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Short communication

Novel chromeno [2,3-*b*]-pyrimidine derivatives as potential anti-microbial agents

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ABSTRACT

An efficient, microwave irradiated synthesis of novel chromeno[2,3-b]-pyrimidine derivatives was carried out. 2-Amino-3,4-dihydro-2*H*-chromene-3-carbonitrile was converted into imine using *N*,*N*-Dimethylacetaldehyde dimethylacetal to give the core intermediate, which was used for the preparation of chromenopyrimidine library, using acetic acid and different amine in microwave irradiation for 5 min. Structures of newly synthesized compounds were confirmed by spectral studies. Compound **6g** was characterized by single crystal X-ray analysis. All the compounds were also screened for their antimicrobial activity. Few of the compounds are found to be potential antimicrobials.

1. Introduction

Condensed heterocyclic systems are of considerable interest not only because of their potential biological activity, but also because of their versatility as synthones in organic transformations [1–3]. A series of 1,6-naphthyrimidines have demonstrated antihuman cytomegalovirus (HCMV) activity [4,5]. Pyrimidine and its derivatives have been studied for over a century due to a variety of chemical and biological significance [6].

Similarly, chromene derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits [7]. Numerous bioactive natural products have been identified, and the presence of the chromene-based structure has been associated with the capacity to prevent disease [8]. Synthetic analogues have been developed over the years, some of them displaying remarkable effects as pharmaceuticals [9], including antifungal [10], anti-microbial [11], molluscidial [12], anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactic characteristics [13]. Moreover, nitrogen-containing heterocycles [14,15] are also of broad pharmaceutical interest and significance, which justifies our continuing efforts in designing novel heterocyclic molecules of biological importance [16,17].

2. Chemistry

2-Imino-2*H*-chromene-3-carbonitrile **3** was prepared using salicylaldehyde and malononitrile in the presence of triethylamine [18]. 2-Imino-2*H*-chromene-3-carbonitrile was reduced using sodium borohydride in methanol to yield 2-amino-3,4-dihydro-2*H*-chromene-3-carbonitrile **4**. Further this amine was converted into imine using *N*,*N*-Dimethylacetaldehyde dimethyl acetal to yield core intermediate **5**, which was used for the preparation of chromenopyrimidine library, using acetic acid and different amine in microwave irradiation (Fig. 1).

3. Antimicrobial studies

All the newly synthesized compounds were screened for their antibacterial activity. For this, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* microorganisms were employed. Antimicrobial study was assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method [19]. Several colonies of *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* were picked off a fresh isolation plate and inoculated in corresponding tubes containing

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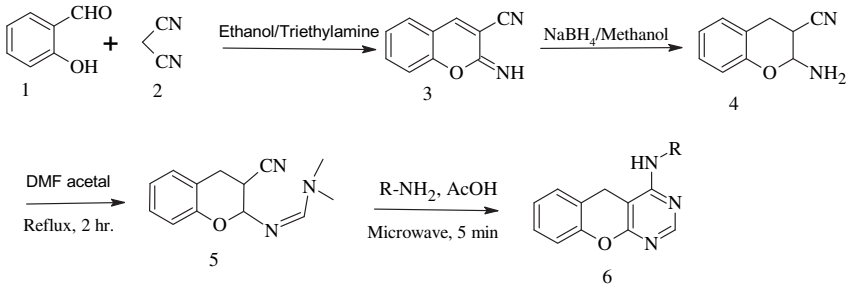

Fig. 1. Scheme for synthesis of Chromeno pyrimidines.

5 mL of trypticase soya broth. The broth was incubated for 6 h at 37 °C until there was visible growth. Mc Farland No.5 standard was prepared by adding 0.05 mL of 1% w/v $BaCl_2 \cdot 2H_2O$ in Phosphate Buffered saline (PBS) to 9.95 mL of 1% v/v H_2SO_4 in PBS. The growth of all the four cultures was adjusted to Mc Farland No.5 turbidity standard using sterile PBS. This gives a 10^8 cfu/mL suspension. The working inoculums of aforementioned four different microorganisms containing 10^5 cfu/mL suspension was prepared by diluting the 10^8 cfu/mL suspension, 10^3 times in trypticase soya broth.

3.1. Preparation of anti-microbial suspension (50 μg/mL)

Dissolved 0.5 mg of each compound in 10 mL of trypticase soya broth to get 50 μg/mL. This suspension was filter sterilized in syringe filters.

3.2. Preparation of dilutions

In all, for each of the 11 anti-microbial compounds and standard anti-microbial i.e. Ceftriaxone, 24 tubes of 5 mL capacity were arranged in 4 rows with each row containing 6 tubes. Then 1.9 mL of trypticase soya broth was added in the first tube in each row and 1 mL in the remaining tubes. Now, 100 μl of filtered anti-microbial suspension was added to the first tube in each row and after mixing the content, 1 mL was serially transferred from these tubes to the second tube in each of the rows. The contents in the second tube of each of the rows were mixed and transferred to the third tube in each of the rows. This serial dilution was repeated till the sixth tube in each of the rows. This provided anti-microbial concentrations of 50, 25, 12.5, 6.25, 3.125, 1.6125 μg/mL in the first to sixth tube respectively in each row. Finally, 1 mL of 10^5 cfu/mL of *S. aureus*, *B. subtilis*, *E. coli* and *P. aerogenosa* suspension were added to the first, second, third and fourth rows of tubes respectively. Along with the test samples and Ceftriaxone (standard), the inoculums control (without anti-microbial compound) and broth control (without anti-microbial compound and inoculum) were maintained. All the test sample and control tubes were then incubated for 16 h at 37 °C.

3.3. Interpretation

After incubation, the tubes showing no visible growth was considered to be representing the MIC. The details of results are furnished in Table 1. Inoculums control showed visible growth, where as the broth control showed no growth (Fig. 1).

4. Results and discussion

Iminocoumarin (2-imino-2H-chromene-3-carbonitrile) **3** was prepared using Knoevenagel condensation procedure, in one–pot reaction from 2-hydroxybenzaldehyde **1** and malononitrile **2** in the presence of triethylamine. The spontaneous cyclization between the ortho hydroxy group and the side-chain cyano group of intermediate **3** led to iminocoumarin derivative **3** in good yield [20]. The structure of the iminocoumarin and coumarin derivatives were determined by IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. A singlet peak at 8.83 ppm in ^{1}H NMR indicates imine-NH and peak at 2231 (CN) in IR confirms the structure. Subsequent reduction of **3** using sodiumborohydride in methanol medium resulted 2-amino-3,4-dihydro-2*H*-chromene-3-carbonitrile **4**.

N′-(3-cyano-3,4-dihydro-2*H*-chromen-2-yl)-*N*,*N*-dimethylimidoformamide **5** was prepared by refluxing **4** in *N*,*N*-Dimethlactaldehyde dimethylacetal for 1 h. Compound **5** is core intermediate for the synthesis of chromeno[2,3-*b*]-pyrimidine library. Microwave irradiation of intermediate **5** with different amines in acetic acid gave chromeno[2,3-*b*]-pyrimidine derivatives **6(a–k)** within 5 min. All compounds are characterized after purification by column chromatography. A single crystal has been developed for compound **6g** and its X-Ray structural analysis was carried out [21]. Spectral data of all the compounds and C, H, N analyses are given in the experimental part.

5. Conclusions

A series of novel chromeno[2,3-b]-pyrimidine derivatives were synthesized by microwave irradiation in reasonably good yields.

Table 1
Antibacterial activity data in MIC (μg/mL).

Compound No.	*S. aureus*	*B.subtilis*	*E.coli*	*P.aeruginosa*
6a	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
6b	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
6c	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
6d	1.6125	1.6125	3.125	Growth in all concentrations
6e	1.6125	1.6125	25.00	Growth in all concentrations
6f	1.6125	1.6125	50.00	Growth in all concentrations
6g	1.6125	1.6125	Growth in all concentrations	Growth in all concentrations
6h	1.6125	1.6125	Growth in all concentrations	Growth in all concentrations
6i	Growth in all concentrations	Growth in all concentrations	50.00	50.00
6j	50.00	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
6k	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	25.00
Ceftriaxone (Standard)	3.125	1.6125	1.6125	1.6125
Inoculum control	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
Broth control	No growth	No growth	No growth	No growth

They were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, IR studies and elemental analyses. Compound **6g** was analyzed for its molecular structure by single crystal X-ray crystallography. All the newly synthesized compounds were screened for antibacterial activity by MIC method. Among the screened samples **6a**, **6b** and **6c** have not showed any antibacterial property against all bacterial strains. However compounds **6d**, **6e**, **6f**, **6g** and **6h** have showed excellent antibacterial activity at 1.6125 μg/mL concentration against *S. aureus* bacteria as compared to the standard drug Ceftriaxone which is active at3.125 μg/mL concentration. Similarly compounds **6d**, **6e**, **6f**, **6g** and **6h** have showed same activity as that of the standard which is active at 1.6125 μg/mL against *B. subtilis*. However none of the compounds were active against bacterial strains *E. coli* and *P. aeruginosa*. Compounds **6d**, **6e**, **6f**, **6g** and **6h** have benzylpiperdine, benzyl, 4-chlorobenzyl, 1-naphthyl and 2,5-dimethylphenyl substituents respectively, which is accounted for their significant antibacterial activity.

6. Experimental

Melting points were determined by open capillary method and were uncorrected. The IR spectra (In KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR and ^{13}C NMR, spectra were recorded on a Perkin–Elmer EM 300 MHz spectrometer using TMS as internal standard. The mass spectra were recorded on a JEOL JMS-D 300 spectrometer operating at 70 eV. Purity of the compounds was checked by TLC silica coated plates obtained from Merck.

6.1. Preparation of 2-imino-2H-chromene-3-carbonitrile (**3**)

To a stirred solution of salicylaldehyde (10 g, 0.08 mol) and malononitrile (5.41 g, 0.081 mol) in ethanol (150 mL) was added triethylamine (1 mL, 0.0081 mol). The resulting mixture was refluxed for 30 min and then allowed to cool at room temperature. The formed precipitate was isolated by filtration and washed with ethanol to get pure product as yellow solid and was recrystallised from ethanol (12 g, 84%). M.p. 140–141 °C. IR (cm^{-1}) 3293 (NH), 2231 (CN), 1653 (CH), 1256 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 7.18–7.21 (1H, m, Ar–H); 7.24–7.29 (1H, m, Ar–H); 7.55–7.61 (2H, m, Ar–H); 8.37 (1H, d, J = 0.9 Hz, 4H); 8.83 (1H, s NH). MS: m/z = 171 (M^+). Anal. calcd. for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.31; H, 3.60; N, 16.37%.

6.2. Preparation of 2-amino-3,4-dihydro-2H-chromene-3-carbonitrile (**4**)

To a mixture of 2-imino-2H-chromene-3-carbonitrile **3**(12 g, 0.069 mol) in methanol (150 mL) was added sodium borohydride (0.83 g, 0.034 mol) at 0 °C. Reaction mixture was stirred for 20 min, TLC analysis confirms the completion of reaction. Reaction mixture was poured to water, precipitated solid was filtered, washed with water and dried to get pure product (10 g, 83%). M.p. 150–152 °C, IR (cm^{-1}); 3406 (NH), 3003 (CH), 1699 (C=N), 1284 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.5 (m, 2H, CH_2), 2.6 (bs, 1H, NH), 3.5 (m, 1H, CH), 4.8 (m, 1H, CH), 7.18–7.21 (m, 1H, Ar–H), 7.24–7.29 (m, 1H, Ar–H), 7.55–7.61 (m, 2H, Ar–H). MS: m/z = 175 (M^+). Anal. calcd. for $C_{10}H_{10}N_2O$: C, 68.97; H, 5.75; N, 16.09; Found: C, 68.95; H, 5.88; N, 16.08%.

6.3. Preparation of N′-(3-cyano-3,4-dihydro-2H-chromen-2-yl)-N, N-dimethylimido formamide (**5**)

A solution of 2-amino-3,4-dihydro-2H-chromene-3-carbonitrile **4** (10 g, 0.057 mol) in N,N-Dimethylformamide dimethylactal (50 mL) was heated to reflux for 1 h. Reaction mixture was concentrated and the residue was triturated with Diethyl ether to get compound **5** as yellow solid (11 g, 84%). IR (cm^{-1}) 3406 (NH), 3003 (CH), 1699 (C=N),1280 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 2.5 (m, 2H, CH_2), 3.5 (m, 1H, CH), 4.8 (m, 1H, CH), 7.18–7.21 (1H, m, Ar–H); 7.24–7.29 (1H, m, Ar–H); 7.55–7.61 (2H, m, Ar–H), 8.4 (s, 1H, CH). MS: m/z = 230 (M^+). Anal. calcd. for $C_{13}H_{15}N_3O$: C, 6812; H, 6.55; N, 18.34; Found: C, 68.08; H, 6.53; N, 18.31%.

6.4. General procedure for synthesis of 5H-chromeno [2,3-d] pyrimidin-4-amine derivatives **6(*a*–*k*)**

A slurry of *N*-(3-cyano-3,4-dihydro-2H-chromen-2-yl)-*N*,*N*-dimethylformamide **5** (4.3 mmol), corresponding amine (4.3 mmol) in acetic acid (2 mL) was irradiated in microwave for 5 min. Resulting dark residue was poured to water, filtered the solid separated, recrystallised from ethanol to get pure compound.

6.4.1. 5H-chromeno [2,3-d]pyrimidin-4-amine (**6a**)

Yield 68%, M.p.190–193 °C, IR (cm^{-1}) 3360 (NH), 3041 (CH), 1606 (C=N), 1254 (C–O).^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.94 (s, 2H, CH_2), 6.6 (bs, 2H, NH_2), 7.1–7.33 (m, 4H, Ar–H), 8.3 (s, 1H, Ar–H). ^{13}C NMR : 161.3, 160.30, 155.6, 129.4, 1 28.27, 123.3, 122.1, 117.2, 99.1, 23.4. MS: m/z = 200.2 (M^+). Anal. calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.43; H, 6.48; N, 21.06%.

6.4.2. Preparation of N-(2,4-dichlorophenyl)-5H-chromeno[2,3-d] pyrimidin-4-amine (**6b**)

Yield 73%, M.p.145–147 °C, IR (cm^{-1}) 3406 (NH), 3053 (CH), 1642 (C=N), 1258 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.01 (s, 2H, CH_2), 7.01–7.40 (m, 7H, Ar–H), 8.44 (s, 1H, Ar–H), 10.4 (bs,1H, NH). ^{13}C NMR : 162.6, 159.9, 157.6, 155.9, 155.2, 149.9, 129.8, 129.3, 128.7, 128.2, 126.2, 124.5, 119.2, 116.7, 116.3, 94.5, 22.25. MS: m/z = 345.0 (M^+). Anal. calcd. for $C_{17}H_{11}Cl_2N_3O$: C, 59.32; H, 3.22; N, 12.21%. Found: C, 59.26; H, 3.18; N, 12.18%.

6.4.3. Preparation of N-[2-methyl-4-(trifluoromethyl)phenyl]-5H-chromeno[2,3-d]pyrimidin-4-amine (**6c**)

Yield 70%, M.p.156–157 °C, IR (cm^{-1}) 3386 (NH), 3062 (CH), 1613 (C=N), 1251 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3) 3.98 (s, 2H, CH_2), 7.01–7.40 (m, 5H, Ar–H), 8.3 (s,1H, Ar–H), 7.6 (d, 1H, Ar–H, J = 12), 7.64 (d, 1H, Ar–H, J = 4), 8.42 (s, 1H, Ar–H), 10.1(bs, 1H, NH). ^{13}C NMR: 162.34, 159.3, 157.4, 152.2, 144.8, 132.8, 129.4, 128.9, 126.8, 125.1, 123.2, 122.7, 121.5117.0, 96.6, 22.5, 20.7. MS: m/z = 358.2 (M^+). Anal. calcd. for $C_{19}H_{14}F_3N_3O$: C, 63.86; H, 3.92; N, 11.76. Found: C, 63.73; H, 3.96; N, 11.69%.

6.4.4. Preparation of N-(1-benzylpiperidin-4-yl)-5H-chromeno [2,3-d]pyrimidine-4-amine (**6d**)

Yield 65%, M.p.248–250 °C, IR (cm^{-1}) 3456 (NH), 3058 (CH), 1603 (C=N), 126(C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.12 (m, 4H, $2CH_2$), 2.71 (bs, 2H, CH_2), 3.12 (m, 2H, CH_2), 3.7 (bs, 2H, CH_2), 3.8 (m, 1H, CH), 4.1 (s, 2H, CH_2), 4.3 (bs, 1H, NH), 7.01–7.25 (m, 2H, Ar–H), 7.32–7.45 (m, 7H, Ar–H), 8.2 (s, 1H, Ar–H). MS: m/z = 373.2 (M^+). Anal. calcd. for $C_{23}H_{24}N_4O$: C, 74.19; H, 6.45; N, 15.04. Found: C, 74.17; H, 6.39; N, 14.98%.

6.4.5. Preparation of N-benzyl-5H-chromeno [2,3-d]pyrimidin-4-amine (**6e**)

Yield 75%, M.p.185–187 °C, IR (cm^{-1}) 3486 (NH), 3054 (CH), 1603 (C=N), 1264 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.8 (s, 2H, CH_2), 4.5 (s, 2H, CH_2), 7.01–7.25 (m, 2H, Ar–H), 7.32–7.45 (m, 7H, Ar–H), 8.3 (s, 1H, Ar–H). ^{13}C NMR : 161.2159.9, 156.0, 150.2, 139.9, 129.4, 128.3, 128.0, 127.6, 126.1, 123.3, 121.0.117.1, 95.6, 44.1,

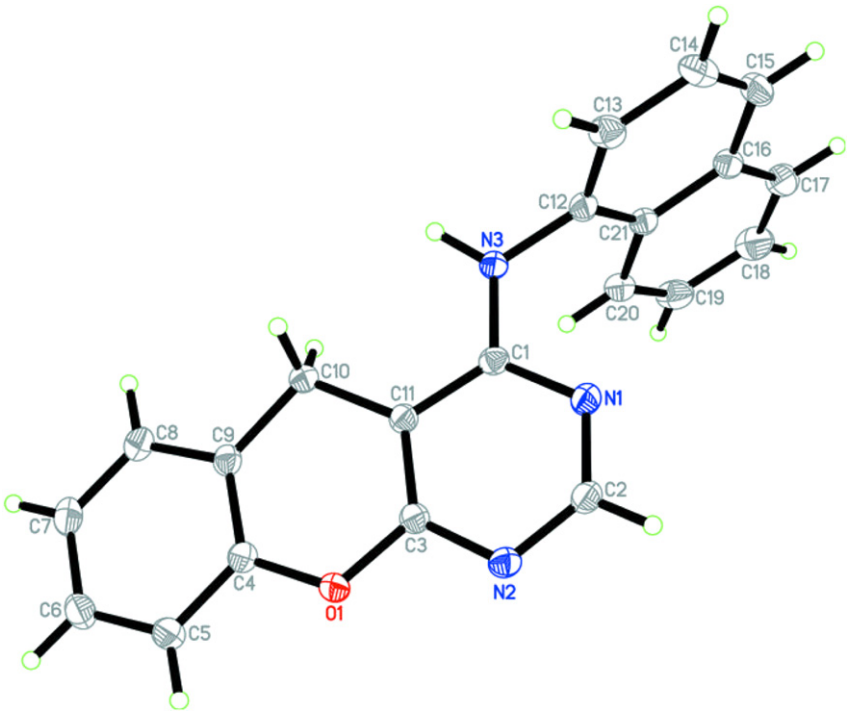

Fig. 2. Molecular structure of **6g**.

24.2. MS: $m/z = 290$ (M^+). Anal. calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.19; N, 14.52. Found: C, 74.67; H, 5.23; N, 14.54%.

*6.4.6. Preparation of 4-(4-chlorobenzyl)-5H-chromeno [2,3-d] pyrimidine (**6f**)*

Yield 71%, M.p.137–139 °C, IR (cm^{-1}) 3896 (NH), 3048 (CH), 1606 (C=N), 1276 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.9 (s, 2H, CH_2), 7.01–7.1 (m, 2H, Ar–H), 7.32–7.45 (m, 7H, Ar–H), 8.45 (s, 1H,Ar–H). ^{13}C NMR: 161.5, 158.8, 155.5, 150.6, 140.1, 133.2, 129.9, 129.4, 129.0, 128.4, 123.4, 120.9, 117.2, 116.1, 25.3. MS: $m/z = 310$ (M^+). Anal. calcd. for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found: C, 65.86; H, 3.83; N, 13.48%.

*6.4.7. Preparation of N-1-naphthyl-5H-chromeno [2,3-d]pyrimidin-4-amine (**6g**)*

Yield 71%, M.p.240–242 °C, IR (cm^{-1}) 345 6(NH), 3058 (CH), 1603 (C=N), 1273 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 3.85 (s, 2H, CH_2), 7.01–7.1 (m, 2H, Ar–H), 7.32–7.45 (m, 7H, Ar–H), 7.80–8.01 (m, 3H, Ar–H), 8.4 (s, 1H, Ar–H). ^{13}C NMR: 161.9, 156.3, 150.2, 135.7, 134.4, 130.5, 129.8, 128.7, 128.6, 128.4, 127.2, 126.6, 126.3, 125.3, 124.7, 124.1, 122.7, 119.9, 117.1, 94.1, 22.8. MS: $m/z = 326$ (M^+). Anal. calcd. for $C_{21}H_{15}N_3O$: C, 77.54; H, 4.62; N, 12.91. Found: C, 77.61; H, 4.65; N, 13.02%.

*6.4.8. Preparation of N-(2,5-dimethylphenyl)-5H-chromeno[2,3-d] pyrimidin-4-amine (**6h**)*

Yield 68%, M.p.198–200 °C, IR (cm^{-1}) 3436 (NH), 3051 (CH), 1600 (C=N), 1274 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.72 (d, 2H, Ar–H), 7.2–7.35 (m, 4H, Ar–H), 7.30–7.45 (m, 3H, Ar–H), 8.35 (s, 1H, Ar–H). ^{13}C NMR: 161.4, 161.1, 150.7, 150.1, 136.8, 136.5, 132.4, 131.0, 130.5, 130.1, 128.8, 128.6, 125.2, 119.8, 117.0, 99.0, 22.5, 20.7, 17.15. MS: $m/z = 304$ (M^+). Anal. calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.61; N, 13.85. Found: C, 75.31; H, 5.55; N, 13.78%.

*6.4.9. Preparation of N-tricyclo[5.2.1.0^{3,8}]dec-1-yl-5H-chromeno [2,3-d]pyrimidin-4-amine (**6i**)*

Yield 61 %, M.p.167–169 °C, IR (cm^{-1}) 3426 (NH), 3043 (CH), 1608 (C=N), 1279 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1–1.2 (m, 4H, $2CH_2$), 1.3–1.5 (m, 6H, CH_2), 1.6–1.8 (m, 3H, CH), 2.2–2.4 (m, 2H, CH_2), 3.8 (s, 3H, CH_3), 7.1 (m, 1H, Ar–H), 7.3 (m, 1H, Ar–H), 7.4 (m, 2H, Ar–H), 8.5 (s, 1H, Ar–H). ^{13}C NMR: 161.1, 159.6, 155.7, 150.2, 129.4, 128.0, 123.3, 121.5, 117.1, 95.6, 64.1, 40.7, 39.6, 37.7, 35.1,

Table 2
Crystal data and structure refinement of compound 6g.

Crystal data	
$C_{21}H_{15}N_3O$	Dx = 1.349 Mg m−3
Mr = 325.36	Melting point = 513–515 K
Orthorhombic, Pbca	Mo K_α radiation
	λ = 0.71073 Å
-Hall symbol: -P 2ac 2ab	Cell parameters from 4673 reflections
a = 13.2762 (3) Å	θ = 1.5–30.0°
b = 8.8700 (2) Å	μ = 0.09 mm^{-1}
c = 27.1997 (5) Å	T = 100 K
V = 3203.03 (12) Å3	Plate, colourless
Z = 8	0.57 × 0.38 × 0.03 mm
F000 = 1360	
Data collection	
Bruker SMART APEXII CCD area-detector	
Diffractometer	4673 independent reflections
Radiation source:	3649 reflections with I > 2σ(I)
fine-focus sealed tube	
Monochromator: graphite	Rint = 0.042
Detector resolution: 8.33 pixels mm^{-1}	θmax = 30.0°
T = 100 K	θmin = 1.5°
ω scans	h = −18 → 18
Absorption correction: multi-scan	
(SADABS; Bruker, 2005)	k = −12 → 12
T_{min} = 0.901, T_{max} = 0.997	l = −37 → 38
27 104 measured reflections	

30.9, 24.7, 14.7. MS: $m/z = 334.3$ (M^+). Anal. calcd. for $C_{21}H_{23}N_3O$: C, 75.68; H, 6.91; N, 12.60. Found: C, 75.61; H, 6.85; N, 12.58%.

*6.4.10. Preparation of N-(3-fluoro-4-methylphenyl)-5H-chromeno [2,3-d]pyrimidin-4-amine (**6j**)*

Yield 69%, M.p.171–172 °C, IR (cm^{-1}) 3456 (NH), 3081 (CH), 1620 (C=N), 1284 (C–O). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.0–7.2 (m, 2H, Ar–H), 7.2–7.35 (m, 4H, Ar–H), 7.5 (m, 1H, Ar–H), 8.3 (s, 1H, Ar–H). ^{13}C NMR: 162.2, 161.3, 158.1, 156.4, 151.1, 140.5, 131.3, 129.4, 128.9, 123.2, 122.2, 118, 117.2, 105.6, 97.1, 26.6,15.1. MS: $m/z = 308.1$ (M^+). Anal. calcd. for $C_{18}H_{14}FN_3O$: C, 70.35; H, 4.59; N, 13.67. Found: C, 70.41; H, 4.65; N, 13.64%.

*6.4.11. Preparation of N-(5-methyl-1,3-thiazol-2-yl)-5H-chromeno [2,3-d]pyrimidin-4-amine (**6k**)*

Yield 64%, M.p.238–240 °C, IR (cm^{-1}) 3449 (NH), 3043 (CH), 1607 (C=N), 1254 (C–O). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.2 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 7.0–7.4 (m, 3H, Ar–H), 7.35 (m, 2H, Ar–H), 7.8 (s, 1H, thiazole-H), 8.45 (s, 1H, Ar–H). ^{13}C NMR: 161.3, 157.8, 157.3, 156.3, 151.1, 133.9, 129.3128.3, 124.4, 122.0.117.3, 110.6, 98.9, 20. MS: $m/z = 297.1$ (M^+). Anal. calcd. for $C_{15}H_{12}N_4OS$: C, 60.81; H, 4.05; N, 18.91. Found: C, 60.71; H, 4.02; N, 18.87% (Fig. 2 and Table 2).

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