m, $CH_2-N-2'',6''$), 3.80 (s, 4'-OCH₃), 5.90 (s, H-5), 6.85 (m, H-7,8), 7.15 (m, H-2',3',5',6'), 7.80 (s, H-4), 8.45 (d, $J = 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.3 (C-4''), 25.8 (C-3'',5''), 50.5 (C-2'',6''), 55.2 (4-OCH₃), 77.1 (C-5), 88.4 (C-1), 114.0 (C-3',5'), 118.1 (CN), 119.8 (C-7), 120.0 (C-10a) 126.4 (C-10), 127.1 (C-9), 127.1 (C-1'), 129.0 (C-2',6'), 129.3 (C-4a), 132.5 (C-8), 141.9 (C-10b), 148.6 (C-4), 154.1 (C-2), 160.0 (C-4'), 164.2 (C-6a); MS: m/z 431 M^+ (65), 430 (100), 402 (30), 396 (40), 388 (10), 324 (15), 268 (10), 219 (10), 149 (20) 136 (15) and 84 (75); Anal. Calcd. for $C_{25}H_{22}ClN_3O_2$: C, 69.52, H, 5.13, N, 9.73. Found C, 69.38, H, 5.04, N, 9.81 %.

9-Chloro-5-(4'-methylphenyl)-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile

(4d). M.p. 173 °C; IR (KBr): 2207 cm^{-1} (CN); UV (MeOH): 222 nm (log ϵ 4.4), 276 nm (log ϵ 4.2), 346 nm (log ϵ 3.6); 1H NMR (200 MHz, $CDCl_3$): δ 1.75 (m, $CH_2-N-3'',4'',5''$), 2.35 (s, 4'-CH₃), 3.60 (m, $CH_2-N-2'',6''$), 5.90 (s, H-5), 6.95 (d, $J = 9.0$ Hz, H-7), 7.15 (m, H-2',3',5',6'), 7.35 (dd, $J = 9.0, 2.0$ Hz, H-8), 7.75 (s, H-4), 8.40 (d, $J = 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.6 (4'-CH₃), 23.8 (C-4''), 25.3 (C-3'',5''), 49.9 (C-2'',6''), 76.3 (C-5), 88.0 (C-1), 117.6 (C-10a), 119.6 (C-7), 120.4 (CN), 125.0 (C-10) 126.0 (C-9), 126.0 (C-1'), 127.1 (C-3',5'), 128.7 (C-2',6'), 132.0 (C-8), 134.0 (C-4a), 138.0 (C-4') 140.9 (C-10b), 148.2 (C-4), 153.6 (C-2), 163.6 (C-6a); MS: m/z 415 M^+ (60), 414 (100), 386 (25), 380 (40), 359 (15), 324 (15), 268 (10) and 84 (30); Anal. Calcd. for $C_{25}H_{22}ClN_3O$: C, 72.20, H, 5.33, N, 10.10. Found C, 72.11, H, 5.43, N, 10.01%.

5-Phenyl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile (4e).

M.p. 161 °C; IR (KBr): 2210 cm^{-1} (CN); UV (MeOH): 218 nm (log ϵ 4.6), 277 nm (log ϵ 4.6) and 335 nm (log ϵ 4.0); 1H NMR (200 MHz, $CDCl_3$): δ 1.60 (m, CH_2-N-4''), 1.75 (m, $CH_2-N-3'',5''$), 3.60 (m, $CH_2-N-2'',6''$), 5.90 (s, H-5), 7.10 (m, H-7,8,9), 7.35 (m, H-2',3',4',5',6'), 7.65 (s, H-4), 8.45 (dd, $J = 9.0, 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.3 (C-4''), 25.5 (C-3'',5''), 50.9 (C-2'',6''), 77.2 (C-5), 89.2 (C-1), 118.3 (C-7), 118.4 (C-10a), 119.9 (CN), 121.3 (C-1'), 122.2 (C-9), 126.9 (C-8), 127.6 (C-2',6'), 128.5 (C-3',5'), 128.7 (C-4'), 132.9 (C-10), 137.6 (C-4a), 143.1 (C-10b), 148.2 (C-4), 155.6 (C-2), 164.5 (C-6a); MS: m/z 367 M^+ (80), 366 (100), 338 (25), 311 (10), 290 (15), 284 (10), 234 (10), 222 (10) and 84 (25); Anal. Calcd. for $C_{24}H_{21}N_3O$: C, 78.45, H, 5.76, N, 11.44. Found C, 78.52, H, 5.69, N, 11.48 %.

5-(4'-Methoxyphenyl)-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile (4f).

M.p. 151°C; IR (KBr): 2215 cm^{-1} (CN); UV (MeOH): 225 nm (log ϵ 4.4), 277 nm (log ϵ 4.3) and 335 nm (log ϵ 3.8); 1H NMR (200 MHz, $CDCl_3$): δ 1.70 (m, $CH_2-N-3'',4'',5''$), 3.60 (m, $CH_2-N-2'',6''$), 3.85 (s, 4'-OCH₃), 5.90 (s, H-5), 7.15 (m, H-8,9), 7.20 (m, H-2',3',5',6'), 7.30 (dd, $J = 9.0,$

2.0 Hz, H-7), 7.65 (s, H-4), 8.45 (dd, $J = 9.0, 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, CDCl_3): δ 24.4 (C-4''), 25.8 (C-3'',5''), 50.6 (C-2'',6''), 55.2 (4-OCH₃), 77.0 (C-5), 89.2 (C-1), 114.0 (C-3',5'), 118. (C-7), 118.5 (C-10a), 119.7 (CN), 121.7 (C-1'), 122.1 (C-9), 126.9 (C-8), 129.1 (C-2',6'), 129.7 (C-4a), 132.9 (C-10), 143.2 (C-10b), 148.4 (C-4), 155.7 (C-2), 159.9 (C-4'), 164.6 (C-6a); MS: m/z 397 M⁺ (10), 396 (15), 380 (15), 366 (100), 338 (20), 290 (15), 234 (5) and 84 (30); Anal. Calcd. for C₂₅H₂₃N₃O₂: C, 75.55, H, 5.83, N, 10.57. Found C, 75.38, H, 5.94, N, 10.64 %.

5-(4'-Methoxyphenyl)-9-methyl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile (4g). M.p. 158 °C; IR (KBr): 2213 cm⁻¹ (CN); UV (MeOH): 223 nm (log ϵ 4.6), 276 nm (log ϵ 4.5), 346 nm (log ϵ 3.9); ^1H NMR (200 MHz, CDCl_3): δ 1.70 (m, CH₂-N-3'',4'',5''), 2.40 (s, 9-CH₃), 3.60 (m, CH₂-N-2'',6''), 3.80 (s, 4'-OCH₃), 5.95 (s, H-5), 6.90 (m, H-7,8), 7.25 (m, H-2',3',5',6'), 7.70 (s, H-4), 8.25 (d, $J = 2.0$ Hz, H-10); ^{13}C NMR (50.3 MHz, CDCl_3): δ 20.8 (9-CH₃), 24.4 (C-4''), 25.8 (C-3'',5''), 50.7 (C-2'',6''), 55.2 (4'-OCH₃), 77.0 (C-5), 89.1 (C-1), 114.0 (C-3',5'), 118.7 (CN), 119.4 (C-7), 121.7 (C-10a), 127.0 (C-9), 127.0 (C-1'), 129.1 (C-2',6'), 129.8 (C-4a), 131.5 (C-8), 133.7 (C-10), 143.4 (C-10b), 148.3 (C-4), 153.5 (C-2), 159.8 (C-4'), 164.6 (C-6a); MS: m/z 411 M⁺ (50), 410 (75), 396 (100), 382 (15), 328 (10), 304 (15), 285 (20), 271 (10) and 84 (20); Anal. Calcd. for C₂₆H₂₅N₃O₂: C, 75.89, H, 6.12, N, 10.21. Found C, 76.02, H, 6.25, N, 10.10 %.

X-ray crystallographic studies

A yellowish cube crystal of compound **4a** was obtained from acetone/water (1:1) The crystal belongs to the monoclinic crystal system, space group Cc with $a = 12.736$ (12), $b = 19.9162$ (19), $c = 8.4531$ (8) Å, $\beta = 108.95$ (0)°, $V = 2027.94$ (33) Å³, $Z = 4$, $\lambda = 0.71073$ Å, μ (MoK α) = 2.086 mm⁻¹, $F_{000} = 840.0$, $T = 273$ (2) K. Data collection yielded 6126 reflections resulting in 3512 unique ($I > 2\sigma I$), θ range: 1.98 – 28.02°. Full matrix least-squares refinement led to a final $R = 0.0464$, $wR = 0.1196$ and $\text{GOF} = 1.029$. Diffraction data were measured at room temperature with a Bruker SMART Apex CCD area detector on a D8 goniometer. Preliminary lattice parameters and orientation matrices were obtained from three sets of frames. Intensity data were collected using graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å) with the ω -scan method.¹⁷ Integration and scaling of intensity data was accomplished using SAINT¹⁷ and absorption corrections were performed using SADABS.¹⁸ The structures were solved by direct methods and refined by a full matrix least-squares procedure based on $F^{19,20}$. Crystallographic data for the structure of 9-chloro-5-phenyl-2-piperidino-5H-chromeno[3,4-c]pyridine-1-carbonitrile **4a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 270792.

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