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ORIGINAL ARTICLE

An efficient one-pot synthesis of functionalized chromeno[4,3-*b*]pyridine derivatives under catalyst-free conditions

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Abstract A concise, efficient one-pot synthesis of functionalized chromeno[4,3-*b*]pyridine derivatives via a three-component reaction of 4-oxo-4*H*-chromene-3-carbaldehydes, malononitrile or cyanoacetates, and aromatic amines under catalyst-free conditions in an environmentally friendly medium (ethanol–water, 3:1 v/v) is described. This synthesis involves a group-assisted purification process, which avoids traditional recrystallization and chromatographic purification methods.

Keywords Chromeno[4,3-*b*]pyridine · Multicomponent reactions (MCRs) · Group-assisted purification (GAP) process

Introduction

Nitrogen-containing heterocyclic compounds are important because of their presence in a broad range of natural products and synthetic organic molecules with various biological activities [1,2]. The chromenopyridine nucleus has a wide range of pharmacological activities, including antibacterial [3], antiinflammotory [4,5], antimicrobial [6,7], anti-HIV [8], and anticancer [9]. Several methods have been developed for the construction of the chromenopyridine skeleton [10–18], but these methods involve long multistep processes and afford low yields of the desired products. There is therefore a need to develop concise and efficient methods for the synthesis of these important molecules [19–21].

The development of a simple and eco-friendly protocol for the construction of nitrogen-containing heterocyclic compound libraries of medical motifs is an attractive area of research in both academia and the pharmaceutical industry. Multicomponent reactions (MCRs) are promising and powerful tools in organic, combinatorial, and medicinal chemistry because of their atom economy, high complexity and diversity of products, multiple bond formation efficiency, and environmental friendliness [22–26]. These features make MCRs suitable for the easy construction of complex heterocyclic scaffolds from readily available starting materials [27–29]. In the past decade, various MCRs have been used for the construction of complex organic heterocyclic molecules [30–35].

The development of environmentally friendly synthetic methods is a challenge in modern organic synthesis. The need to reduce the amount of toxic wastes and byproducts arising from chemical processes has resulted in an increasing emphasis on the use of less-toxic and environmentally compatible materials in the design of new synthetic methods. Traditional purification methods such as recrystallization and column chromatography have problems in terms of consumption of organic solvents and energy, waste generation, and pollution. The concept of group-assisted purification (GAP) techniques, which avoid traditional recrystallization and chromatographic purification methods and reduce waste generation from silica and solvents, particularly toxic solvents, was first developed by the Li group in the design of asymmetric synthesis of new imine reagents [36,37]. To date, GAP chemistry has been used in many asymmetric synthetic reactions [38–43] and MCRs [44–49]. As part of our current studies on the development of environmentally friendly

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routes to heterocyclic systems [50–55], we now report an efficient and clean synthesis of chromeno[4,3-*b*]pyridine derivatives under catalyst-free conditions in an environmentally friendly medium (ethanol–water, 3:1 v/v).

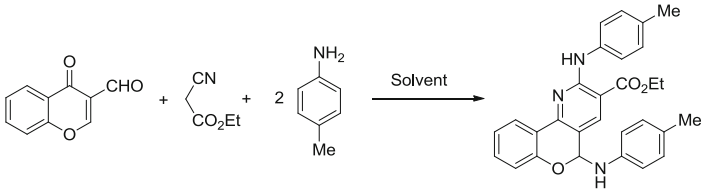
Results and discussion

We initially evaluated the three-component reaction of a 1:1:2 mixtures of 4-oxo-4*H*-chromene- 3-carbaldehyde (**1a**), ethyl cyanoacetate (**2a**), and 4-methylaniline (**3a**) under various conditions. The results are summarized in Table 1. The desired product **4a** was obtained in 89% yield when the reaction was carried out in ethanol at 80 °C for 2 h under catalyst-free conditions (Table 1, entry 1). Various solvents were then evaluated to determine the impact of the solvent on the yield. Of all the solvents tested, *i.e.*, ethanol, toluene, 1,4-dioxane, water, chloroform, and DMF, ethanol gave the best result (Table 1, entries 1–6). Water is a greener solvent; therefore, we evaluated the effect on the yield of mixing ethanol and water in different ratios. Screening experiments showed that a 3:1 (v/v) mixture of ethanol and water was the best solvent for this transformation (Table 1, entries 7–11). The optimum reaction temperature was determined by performing the reaction at ambient temperature, room temperature, and 40, 60, and 80 °C; the best reaction temperature was 80 °C (Table 1, entries 11 and 12–14). These experiments showed that the optimum reaction conditions were ethanol–water (3:1 v/v) as the solvent, 80 °C for 2 h, and catalyst-free conditions.

With the optimum reaction conditions in hand, we then evaluated the substrate scope using various 4-oxo-4*H*-chromene-3-carbaldehydes, malononitrile or cyanoacetates, and amines. The results are summarized in Table 2. In this reaction, when malononitrile, methyl cyanoacetate, and ethyl cyanoacetate were used, the desired products were obtained in excellent yields. The data in Table 2 show that 4-oxo- 4*H*-chromene-3-carbaldehydes with no substituents or with electron-withdrawing groups were tolerated under the reaction conditions. However, when 4-oxo-4*H*-chromene-3-carbaldehydes with electron-donating groups were used, the desired products were not obtained (Table 2, entries 31–33). It can been seen from Table 2 that aromatic amines with either electron-donating or electron-withdrawing groups were also tolerated under these reaction conditions. However, when an aliphatic amine or heterocyclic amine was used in this transformation, the desired products **4** were not obtained (Table 2, entries 34 and 35).

It is important that this synthesis followed a GAP process, which avoids traditional recrystallization or column

Table 1 Optimization of reaction conditions for synthesis of **4a**

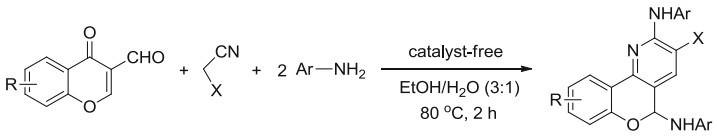


1a **2a** **3a** **4a**

Entry	Solvent (V/V)	Temperature (°C)	Time (h)	Isolated yield (%)
1	EtOH	80	2	89
2	Toluene	80	2	Trace
3	1,4-Dioxane	80	2	Trace
4	H_2O	80	2	55
5	$CHCl_3$	65	2	40
6	DMF	80	2	37
7	EtOH/H_2O (1:3)	80	2	70
8	EtOH/H_2O (1:2)	80	2	70
9	EtOH/H_2O (1:1)	80	2	82
10	EtOH/H_2O (2:1)	80	2	83
11	EtOH/H_2O (3:1)	80	2	88
12	EtOH/H_2O (3:1)	25	2	Trace
13	EtOH/H_2O (3:1)	40	2	Trace
14	EtOH/H_2O (3:1)	60	2	70

Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3a** (2 mmol), solvent (2 mL)

Table 2 Synthesis of functionalized chromeno[4,3-*b*]pyridine derivatives **4** via three-component reaction



1 2 3 4

Entry	R	X	Ar	Product	Isolated yield (%)
1	H	CO_2Et	4-MeC_6H_4	**4a**	88
2	H	CO_2Et	C_6H_5	**4b**	90
3	H	CO_2Et	4-$MeOC_6H_4$	**4c**	89
4	H	CO_2Et	2-MeC_6H_4	**4d**	84
5	H	CO_2Et	2,4-$Me_2C_6H_3$	**4e**	88
6	H	CO_2Et	3,5-$Me_2C_6H_3$	**4f**	88
7	H	CO_2Me	4-MeC_6H_4	**4g**	88
8	H	CO_2Me	4-BrC_6H_4	**4h**	83
9	H	CN	4-$MeOC_6H_4$	**4i**	92
10	H	CN	C_6H_5	**4j**	90
11	H	CN	4-MeC_6H_4	**4k**	92
12	H	CN	3,5-$Me_2C_6H_3$	**4l**	90
13	6-F	CO_2Et	4-$MeOC_6H_4$	**4m**	89
14	6-F	CO_2Et	C_6H_5	**4n**	90
15	6-F	CO_2Et	3-$Me_2CHC_6H_4$	**4o**	88
16	6-F	CO_2Me	3-$Me_2CHC_6H_4$	**4p**	88
17	6-F	CN	4-$Me_2CHC_6H_4$	**4q**	88
18	7-F	CO_2Et	4-$MeOC_6H_4$	**4r**	89
19	7-F	CO_2Et	4-MeC_6H_4	**4s**	90
20	7-F	CO_2Et	3-$Me_2CHC_6H_4$	**4t**	88
21	7-F	CO_2Me	4-$MeOC_6H_4$	**4u**	89
22	7-F	CO_2Me	4-MeC_6H_4	**4v**	88
23	7-F	CO_2Me	3-$Me_2CHC_6H_4$	**4w**	88
24	7-F	CN	4-MeC_6H_4	**4x**	89
25	6-Cl	CO_2Et	4-$MeOC_6H_4$	**4y**	89
26	6-Cl	CO_2Et	4-MeC_6H_4	**4z**	88
27	6-Cl	CO_2Et	4-BrC_6H_4	**4a′**	85
28	6-Cl	CO_2Me	4-MeC_6H_4	**4b′**	88
29	6-Cl	CN	4-$MeOC_6H_4$	**4c′**	90
30	6-Cl	CN	4-MeC_6H_4	**4d′**	90
31	6-Me	CO_2Et	4-MeC_6H_4	**4e′**	Trace
32	6-Me	CO_2Et	4-BrC_6H_4	**4f′**	Trace
32	6-MeO	CO_2Et	4-BrC_6H_4	**4g′**	Trace
33	H	CO_2Et	*n*-C_4H_9	**4h′**	Trace
34	H	CO_2Et	Pyrid-2-yl	**4i′**	Trace

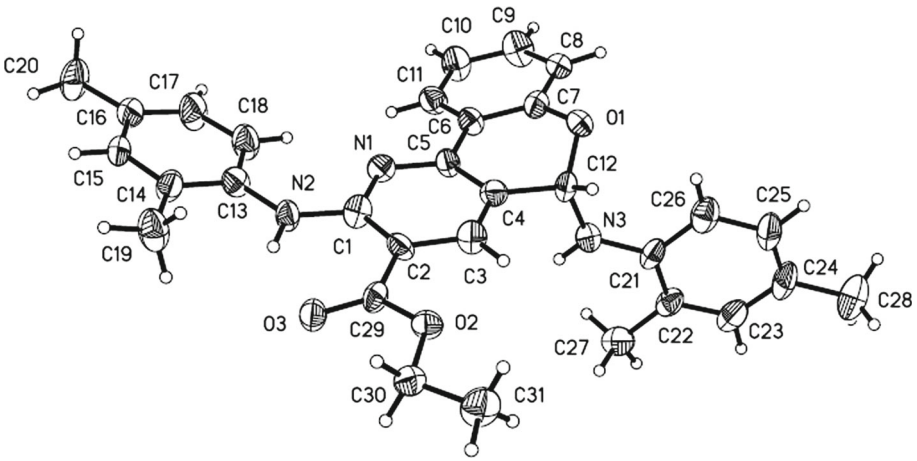
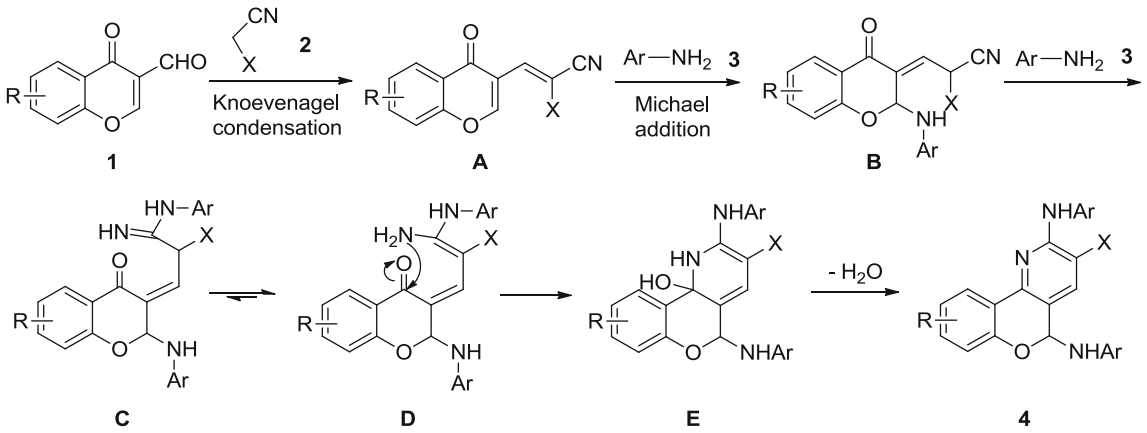


Fig. 1 Crystal structure of compound **4e**



Scheme 1 Proposed mechanism for the formation of compounds **4**

chromatographic purification methods. Pure products were obtained simply by filtration and washing the solid with a little cold ethanol.

The structures of compounds **4** were identified from their IR, ^{1}H NMR, and ^{13}C NMR spectra, and by HRMS analysis. The structure of compound **4e** was further confirmed using single-crystal X-ray diffraction analysis (Fig. 1).

Based on the experimental observations, we propose the following mechanism for this new three-component reaction (Scheme 1). The initial Knoevenagel condensation of a 4-oxo-4*H*-chromene- 3-carbaldehyde **1** with malononitrile or a cyanoacetate **2** gives intermediate **A**. Michael addition of an aromatic amine **3** to intermediate **A** gives intermediate **B**. Then another aromatic amine **3** adds to intermediate **B** to give intermediate **C**, which tautomerizes to give intermediate **D**. Intermediate **D** undergoes intramolecular cyclization and dehydration to give the product **4**. When the 4-oxo-4*H*-chromene- 3-carbaldehydes with electron-donating groups (such as methyl and methoxy) at C_6 position were used, the desired products were not obtained. The reason was that the electron-donating groups reduced the reaction activity of intermediate **A** to anilines **3**.

In summary, we have developed a highly efficient, catalyst-free, green protocol for the one-pot three-component synthesis of chromeno[4,3-*b*] pyridine derivatives; these occur as structural units in a number of biologically active compounds. This protocol has the advantages of mild reaction conditions, high yields, convenient operation, and environmental friendliness.

Experimental section

General

All reagents and solvents were commercially available with analytical grade and used as received. All evaporations of organic solvents were carried out with a rotary evaporator in conjunction with a water aspirator. Melting points were measured using an electrothermal XT-5 apparatus and uncorrected. IR spectra were recorded with a Varian F-1000 spectrometer in KBr with absorption in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 solution, using a Bruker 400 MHz spectrometer. *J* values are reported in hertz. Chemical shifts are expressed in ppm

downfield from internal standard TMS. The abbreviations used for NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. HRMS analyses were carried out using a Bruker micrOTOF-Q instrument. X-ray data were collected on a Bruker SMART diffractometer. 4-oxo-4*H*-chromene-3-carbaldehydes were obtained from Alfa Aesar Company.

General procedure for synthesis of functionalized chromeno[4,3-b]pyridine derivatives **4**

A 25-mL flask was charged with a 4-oxo-4*H*-chromene-3-carbaldehyde **1** (1 mmol), malononitrile or a cyanoacetate **2** (1 mmol), an aromatic amine **3** (2 mmol), ethanol (1.5 mL), and water (0.5 mL). The mixture was stirred at 80 °C for 2 h. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The crystalline solids were collected and washed with a small amount of cold ethanol to give the pure products **4a–4d'** for analysis.

*Ethyl 2,5-bis(p-tolylamino)-5H-chromeno[4,3-b] pyridine-3-carboxylate (***4a***)*

Yellow solid, yield 88%. m.p. 212–214 °C. IR (KBr): 3450, 2925, 1676, 1615, 1526, 1415, 1230, 1104, 939, 813, 793, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.25 (s, 1H, NH), 8.29 (s, 1H, ArH), 8.13–8.11 (m, 1H, ArH), 7.73 (d, J = 8.8 Hz, 2H, ArH), 7.40–7.35 (m, 1H, ArH), 7.24 (d, J = 8.0 Hz, 2H, ArH), 7.14 (t, J = 6.8 Hz, 1H, ArH), 6.98 (d, J = 8.8 Hz, 2H, ArH), 6.91–6.88 (m, 2H, ArH), 6.83 (d, J = 8.8 Hz, 2H, ArH + CH), 6.74 (d, J = 8.8 Hz, 1H, NH), 4.37 (q, J = 7.2 Hz, 2H, CH_2O), 2.32 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 167.2, 156.0, 154.6, 142.0, 138.3, 137.1, 132.2, 129.8, 129.3, 125.6, 122.0, 121.7, 120.8, 118.4, 115.8, 114.6, 106.1, 100.0, 81.9, 61.3, 20.9, 20.5, 14.3. HRMS (ESI) Calcd. for $C_{29}H_{28}N_3O_3$ ([M + H]$^+$): 466.2131. Found: 466.2132.

Ethyl 2,5-bis(phenylamino)-5H-chromeno[4,3-b] pyridine-3-carboxylate **(4b)**

Yellow solid, yield 90%. m.p. 230–232 °C. IR (KBr): 3394, 2970, 1679, 1602, 1519, 1436, 1371, 1293, 1231, 1105, 922, 794, 749 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H, NH), 8.33 (s, 1H, ArH), 8.15 (d, J = 7.6 Hz, 1H, ArH), 7.86 (d, J = 8.0 Hz, 2H, ArH), 7.46–7.37 (m, 3H, ArH), 7.20–7.06 (m, 5H, ArH), 6.92 (d, J = 7.6 Hz, 3H, ArH), 6.79 (t, J = 8.8 Hz, 1H, CH), 6.73 (t, J = 7.2 Hz, 1H, NH), 4.38 (q, J = 7.2 Hz, 2H, CH_2O), 1.36 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.8, 155.1, 154.8, 150.0, 145.5, 139.7, 138.9, 132.5, 129.0, 125.1, 122.7, 121.9, 121.5, 120.2, 118.3, 116.6, 113.8, 106.2, 80.7, 61.5, 14.2. HRMS (ESI) Calcd. for $C_{27}H_{24}N_3O_3$ ([M+H]$^+$): 438.1818. Found: 438.1812.

Ethyl 2,5-bis((4-methoxyphenyl)amino)-5H-chromeno [4,3-b]pyridine-3-carboxylate **(4c)**

Yellow solid, yield 89%. m.p. 180–182 °C. IR (KBr): 3371, 2972, 2931, 2834, 1677, 1614, 1510, 1421, 1301, 1090, 1029, 944, 821, 764 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.16 (s, 1H, NH), 8.27 (s, 1H, ArH), 8.11–8.09 (m, 1H, ArH), 7.75–7.72 (m, 2H, ArH), 7.39–7.35 (m, 1H, ArH), 7.13 (t, J = 8.0 Hz, 1H, ArH), 7.01 (d, J = 8.8 Hz, 2H, ArH), 6.88 (t, J = 9.2 Hz, 3H, ArH), 6.79 (d, J = 9.2 Hz, 2H, ArH), 6.74 (d, J = 8.8 Hz, 1H, CH), 6.68 (d, J = 8.8 Hz, 1H, NH), 4.36 (q, J = 7.2 Hz, 2H, CH_2O), 3.78 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 1.35 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.8, 155.2, 155.1, 154.9, 152.3, 150.0, 139.3, 138.8, 132.7, 132.4, 125.1, 122.0, 121.7, 121.6, 118.3, 116.3, 115.0, 114.6, 114.1, 105.5, 81.7, 61.4, 55.4, 55.3, 14.2. HRMS (ESI) Calcd. for $C_{29}H_{28}N_3O_5$ ([M+H]$^+$): 498.2029. Found: 498.2027.

Ethyl 2,5-bis(o-tolylamino)-5H-chromeno[4,3-b] pyridine-3-carboxylate **(4d)**

Yellow solid, m.p. 190–192 °C. IR (KBr): 3444, 2985, 1676, 1596, 1520, 1460, 1344, 1234, 1109, 903, 803, 734 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.20 (s, 1H, NH), 8.48 (d, J = 7.6 Hz, 1H, ArH), 8.31 (s, 1H, ArH), 8.07–8.05 (m, 1H, ArH), 7.39–7.24 (m, 4H, ArH), 7.16–7.01 (m, 4H, ArH), 6.91 (d, J = 8.0 Hz, 1H, ArH), 6.80–6.71 (m, 2H, ArH+CH), 6.16 (d, J = 8.8 Hz, 1H, NH), 4.37 (q, J = 7.2 Hz, 2H, CH_2O), 2.37 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.2, 156.2, 154.5, 150.6, 142.6, 138.4, 138.1, 132.3, 130.4, 128.8, 127.2, 126.2, 125.6, 123.2, 122.1, 121.9, 121.5, 119.7, 118.4, 115.9, 112.9, 106.4, 81.6, 61.3, 18.5, 17.5, 14.3. HRMS (ESI) Calcd. for $C_{29}H_{28}N_3O_3$ ([M+H]$^+$): 466.2131. Found: 466.2132.

Ethyl 2,5-bis((2,4-dimethylphenyl)amino)-5H-chromen [4,3-b]pyridine-3-carboxylate **(4e)**

Yellow solid, yield 88%. m.p. 183–185 °C. IR (KBr): 3402, 2991, 2912, 1686, 1601, 1517, 1440, 1300, 1245, 1225, 1135, 946, 819, 798, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.09 (s, 1H, NH), 8.29 (d, J = 9.2 Hz, 2H, ArH), 8.04–8.01 (m, 1H, ArH), 7.38–7.34 (m, 1H, ArH), 7.15–7.01 (m, 4H, ArH), 6.94–6.84 (m, 3H, ArH), 6.71 (d, J = 9.2 Hz, 2H, CH), 5.99 (d, J = 9.2 Hz, 1H, NH), 4.36 (q, J = 6.8 Hz,

2H, CH_2O), 2.30 (d, J = 5.6 Hz, 6H, 2 × CH_3), 2.19 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.34 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.3, 156.2, 154.5, 150.6, 140.3, 138.4, 135.4, 132.7, 132.2, 131.2, 131.0, 129.0, 128.9, 127.5, 126.6, 125.6, 123.3, 122.2, 122.0, 121.6, 118.4, 115.8, 113.2, 106.2, 82.1, 61.2, 20.9, 20.5, 18.4, 17.4, 14.3. HRMS (ESI) Calcd. for $C_{31}H_{32}N_3O_3$ ($[M+H]^+$): 494.2444. Found: 494.2436.

Ethyl 2,5-bis((3,5-dimethylphenyl)amino)-5H-chromeno [4,3-b]pyridine-3-carboxylate **(4f)**

Yellow solid, yield 88%. m.p. 229–230 °C. IR (KBr): 3442, 2921, 1686, 1602, 1521, 1425, 1230, 1180, 1105, 923, 828, 798, 768, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.32 (s, 1H, NH), 8.26–8.24 (m, 1H, CH), 8.17 (s, 1H, NH), 7.55 (s, 2H, ArH), 7.37–7.32 (m, 1H, ArH), 7.12 (t, J = 7.2 Hz, 1H, ArH), 7.00 (d, J = 8.8 Hz, 1H, ArH), 6.76 (s, 1H, ArH), 6.56 (d, J = 10.4 Hz, 4H, ArH), 4.36 (q, J = 6.8 Hz, 2H, CH_2O), 2.38 (s, 6H, 2 × CH_3), 2.29 (s, 6H, 2 × CH_3), 1.40 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.1, 155.9, 154.6, 150.5, 144.4, 139.6, 139.1, 138.2, 132.2, 125.5, 124.4, 122.0, 121.7, 121.7, 118.5, 118.4, 115.8, 112.1, 106.2, 81.5, 61.3, 21.5, 14.3. HRMS (ESI) Calcd. for $C_{31}H_{32}N_3O_3$ ($[M+H]^+$): 494.2444. Found: 494.2434.

Methyl 2,5-bis(p-tolylamino)-5H-chromeno[4,3-b] pyridine-3-carboxylate **(4g)**

Yellow solid, yield 88%. m.p. 178–180 °C. IR (KBr): 3402, 3021, 2947, 2921, 1677, 1612, 1519, 1440, 1296, 1232, 1105, 929, 804, 754 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.21 (s, 1H, NH), 8.25 (s, 1H, ArH), 8.11 (d, J = 7.6 Hz, 1H, ArH), 7.73 (d, J = 8.0 Hz, 2H, ArH), 7.37–7.32 (m, 1H, ArH), 7.23 (d, J = 8.8 Hz, 2H, ArH), 7.14 (t, J = 7.2 Hz, 1H, ArH), 6.98 (d, J = 8.0 Hz, 2H, ArH), 6.91–6.88 (m, 2H, ArH), 6.82 (d, J = 8.4 Hz, 2H, ArH+CH), 6.69 (d, J = 8.8 Hz, 1H, NH), 3.89 (s, 3H, CH_3O), 2.32 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.5, 155.9, 154.6, 150.8, 142.0, 138.2, 137.0, 132.3, 129.8, 129.3, 129.1, 125.6, 122.0, 121.6, 120.8, 118.4, 115.8, 114.6, 105.7, 81.9, 52.2, 20.9, 20.5. HRMS (ESI) Calcd. for $C_{28}H_{26}N_3O_3$ ($[M+H]^+$): 452.1974. Found: 452.1973.

Methyl 2,5-bis((4-bromophenyl)amino)-5H-chromeno [4,3-b]pyridine-3-carboxylate **(4h)**

Yellow solid, yield 83%. m.p. 182–184 °C. IR (KBr): 3413, 3033, 2957, 2931, 1670, 1616, 1520, 1455, 1300, 1255, 1137, 939, 811, 768 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.30 (s, 1H, NH), 8.32 (s, 1H, ArH), 8.13 (d, J = 7.2 Hz, 1H, ArH), 7.84 (d, J = 8.0 Hz, 2H, ArH), 7.60 (d, J = 8.0 Hz, 2H, ArH), 7.41–7.14 (m, 5H, ArH), 6.93–6.86 (m, 3H, ArH+CH), 6.75 (d, J = 8.0 Hz, 1H, NH), 3.90 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 167.0, 154.7, 154.6, 149.9, 144.8, 138.9, 132.7 131.7, 131.6, 125.2, 122.2, 122.1, 121.3, 118.3, 116.7, 115.9, 114.2, 109.3, 106.4, 80.4, 52.7. HRMS (ESI) Calcd. for $C_{26}H_{20}Br_2N_3O_3$ ($[M+H]^+$): 579.9873. Found: 579.9871.

2,5-Bis((4-methoxyphenyl)amino)-5H-chromeno[4,3-b] pyridine-3-carbonitrile **(4i)**

Yellow solid, yield 92%. m.p. 187–188 °C. IR (KBr): 3330, 2955, 2834, 2218, 1601, 1510, 1446, 1425, 1240, 1034, 823, 753 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.11 (s, 1H, NH), 8.10 (s, 1H, ArH), 7.96 (d, J = 7.2 Hz, 1H, ArH), 7.60 (d, J = 8.8 Hz, 2H, ArH), 7.35 (t, J = 7.2 Hz, 1H, ArH), 7.08 (t, J = 7.6 Hz, 1H, ArH), 6.98 (d, J = 8.8 Hz, 2H, ArH), 6.90–6.73 (m, 6H, ArH+CH), 6.57 (d, J = 8.4 Hz, 1H, NH), 3.78 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 155.9, 155.5, 154.7, 152.4, 149.3, 141.7, 139.3, 132.6, 132.5, 125.0, 123.5, 121.8, 121.4, 118.3, 116.9, 116.7, 115.0, 114.6, 113.7, 90.8, 81.5, 55.4, 55.3. HRMS (ESI) Calcd. for $C_{27}H_{22}N_4NaO_3$ ($[M+Na]^{+)}$: 473.1590. Found: 473.1582.

2,5-Bis(phenylamino)-5H-chromeno[4,3-b]pyridine-3-carbonitrile **(4j)**

Yellow solid, yield 90%. m.p. 215–217 °C. IR (KBr): 3398, 3313, 2225, 1599, 1521, 1496, 1443, 1300, 1242, 1195, 1099, 929, 749 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.17–8.14 (m, 1H, NH), 7.75–7.72 (m, 3H, ArH), 7.46–7.42 (m, 2H, ArH), 7.39–7.34 (m, 1H, ArH), 7.29–7.25 (m, 2H, ArH), 7.20–7.10 (m, 3H, ArH), 6.98–6.89 (m, 4H, ArH), 6.53 (d, J = 9. 6 Hz, 1H, CH), 4.63 (d, J = 9.2 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.6, 154.5, 150.4, 143.9, 139.4, 138.5, 132.9, 129.4, 129.0, 125.6, 123.9, 122.4, 121.0, 120.5, 120.2, 118.5, 116.7, 116.4, 114.7, 91.5, 81.1. HRMS (ESI) Calcd. for $C_{25}H_{18}N_4NaO$ ($[M+Na]^+$): 413.1378. Found: 413.1374.

2,5-Bis(p-tolylamino)-5H-chromeno[4,3-b]pyridine-3-carbonitrile **(4k)**

Yellow solid, yield 92%. m.p. 187–188 °C. IR (KBr): 3421, 2921, 2212, 1602, 1520, 1450, 1420, 1245, 1205, 1090, 808, 753 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H, NH), 8.12 (s, 1H, CH), 7.98 (d, J = 7.6 Hz, 1H, NH), 7.60 (d, J = 7.6 Hz, 2H, ArH), 7.36 (t, J = 7.2 Hz, 1H, ArH), 7.20 (d, J = 8.4 Hz, 2H, ArH), 7.10 (t, J = 7.2 Hz, 1H, ArH), 6.99 (d, J = 8.0 Hz, 2H, ArH), 6.90 (d, J = 8.4 Hz, 2H, ArH), 6.81 (d, J = 8.4 Hz, 2H, ArH), 6.62 (d, J = 8.4 Hz, 1H, ArH), 2.32 (s, 3H, CH_3), 2.19 (s, 3H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 155.7, 154.7, 149.3, 143.0, 141.7, 137.2, 132.6, 132.1, 129.5, 129.0, 126.9, 125.0, 121.9, 121.5, 121.4, 118.3, 116.9, 116.8, 113.9, 91.4, 80.9, 20.6, 20.3. HRMS (ESI) Calcd. for $C_{27}H_{22}N_4NaO$ ([M+Na]$^+$): 441.1691. Found: 441.1690.

2,5-Bis((3,5-dimethylphenyl)amino)-5H-chromeno[4,3-b] pyridine-3-carbonitrile **(4l)**

Yellow solid, yield 90%. m.p. 190–192 °C. IR (KBr): 3410, 2916, 2208, 1526, 1450, 1329, 1240, 1178, 1104, 923, 833, 754 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.17 (d, J = 7.6 Hz, 1H, NH), 7.65 (s, 1H, ArH), 7.37 (t, J = 7.6 Hz, 3H, ArH), 7.12 (t, J = 7.6 Hz, 1H, ArH), 7.00 (t, J = 8.0 Hz, 2H, ArH), 6.83 (s, 1H, ArH), 6.57–6.48 (m, 4H, CH+ArH), 4.57 (d, J = 9.6 Hz, 1H, NH), 2.40 (s, 6H, 2 × CH_3), 2.29 (s, 6H, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.6, 154.6, 150.3, 144.0, 139.3, 139.1, 138.5, 138.3, 132.8, 125.5, 122.2, 122.1, 121.1, 118.5, 118.2, 116.6, 116.4, 112.5, 91.4, 81.2, 21.5, 21.4. HRMS (ESI) Calcd. for $C_{29}H_{26}N_4NaO$ ([M+Na]$^+$): 469.2004. Found: 469.2006.

Ethyl 9-fluoro-2,5-bis((4-methoxyphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4m)**

Yellow solid, yield 89%. m.p. 190–192 °C. IR (KBr): 3442, 2996, 2930, 1686, 1616, 1516, 1455, 1213, 1099, 1044, 949, 828, 798, 698 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.13 (s, 1H, NH), 8.29 (s, 1H, ArH), 7.71–7.68 (m, 3H, ArH), 7.25–7.20 (m, 1H, ArH), 7.02 (d, J = 8.8 Hz, 2H, ArH), 6.95–6.92 (m, 1H, ArH), 6.87 (d, J = 9.2 Hz, 2H, ArH), 6.81–6.75 (m, 3H, ArH+CH), 6.68 (d, J = 9.2 Hz, 1H, NH), 4.37 (q, J = 6.8 Hz, 2H, CH_2O), 3.79 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 1.36 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.0, 155.7, 154.9 (d, J = 234 Hz), 150.4, 149.7, 138.3, 138.1, 132.6, 122.6, 119.6, 118.9 (d, J = 25 Hz), 116.1, 115.7, 114.8, 114.0, 111.4, 111.1, 106.3, 82.6, 61.4, 55.7, 55.5, 14.3. HRMS (ESI) Calcd. for $C_{29}H_{26}FN_3NaO_5$ ([M+Na]$^+$): 538.1754. Found: 538.1751.

Ethyl 9-fluoro-2,5-bis(phenylamino)-5H-chromeno [4,3-b]pyridine-3-carboxylate **(4n)**

Yellow solid, yield 90%. m.p. 237–239 °C. IR (KBr): 3398, 2990, 1681, 1602, 1526, 1445, 1289, 1219, 1109, 933, 877, 798 752, 698 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.31 (s, 1H, NH), 8.36 (s, 1H, ArH), 7.81 (d, J = 8.0 Hz, 2H, ArH), 7.76–7.73 (m, 1H, ArH), 7.44 (t, 2H, ArH), 7.24–7.07 (m, 5H, ArH), 6.97–6.90 (m, 3H, ArH), 6.81 (d, J = 8.4 Hz, 1H, CH), 6.73 (t, 1H, NH), 4.38 (q, J = 7.2 Hz, 2H, CH_2O), 1.36 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm): 116.6, 157.1 (d, J = 237 Hz), 155.0, 150.9, 148.9, 145.3, 139.4, 139.1, 129.0 (d, J = 5 Hz), 123.0, 120.5, 119.3, 119.1, 118.4, 116.8, 113.8, 110.3 (d, J = 24 Hz), 106.8. HRMS (ESI) Calcd. for $C_{27}H_{23}FN_3O_3$ ([M+H]$^+$): 456.1723. Found: 456.1733.

Ethyl 9-fluoro-2,5-bis((3-isopropylphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4o)**

Yellow solid, yield 88%. m.p. 187–189 °C. IR (KBr): 3404, 2960, 2878, 1681, 1611, 1526, 1450, 1225, 1129, 943, 884, 793, 702 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H, NH), 8.34 (s, 1H, CH), 7.92 (s, 1H, NH), 7.84–7.81 (m, 1H, ArH), 7.44 (d, J = 8.0 Hz, 1H, ArH), 7.33 (t, J = 8.0 Hz, 1H, ArH), 7.26–7.21 (m, 1H, ArH), 7.09 (t, J = 8.4 Hz, 1H, ArH), 7.02–6.95 (m, 3H, ArH), 6.77 (t, J = 7.2 Hz, 3H, ArH), 6.62 (d, J = 7.6 Hz, 1H, ArH), 4.40-4.35 (m, 2H, CH_2O), 2.99-2.92 (m, 1H, CH), 2.79-2.74 (m, 1H, CH), 1.36 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$), 1.17 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.0, 156.0, 150.4, 149.7, 144.3, 139.4, 138.4, 129.4, 128.7, 122.6, 121.5, 119.8, 119.7, 119.1, 119.0, 118.3, 118.2, 115.9, 112.8, 111.7, 111.4 (d, J = 25 Hz), 106.7, 81.7, 61.5, 34.4, 34.2, 24.1, 24.0, 23.9, 14.3. HRMS (ESI) Calcd. for $C_{33}H_{35}FN_3O_3$ ([M+H]$^+$): 540.2662. Found: 540.2659.

Methyl 9-fluoro-2,5-bis((3-isopropylphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4p)**

Yellow solid, yield 88%. m.p. 184–185 °C. IR (KBr): 3402, 2958, 2880, 1681, 1611, 1526, 1446, 1295, 1220, 1130, 940, 889, 794, 698 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H, NH), 8.32 (s, 1H, ArH), 7.91 (s, 1H, ArH), 7.83–7.79 (m, 1H, ArH), 7.43 (d, J = 8.4 Hz, 1H, ArH), 7.32 (t, J = 8.0 Hz, 1H, ArH), 7.25–7.20 (m, 1H, ArH), 7.09 (t, J = 8.0 Hz, 1H, ArH), 7.02–6.94 (m, 3H, ArH), 6.75 (s, 3H, ArH+CH), 6.62 (d, J = 7.6 Hz, 1H, NH), 3.90 (s, 3H, CH_3O), 2.97–2.92 (m, 1H, CH), 2.79–2.75 (m, 1H, CH), 1.30–1.28 (m, 6H, 2 × CH_3), 1.17 (d, J = 6.8 Hz, 6H, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.4, 155.9, 150.3, 149.7, 144.3, 139.4, 138.4, 129.3, 128.7, 122.6, 122.5, 121.6, 119.7, 119.6, 119.2, 119.0, 118.4, 118.2, 115.9, 112.8, 111.8, 111.4 (d, J = 24 Hz), 106.4, 81.8, 52.3, 34.4, 34.2, 24.1, 24.0, 23.9. HRMS (ESI) Calcd. for $C_{32}H_{33}FN_3O_3$ ([M+H]$^+$): 526.2506. Found: 526.2509.

9-Fluoro-2,5-bis((4-isopropylphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carbonitrile **(4q)**

Yellow solid, yield 88%. m.p. 161–163 °C. IR (KBr): 3417, 2958, 2870, 2218, 1611, 1517, 1455, 1260, 1176, 1135, 939, 824 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81–7.78 (m, 1H, NH), 7.74 (s, 1H, ArH), 7.62 (d, J = 8.4 Hz, 2H,

ArH), 7.31 (d, J = 8.4 Hz, 2H, ArH), 7.13 (t, J = 8.4 Hz, 3H, ArH), 7.08–7.03 (m, 1H, ArH), 6.94–6.91 (m, 1H, ArH), 6.86 (d, J = 8.4 Hz, 2H, ArH), 6.49 (d, J = 9.2 Hz, 1H, CH), 4.54 (d, J = 9.2 Hz, 1H, NH), 3.00–2.93 (m, 1H, CH), 2.90–2.83 (m, 1H, CH), 1.31 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$), 1.24 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.0 (d, J = 239 Hz), 155.7, 150.5, 149.7, 145.0, 141.7, 141.0, 139.5, 135.9, 127.3, 127.0, 120.7, 119.9, 119.8, 119.6, 116.8, 116.3, 114.8, 111.4 (d, J = 25 Hz), 92.0, 81.7, 33.6, 33.3, 24.2, 24.0. HRMS (ESI) Calcd. for $C_{31}H_{29}FN_4NaO$ ($[M+Na]^+$): 515.2223. Found: 515.2224.

Ethyl 8-fluoro-2,5-bis((4-methoxyphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4r)**

Yellow solid, yield 89%. m.p. 218–220 °C. IR (KBr): 3442, 3041, 2966, 1681, 1621, 1510, 1420, 1365, 1240, 1034, 929, 834, 743 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.15 (s, 1H, NH), 8.24 (s, 1H, CH), 8.09 (t, J = 8.0 Hz, 1H, NH), 7.71 (t, J = 8.8 Hz, 2H, ArH), 7.01–6.70 (m, 10H, ArH), 4.35 (q, J = 7.2 Hz, 2H, CH_2O), 3.78 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 1.35 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.7, 164.7 (d, J = 247 Hz), 156.6, 156.5, 155.2, 152.5, 149.4, 139.1, 138.7, 132.6, 127.1, 122.1, 118.3, 115.4, 115.1, 114.6, 114.1, 109.2 (d, J = 23 Hz), 105.5, 105.1, 82.6, 61.4, 55.4, 55.3, 14.2. HRMS (ESI) Calcd. for $C_{29}H_{27}FN_3O_5$ ($[M+H]^+$): 516.1935. Found: 516.1925.

Ethyl 8-fluoro-2,5-bis(p-tolylamino)-5H-chromeno [4,3-b]pyridine-3-carboxylate **(4s)**

Yellow solid, yield 90%. m.p. 231–233 °C. IR (KBr): 3402, 2976, 2921, 1677, 1616, 1516, 1415, 1290, 1209, 1105, 969, 893, 808, 708 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H, NH), 8.26 (s, 1H, ArH), 8.12 (t, J = 7.6 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 2H, ArH), 7.22 (d, J = 7.6 Hz, 2H, ArH), 6.98 (t, J = 6.8 Hz, 4H, ArH), 6.83–6.76 (m, 4H, ArH+CH+NH), 4.35 (q, J = 6.8 Hz, 2H, CH_2O), 2.32 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.34 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.1, 156.1, 141.8, 138.3, 137.0, 132.5, 129.9, 129.4, 129.3, 127.3, 127.2, 120.9, 118.1, 114.8, 114.5, 109.7 (d, J = 22 Hz), 105.9, 105.8, 105.5, 82.5, 61.3, 20.9, 20.5, 14.3. HRMS (ESI) Calcd. for $C_{29}H_{27}FN_3O_3$ ($[M+H]^+$): 484.2036. Found: 484.2046.

Ethyl 8-fluoro-2,5-bis((3-isopropylphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4t)**

Yellow solid, yield 88%. m.p. 231–233 °C.; IR (KBr): 3452, 2956, 2930, 1686, 1608, 1526, 1445, 1209, 1104, 973, 788, 698 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.31 (s, 1H, NH), 8.31 (s, 1H, ArH), 8.18 (t, J = 7.2 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.61 (d, J = 8.0 Hz, 1H, ArH), 7.33 (t, J = 8.0 Hz, 1H, ArH), 7.12–7.06 (m, 2H, ArH), 6.99 (t, J = 6.8 Hz, 2H, ArH), 6.86–6.76 (m, 4H, ArH+CH), 6.63 (d, J = 7.6 Hz, 1H, NH), 4.35 (q, J = 6.8 Hz, 2H, CH_2O), 2.98–2.91 (m, 1H, CH), 2.81–2.74 (m, 1H, CH), 1.35 (t, J = 6.8 Hz, 3H, CH_3), 1.28 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$), 1.18 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.1, 156.0, 150.4, 150.0, 149.6, 144.1, 139.5, 138.4, 129.4, 128.6, 127.4, 127.3, 121.4, 118.9, 118.3, 118.1, 114.9, 112.8, 111.7, 109.6 (d, J = 22 Hz), 106.1, 105.9, 105.6, 82.3, 61.4, 34.3, 34.2, 24.1, 24.0, 23.9, 14.3. HRMS (ESI) Calcd. for $C_{33}H_{35}FN_3O_3$ ($[M+H]^+$): 540.2662. Found: 540.2653.

Methyl 8-fluoro-2,5-bis((4-methoxyphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4u)**

Yellow solid, yield 89%. m.p. 208–210 °C. IR (KBr): 3408, 1691, 1626, 1512, 1420, 1310, 1209, 1104, 1034, 979, 823, 793 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.09 (s, 1H, NH), 8.24 (s, 1H, ArH), 8.10–8.07 (m, 1H, ArH), 7.70 (d, J = 9.2 Hz, 2H, ArH), 7.01–6.94 (m, 3H, ArH), 6.87–6.69 (m, 7H, ArH+CH+NH), 3.89 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.5, 155.6, 154.9 (d, J = 223 Hz), 150.2, 138.3, 137.9, 132.7, 127.3, 127.2, 122.6, 116.1, 114.8, 113.9, 109.6 (d, J = 22 Hz), 105.4, 105.3, 83.3, 55.7, 55.5, 52.2. HRMS (ESI) Calcd. for $C_{28}H_{24}FN_3NaO_5$ (M+Na]$^+$): 524.1598. Found: 524.1592.

Methyl 8-fluoro-2,5-bis(p-tolylamino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4v)**

Yellow solid, yield 88%. m.p. 231–233 °C. IR (KBr): 3402, 3025, 2955, 1686, 1616, 1526, 1431, 1295, 1209, 1105, 974, 848, 793 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.19 (s, 1H, NH), 8.27 (s, 1H, CH), 8.13–8.10 (m, 1H, NH), 7.70 (d, J = 8.4 Hz, 2H, ArH), 7.23 (d, J = 8.4 Hz, 2H, ArH), 7.02–6.95 (m, 4H, ArH), 6.83–6.77 (m, 4H, ArH), 3.89 (s, 3H, CH_3O), 2.32 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.5, 156.0, 150.2, 141.7, 138.3, 136.9, 132.5, 129.9, 129.4, 129.3, 127.4, 127.3, 120.9, 118.1, 114.9, 114.6, 109.6 (d, J = 23 Hz), 105.7, 105.6, 82.6, 52.2, 20.9, 20.5. HRMS (ESI) Calcd. for $C_{28}H_{25}FN_3O_3$ ($[M+H]^+$): 470.1877. Found: 470.1871.

Methyl 8-fluoro-2,5-bis((3-isopropylphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4w)**

Yellow solid, yield 88%. m.p. 183–184 °C. IR (KBr): 3442, 2966, 1692, 1608, 1526, 1436, 1385, 1210, 1110, 979, 789,

702 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.26 (s, 1H, NH), 8.30 (s, 1H, ArH), 8.19–8.15 (m, 1H, ArH), 7.74 (s, 1H, ArH), 7.61 (d, J = 8.0 Hz, 1H, ArH), 7.33 (t, J = 8.0 Hz, 1H, ArH), 7.12–7.06 (m, 2H, ArH), 7.00–6.95 (m, 2H, ArH), 6.84–6.77 (m, 4H, ArH+CH), 6.63 (d, J = 7.6 Hz, 1H, NH), 3.90 (s, 3H, CH_3O), 2.98–2.91 (m, 1H, CH), 2.81–2.74 (m, 1H, CH), 1.28 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$), 1.17 (d, J = 6.8 Hz, 6H, $(CH_3)_2C$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.1, 164.7 (d, J = 248 Hz), 156.7, 156.5, 155.0, 149.3, 149.2, 145.2, 139.5, 138.9, 129.0, 128.9, 127.0, 126.8, 121.1, 118.3, 118.2, 117.9, 116.7, 115.8, 112.2, 111.2, 109.1 (d, J = 22 Hz), 105.8, 105.5, 105.3, 81.8, 52.5, 33.7, 24.0. HRMS (ESI) Calcd. for $C_{32}H_{33}FN_3O_3$ ($[M+H]^+$): 526.2506. Found: 526.2529.

8-Fluoro-2,5-bis((4-methylphenyl)amino)-5H-chromeno [4,3-b]pyridine-3-carbonitrile **(4x)**

Yellow solid, yield 89%. m.p. 209–210 °C. IR (KBr): 3330, 3025, 2920, 2225, 1616, 1516, 1461, 1345, 1245, 1010, 969, 813 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.19 (s, 1H, NH), 8.11 (s, 1H, ArH), 8.00–7.96 (m, 1H, ArH), 7.58 (d, J = 8.4 Hz, 2H, ArH), 7.19 (d, J = 8.0 Hz, 2H, ArH), 7.00–6.94 (m, 4H, ArH), 6.82–6.76 (m, 3H, ArH+CH), 6.67 (d, J = 8.4 Hz, 1H, NH), 2.31 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.0, 163.5, 156.4, 156.3, 155.7, 148.6, 142.8, 141.8, 137.1, 132.2, 129.5, 129.0, 127.2, 127.1, 127.0, 121.6, 118.2, 116.8, 116.2, 114.0, 109.4 (d, J = 23 Hz), 105.5, 105.3, 91.4, 81.8, 20.6, 20.3. HRMS (ESI) Calcd. for $C_{27}H_{22}FN_4O$ ($[M+H]^+$): 437.1778. Found: 437.1788.

Ethyl 9-chloro-2,5-bis((4-methoxyphenyl)amino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4y)**

Yellow solid, yield 89%. m.p. 209–211 °C. IR (KBr): 3368, 1682, 1621, 1516, 1440, 1230, 1090, 1039, 949, 828, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.20 (s, 1H, NH), 8.18 (s, 1H, ArH), 8.09 (s, 1H, ArH), 7.69 (d, J = 8.8 Hz, 2H, ArH), 7.24 (d, J = 8.8 Hz, 1H, ArH), 6.96 (d, J = 8.8 Hz, 2H, ArH), 6.89–6.83 (m, 5H, ArH), 6.45 (d, J = 9.2 Hz, 1H, CH), 6.44 (d, J = 9.6 Hz, 1H, NH), 4.37 (q, J = 7.2 Hz, 2H, CH_2O), 3.86 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 1.41 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.0, 156.0, 155.7, 153.8, 152.9, 149.4, 138.4, 138.0 132.6, 131.8, 127.1, 125.1, 122.9, 122.5, 119.8, 116.1, 115.5, 114.8, 114.0, 106.4, 82.7, 61.4, 55.7, 55.5, 14.3. HRMS (ESI) Calcd. for $C_{29}H_{27}ClN_3O_5$ ($[M+H]^+$): 532.1639. Found: 532.1637.

Ethyl 9-chloro-2,5-bis(p-tolylamino)-5H-chromeno[4,3-b]pyridine-3-carboxylate **(4z)**

Yellow solid, yield 88%. m.p. 242–244 °C. IR (KBr): 3370, 2986, 2920, 1681, 1616, 1520, 1440, 1280, 1230, 1099, 954, 814, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.31 (s, 1H, NH), 8.20 (s, 1H, ArH), 8.14 (s, 1H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH), 7.27–7.22 (m, 3H, ArH), 7.08 (d, J = 8.4 Hz, 2H, ArH), 6.90–6.83 (m, 3H, ArH), 6.53 (d, J = 9.2 Hz, 1H, CH), 4.52 (d, J = 9.2 Hz, 1H, NH), 4.38 (q, J = 7.2 Hz, 2H, CH_2O), 2.38 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.41 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.0 156.0, 153.0, 149.4, 141.8, 138.4, 136.8, 132.6, 131.9, 129.9, 129.3, 127.2, 125.2, 122.9, 120.8, 119.9, 115.6, 114.6, 106.6, 82.1, 61.4, 30.9, 20.9, 20.5, 14.3. HRMS (ESI) Calcd. for $C_{29}H_{27}ClN_3O_3$ ($[M+H]^+$): 500.1741. Found: 500.1749.

*Ethyl 2,5-bis((4-bromophenyl)amino)-9-chloro-5H-chrome[4,3-b]pyridine-3-carboxylate (***4a′***)*

Yellow solid, yield 85%. m.p. 242–244 °C. IR (KBr): 3364, 2986, 2930, 1677, 1612, 1521, 1451, 1296, 1230, 1070, 955, 819, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.45 (s, 1H, NH), 8.21 (s, 1H, ArH), 8.10 (s, 1H, ArH), 7.72 (d, J = 8.4 Hz, 2H, ArH), 7.52 (d, J = 8.8 Hz, 2H, ArH), 7.36 (d, J = 8.8 Hz, 2H, ArH), 7.31–7.28 (m, 1H, ArH), 6.90 (d, J = 8.8 Hz, 1H, ArH), 6.81 (d, J = 8.8 Hz, 2H, ArH), 6.50 (d, J = 8.8 Hz, 1H, CH), 4.62 (d, J = 9.2 Hz, 1H, NH), 4.45 (q, J = 7.2 Hz, 2H, CH_2O), 1.42 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.5, 154.7, 149.2, 145.3, 141.7, 139.7, 138.0, 137.4, 132.6, 124.9, 124.5, 121.8, 121.4, 120.3, 118.8, 118.4, 117.1, 116.7, 111.8, 91.8, 80.7, 21.4, 21.3. HRMS (ESI) Calcd. for $C_{27}H_{20}Br_2ClN_3NaO_3$ ($[M+Na]^+$): 649.9458. Found: 649.9459.

*Methyl 9-chloro-2,5-bis(p-tolylamino)-5H-chromeno [4,3-b]pyridine-3-carboxylate (***4b′***)*

Yellow solid, yield 88%. m.p. 239–241 °C. IR (KBr): 3398, 2956, 2921, 1677, 1611, 1521, 1436, 1296, 1235, 1105, 929, 798 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.28 (s, 1H, NH), 8.22 (s, 1H, ArH), 8.15 (s, 1H, ArH), 7.71 (d, J = 8.4 Hz, 2H, ArH), 7.29–7.24 (m, 3H, ArH), 7.09 (d, J = 8.0 Hz, 2H, ArH), 6.91–6.84 (m, 3H, ArH), 6.53 (d, J = 9.2 Hz, 1H, CH), 4.53 (d, J = 9.2 Hz, 1H, NH), 3.94 (s, 3H, CH_3O), 2.40 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.4, 155.9, 153.1, 149.6, 149.2, 141.8, 138.5, 136.8, 132.7, 131.9, 129.9, 129.3, 127.2, 125.2, 122.8, 120.9, 119.9, 115.7, 114.6, 106.3, 82.1, 52.3, 20.9, 20.5. HRMS (ESI) Calcd. for $C_{28}H_{25}ClN_3O_3$ ($[M+H]^+$): 486.1584. Found: 486.1581.

*9-Chloro-2,5-bis((4-methoxyphenyl)amino)-5H-chromeno [4,3-b]pyridine-3-carbonitrile (**4c′**)*

Yellow solid, yield 90%. m.p. 212–213 °C. IR (KBr): 3387, 3336, 2995, 2952, 2840, 2218, 1601, 1516, 1450, 1346, 1247, 1034, 888, 813 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (s, 1H, NH), 7.82 (s, 1H, ArH), 7.62–7.60 (m, 2H, ArH), 7.34–7.31 (m, 1H, ArH), 7.08–7.03 (m, 3H, ArH), 6.95–6.88 (m, 5H, ArH), 6.49 (d, J = 9.6 Hz, 1H, CH), 4.45 (d, J = 10.0 Hz, 1H, NH), 3.92 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.0, 154.1, 153.0, 149.3, 139.7, 137.5, 132.5, 131.1, 127.4, 125.2, 123.1, 122.3, 119.9, 116.6, 114.8, 114.2, 91.7, 82.5, 55.6. HRMS (ESI) Calcd. for $C_{27}H_{21}ClN_4NaO_3$ ($[M+Na]^+$): 507.1200. Found: 507.1204.

9-Chloro-2,5-bis(p-tolylamino)-5H-chromeno[4,3-b] pyridine-3-carbonitrile (**4d′**)

Yellow solid, yield 90%. m.p. 229–231 °C. IR (KBr): 3416, 3031, 2918, 2212, 1597, 1521, 1451, 1351, 1261, 1200, 1141, 899, 808 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (s, 1H, NH), 7.77 (s, 1H, ArH), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.30 (t, J = 10.0 Hz, 3H, ArH), 7.09 (d, J = 7.6 Hz, 3H, ArH), 6.92–6.83 (m, 3H, ArH), 6.52 (d, J = 10.0 Hz, 1H, CH), 4.52 (d, J = 9.6 Hz, 1H, NH), 2.42 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.7, 153.0, 149.3, 141.3, 139.6, 135.6, 134.0, 132.5, 129.9, 129.6, 127.4, 125.2, 122.2, 120.9, 120.0, 116.6, 114.9, 92.0, 81.8, 20.9, 20.5. HRMS (ESI) Calcd. for $C_{27}H_{22}ClN_4O$ ($[M+H]^+$): 453.1482. Found: 453.1487.

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