# Synthesis of New Substituted 2-amino-4*H*-benzo[*h*]chromene-3-carbonitrile Derivatives

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**Summary:** A series of novel substituted 2-amino-4*H*-benzo[h]chromene-3-carbonitrile derivatives was synthesised by condensation of different halogen derivatives with the hydroxy-group of 2-amino-8-hydroxy-4-styryl- 4*H*-benzo[h]chromene-3-carbonitrile and 2-amino-8-hydroxy-4-phenethyl-4*H*-benzo-[h]chromene-3-carbonitrile, which were prepared from cinnamaldehyde, malononitrile and naphthalene-1,6-diol through Knoevenagel condensation and cyclization reaction and then reduction with hydrogen in the presence of Pd/C at room temperature. Each intermediates and target compounds were obtained in good yields.

**Keywords**: benzo[h]chromene-3-carbonitrile, Alkylation, Derivative, Knoevenagel condensation, Etherification.

## Introduction

In the past few decades, it has been found compounds containing chromenes and fused chromenes structural units are an important class of heterocyclic compounds and have attracted the attention of medicinal chemists due to their biological and chemotherapeutic importance.[1, 2] Among them, 4*H*-chromene and its derivatives are biologically interesting compounds known for their anticancer, [3] antimicrobial and antifungal, [4] antioxidant, [5] antileishmanial, [6] hypotensive, [7] local anesthetic [8] activities and effects. Moreover, fused chromene ring systems have platelet antiaggregating, local anesthetic, [9] antihistaminic [10] and anticancer activities. [3] They also exhibit antidepressant effects, [11] inhibitory effect on influenza virus sialidases, [12] DNA breaking activities and mutagenicity, [13] antiviral activities. [14] In order to find novel bioactive compounds, several new kind of fused heterocycles which showed excellent potencies have been synthesized in our laboratory. [15, 16] As part of our ongoing research program on heterocyclic compounds which may serve as leads for designing novel chemotherapeutic agents, we now reported the synthesis a new series of substituted 2-amino-4*H*-benzo[h]chromene-3-carbonitrile derivatives.

## Experimental

*General*

Unless specified otherwise, all starting materials and reagents were obtained from commercial supplies without further purification. All melting points were taken on a Beijing Taike X-4 microscopy melting point apparatus and were uncorrected. $^1$H-NMR spectra were recorded on a Bruker Biospin 600 MHz or Bruker Biospin 300 MHz instrument using TMS as the internal standard. All chemical shifts were reported in ppm. IR spectra were recorded as KBr pellets on a Perkin-Elmer Spcetrum one FT-IR spectrometer. MS spectra were obtained on an 6460 QQQ mass spectrometer (Agilent, USA) analysis system. Elemental analysis of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer and are found within the range of theoretical value.

*Synthesis of 2-(3-phenylallylidene)malononitrile* (**2**):

To the suspension of malononitrile (3.00 g, 45.41 mmol) and cinnamaldehyde **1** (7.20 g, 54.49 mmol) in EtOH (100 mL), twenty drops of $Et_3N$ was added, and the mixture was stirred at room temperature for 4 hours. The resultant precipitate was filtered, washed with EtOH and dried under vacuum to give 6.60 g of 2-(3-phenylallylidene)malononitrile **2** as yellow solid. M.p.: 125-127 °C (lit. [17] 124-126 °C); Yield: 81 %. IR (KBr, cm$^{-1}$): 3032(Ar), 2224(CN), 1609, 1576, 1560, 1449, 1321, 1278, 1178, 1150; $^1$H-NMR (DMSO-$d_6$, 600 MHz): $\delta$ 8.30 (d, 1H, $J$ = 11.4 Hz, CH), 7.78 (t, 2H, $J$ = 7.2 Hz, Ar-H), 7.62 (d, 1H, $J$ = 15.0 Hz, CH), 7.46-7.53 (m, 3H, Ar-H), 7.26-7.31 (m, 1H, CH).

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*Synthesis of 2-amino-8-hydroxy-4-styryl-4H-benzo[h]chromene-3-carbonitrile* (**4**):

A mixture of 2-(3-phenylallylidene)malononitrile **2** (3.60 g, 19.98 mmol), naphthalene-1,6-diol **3** (3.20 g, 19.98 mmol), EtOH (90 mL) and triethylamine (0.5 mL) was heated at 50 °C for 20 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The resulting mixture was dissolved in dichloromethane (150 mL), sequentially washed with 10% $K_2CO_3$ (60 mL × 3) and brine (60 mL × 3), and the organic phase was separated, dried, and evaporated. The crude product obtained was purified by silica gel chromatography to give 5.20 g of 2-amino-8-hydroxy-4-styryl-4*H*-benzo[h]chromene-3-carbonitrile **4** as a light yellow solid. Yield: 77 %. M.p.: 192-194 °C; IR(KBr. $cm^{-1}$): 3398 ($NH_2$), 3324 ($NH_2$), 3205 (OH), 2199 (CN), 1697, 1662, 1608, 1579, 1388, 1265, 1238, 1179, 1101, 1045; $^1$H-NMR (DMSO-$d_6$, 600 MHz,): $\delta$ 10.01 (br, 1H, OH), 8.05 (d, 1H, *J* = 9.6 Hz, Ar-H), 7.45 (d, 3H, *J* = 8.4 Hz, Ar-H), 7.32 (t, 2H, *J* = 7.2 Hz, Ar-H), 7.24 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.18 (t, 2H, *J* = 7.2Hz, Ar-H), 7.14 (d, 1H, *J* = 2.4 Hz, Ar-H), 6.60 (d, 1H, *J* = 15.6Hz, C=CH), 6.20-6.28 (m, 1H, C=CH), 4.36 (d, 1H, *J* = 9.0 Hz, CH), 4.03 (br, 2H, $NH_2$) ; MS (ESI) m/z(%): 341.1 $[M+H]^+$; Anal. calcd. for $C_{22}H_{16}N_2O_2$ (%): C, 77.63; H, 4.74; N, 8.23. Found (%): C, 77.71; H, 4.80; N, 8.28.

*Synthesis of 2-amino-8-hydroxy-4-phenethyl-4H-benzo[h]chromene-3-carbonitrile* (**5**):

2-amino-8-hydroxy-4-styryl-4*H*-benzo[h]chromene-3-carbonitrile **4** (8.0g, 23.50 mmol), Palladium 10% on Carbon (1.50 g), dichloromethane (50 mL) and methanol (30 mL) were placed in a Schlenk flask (20 mL). The flask was purged with $H_2$ three times to remove air, and the reaction mixture was stirred with a balloon of $H_2$ at room temperature for 12 hours. After the reaction, the resultant mixture was transferred into a tube and the solid was separated by centrifugation. The organic phase was concentrated under reduced pressure. The crude product obtained was purified by silicagel chromatography to afford 7.30 g compound **5** as white solid in 91 % yield. M.p.: 144-1147 °C; IR (KBr, $cm^{-1}$): 3401($NH_2$, OH), 2858 ($CH_2$), 2185 (CN), 1649, 1606, 1580, 1384, 1311, 1219, 1182, 1104; $^1$H-NMR (DMSO-$d_6$, 600 MHz): δ 10.50 (s, 1H, OH), 8.02 (d, 1H, *J* = 8.4Hz, Ar-H, Ar-H), 7.47 (d, 1H, *J* = 8.4 Hz, Ar-H, Ar-H), 7.26 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.21 (t, 2H, *J* = 7.8 Hz, Ar-H), 7.10-7.16 (m, 3H, Ar-H), 7.09 (d, 2H, *J* = 7.2 Hz, Ar-H), 6.99 (br, 2H, Ar-H), 3.75 (t, 1H, *J* = 4.8 Hz, -CH), 2.60-2.39 (m, 1H, -$CH_2$), 2.20-2.30 (m, 1H, -$CH_2$), 1.89-2.06 (m, 2H, $CH_2$); MS (ESI) m/z(%): 343.1 $[M+H]^+$; Anal. calcd. for $C_{22}H_{18}N_2O_2$ (%): C, 77.17; H, 5.30; N, 8.18. Found (%): C, 77.30; H, 5.39; N, 8.25.

*General procedure for Preparation of target compounds* (**6~8** and **9~11**):

A mixture of intermediate 2-amino-8-hydroxy-4-styryl-4*H*-benzo[h]chromene-3-carbonitrile **4** or 2-amino-8-hydroxy-4-phenethyl-4*H*-benzo[h]chromene-3-carbonitrile **5** (1.00 mmol), corresponding chloride (1.20 mmol), potassium carbonate (3.00 mmol) and potassium iodide (1.20 mmol) in acetonitrile (50 mL) was stirred at 80 °C overnight. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was then extracted with ethyl acetate (30 mL × 3). The combined organic extracts were sequentially washed with water (30 mL × 3), brine (80 mL × 3) and dried over anhydrous $Na_2SO_4$. After evaporation of the organic solvent, the residue was purified by column chromatography to afford corresponding target compounds as milky yellow powder.

*2-amino-8-(3-morpholinopropoxy)-4-styryl-4H-benzo[h]chromene-3-carbonitrile* (**6**): Yield: 73 %; M.p.: 98-102 °C; IR (KBr, cm-1): 3347 ($NH_2$), 2957 ($CH_2$), 2827 ($CH_2$), 2189 (CN), 1663, 1606, 1403, 1375, 1264, 1248, 1187, 1166, 1117, 1034 ; $^1$H-NMR (DMSO-$d_6$, 600 MHz): $\delta$ 8.08 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.55 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.43 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.29-7.31 (m, 3H, Ar-H), 7.19-7.22 (m, 3H, Ar-H), 7.10 (s, 2H, Ar-H), 6.57 (d, 1H, *J* = 15.6 Hz, C=CH), 6.19-6.27 (m, 1H, C=CH), 4.36 (d, 1H, *J* = 9.0 Hz, -CH), 4.11 (t, 2H, *J* = 6.6Hz, -$NH_2$), 3.55 (br, 4H, -$CH_2$), 2.44 (t, 2H, *J* = 6.6 Hz, -$CH_2$), 2.36(br, 4H, -$CH_2$), 1.89-1.94 (m, 2H, -$CH_2$); MS (ESI) m/z(%): 468.2 $[M+H]^+$; Anal. calcd. for $C_{29}H_{29}N_3O_3$ (%): C, 74.50; H, 6.25; N, 8.99. Found (%): C, 74.37; H, 6.35; N, 9.09.

*ethyl 4-(2-amino-3-cyano-4-(E)-styryl-4H-benzo[h]chromen-8-yloxy)but-2-enoate* (**7**): Yield: 68 %; M.p.: 139-144 °C; IR (KBr, $cm^{-1}$): 3392 ($NH_2$), 3324 ($NH_2$), 3058, 2981($CH_3$), 2851($CH_2$), 2188 (CN), 1714 (C=O), 1605, 1402, 1377, 1307, 1267, 1247, 1185, 1028; $^1$H-NMR (DMSO-$d_6$, 600 MHz): δ 8.12 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.55 (d, 1H, *J* = 8.4Hz, Ar-H), 7.43 (d, 2H, *J* = 7.8Hz, Ar-H), 7.32-7.38 (m, 2H, Ar-H), 7.29 (t, 2H, *J* = 7.2 Hz, Ar-H), 7.25 (d, 1H, *J* = 8.4 Hz, Ar-H),

7.19-7.23 (m, 1H, Ar-H), 7.10 (s, 2H, Ar-H), 7.00-7.09 (m, 1H, C=CH), 6.58 (d, 1H, *J* = 15.6 Hz, C=CH), 6.20-6.27 (m, 1H, C=CH), 6.16 (d, 1H, *J* = 15.6Hz, C=CH), 4.91 (d, 2H, *J* = 2.4 Hz, -$CH_2$), 4.37 (d, 1H, *J* =8.4 Hz, -CH), 4.13 (q, 2H, *J* = 7.2 Hz, -$CH_2$), 1.20 (t, 3H, *J* = 7.2 Hz, -$CH_3$); MS (ESI) m/z(%): 453.2 $[M+H]^+$; Anal. calcd. for $C_{28}H_{24}N_2O_4$ (%): C, 74.32; H, 5.35; N, 6.19. Found (%): C, 74.39; H, 5.38; N, 6.26.

*2-amino-8-[(2-(4-chlorophenyl)-2-oxoethoxy]-4-styryl-4H-benzo[h]chromene-3-carbonitrile* (**8**): Yield: 76 %; M.p.: 188-190 °C; IR (KBr, $cm^{-1}$): 3468($NH_2$), 3332($NH_2$), 3058, 2194 (CN), 1701(C=O), 1670, 1603, 1488, 1397, 1357, 1284, 1266, 1250, 1224, 1190, 1173, 1103, 1092, 984; $^1$H-NMR (DMSO-$d_6$, 600 MHz): $\delta$ 8.12 (d, 1H, *J* = 9.6 Hz, Ar-H), 8.06 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.65 (d, 2H, *J* = 9.6 Hz, Ar-H), 7.52 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.43 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.39 (d, 1H, *J* = 2.4Hz, Ar-H), 7.37 (dd, 1H, *J* = 9.0 Hz, 2.4 Hz, Ar-H), 7.29 (t, 2H, *J* = 7.2 Hz, Ar-H), 7.18-7.28 (m, 2H, Ar-H), 7.11 (s, 2H, Ar-H), 6.59 (d, 1H, *J* = 15.6 Hz, C=CH), 6.21-6.27 (m, 1H, C=CH), 5.69 (s, 2H, -$NH_2$), 4.37 (d, 1H, *J* = 9.0 Hz, -CH); MS (ESI) m/z(%): 493.1 $[M+H]^+$; Anal. calcd. for $C_{30}H_{21}ClN_2O_3$ (%): C, 73.09; H, 4.29; N, 5.68. Found (%): C, 73.27; H, 4.36; N, 5.77.

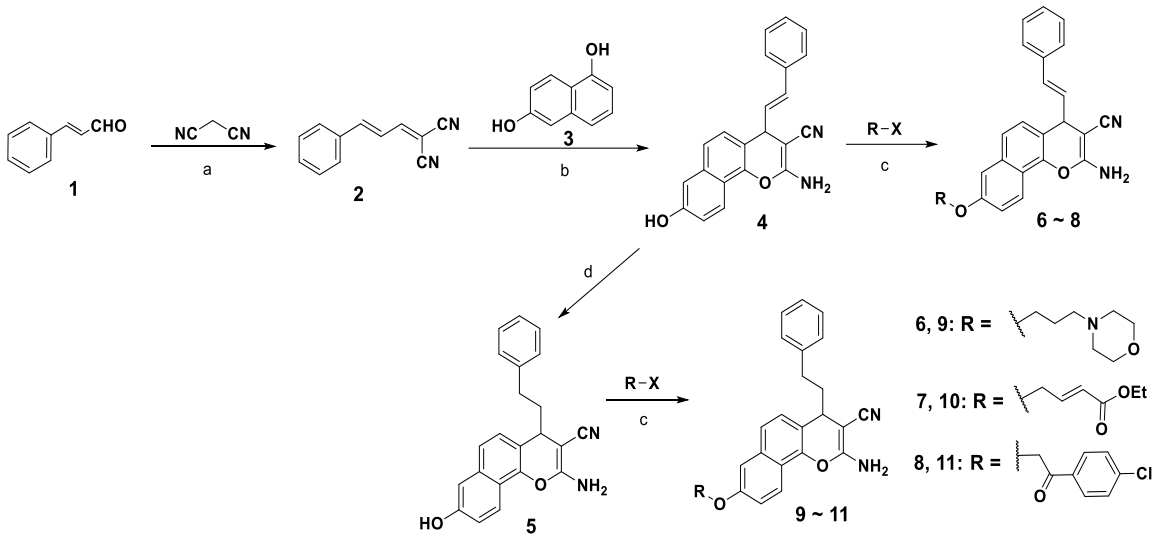
*Synthesis of 2-amino-8-(3-morpholinopropoxy)-4-phenethyl-4H-benzo[h]chromene-3-carbonitrile* (**9**): Yield: 76 %; M.p.: 117-120 °C; IR (KBr, $cm^{-1}$): 3413 ($NH_2$), 2855($CH_2$), 2185 (CN), 1649, 1606, 1413, 1384, 1311, 1219, 1182, 1104, 852; $^1$H-NMR (DMSO-$d_6$, 600 MHz): $\delta$ 8.06 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.59 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.33 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.20-7.24 (m, 3H, Ar-H), 7.08-7.13 (m, 3H, Ar-H), 7.05 (s, 2H, Ar-H), 4.11(t, 2H, *J* = 6.6 Hz, -$NH_2$), 3.76 (t, 1H, *J* = 4.2 Hz, -CH), 3.56 (s, 4H, -$CH_2$), 2.48-2.59 (m, 1H, -$CH_2$), 2.43 (t, 2H, *J* = 7.2 Hz, -$CH_2$), 2.36 (br, 4H, -$CH_2$), 2.10-2.30 (m, 1H, -$CH_2$), 2.00-2.05 (m, 1H, -$CH_2$), 1.85-1.95 (m, 3H, -$CH_2$); MS (ESI) m/z(%): 470.2 $[M+H]^+$; Anal. calcd. for $C_{29}H_{31}N_3O_3$ (%): C, 74.18; H, 6.65; N, 8.95. Found (%): C, 74.31; H, 6.60; N, 9.01.

*Synthesis of ethyl 4-(2-amino-3-cyano-4-phenethyl-4H-benzo[h]chromen-8-yloxy)but-2-enoate* (**10**): Yield: 72 %; M.p.: 146-149 °C; IR (KBr, $cm^{-1}$): 3396 ($NH_2$), 3322 ($NH_2$), 2982($CH_3$), 2927($CH_2$), 2859($CH_2$), 2180 (CN), 1711 (C=O), 1659, 1606, 1579, 1410, 1376, 1310, 1247, 1188, 1107, 1077, 1027; $^1$H-NMR (DMSO-$d_6$, 600 MHz): $\delta$ 8.11 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.57 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.40-7.30 (m, 3H, Ar-H), 7.21 (t, 2H, *J* = 7.2 Hz, Ar-H), 7.12 (d, 1H, *J* = 7.2 Hz, Ar-H), 7.09-7.15 (m, 3H, Ar-H, C=CH), 7.04 (s, 2H, Ar-H), 6.10-6.22 (m, 1H, C=CH), 4.83-4.96 (m, 2H, -$NH_2$), 4.13 (q, 2H, *J* = 7.2 Hz, -$CH_2$), 3.78 (t, 1H, *J* = 4.8 Hz), 2.68-2.50 (m, 1H, -$CH_2$), 2.39-2.18 (m, 1H, -$CH_2$), 1.99-2.07 (m, 1H, -$CH_2$), 1.95-1.88 (m, 1H, -$CH_2$), 1.20 (t, 3H, *J* = 7.2 Hz, -$CH_3$); MS (ESI) m/z(%): 455.2 $[M+H]^+$; Anal. calcd. for $C_{28}H_{26}N_2O_4$ (%): C, 73.99; H, 5.77; N, 6.16. Found (%): C, 74.14; H, 6.25; N, 6.25.

*2-amino-8-[2-(4-chlorophenyl)-2-oxoethoxy]-4-phenethyl-4H-benzo[h]chromene-3-carbonitrile* (**11**): Yield: 77 %; M.p.: 181-183 °C; IR (KBr, $cm^{-1}$): 3387 ($NH_2$), 3322 ($NH_2$), 3062, 2923($CH_2$), 2855, 2194 (CN), 1700 (C=O), 1660, 1605, 1483, 1406, 1378, 1312, 1230, 1192, 1172, 1093, 989; $^1$H-NMR (DMSO-$d_6$, 600 MHz): $\delta$ 8.10 (d, 1H, *J* = 9.0 Hz, Ar-H), 8.07 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.66 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.54 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.39 (d, 1H, *J* = 2.4 Hz, Ar-H), 7.37-7.32 (m, 2H, Ar-H), 7.25-7.17 (m, 2H, Ar-H), 7.14-7.09 (m, 3H, Ar-H), 7.04 (s, 2H, Ar-H), 5.70 (s, 2H, -$NH_2$), 3.78 (t, 1H, *J* = 4.8 Hz, -CH), 2.69-2.52 (m, 1H, -$CH_2$), 2.40-2.19 (m, 1H, -$CH_2$), 2.04-2.10 (m, 1H, -$CH_2$), 2.00-1.94 (m, 1H, -$CH_2$) ; MS (ESI) m/z(%): 495.1 $[M+H]^+$; Anal. calcd. for $C_{30}H_{23}ClN_2O_3$ (%): C, 72.80; H, 4.68; N, 5.66. Found (%): C, 72.94; H, 4.65; N, 5.60.

**Results and Discussion**

The synthetic method for compounds **6~11** is outlined in Scheme 1. The condensation of cinnamaldehyde (**1**) with malononitrile in EtOH afforded 2-(3-phenylallylidene)malononitrile (**2**) as light yellow rystals . The cyclization of **2** with naphthalene-1,6-diol in EtOH at 50 °C condition for 20 hours given 2-amino-8-hydroxy-4-styryl-4*H*-benzo[h]chromene-3-carbonitrile (**4)**, which was then hydrogenated hydrogen in the presence of Pd/C at room temperature provided 2-amino-8-hydroxy-4-phenethyl-4*H*-benzo[h]chromene-3-carbonitrile (**5**). Compound **4** and compound **5** were then condensed with 4-(3-chloropropyl)morpholine, ethyl 4-bromobut-2-enoate and 2-bromo-1-(4-chlorophenyl)ethanone to afford the target substituted 2-amino-4*H*-benzo[h]chromene-3-carbonitrile derivatives **6~11**. Compounds **6~11** were appropriately established by spectroscopic and analytical methods. All data were consistent with the structures of **6~11**, for example, IR shows the peak at about 2189 $cm^{-1}$ results from the nitrile group stretching vibration of **6**. The $^1$H-NMR spectrum for compound **6** exhibits a double peaks at 4.36 ppm, corresponding to the methenyl proton at position 4 of benzo[h]chromene. In the mass spectrum of **6**, the peak appeared at m/z 468 ($[M+H]^+$, 100%), which is in accordance with its molecular formula. IR, $^1$H-NMR, MS and elemental analyses of the target compounds confirmed their structural integrity.




Reagents and conditions. (a) EtOH, $Et_3N$ at RT; (b) EtOH, $Et_3N$ at 50 °C; (c) $K_2CO_3$, KI, $CH_3CN$ at 80 °C; (d) Palladium 10% on Carbon, $H_2$, $CH_2Cl_2$, $CH_3OH$, at RT.

Scheme-1: Synthetic route of the target compounds.

## Conclusion

Some novel substituted 2-amino-4*H*-benzo [h]chromene-3-carbonitrile derivatives were synthesized and all the target compounds have not been reported in other literatures. The novel compounds may serve as leads for designing novel chemotherapeutic agents. Further studies on biological activities about these derivatives are still underway in our laboratory and will be reported in the future.

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