Efficient access to benzochromeno[2,3-*d*]pyrimidine derivatives from *β*-enamino nitriles by bis(trichloromethyl) carbonate and triphenylphosphine oxide

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A mild and efficient synthesis of novel benzochromeno[2,3-*d*]pyrimidine derivatives is described. A number of 8,10-dichloro-7-aryl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidines and 9,11-dichloro-12-aryl-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidines were synthesised by the cyclisation of 2-amino-4-aryl-4H-benzo[*h*]chromene-3-carbonitriles or 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles with bis(trichloromethyl) carbonate and triphenylphosphine oxide in moderate to good yields.

Keywords: benzochromeno[2,3-*d*]pyrimidine, cyclisation, bis(trichloromethyl) carbonate, triphenylphosphine oxide

Pyrano[2,3-*d*]pyrimidine derivatives are an important class of heterocycles that have received considerable attention due to their pharmacological properties such as antimicrobial,[1–3] anticancer,[4,5] antifungal[6] and antiviral[7] activities. They possess wide utility but the availability of synthetic methods is limited, typically relying on two-component condensation of 2-benzylidenemalononitrile with barbituric acid.[8,9]

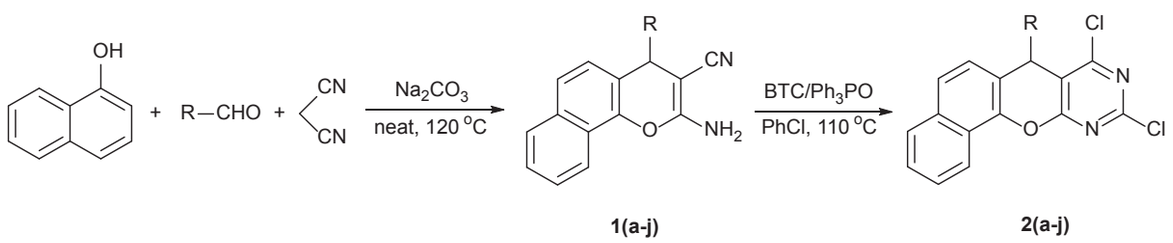
In recent years, improvement were made by the reaction of benzylidenemalononitriles with barbituric acids in ionic liquids,[10] or under microwave irradiation[11,12] to shorten the reaction time and raise the yields. Some novel strategies[13–17] have also been developed to prepare pyrano[2,3-*d*]pyrimidine derivatives. Limitations of these methods, however, include requirement for longer reaction times, use of expensive reagents, complex synthetic pathways, and unsuitability for industrialisation. So the development of new and convenient synthetic approaches to these scaffolds is of great interest to the medicinal chemistry community.

In the development of highly expedient methods for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives, we report here a convenient and versatile method directly from the cyclisation of widely available 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles or 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles leading to 8,10-dichloro-7-aryl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidines or 9,11-dichloro-12-aryl-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidines by bis(trichloromethyl) carbonate (BTC) and Ph_3PO.

Results and discussion

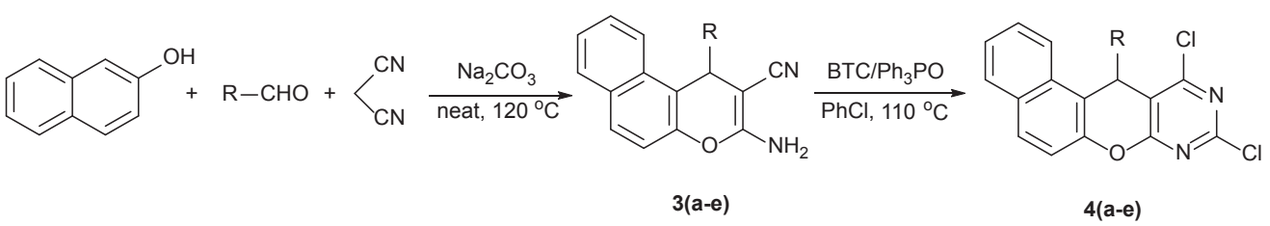
2-Amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles **1a–j** and 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles **3a–e** were synthesised by three-component solvent-free condensation of α/β-naphthol, substituted arylaldehydes and malononitrile in the presence of Na_2CO_3 as an efficient catalyst with excellent yields.[18] We subsequently carried out the reaction of compounds **1a–j** and **3a–e** with BTC and Ph_3PO in chlorobenzene at 110 °C to produce the corresponding 8,10-dichloro-7-aryl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine **2a–j** and the 9,11-dichloro-12-aryl-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine **4a–e** in moderate to good yields (Schemes 1 and 2, Table 1).

The activity of this reaction was found to be solvent-dependent. Various solvents were examined for the cyclisation reaction, including dichloromethane, 1,2-dichlorethane, acetonitrile, toluene and chlorobenzene. The best results were obtained in chlorobenzene with good yield (84%) after a short reaction time (60 min).



1(a-j) **2(a-j)**

Scheme 1 Synthesis of 8,10-dichloro-7-aryl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine.



3(a-e) **4(a-e)**

Scheme 2 Synthesis of 9,11-dichloro-12-aryl-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine.

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Table 1 Synthesis of benzo chromene[2,3-*d*]pyrimidine derivatives

Entry[a]	R	Time/min	Product	Yield/%[b]
1	C_6H_5	60	**2a**	80
2	2-$OCH_3C_6H_4$	60	**2b**	81
3	4-$OCH_3C_6H_4$	60	**2c**	84
4	4-$CH_3C_6H_4$	60	**2d**	82
5	1-Naphthalene	60	**2e**	79
6	4-FC_6H_4	70	**2f**	74
7	4-ClC_6H_4	90	**2g**	73
8	4-BrC_6H_4	90	**2h**	71
9	2-BrC_6H_4	90	**2i**	73
10	2,4-$Cl_2C_6H_3$	90	**2j**	70
11	C_6H_5	60	**4a**	78
12	4-$OCH_3C_6H_4$	70	**4b**	83
13	4-$CH_3C_6H_4$	70	**4c**	84
14	2-BrC_6H_4	90	**4d**	73
15	4-ClC_6H_4	90	**4e**	74

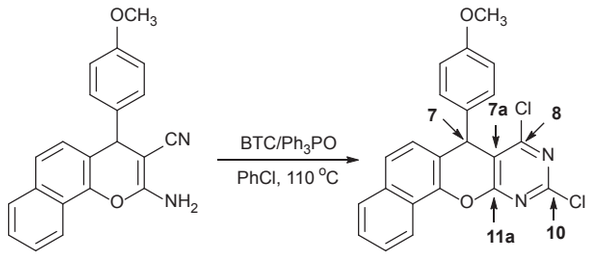
[a]Reaction condition: 2-amino-4-aryl-4*H*-chromene-3-carbonitrile (1 mmol), BTC (1 mmol), Ph_3PO (3 mmol), 110 °C.
[b]Isolated yields.

In order to determine the optimal conditions, we screened various ratios of reactants at different temperatures for the above reaction. The model reaction was carried out simply by reaction of 2-amino-4-(4-methoxyphenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile **1c** with BTC and Ph_3PO in chlorobenzene (Table 2). The absence of Ph_3PO resulted in the failure of the reaction to give the corresponding pyrano[2,3-*d*]pyrimidine derivative (Table 2, entry 1). The use of catalytic amount of Ph_3PO also would not promote this cyclisation, only giving a trace of the product (Table 2, entry 2). Note that the reaction proceeded by smooth 1 : 1 : 3 addition in chlorobenzene to produce **2c** in 84% yield at 110 °C (Table 2, entry 8). Furthermore, in an effort to improve the yield, we increased the amount of BTC or Ph_3PO and observed no obvious change in the product yield (Table 2, entries 9 and 10). A brief examination of reaction temperature revealed that the reaction proceeded most efficiently in chlorobenzene at 110 °C (Table 2, entry 8). When the reaction temperature dropped, the corresponding yield also dropped. (Table 2, entries 11 and 12). We also observed a decrease in yield when the reaction temperature was > 110 °C, coupled with the formation of unidentified impurities (Table 2, entry 13).

The structure of all products **2a–j** and **4a–e** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS, and HRMS. From the IR spectrum of the product (**2c**), the disappearance of characteristic bands at 3416, 3324 cm^{-1} for the NH_2 and at 2194 cm^{-1} for the CN in the starting material, meanwhile, the appearance of a strong band at 1528 cm^{-1} for C=N of the pyrimidine ring indicated the formation of product. From the ^{1}H NMR spectrum, the absence of two singlets at 4.75 ppm (two amine protons) and 4.80 ppm (proton attached to C-7) in the starting material and the disappearance of signals at 61.8 ppm (C-7a), 117.4 ppm (C-8) and 158.6 ppm (C-11a) and the appearance of signals at 114.6 ppm (C-7a), 157.7 ppm (C-8), 158.9 ppm (C-10), and 165.0 ppm (C-11a) in the ^{13}C NMR spectra confirm the structure of compound **2c**. Besides, MS, and HRMS also supported the structural formation.

Utilising these optimal conditions (Table 2, entry 8), the reaction was extended to other aryl substrate (**2a–j** and **4a–e**) in moderate to good yields (Table 1). Moreover, the structures of aryl bearing electron-donating groups (Table 1, entries 2–4, 12 and 13) often led to higher yields than those with electron-withdrawing groups (Table 1, entries 6–10, 14 and 15).

Table 2 Synthesis of **2c** under different conditions



1c **2c**

Entry	Ratio **1c** : BTC : Ph_3PO	Reaction temperature/°C	Yield/%[a]
1	1 : 0.3 : 0	110	0
2	1 : 0.3 : 0.3	110	Trace
3	1 : 0.3 : 1	110	25
5	1 : 0.3 : 2	110	20
6	1 : 1 : 1	110	55
7	1 : 1 : 2	110	68
8	**1 : 1 : 3**	**110**	84
9	1 : 2 : 3	110	81
10	1 : 1 : 4	110	82
11	1 : 1 : 3	90	53
12	1 : 1 : 3	100	70
13	1 : 1 : 3	120	77

[a]Isolated yields based on **1c**.

The possible mechanism of the formation of benzochromeno[2,3-*d*]pyrimidine is shown in Scheme 3. Initially, the amino-group of **1** was reacted with BTC to form an intermediate **5**,[19,20] which reacted with Ph_3PCl_2 generated *in situ* from BTC and Ph_3PO, formed the O–P bond and converted to **6**. The chlorination of C-8 position of **6** acquired the intermediate **7**. Finally, the chlorination of C-10 position was accomplished by the replacement of Ph_3PO with chloride and afforded the final product **2**.

Conclusion

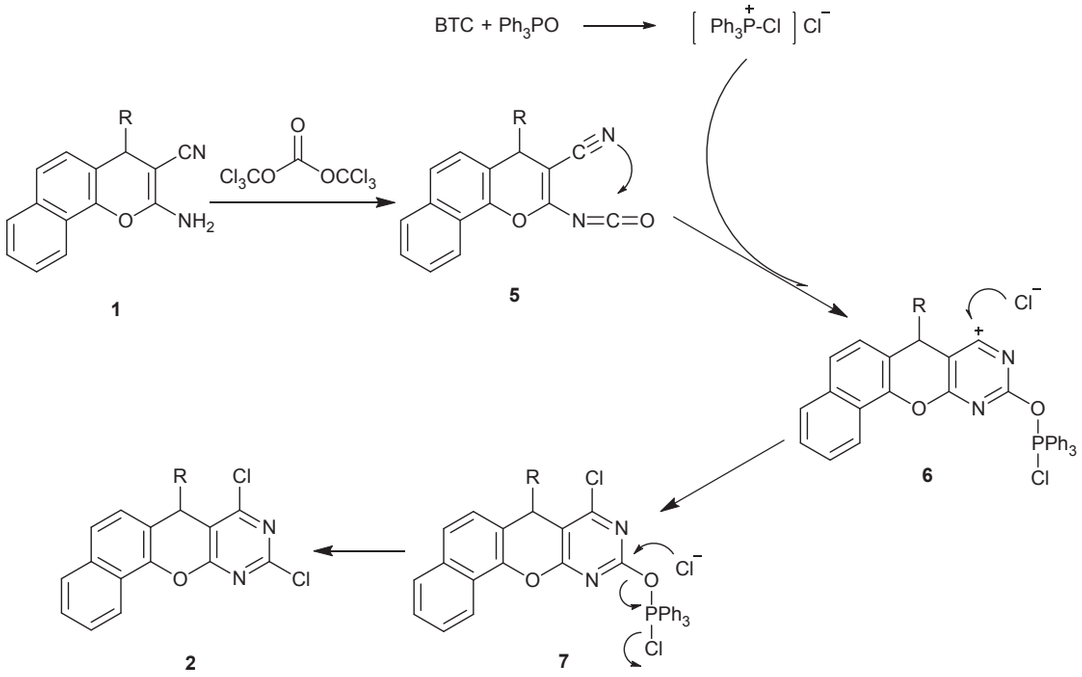
In conclusion, we have developed a new and efficient strategy for convenient synthesis of 8,10-dichloro-7-aryl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine and 9,11-dichloro-12-aryl-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidines with moderate to good yields in the BTC/Ph_3PO system. This method has been applied to a range of substrates. The yield of the reaction depends on the substituents in the phenyl ring. The advantages of the present procedure are experimental simplicity and easy work-up. Further biological applications of these compounds are currently in progress in our laboratory.

Experimental

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. Melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were measured in KBr on an AVATAR-370 spectrometer. ^{1}H (400 MHz) NMR and ^{13}C (100 Hz) NMR spectra were recorded on a Varian spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standards, chemical shifts are expressed in ppm. LRMS (lower resolution mass spectra) and HRMS (high resolution mass spectra) were obtained on Finnigan Trace DSQ (ESI) and Bruker Daltonics micrOTOF-Q II instrument, respectively.

Synthesis of **2a–j** *and* **4a–e***; general procedure*

BTC (0.89 g, 3 mmol / 8 mL PhCl) was added to a stirred solution of Ph_3PO (2.50 g, 9 mmol) in PhCl (15 mL) dropwise at 0–5 °C. After complete addition the mixture was stirred for 30 min at room



Scheme 3 Possible reaction pathways of the formation of benzochromeno[2,3-*d*]pyrimidine.

temperature. Then **1a–j**/**3a–e** (3 mmol) was added, and the mixture was heated to 110 °C until completion of reaction (followed by TLC, hexane: ethyl acetate = 3 : 1). After the reaction mixture had been washed with water and extracted with dichloromethane, the organic layer was dried over anhydrous Na_2SO_4, concentrated and purified over column chromatography to afford the pure product.

*8,10-Dichloro-7-phenyl-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2a)**: White solid, m.p. 217.0–219.3 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1260 (C–O–C at pyran ring), 666 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.64–7.51 (m, 3H), 7.29–7.15 (m, 6H), 5.39 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, ppm) δ 165.1, 162.4, 157.9, 143.4, 142.7, 133.4, 128.9, 128.1, 127.6, 127.5, 127.1, 127.0, 125.6, 125.4, 123.6, 121.4, 117.9, 114.4, 42.6; MS (ESI): 379 ([M+H]$^+$); HRMS (ESI) calcd for $C_{21}H_{13}Cl_2N_2O$ ([M+H]$^+$): 379.0399; found: 379.0411.

*8,10-Dichloro-7-(2-methoxyphenyl)-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2b):** White solid, m.p. 214.8–216.4 °C; IR (KBr): 2836 (–OCH_3), 1530 (–C=N at pyrimidine ring), 1259 (C–O–C at pyran ring), 666 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.61–7.55 (m, 1H), 7.54–7.48 (m, 2H), 7.26 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.23–7.17 (m, 2H), 6.90 (td, *J* = 7.5, 1.0 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 3.63 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$, ppm) δ 165.8, 161.5, 157.5, 156.7, 143.7, 133.3, 131.4, 130.7, 130.3, 129.1, 127.4, 126.8, 125.5, 124.9, 123.4, 121.2, 120.7, 117.1, 114.1, 111.6, 55.5, 38.5; MS (ESI): 409 ([M+H]$^+$); HRMS (ESI) calcd for $C_{22}H_{15}Cl_2N_2O_2$ ([M+H]$^+$): 409.0505; found: 409.0511.

*8,10-Dichloro-7-(4-methoxyphenyl)-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2c):** White solid, m.p. 146.4–147.5 °C; IR (KBr): 2835 (–OCH_3), 1528 (–C=N at pyrimidine ring), 1257 (C–O–C at pyran ring), 663 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.46–8.40 (m, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.64–7.50 (m, 3H), 7.19–7.09 (m, 3H), 6.81–6.73 (m, 2H), 5.34 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$, ppm) δ 165.0, 162.4, 158.9, 157.8, 143.4, 135.1, 133.4, 129.2, 127.5, 127.1, 127.0, 125.6, 125.5, 123.7, 121.4, 118.3, 114.7, 114.4, 55.3, 41.8; MS (ESI): 409 ([M+H]$^+$); HRMS (ESI) calcd for $C_{22}H_{13}Cl_2N_2O_2$ ([M−H]$^+$): 407.0360; found: 407.0370.

*8,10-Dichloro-7-(4-methylphenyl)-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2d):** White solid, m.p. 179.7–181.4 °C; IR (KBr): 1527 (–C=N at pyrimidine ring), 1258 (C–O–C at pyran ring), 661 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.42 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.56 (ddt, *J* = 13.8, 9.5, 6.9 Hz, 3H), 7.10 (dt, *J* = 20.3, 8.3 Hz, 5H), 5.31 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$, ppm) δ 165.1, 162.4, 157.8, 143.4, 139.8, 137.3, 133.4, 129.6, 127.9, 127.5, 127.1, 126.9, 125.6, 125.4, 123.6, 121.3, 118.2, 114.5, 42.2, 21.1; MS (ESI): 393 ([M+H]$^+$); HRMS (ESI) calcd for $C_{22}H_{15}Cl_2N_2O$ ([M+H]$^+$): 393.0565; found: 393.0559.

*8,10-Dichloro-7-(naphthalen-1-yl)-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2e):** White solid, m.p. 241.8–242.7 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1256 (C–O–C at pyran ring), 668 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.46 (t, *J* = 9.9 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.68 (dd, *J* = 19.6, 7.9 Hz, 3H), 7.63–7.48 (m, 3H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.24 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, ppm) δ 165.0, 162.8, 157.8, 142.5, 140.2, 133.6, 133.2, 130.6, 129.2, 128.1, 127.4, 127.1, 127.0, 127.0, 125.9, 125.7, 125.4, 124.7, 123.5, 122.3, 121.3, 118.2, 114.8; MS (ESI): 429 ([M+H]$^+$); HRMS (ESI) calcd for $C_{25}H_{15}Cl_2N_2O$ ([M+H]$^+$): 429.0567; found: 429.0578.

*8,10-Dichloro-7-(4-fluorophenyl)-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2f):** White solid, m.p. 175.9–178.2 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1260 (C–O–C at pyran ring), 1226 (C–F), 664 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.39 (m, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.63–7.51 (m, 3H), 7.22–7.15 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.98–6.90 (m, 2H), 5.35 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, ppm) δ 164.9, 163.0, 162.4, 160.6, 157.9, 143.3, 138.5, 133.4, 129.8, 127.5, 127.2, 125.7, 125.2, 123.5, 121.3, 117.6, 115.9, 114.1, 41.8; MS (ESI): 397 ([M+H]$^+$); HRMS (ESI) calcd for $C_{21}H_{12}Cl_2FN_2O$ ([M+H]$^+$): 397.0315; found: 397.0322.

*8,10-Dichloro-7-(4-chlorophenyl)-7*H-*benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2g):** White solid, m.p. 170.9–172.3 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1257 (C–O–C at pyran ring), 664 (C–Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (dd, *J* = 8.4, 0.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64– 7.52 (m, 3H), 7.26–7.20 (m, 2H), 7.20–7.10 (m, 3H), 5.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.8, 162.4, 158.0, 143.2, 141.0, 133.5, 133.3, 129.5, 129.1, 127.5, 127.3, 127.1, 125.7, 125.1, 123.4, 121.3, 117.2, 113.8, 41.9; MS (ESI): 413 ([M+H]$^+$); HRMS (ESI) calcd for $C_{21}H_{12}Cl_3N_2O$ ([M+H]$^+$): 413.0010; found: 413.0008.

*7-(4-Bromophenyl)-8,10-*d*ichloro-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2h):** White solid, m.p. 175.8–178.0 °C; IR (KBr): 1528 (–C=N at pyrimidine ring), 1258 (C–O–C at pyran ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.42 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.66–7.51 (m, 3H), 7.42 –7.35 (m, 2H), 7.16–7.06 (m, 3H), 5.36 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.9, 162.4, 158.2, 143.4, 141.6, 133.5, 132.1, 129.8, 127.5, 127.3, 127.2, 125.8, 125.1, 123.6, 121.7, 121.3, 117.3, 113.8, 42.1; MS (ESI): 457 ($[M+H]^+$); HRMS (ESI) calcd for $C_{21}H_{10}BrCl_2N_2O$ ($[M-H]^+$): 454.9359; found: 454.9352.

*7-(2-Bromophenyl)-8,10-*d*ichloro-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2i):** White solid, m.p. 258.4–259.6 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1259 (C–O–C at pyran ring), 659 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.40 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.62–7.50 (m, 4H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.18–6.94 (m, 3H), 6.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.1, 162.8, 158.2, 142.8, 142.4, 133.4, 133.1, 131.0, 128.9, 128.4, 127.5, 127.2, 127.0, 125.6, 124.7, 123.4, 123.1, 121.3, 117.1, 113.8, 40.8; MS (ESI): 457 ($[M+H]^+$); HRMS (ESI) calcd for $C_{21}H_{10}BrCl_2N_2O$ ($[M-H]^+$): 454.9359; found: 454.9350.

*8,10-Dichloro-7-(2,4-*d*ichlorophenyl)-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine* **(2j):** Yellow solid, m.p. 237.0–238.5 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1259 (C–O–C at pyran ring), 663 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.41 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.57 (tt, *J* = 6.9, 5.4 Hz, 3H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.3, 162.6, 158.5, 143.2, 139.2, 134.1, 133.6, 133.3, 131.7, 129.8, 128.2, 127.5, 127.4, 127.2, 125.8, 124.6, 123.5, 121.4, 116.4, 113.2, 38.4; MS (ESI): 447 ($[M+H]^+$); HRMS (ESI) calcd for $C_{21}H_9Cl_4N_2O$ ($[M-H]^+$): 444.9474; found: 444.9467.

*9,11-Dichloro-12-phenyl-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine* **(4a):** White solid, m.p. 188.4–189.2 °C; IR (KBr): 1529 (–C=N at pyrimidine ring), 1286 (C–O–C at pyran ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.81 (t, *J* = 8.4 Hz, 2H), 7.54–7.34 (m, 5H), 7.25–7.20 (m, 2H), 7.16–7.09 (m, 1H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 164.8, 161.6, 147.1, 141.2, 131.6, 130.3, 130.2, 128.8, 128.3, 127.5, 125.5, 122.8, 117.2, 116.4, 115.0, 39.2; MS (ESI): 379 ($[M+H]^+$); HRMS (ESI) calcd for $C_{21}H_{13}Cl_2N_2O$ ($[M+H]^+$): 379.0399; found: 379.0391.

*9,11-Dichloro-12-(4-methoxyphenyl)-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine* **(4b):** White solid, m.p. 221.5–223.9 °C; IR (KBr): 2837 ($–OCH_3$), 1530 (–C=N at pyrimidine ring), 1255 (C–O–C at pyran ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 8.3, 4.6 Hz, 2H), 7.53–7.47 (m, 1H), 7.46–7.38 (m, 2H), 7.30–7.22 (m, 2H), 6.77–6.71 (m, 2H), 5.85 (s, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.6, 161.5, 158.6, 157.2, 146.9, 133.5, 131.6, 130.2, 130.0, 128.8, 127.5, 125.5, 122.8, 117.1, 116.5, 115.2, 114.1, 55.2, 38.3; MS (ESI): 409 ($[M+H]^+$); HRMS (ESI) calcd for $C_{22}H_{15}Cl_2N_2O_2$ ($[M+H]^+$): 409.0505; found: 409.0500.

*9,11-Dichloro-12-(4-methylphenyl)-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine* **(4c):** White solid, m.p. 204.9–206.6 °C; IR (KBr): 1530 (–C=N at pyrimidine ring), 1286 (C–O–C at pyran ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.4 Hz, 2H), 7.54–7.39 (m, 3H), 7.24 (d, *J* = 2.9 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.89 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.7, 161.5, 157.3, 146.9, 138.3, 137.3, 131.6, 130.3, 130.0, 129.4, 128.7, 128.1, 127.5, 125.4, 122.8, 117.1, 116.5, 115.1, 38.8, 21.1; MS (ESI): 393 ($[M+H]^+$); HRMS (ESI) calcd for $C_{22}H_{15}Cl_2N_2O$ ($[M+H]^+$): 393.0565; found: 393.0560.

*12-(2-Bromophenyl)-9,11-*d*ichloro-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine* **(4d):** White solid, m.p. 285.6–287.4 °C; IR (KBr): 1530 (–C=N at pyrimidine ring), 1214 (C–O–C at pyran ring), 686 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45 (d, *J* = 8.5 Hz, 1H), 7.81 (t, *J* = 9.0 Hz, 2H), 7.59–7.48 (m, 2H), 7.47–7.40 (m, 2H), 7.28–7.24 (m, 1H), 7.13 (td, *J* = 7.7, 1.3 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 6.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 181.5, 165.0, 162.3, 147.2, 141.0, 133.9, 131.9, 131.6, 130.7, 130.5, 129.1, 128.8, 128.3, 127.5, 125.6, 123.9, 122.5, 117.2, 114.4, 38.9; Mass: 457 ($[M+H]^+$); HRMS (ESI) calcd for $C_{21}H_{10}BrCl_2N_2O$ ($[M-H]^+$): 454.9359; found: 454.9350.

*9, 11-Dichloro-12-(4-chlorophenyl)-12*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine* **(4e):** White solid, m.p. 208.7–210.2 °C; IR (KBr): 1533 (–C=N at pyrimidine ring), 1213 (C–O–C at pyran ring), 643 (C–Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.83 (t, *J* = 8.8 Hz, 2H), 7.51 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.48–7.40 (m, 2H), 7.34–7.26 (m, 2H), 7.22–7.15 (m, 2H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.7, 161.6, 157.7, 147.1, 139.6, 133.5, 131.7, 130.4, 130.1, 129.6, 129.0, 128.9, 127.7, 125.6, 122.6, 117.1, 115.8, 114.5, 38.6; Mass: 413 ($[M+H]^+$); HRMS (ESI) calcd for $C_{21}H_{12}Cl_3N_2O$ ($[M+H]^+$): 413.0010; found: 413.0013.

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References

1 M.M. Ghorab and A.Y. Hassan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1998, **141**, 251.
2 A.H. Bedair, H.A. Emam, N.A. El-Hady, K.A.R. Ahmed and A.M. El-Agrody, *Farmaco*, 2001, **56**, 965.
3 H.M. Alya and M.M. Kamal, *Eur. J. Med. Chem.*, 2012, **47**, 18.
4 A.A. Shestopalov, L.A. Rodinovskaya, A.M. Shestopalov and V.P. Litvinov, *Russ. Chem. Bull.*, 2004, **53**, 2342.
5 M.M. Ghorab, F.A. Ragab, H.I. Heiba and R.M. El-Hazek, *Eur. J. Med. Chem.*, 2011, **46**, 5120.
6 V.K. Ahluwalia, R. Batla, A. Khurana and R. Kumar, *Indian J. Chem.*, 1990, **29**, 1141.
7 A.H. Shamroukh, M.E.A. Zaki, E.M.H. Morsy, F.M. Abdel-Motti and F.M.E. Abdel-Megeid, *Arch. Pharm.*, 2007, **340**, 236.
8 S. Mashkouri and M.R. Naimi-Jamal, *Molecules*, 2009, **14**, 474.
9 M.M. Heravi, A. Ghods, K. Bakhtiari and F. Derikvand, *Synth. Commun.*, 2010, **40**, 1927.
10 J. Yu and H.Q. Wang, *Synth. Commun.*, 2005, **35**, 3133.
11 Y. Gao, S.J. Tu, T.J. Li, X.J. Zhang, S.L. Zhu, F. Fang and D.Q. Shi, *Synth. Commun.*, 2004, **34**, 1295.
12 I. Devi, H.N. Borah and P.J. Bhuyan, *Tetrahedron Lett.*, 2004, **45**, 2405.
13 X.S. Fan, Y.Y. Wang, Y.Y. Qu, H.Y. Xu, Y. He, X.Y. Zhang and J.J. Wang, *J. Org. Chem.*, 2011, **76**, 982.
14 M. Bayat, Y. Bayat and S.S. Asayesh, *Monatsh. Chem.*, 2012, **143**, 479.
15 G. Mehdi, M. Elham, S. Masoud and H.B. Abolfazl, *Tetrahedron*, 2011, **67**, 8484.
16 M.D. Hill and M. Movassaghi, *Chem. Eur. J.*, 2008, **14**, 6836.
17 J.W. Yan, M. Cheng, F. Hu and Y.H. Hu, *Org. Lett.*, 2012, **14**, 3206.
18 M.R. Naimi-Jamal, S. Mashkouri and A. Sharifi, *Mol. Divers.*, 2010, **14**, 473.
19 J.H. Lee, B.S. Lee, H. Shin, D.H. Nam and D.Y. Chi. *Synlett*., 2006, 65.
20 Z.H. Li, D.L. Wu and W.H. Zhong. *Heterocycles,* 2012, **85**, 1417.