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SOLVENT-FREE SYNTHESIS OF NOVEL 5-OXO-5*H*-CHROMENO[4,3-*b*]PYRIDINE DERIVATIVES

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An efficient and simple method for the synthesis of new 5-oxo-5H-chromeno[4,3-b]pyridine derivatives via Michael addition of 4-aminocoumarin to arylidenemalononitrile for 20 min at 150°C without any solvent is proposed. The advantages of this procedure are mild reaction conditions, high yields of products, and operational simplicity.

Keywords: 5-oxo-5*H*-chromeno[4,3-*b*]pyridine, Michael addition, solvent-free synthesis.

Various coumarin derivatives, particularly those fused with other heterocycles, have attracted much attention in recent years due to their biological activities [1, 2], and encouraged research to improve the availability of these compounds with regard to procedures and substrates. Coumarins condensed to pyridine ring (chromeno[3,4-*b*]pyridin-5-ones) are also under investigation, as they constitute the backbone of naturally occurring alkaloids, e.g. santiagonamine [3]. Some of them, both natural and non-natural products, are currently in clinical trials [4-7].

Previously we reported the synthesis and cytotoxic activity of novel coumarin derivatives, chromeno[4,3-*b*]-quinolines, benzopyrano[3,2-*c*]chromene-6,8-diones and chromeno[3',4']pyrano[2,3-*b*]quinoline-6,9-diones [8-10]. In continuation of our studies, and owing to the importance of chromenopyridines, we decided to investigate the synthesis of new 5-oxo-5*H*-chromeno[4,3-*b*]pyridine derivatives by a simple method.

The literature data on existing synthetic routes to 5-oxo-5*H*-chromeno[4,3-*b*]pyridines can be classified based on the functionality of the starting materials. Synthetically significant approaches include multistep ring formation by reaction of 4-aminocoumarin with alkyl vinyl ketones [11], 4-amino-3-formylcoumarin with C–H acids [12], 4-chloro-3-formylcoumarin with Wittig phosphoranes [13], or 4-oxo-4*H*-chromene-3-carbaldehydes with enamines followed by oxidation [14]. In another procedure, 7-trifluoromethyl group-containing 5-oxo-5*H*-chromeno[4,3-*b*]pyridine derivatives were prepared by reaction of 4-chloro-3-(trifluoroacetyl)-2*H*-chromen-2-one and aniline followed by intramolecular cyclization in the presence of concentrated sulfuric acid [15]. However, these methods have disadvantages such as harsh reaction conditions, sensitivity of starting materials and reagents to moisture, and use of toxic reagents ($POCl_3$, TMSCl) or oxidants (CrO_3, conc. H_2SO_4).

In the present work, we have developed the synthesis of new 2-amino-4-aryl-5-oxo-5*H*-chromeno-[4,3-*b*]pyridine-3-carbonitriles **3a-n** *via* Michael addition of 4-aminocoumarin (**1**) to arylidenemalononitrile **2a-n** in 60–80% yields in a solvent-free system at 150°C.

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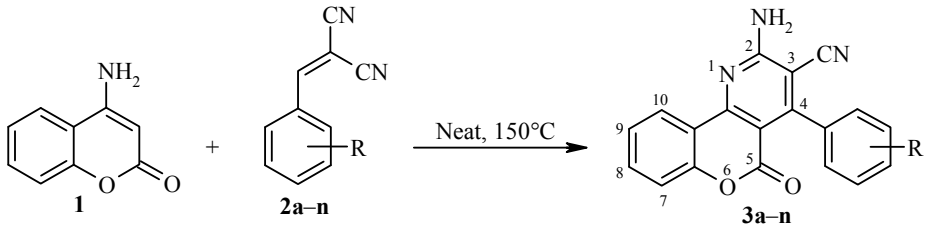
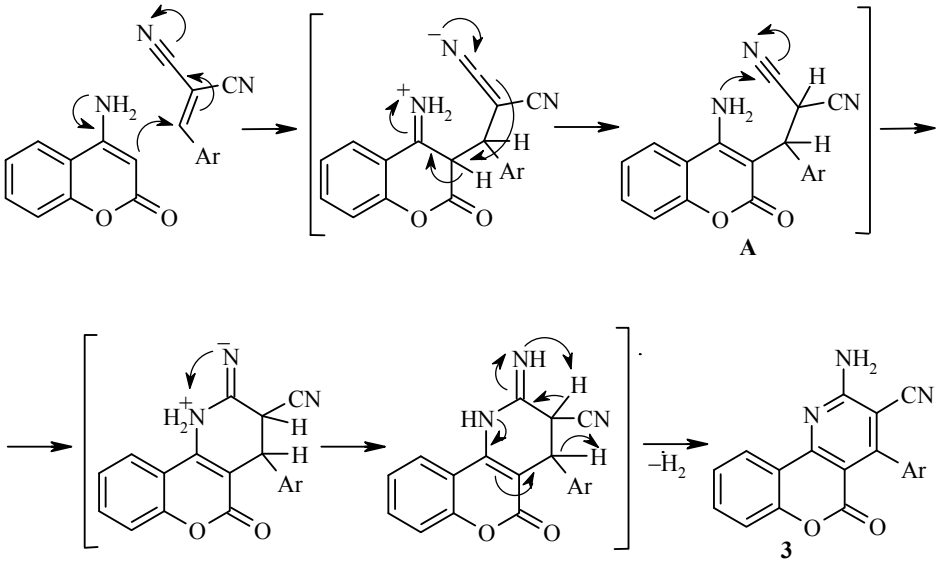
The starting materials, 4-aminocoumarin (**1**) and arylidenemalononitriles **2a-n** were obtained by known methods [10, 16-20]. In our condensation protocol, no organic solvents or catalysts were used in the reaction process. The crude products **3a-n** were obtained as solids which were further purified by flash column chromatography and characterized by ^{1}H NMR, FT-IR, and mass spectra.



2, **3 a** R = 3-NO_2, **b** R = 4-NO_2, **c** R = 2-Cl, **d** R = 3-Cl, **e** R = 4-Cl, **f** R = 2-Br, **g** R = 3-Br, **h** R = 4-Br, **i** R = 2-MeO, **j** R = 3-MeO, **k** R = 4-MeO, **l** R = 2-Me, **m** R = 3-Me, **n** R = 4-Me

The ^{1}H NMR spectra of compounds **3a-n** contain the corresponding signals of coumarin and aryl protons at 7.00-8.39 ppm, and the broad signal of the NH_2 group protons at 8.05-8.35 ppm. Also, the IR spectra revealed the presence of amino and cyano functions by the respective absorption bands at 3330-3500 and 2211-2228 cm^{-1}.

A putative mechanism for the formation of the products **3** is outlined below.



The reaction occurs *via* the initial formation of the intermediate **A** as a result of Michael addition of substituted arylidenemalononitriles **2** and 4-aminocoumarin (**1**). The Michael adduct **A** then cyclizes, isomerizes, and subsequently loses a hydrogen molecule to afford the fully aromatized compounds **3**.

In summary, a new Michael addition approach to novel 5-oxo-5*H*-chromeno[4,3-*b*]pyridines is reported, starting from easily accessible arylidenemalononitrile and 4-aminocoumarin. The described method can be applied to achieve good yields and short reaction times in a solvent-free system to obtain chromenopyridin-5-one (benzopyranopyridin-5-one) derivatives substituted at position 4 with the aromatic moiety, which are not easily accessible by other methods.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Magna 550 FT-IR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded with a Finnegan MAT TSQ-70 spectrometer (EI, 70 eV). Melting points were determined on a Kofler hot stage apparatus. Elemental analysis was carried out on a Vario EL III CHNS-analyzer. The purity of obtained compounds was confirmed by TLC using different mobile phases. All chemicals and solvents used in this study were purchased from Merck and Sigma-Aldrich.

4-Aminocoumarin (**1**) was obtained in 90% yield by melting 4-hydroxycoumarin in the presence of excess NH_4OAc for 30 min. ^{1}H NMR and mass spectra of the product were in agreement with those reported in the literature [10]. The arylidenemalononitriles **2a-n** were synthesized by the Knoevenagel condensation of the corresponding arylaldehydes with malononitrile in aqueous MeOH (H_2O–MeOH, 1:1) at room temperature in 90-95% yields. The structures of compounds **2a-n** were confirmed by comparison of their spectroscopic data (IR, ^{1}H NMR, and mass spectra) with those reported in the literature [16-20].

2-Amino-4-aryl-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles 3 (General Method). The corresponding arylidenemalononitrile **2a-n** (5.4 mmol) and 4-aminocoumarin (**1**) (870 mg, 5.4 mmol) were thoroughly mixed in a beaker using spatula. Then the beaker was placed in an autoclave (150°C) for 20 min, after which the reaction was completed (TLC). The solid crude product was purified by flash column chromatography, eluting with EtOAc–petroleum ether (20:70) to give pure yellowish crystals of compounds **3a-n**.

2-Amino-4-(3-nitrophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3a). Yield 1.55 g (80%). Mp 276-278°C. IR spectrum, ν, cm^{-1}: 3333, 3452 (NH_2), 3223 (C–H), 2228 (CN), 1739 (C=O), 1554, 1348 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.37 (1H, d, *J* = 8.0, H-7); 7.45 (1H, t, *J* = 8.0, H-9); 7.69 (1H, dt, ^3J = 8.0, ^4J = 1.5, H-8); 7.80 (1H, t, *J* = 8.0, H-5'); 7.88 (1H, d, *J* = 8.0, H-6'); 8.32 (2H, br. s, NH_2); 8.33-8.35 (2H, m, H-2',4'); 8.39 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 358 $[M]^+$ (25), 326 (30), 311 (15), 262 (100), 57 (35). Found, %: C 63.63; H 2.79; N 15.63. $C_{19}H_{10}N_4O_4$. Calculated, %: C 63.69; H 2.81; N 15.64.

2-Amino-4-(4-nitrophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3b). Yield 1.47 g (76%). Mp 316-317°C. IR spectrum, ν, cm^{-1}: 3338, 3431 (NH_2), 3234 (C–H), 2222 (CN), 1733 (C=O), 1558, 1350 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.37 (1H, d, *J* = 8.0, H-7); 7.45 (1H, t, *J* = 8.0, H-9); 7.69-7.73 (3H, m, H-8,2',6'); 8.10 (2H, br. s, NH_2); 8.34 (2H, d, *J* = 8.4, H-3',5'); 8.38 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 358 $[M]^+$ (100), 328 (56), 311 (25), 238 (9). Found, %: C 63.67; H 2.77; N 15.61. $C_{19}H_{10}N_4O_4$. Calculated, %: C 63.69; H 2.81; N 15.64.

2-Amino-4-(2-chlorophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3c). Yield 1.63 g (87%). Mp 258-260°C. IR spectrum, ν, cm^{-1}: 3483, 3334 (NH_2), 3214 (C–H), 2217 (CN), 1732 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.37 (1H, d, *J* = 8.0, H-7); 7.39 (1H, d, *J* = 8.0, H-6'); 7.43-7.51 (3H, m, H-9,4',5'); 7.58 (1H, d, *J* = 8.0, H-3'); 7.70 (1H, t, *J* = 8.0, H-8); 8.31 (2H, br. s, NH_2); 8.38 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 349 $[M+2]^+$ (22), 347 $[M]^+$ (72), 330 (2), 312 (10), 201 (30), 104 (100), 77 (30). Found, %: C 65.58; H 2.88; N 12.05. $C_{19}H_{10}ClN_3O_2$. Calculated, %: C 65.62; H 2.90; N 12.08.

2-Amino-4-(3-chlorophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3d). Yield 1.69 g (90%). Mp 254-256°C. IR spectrum, ν, cm^{-1}: 3379 (NH_2), 3197 (C–H), 2208 (CN), 1697 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.32 (1H, dt, ^3J = 7.0, ^4J = 2.0, H-6'); 7.36 (1H, d, *J* = 8.0, H-7); 7.42 (1H, t, *J* = 8.0, H-9); 7.48-7.53 (3H, m, H-2',4',5'); 7.67 (1H, dt, ^3J = 8.0, ^4J = 1.5, H-8); 8.35 (2H, br. s, NH_2); 8.37 (1H, dd, ^3J = 8.0, ^4J = 1.5, H-10). Mass spectrum, *m/z* (I_{rel}, %): 349 $[M+2]^+$ (22), 347 $[M]^+$ (72), 346 (100), 330 (4.5), 312 (4.5), 228 (4), 201 (5). Found, %: C 65.59; H 2.89; N 12.04. $C_{19}H_{10}ClN_3O_2$. Calculated, %: C 65.62; H 2.90; N 12.08.

2-Amino-4-(4-chlorophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3e). Yield 1.26 g (67%). Mp 305-307°C. IR spectrum, ν, cm^{-1}: 3396, 3500 (NH_2), 3077 (C–H), 2212 (CN), 1725 (C=O). ^{1}H NMR

spectrum, δ, ppm (*J*, Hz): 7.36 (1H, d, *J* = 8.0, H-7); 7.39 (2H, d, *J* = 8.5, H-3',5'); 7.42 (1H, t, *J* = 8.0, H-9); 7.53 (2H, d, *J* = 8.5, H-2',6'); 7.68 (1H, dt, ^3J = 8.0, ^4J = 1.5, H-8); 8.19 (2H, br. s, NH_2); 8.38 (1H, dd, ^3J = 8.0, ^4J = 1.5, H-10). Mass spectrum, *m/z* (I_{rel}, %): 349 $[M+2]^+$ (22), 347 $[M]^+$ (67), 346 (100), 330 (5), 318 (5), 228 (5), 201 (5). Found, %: C 65.58; H 2.87; N 12.05. $C_{19}H_{10}ClN_3O_2$. Calculated, %: C 65.62; H 2.90; N 12.08.

2-Amino-4-(2-bromophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3f). Yield 1.80 g (85%). Mp 242-244°C. IR spectrum, ν, cm^{-1}: 3323, 3469 (NH_2), 3213 (C–H), 2214 (CN), 1727 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.36-7.39 (2H, m, H-7,4'); 7.42-7.46 (2H, m, H-9,6'); 7.61-7.70 (3H, m, H-8,3',5'); 8.15 (2H, br. s, NH_2); 8.38 (1H, dd, ^3J = 8.0, ^4J = 1.5, H-10). Mass spectrum, *m/z* (I_{rel}, %): 393/391 $[M]^+$ (66), 392 (100), 312 (33), 228 (17), 201 (20), 76 (32), 63 (32). Found, %: C 58.14; H 2.50; N 10.75. $C_{19}H_{10}BrN_3O_2$. Calculated, %: C 58.18; H 2.57; N 10.71.

2-Amino-4-(3-bromophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3g). Yield 1.48 g (70%). Mp 244-246°C. IR spectrum, ν, cm^{-1}: 3321, 3463 (NH_2), 3218 (C–H), 2212 (CN), 1726 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.37-7.39 (2H, m, H-7,2'); 7.41 (1H, dt, ^3J = 8.0, ^4J = 1.5, H-6'); 7.45 (1H, t, *J* = 8.0, H-9); 7.51 (1H, t, *J* = 7.5, H-5'); 7.68 (1H, t, *J* = 8.0, H-8); 7.74 (1H, d, *J* = 8.0, H-4'); 8.05 (2H, br. s, NH_2); 8.38 (1H, dd, ^3J = 8.0, ^4J = 1.5, H-10). Mass spectrum, *m/z* (I_{rel}, %): 393/391 $[M]^+$ (64), 312 (100), 284 (5), 125 (5). Found, %: C 58.15; H 2.52; N 10.68. $C_{19}H_{10}BrN_3O_2$. Calculated, %: C 58.18; H 2.57; N 10.71.

2-Amino-4-(4-bromophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3h). Yield 1.59 g (75%). Mp 290-292°C. IR spectrum, ν, cm^{-1}: 3393, 3489 (NH_2), 3100 (C–H), 2219 (CN), 1722 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.33 (2H, d, *J* = 9.0, H-2',6'); 7.37 (1H, d, *J* = 8.0, H-7); 7.42 (1H, t, *J* = 8.5, H-9); 7.66 (1H, t, *J* = 8.0, H-8); 7.68 (2H, d, *J* = 9.0, H-3',5'); 8.10 (2H, br. s, NH_2); 8.37 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 393/391 $[M]^+$ (63), 392 (100), 312 (9), 284 (7), 228 (8), 201 (9). Found, %: C 58.13; H 2.53; N 10.64. $C_{19}H_{10}BrN_3O_2$. Calculated, %: C 58.18; H 2.57; N 10.71.

2-Amino-4-(2-methoxyphenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3i). Yield 0.65 g (35%). Mp 209-211°C. IR spectrum, ν, cm^{-1}: 3349, 3431 (NH_2), 3214 (C–H), 2223 (CN), 1722 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.07 (3H, s, OCH_3); 7.12 (1H, d, *J* = 8.0, H-3'); 7.47-7.53 (2H, m, H-5',6'); 7.68-7.76 (3H, m, H-7,9,4'); 8.03 (1H, t, *J* = 8.0, H-8); 8.20 (2H, br. s, NH_2); 8.32 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 343 $[M]^+$ (19), 300 (6), 167 (25), 149 (100), 105 (75), 76 (50), 43 (25). Found, %: C 69.92; H 3.78; N 12.22. $C_{20}H_{13}N_3O_3$. Calculated, %: C 69.96; H 3.82; N 12.24.

2-Amino-4-(3-methoxyphenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3j). Yield 1.44 g (78%). Mp 260-262°C. IR spectrum, ν, cm^{-1}: 3374 (NH_2), 3181 (C–H), 2192 (CN), 1707 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.76 (3H, s, OCH_3); 6.88 (1H, d, *J* = 8.0, H-6'); 6.92 (1H, s, H-2'); 7.01 (1H, dt, ^3J = 8.0, ^4J = 2.0, H-4'); 7.34 (1H, d, *J* = 8.0, H-7); 7.38 (1H, t, *J* = 8.0, H-5'); 7.41 (1H, t, *J* = 8.0, H-9); 7.66 (1H, dt, ^3J = 8.0, ^4J = 1.5, H-8); 8.05 (2H, br. s, NH_2); 8.37 (1H, dd, ^3J = 8.0, ^4J = 1.5, H-10). Mass spectrum, *m/z* (I_{rel}, %): 343 $[M]^+$ (100), 328 (23), 312 (23), 300 (31), 270 (10), 201 (13), 190 (20), 76 (23), 63 (67). Found, %: C 69.92; H 3.79; N 12.24. $C_{20}H_{13}N_3O_3$. Calculated, %: C 69.96; H 3.82; N 12.24.

2-Amino-4-(4-methoxyphenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3k). Yield 1.39 g (75%). Mp 259-261°C. IR spectrum, ν, cm^{-1}: 3349, 3431 (NH_2), 3239 (C–H), 2214 (CN), 1734 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, OCH_3); 7.00 (2H, d, *J* = 8.5, H-2',6'); 7.30 (2H, d, *J* = 8.5, H-3',5'); 7.33 (1H, d, *J* = 8.0, H-7); 7.40 (1H, t, *J* = 8.0, H-9); 7.65 (1H, t, *J* = 8.0, H-8); 8.10 (2H, br. s, NH_2); 8.37 (1H, d, *J* = 8.0, H-10). ^{13}C NMR spectrum, δ, ppm: 55.1; 94.2; 105.2; 113.3 (2C); 115.3; 116.6; 118.3; 124.3; 125.3; 129.0 (2C); 129.2; 133.4; 153.1; 155.1; 157.3; 159.5; 160.0; 160.9. Mass spectrum, *m/z* (I_{rel}, %): 343 $[M]^+$ (100), 328 (3), 314 (2), 300 (13), 271 (2), 201 (2), 190 (3). Found, %: C 69.85; H 3.89; N 12.20. $C_{20}H_{13}N_3O_3$. Calculated, %: C 69.96; H 3.82; N 12.24.

2-Amino-4-(2-methylphenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3l). Yield 1.15 g (65%). Mp 270-272°C. IR spectrum, ν, cm^{-1}: 3331, 3468 (NH_2), 3218 (C–H), 2211 (CN), 1730 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.05 (3H, s, CH_3); 7.10 (1H, d, *J* = 6.5, H-3'); 7.26 (1H, t, *J* = 6.5, H-4'); 7.31-7.33 (2H, m, H-5',6'); 7.35 (1H, d, *J* = 8.0, H-7); 7.44 (1H, t, *J* = 8.0, H-9); 7.67 (1H, t, *J* = 8.0, H-8); 8.10

(2H, br. s, NH_2); 8.39 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 327 $[M]^+$ (26), 312 (26), 310 (100), 299 (6), 201 (5), 163 (7). Found, %: C 73.34; H 3.97; N 12.82. $C_{20}H_{13}N_3O_2$. Calculated, %: C 73.38; H 4.00; N 12.84.

2-Amino-4-(3-methylphenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3m). Yield 0.71 g (40%). Mp 241-243°C. IR spectrum, ν, cm^{-1}: 3327, 3456 (NH_2), 3216 (C–H), 2211 (CN), 1729 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, CH_3); 7.11 (1H, d, *J* = 7.5, H-6'); 7.13 (1H, s, H-2'); 7.26 (1H, d, *J* = 7.5, H-4'); 7.35 (1H, d, *J* = 7.5, H-7); 7.35 (1H, t, *J* = 7.5, H-5'); 7.41 (1H, t, *J* = 7.5, H-9); 7.66 (1H, t, *J* = 7.5, H-8); 8.10 (2H, br. s, NH_2); 8.38 (1H, d, *J* = 7.5, H-10). Mass spectrum, *m/z* (I_{rel}, %): 327 $[M]^+$ (87), 326 (100), 312 (6), 298 (6), 274 (6), 144 (16), 105 (20). Found, %: C 73.35; H 3.92; N 12.80. $C_{20}H_{13}N_3O_2$. Calculated, %: C 73.38; H 4.00; N 12.84.

2-Amino-4-(4-methylphenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (3n). Yield 0.97 g (55%). Mp 294-296°C. IR spectrum, ν, cm^{-1}: 3348, 3468 (NH_2), 3213 (C–H), 2212 (CN), 1716 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 7.22 (2H, d, *J* = 8.5, H-3',5'); 7.26 (2H, d, *J* = 8.5, H-2',6'); 7.33 (1H, d, *J* = 8.0, H-7); 7.41 (1H, t, *J* = 8.0, H-9); 7.66 (1H, t, *J* = 8.0, H-8); 8.10 (2H, br. s, NH_2); 8.37 (1H, d, *J* = 8.0, H-10). Mass spectrum, *m/z* (I_{rel}, %): 327 $[M]^+$ (68), 326 (100), 310 (4), 298 (4), 210 (12), 105 (62), 77 (14). Found, %: C 73.33; H 3.95; N 12.82. $C_{20}H_{13}N_3O_2$. Calculated, %: C 73.38; H 4.00; N 12.84.

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