Synthesis of New Chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridines Derivatives with Antimicrobial Evaluation

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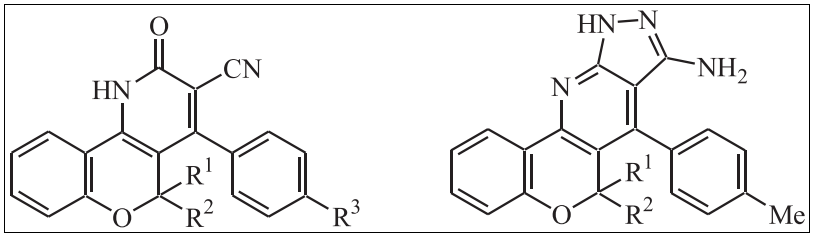

A series of 2-oxo-2,5-dihydro-1*H*-chromeno[4,3-*b*]pyridine derivatives were obtained by using a one-pot three component reaction of 2,2-disubstituted chroman-4-one with aromatic aldehydes and 2-cyanoacetamide in the presence of sodium hydroxide under solvent-free conditions. Heating chromenopyridine derivatives with phosphoryl chloride gave the corresponding chloro derivatives. The reaction of the chloro derivatives with hydrazine hydrate afforded dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridines derivatives. Condensation of the dimethyl derivative compound with the aromatic aldehydes gave 8-Arylideneamino-6,6-dimethyl-10*H*-chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine.

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INTRODUCTION

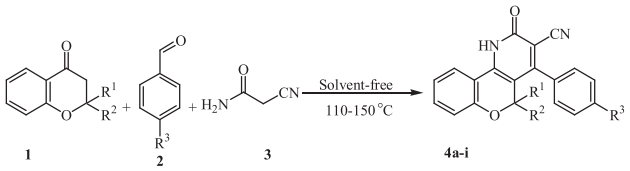
Chromenes and fused chromenes are biologically interesting compounds with antimicrobial activities [1–3], inhibitors of influenza virus sialidases [4,5], DNA stand-breaking activity, and mutagenicity [6]. It is also known that many chromene containing compounds exhibit a wide spectrum of pharmacological activities [7,8], anti-HIV agents [9,10], antibacterials [11,12], and antifungals [13]. In general, a number of biologically active chromenes and chromanes have been isolated from several natural sources. These substances have been identified as apoptosis-inducing [14]. In the past several years, benzopyrano [4,3-*b*]pyridine derivatives have attracted attention as pharmacologically interesting compounds. They have been reported to possess inotropic, anti-allergic, analgesic, and anti-inflammatory activity [15,16]. In addition, 1*H*-pyrazolo [3,4-*b*]pyridines comprise a very interesting class of compounds because of their significant and versatile biological and pharmacological activities, such as antimalarial [17], antiproliferative [18], antimicrobial [19], inhibition of cyclin-dependent kinases [20], cardiovascular [21], antiviral [22], and antileishmanial activities [23]. Our goal, in the past, and recent work is to synthesize a new heterocyclic compounds incorporating pyrazolo[3,4-*b*] pyridine and 2,2-disubstituted chromane-4-one derivatives [24–29]. We reported here the development of tricyclic and tetracyclic ring systems from 2,2-disubstituted chroman-4-one.

RESULTS AND DISCUSSION

2,2-Dialkylchroman-4-ones **1a–c** were synthesized according to reported method [30] by the reaction of 2-hydroxyacetophenone with the appropriate dialkylketone in the presence of pyrrolidine. The one-pot solvent free reaction of the chromanones **1a–c** with aromatic aldehydes **2a–c** and 2-cyanoacetamide **3**, in presence of sodium hydroxide, according to the recent reported method [31], afforded the 4-aryl-5,5-dialkyl-2-oxo)-1,2-dihydro-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile **4a–i**. The structure of the latter compounds was proved by elemental and spectral analysis. The IR spectra showed characteristic CN bands at 2201–2214 cm^{-1} region. The ^1H NMR spectra showed the NH signal at δ 10.99–13.08 ppm, as broad singlet. All the other aromatic and aliphatic protons were observed at the expected regions. Mass spectra (MS, EI) of the derivatives showed a $[M^+]$ and $[M^++1]$ peaks, in agreement with their molecular formula. The ^{13}C NMR spectra of derivatives **4a–i** showed the signal of C-5 at 79.20–86.09 ppm and the signal of CN at 97.76–111.13 ppm. All the other aromatic and aliphatic carbons were observed at the expected regions (Scheme 1).

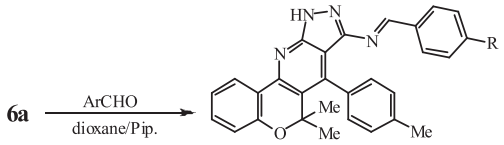
Heating **4a–c** in phosphoryl chloride under reflux gave the corresponding 2-chloro-5,5-dialkyl-4-(4-methylphenyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles **5a–c**. The NMR spectral data were consistent with the structure of the obtained chloro nitrile derivatives **5a–c**. The latter compounds **5a–c** proved to be versatile intermediates for the synthesis of a

Scheme 1. Synthesis routes of the chromenopyridine derivatives.



4	a	b	c	d	e	f	g	h	i
R^1	Me	Et	Et	Me	Et	Et	Me	Et	Et
R^2	Me	Me	Et	Me	Me	Et	Me	Me	Et
R^3	Me	Me	Me	OMe	OMe	OMe	Cl	Cl	Cl

Scheme 3. Synthesis of benzylidene derivatives.



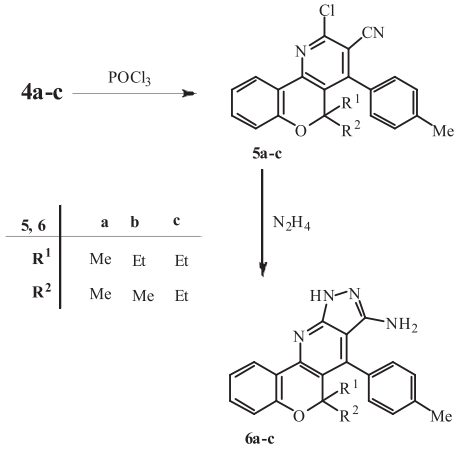
7a-c	R
a	Cl
b	NO_2
c	OMe

new series of chrominopyrazolopyridine derivatives **6a–c**. Thus, the reaction of **5a–c** with hydrazine hydrate in ethanol at reflux temperature, afforded the corresponding 8-amino-6,6-dialkyl-7-(4-methylphenyl)-6*H*,10*H*-chromeno[4,3-*b*] pyrazolo[4,3-*e*]pyridines **6a–c**. (Scheme 2)

When 8-amino-6,6-dimethyl-7-(4-methylphenyl)-6*H*,10*H*-chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine (**6a**) was allowed to react with the appropriate aldehydes in dioxane in the presence of piperidine, the corresponding 8-arylideneamino derivatives **7a–c** were obtained as reported in Scheme 3. The structures of the products **7a–c** were inferred from their analytical and spectral data. Thus, their IR spectra showed characteristic absorption band at 3350–3240 cm^{-1} corresponding to NH group, and the ^1H NMR spectra showed the absence of NH_2 and showed the presence of azomethine proton at δ 8.93–9.75 ppm (Scheme 3).

Biological screening. ***Antibacterial activity.*** The newly synthesized compounds were screened for their antibacterial activity against four strains of bacteria: two gram-positive strains namely *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579), and two gram-negative ones namely *Serratia marcescens* (IMRU-70) and *Proteus mirabilis* (NCTC-289) using Ampicillin (25 μg) as reference antibiotic [32]. The tested compounds were dissolved in DMF to obtain a solution of 1% concentration. Filter paper disks (white-man No. 3 filter, 5 mm diameter) were saturated with former solution. The saturated filter paper disks were placed on the nutrient agar (Difco) dishes seeded by test bacterial. The inhibition zone was measured in millimeter at the end of an incubation period of 48 h at 25°C. DMF showed no inhibition zone. The results are illustrated in Table 1.

Scheme 2. Formation of aminopyrazole derivative.



5, 6	a	b	c
R^1	Me	Et	Et
R^2	Me	Me	Et

The results revealed that compounds **4b**, **4f**, **6c**, and **7b** possess high activity against *S. aureus*, *S. marcescens*, and *P. mirabilis*, whereas compounds **4d** and **6a** showed high activity against *S. marcescens* and *P. mirabilis*.

From the antimicrobial activity results and structure activity relationship correlation, it can be concluded that the chromenopyridine-3-carbonitrile derivative with ethyl and methyl groups located at the C-2 in the chromen ring and incorporating p-tolyl ring exhibited the highest activity against *S. aureus*. This was not the case for *S. marcescens* and *P. mirabilis* because chromenopyridine-3-carbonitrile derivatives with either two ethyl groups or two methyl groups and (p-methoxyphenyl) showed the highest inhibition activity. The tetracyclic amine derivative **6c** with two ethyl subsistent and the arylidine **7b** containing p-nitrophenyl also revealed high inhibition activities against *S. aureus*. In addition, the tetracyclic amine derivatives with either two methyl groups or two ethyl groups showed the highest activates against *S. marcescens* and *P. mirabilis*.

EXPERIMENTAL

All reagents were of commercial quality and used without purification. Melting points were uncorrected and determined using *Kofter* block instrument. TLC was performed on plastic plates Silica Gel 60 F254 (E. Merck, layer thickness 0.2 mm). NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 300 MHz for ^1H NMR and at 75.5 MHz for ^{13}C NMR with *TMS* as an internal standard. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were measured in a Kratos 50 TC spectrometers. The microanalyses were performed at the Microanalytical Unit, Cairo University, Egypt and were found to agree favorably with the calculated values.

Table 1

Antibacterial activity of the synthesized compounds (diameter of inhibition zone in mm).

Compound	*Staphylococcus aureus* (NCTC-447)	*Bacillus cereus* (ATCC-14579)	*Serratia marcescens* (IMRU-70)	*Proteus mirabilis* (NTCC-289)
4a	20	21	26	25
4b	28	20	27	26
4c	26	25	25	26
4d	22	19	27	28
4e	21	22	24	23
4f	27	20	28	27
4g	21	26	20	22
4h	23	21	26	25
4i	22	18	22	21
5a	20	20	20	18
5b	19	21	19	20
5c	20	22	20	21
6a	22	14	28	27
6b	18	20	18	15
6c	27	23	28	27
7b	28	25	26	27
7c	23	27	24	25
Ampicillin (25 μg)	26	25	26	25

Table 1 shows the results of antibacterial activity of newly synthesized compounds and ampicillin against selected standard strain, the results represented the diameter of inhibition zones in mm.

General procedure for the syntheses of 4-aryl-5,5-dialkyl-2-oxo-2,5-dihydro-1H-chromeno[4,3-b]pyridine-3-carbonitrile (4a–i). To a mixture of chromone derivative **1** (10 mmol), appropriate aromatic aldehyde **2** (10 mmol), 0.84 g 2-cyanoacetamide (**3**) (10 mmol), and 1.0 g sodium hydroxide (25 mmol) was added. The reaction mixture was fused at temperature between 110–150°C for 20–30 min, and the reaction mixture was poured into cold water with stirring until the solid product appeared. The product was collected by filtration, dried, and recrystallized from methanol to afford **4a–i** in good yield 80–92%.

5,5-Dimethyl-2-oxo-4-p-tolyl-2,5-dihydro-1H-chromeno[4,3-b] pyridine-3-carbonitrile (4a). Yellow powder, yield 2.95 g (86%), mp 290–292°C; IR (KBr) ν 3270 (NH), 2206 (CN), 1630 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.49 (s, 3H, CH_3), 1,54 (s, 3H, CH_3), 2.49 (s, 3H, $CH_3C_6H_4$), 7.29–7.33 (m, 5H, ArH), 7.39–8.03 (m, 3H, ArH), 12.22 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 21.51, 23.25, 24.55 (3 CH_3), 85.13 (C-5), 109.16 (CN), 112.56, 117.66, 118.22, 121.77, 125.12, 127.32, 129.24 (2C), 134.16 (2C), 137.04, 138.44, 140.31, 143.77, 144.12, 152.16 (Ar–C), 163.08 (CO); MS (EI): *m/z* = 342.0 (M^+, 100), 299 (12), 207 (10), 180 (65), 174 (33). *Anal*. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.13: Found: C, 77.22; H, 518; N, 8.29.

5-Ethyl-5-methyl-2-oxo-4-p-tolyl-2,5-dihydro-1H-chromeno [4,3-b]pyridine-3-carbonitrile (4b). Pale yellow powder, yield 2.87 g (80%); mp 276–278°C; IR (KBr) ν = 3267 (NH), 2205 (CN), 1622 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.15 (t, 3H, *J* = 7.5 Hz, CH_3CH_2), 1.45 (s, 3H, CH_3), 2.25 (q, 2H, *J* = 7.5 Hz, CH_3CH_2), 2.36 (s, 3H, $CH_3C_6H_4$), 7.25–7.30 (m, 5H, ArH), 7.38–7.88 (m, 3H, ArH), 11.89 (bs, 1H, NH) ppm; MS (EI): *m/z* 356 (M^+, 30), 312 (100). *Anal*. Calcd for $C_{23}H_{20}N_2O_2$; C, 77.51; H, 5.66; N, 7.86. Found: C, 77.44; H, 5.75; N, 7.54.

5,5-Diethyl-2-oxo-4-p-tolyl-2,5-dihydro-1H-chromeno[4,3-b] pyridine-3-carbonitrile (4c). Yellow powder, yield 2.98 g 80%; mp 243–245°C, IR (KBr) ν 3263 (NH), 2204 (CN), 1621 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.09–1.15 (m, 6H, 2 CH_3CH_2), 2.22–2.29 (m, 4H, 2 CH_3CH_2), 2.33 (s, 3H, $CH_3C_6H_4$), 7.27 (d, 2H, *J* = 8.2 Hz, ArH), 7.31–7.37 (m, 5H, ArH), 7.48–8.00 (m, 3H, ArH), 12.78 (bs, 1H, NH); MS (EI): *m/z* 371 (M^+ + 1, 60), 370 (M^+, 100). *Anal*. Calcd for $C_{24}H_{22}N_2O_2$; C, 77.81; H, 5.99; N, 7.56. Found: C, 77.61; H, 5.77; N, 7.39.

5,5-Dimethyl-4-(4-methoxyphenyl)-2-oxo-2,5-dihydro-1H-chromeno[4,3-b]pyridine-3-carbonitrile (4d). Yellow powder, yield 3.22 g (90%); mp 281–282°C; IR (KBr) ν 3273 (NH), 2210 (CN), 1635 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.48 (s, 3H, CH_3), 1,55 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 7.11–734 (m, 3H, *J* = 8.2 Hz, ArH), 7.39–7.93 (m, 5H, ArH), 13.08 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 16.92, 19.25 (2 CH_3), 52.97 (OCH_3), 84.05 (C-5), 111.13 (CN), 118.15, 121.78, 122.81, 123.38, 125.26, 126.78, 127.79 (2C), 128.27 (2C), 128.49, 133.05, 134.49, 137.99, 141.61, 148.48 (Ar–C), 167.83 (CO) ppm; MS (EI): *m/z* 358 (M^+, 20), 328 (100). *Anal*. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.86; H, 5.12; N, 7.96.

5-Ethyl-4-(4-methoxyphenyl)-5-methyl-2-oxo-2,5-dihydro-1H-chromeno[4,3-b]pyridine-3-carbonitrile (4e). Pale yellow powder, yield 3.25 g (87%); mp 251–252°C; IR (KBr) ν 3281 (NH), 2212 (CN), 1628 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.04 (t, 3H, *J* = 7.5 Hz, CH_3CH_2), 1.35 (s, 3H, CH_3), 2.32 (q, 2H, *J* = 7.5 Hz, CH_3CH_2), 3.65 (s, 3H, OCH_3), 7.06–7.33 (m, 6H, ArH), 7.39–8.8.17 (m, 2H, ArH), 12.25 (bs, 1H, NH); MS (EI): *m/z* 373 (M^+ + 1, 70), 372 (M^+, 100). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.25; H, 5.67; N, 7.77.

5,5-Diethyl-4-(4-methoxyphenyl)-2-oxo-2,5-dihydro-1H-chromeno[4,3-b]pyridine-3-carbonitrile (4f). Pale yellow crystal, yield 3.56 g (92%); mp 222–224°C; IR (KBr) ν 3259 (NH), 2201 (CN), 1619 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.99–1.06 (m, 6H, 2 CH_3CH_2), 2.18–2.24 (m, 4H, 2 CH_3CH_2), 3.45

(s, 3H, OCH_3), 7.09–7.31 (m, 3H, ArH), 7.35–7.39 (m, 3H, ArH), 7.41–9.11 (m, 2H, ArH), 11.53 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 7.43, 7.67 (2 CH_3CH_2), 23.50, 23.87 (2 CH_3CH_2), 51.77 (OCH_3), 79.20 (C-5), 97.76 (CN), 115.85 (2C), 117.62, 118.92, 120.12, 120.54, 120.68, 121.77, 127.77, 129.69 (2C), 135.88, 144.64, 153.80, 153.92, 156.99 (Ar–C), 163.77 (CO); MS (EI): *m/z* 387 (M^+ + 1, 10), 386 (M^+, 50), 298 (100). *Anal*. Calcd for $C_{24}H_{22}N_2O_3C$: 74.59; H, 5.74; N, 7.25. Found: C, 74.70; H, 5.83; N, 7.45.

4-(4-Chlorophenyl)-5,5-dimethyl-2-oxo-2,5-dihydro-1H-chromeno[4,3-b]pyridine-3-carbonitrile (4g). Pale yellow powder, yield 3.1 g (85%); mp 190–191°C; IR (KBr) ν 3284 (NH), 2212 (CN), 1650 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.50 (s, 3H, CH_3), 1,52 (s, 3H, CH_3), 7.53–7.63 (m, 3H, ArH), 7.69–8.22 (m, 5H, ArH), 13.65 (, bs, 1H, NH); MS (EI): *m/z* 362 (M^+, 30), 297 (100). *Anal*. Calcd for $C_{21}H_{15}ClN_2O_2C$, 69.52; H, 4.17; N, 7.72. Found: C,69.73; H, 4.22; N, 7.85.

4-(4-Chlorophenyl)-5-ethyl-5-methyl-2-oxo-2,5-dihydro-1H-chromeno[4,3-b]pyridine-3-carbonitrile (4h). Yellow crystal, yield 3.45 g (92%); mp 150–151°C; IR (KBr) ν 3274 (NH), 2206 (CN), 1644 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.10 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.25 (s, 3H, CH_3), 2.29 (q, 2H, J = 7.5 Hz, CH_3CH_2), 7.50–7.58 (m, 3H, ArH), 7.60–7.87 (m, 5H, ArH), 13.05 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 7.55 (CH_3CH_2), 21.74 (CH_3), 28.56 (CH_2CH_3), 83.96 (C-5), 108.88 (CN), 116.58, 117.74 (2C), 118.94, 118.98, 119.17, 120.30, 120.67, 121.71, 121.74, 121.81, 135.80 (2C), 144.29, 149.12, 152.70 (Ar–C), 168.76 (CO); MS (EI): *m/z* 377 (M^+ + 1, 25), 376 (M^+, 30), 347 (100). *Anal*. Calcd for $C_{22}H_{17}ClN_2O_2C$, 70.12; H, 4.55; N, 7.43. Found: C,70.31; H, 4.70; N, 7.55.

4-(4-Chlorophenyl)-5,5-diethyl-2-oxo-2,5-dihydro-1H-chromeno [4,3-b]pyridine-3-carbonitrile (4i). Yellow crystal, mp 130–132°C; IR (KBr) ν 3270 (NH), 2214 (CN), 1643 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.98–1.04 (m, 6H, 2 CH_3CH_2), 2.22–2.28 (m, 4H, 2 CH_3CH_2), 7.48–7.55 (m, 3H, ArH), 7.61–8.19 (m, 5H, ArH), 12.86 (bs, 1H, NH); MS (EI): *m/z* 391 (M^+ + 1, 16), 317 (15), 296 (70), 125 (100). *Anal*. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C,79.52; H, 4.75; N, 7.08.

General procedure for the syntheses of 2-chloro-5,5-dialkyl-4-p-tolyl-5H-chromeno[4,3-b]pyridine-3-carbonitrile (5a–c). Chromenopyridine derivatives **4a–c** (10 mmol) were added to an amount corresponding to five times their weight of $POCl_3$, and the mixture was refluxed until the starting material had disappeared at TLC analysis (eluent toluene/acetone 8:2). The suspension was then cooled first to room temperature and poured carefully into water/ice with stirring. The resulting precipitate was collected, washed many times with water, dried and recrystallized from hexane-THF afforded a pale yellow powder of **5a–c** in good yields.

2-Chloro-5,5-dimethyl-4-p-tolyl-5H-chromeno[4,3-b]pyridine-3-carbonitrile (5a). Yield 2.65 g (73%); mp 112.0–114.0°C; IR (KBr) ν 2222 (CN),1570 (N=C) cm^{-1}; ^{1}H NMR (MHz, $CDCl_3$): δ 1.53 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.45 (s, 3H, $CH_3C_6H_4$), 7.13–7.36 (m, 3H, ArH), 7.67–7.92 (m, 5H, ArH); ^{13}C NMR (MHz, $CDCl_3$): δ = 20.28, 21.61, 24.15 (3 CH_3), 85.38 (C-5), 109.91 (CN), 117.56, 118.36, 118.98, 119.44, 121.78, 122.0.55, 128.47 (2C), 129.32 (2C), 136.35, 141.86, 142.33, 145.40, 148.66, 149.55, 156.49 (Ar–C); MS (EI): *m/z* 361 (M^+, 70), 360 (100). *Anal*. Calcd for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76; Found C, 73.12; H, 4.43; N, 7.57.

2-Chloro-5-ethyl-5-methyl-4-p-tolyl-5H-chromeno[4,3-b]pyridine-3-carbonitrile (5b). Yield 2.33 g 62%; mp 118–119°C; IR (KBr) ν 2217 (CN), 1566 (N=C) cm^{-1}; ^{1}H NMR (MHz, $CDCl_3$): δ = 1.12 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.32 (s, 3H, CH_3), 2.21 (q, 2H, J = 7.5 Hz, CH_3CH_2), 2.44 (s, 3H, $CH_3C_6H_4$), 7.30–7.41 (m, 5H), 7.56–7.84 (m, 3H, ArH); MS (EI): *m/z* 375 (M^+ + 1, 25), 374 (M^+, 60), 279 (100). *Anal*. Calcd for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.11; N, 7.47; Found: C, 73.88; H, 5.04; N, 7.65.

2.1.3 2-Chloro-5,5-diethyl-4-p-tolyl-5H-chromeno[4,3-b]pyridine-3-carbonitrile (5c). Yield 2.73 g (70%); mp 88–90°C;. IR (KBr) ν 2219 (CN), 1550 (N=C) cm^{-1}; ^{1}H NMR (MHz, $CDCl_3$): δ 1.00 (t, 3H, CH_3CH_2), 1.18 (t, 3H, CH_3CH_2), 1.73–2.36 (m, 4H, 2 CH_3CH_2), 2.47 (s, 3H, $CH_3C_6H_4$), 7.20–7.35 (m, 5H, ArH), 7.42–7.66 (m, 3H, ArH); MS (EI): *m/z* 389 (M^+ + 1, 5), 388 (M^+, 20), 332 (70), 280 (100). *Anal*. Calcd for $C_{24}H_{21}ClN_2O$: C, 74.12; H, 5.44; N, 7.20. Found: C, 74.22; H, 5.61; N, 7.12.

General procedure for the syntheses of 6,6-dialkyl-7-*p*-tolyl-6,10-dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-8-amine (6a–c). A mixture of choropyridochromane derivatives **5a–c** (10 mmol) and 1.25 g hydrazine hydrate (25 mmol) in 30 mL ethanol was heated under reflux for 4–6 h. The excess ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from methanol-DMF to give bright orange solid of **6a–c**.

6,6-Dimethyl-7-p-tolyl-6,10-dihydrochromeno[4,3-b]pyrazolo [4,3-e]pyridin-8-amine (6a). Yield 2.67 g (75%); mp 315–316°C;.IR (KBr) ν 3380–3270 (NH, NH_2),1615 (N=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.45 (s, 3H, CH_3), 1,49 (s, 3H, CH_3), 2.57 (s, 3H, $CH_3C_6H_4$), 5.40 (bs, 2H, NH_2), 7.11–7.20 (m, 3H, ArH), 7.66–8.03 (m, 5H, ArH), 11.99 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 21.61, 22.06, 26.43 (3 CH_3), 78.97 (C-5), 118.14, 118.57, 120.47, 121.45, 123.86 (2C), 128.47, 138.29, 129.30 (2C), 136.35, 140.94, 141.86, 142.79, 145.55, 147.13, 149.55, 154.81 (Ar–C); MS (EI): *m/z* 357 (M^+ + 1, 35), 356 (M^+ + 75), 315 (55), 238 (100). *Anal*. Calcd for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.05; H, 5.76; N, 15.42.

6-Ethyl-6-methyl-7-p-tolyl-6,10-dihydrochromeno[4,3-b]pyrazolo [4,3-e]pyridin-8-amine (6b). Yield 2.47 g 67%; mp 288–290°C; IR (KBr) ν 3320–3250 (NH, NH_2), 1605 (N=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.40 (s, 3H, CH_3), 1.85 (q, 2H, J = 7.5 Hz, CH_3CH_2), 2.51 (s, 3H, $CH_3C_6H_4$), 5.78 (s, 2H, NH_2), 7.06–717 (m, 5H, ArH), 7.49–7.83 (m, 3H, ArH); 11.77 (bs, 1H, NH); MS (EI): *m/z* 371 (M^+ + 1, 10), 370 (M^+, 35), 328 (100). *Anal*. Calcd for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99, N, 15.12. Found: C, 74.45; H, 6.03; N, 15.25.

6,6-Diethyl-7-p-tolyl-6,10-dihydrochromeno[4,3-b]pyrazolo[4,3-e] pyridin-8-amine (6c). Yield 3.84 g (72%); mp 277–278°C; IR (KBr) ν 3299–3188 (NH, NH_2), 1587 (N=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.95–1.22 (m, 6H, 2 CH_3CH_2), 1.80–2.25 (m, 4H, 2 CH_3CH_2), 2.57 (s, 3H, $CH_3C_6H_4$), 5.09 (bs, 2H, NH_2), 6.76–7.09 (m, 5H, ArH), 7.26–7.67 (m, 3H, ArH), 11.54 (bs, 1H, NH); MS (EI): *m/z* 385 (M^+ + 1, 25), 384 (M^+, 55), 355 (15), 310 (100). *Anal*. Calcd for $C_{24}H_{24}N_4O$: C, 74.97; H, 6.29; N, 14.57. Found: C, 74.75; H, 6.17; N, 14.69.

General procedure for the syntheses of *N*-substituted benzylidine-7-*p*-tolyl-dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*] pyridin-8-amine (7a–d). A mixture of 0.360 g **6a** (1 mmol), an appropriate aromatic aldehydes (1 mmol), 10 mL dioxane and 0.3 mL piperidine was refluxed for 6 h. The solid product, which formed, was collected by filtration and recrystallized from suitable solvent to give **7a–c**.

N-(4-Chlorobenzylidene)-6,6-dimethyl-7-p-tolyl-6,10-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-8-amine (7a). Yellow crystals, yield 3.10 g (65%); mp 224–226°C (ethanol); IR (KBr) ν 3340 (NH), 1597 (N=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.55 (s, 3H, CH_3), 1,57 (s, 3H, CH_3), 2.66 (s, 3H, $CH_3C_6H_4$), 7.21–7.30 (m, 4H, ArH), 7.72–8.02 (m, 8H, ArH), 8.93 (s, 1H, N=CH), 12.54 (bs, 1H, NH); MS (EI): *m/z* 478 (M^+ , 100), 352 (35), 337 (33), 260 (15). *Anal*. Calcd for $C_{29}H_{23}ClN_4O$: C, 72.72; H, 4.84; N, 11.70. Found: C, 72.80; H, 4.91; N, 11.81.

6,6-Dimethyl-N-(4-nitrobenzylidene)-7-p-tolyl-6,10-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-8-amine (7b). Pale yellow powder, yield 3.50 g (71%); mp 246–247°C (methanol); IR (KBr) ν 3333 (NH), 1605 (N=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.53 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.69 (s, 3H, $CH_3C_6H_4$), 7.25–7.33 (m, 4H, ArH), 7.70–7.98 (m, 8H, ArH), 9.75 (s, 1H, N=CH), 13.13 (bs, 1H, NH); MS (EI): *m/z* 489 (M^+ , 15), 444 (100), 337 (25), 260 (61). *Anal*. Calcd for $C_{29}H_{23}N_5O_3$: C, 71.15; H, 4.74; N, 14.31. Found: C, 71.22; H, 4.81; N, 14.46.

N-(4-Methoxybenzylidene)-6,6-dimethyl-7-p-tolyl-6,10-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridin-8-amine (7c). Bright yellow powder, yield 2.90 g (59%); mp 229–230°C (methanol); IR (KBr) ν 3256 (NH), 1612 (N=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.41 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.55 (s, 3H, $CH_3C_6H_4$), 3.45 (s, 3H, OMe), 7.11–7.29 (m, 5H, ArH), 7.65–7.91 (m, 7H, ArH), 9.37 (s, 1H, N=CH), 12.77 (bs, 1H, NH); MS (EI): *m/z* 489 (M^+ , 15), 444 (100), 337 (25), 260 (61). *Anal*. Calcd for $C_{30}H_{26}N_4O_2$: C, 75.93; H, 5.52; N, 11.81. Found: C, 76.04; H, 5.61; N, 11.89.

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