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Synthesis of New Benzo[*h*]- and Benzo[*f*]chromeno[2,3-*b*]-pyridine-5-ones

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ABSTRACT: *A number of new benzo[h]- and benzo[f]chromeno[2,3-b] pyridine-5-ones derivatives were synthesized from benzo[h]- and benzo[f]-chromone-carbonitriles and amino-benzo[h]- and benzo[f]chromone-carbaldehydes.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:2–7, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20152

INTRODUCTION

Several 5-oxo-5H[1]benzopyrano[2,3-*b*]pyridine derivatives have received increased attention due to their medicinal applications particularly as antiallergic and antiulcer drugs [1–7]. However, many benzopyrano[2,3-*b*]pyridine derivatives have been synthesized for pharmacological screening, only few reports on the synthesis of benzo[*h*]- and benzo[*f*]chromeno [2,3-*b*] pyridine-5-ones [2], 2,3-cyclic substituted [8], and 2,3-heterocyclic substituted benzo[*h*]- and benzo[*f*]chromeno [2,3-*b*] pyridine-5-ones [9] have appeared. Prompted by the reported results on the effects of fused aromatic substitution of benzopyrone ring system on the receptor-binding affinity [10] and in view of the structure-activity relationship, we regarded it is interesting to synthesize two angular isomeric naphthpyranopyridine derivatives. Therefore, we report herein the synthesis of new derivatives of benzo[*h*]- and benzo[*f*]chromeno [2,3-*b*] pyridine-5-ones including 2,3-cyclic and 2,3-heterocyclic derivatives.

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RESULTS AND DISCUSSION

Two methods were used to prepare the desired pyridine-containing products starting from benzo[*h*]- and benzo[*f*]chromone-carbonitriles (**1a, 2a**) and amino-benzo[*h*]- and benzo[*f*]chromone-carbaldehydes (**1b, 2b**) (Fig. 1).

As summarized in Scheme 1, one method involves reaction of **1a, 2a** with enamines to give pyridine derivatives **3–5**.

However, the reaction of enamines with 3-formylchromones is well documented [11,12]. There is no report on their reaction with the 3-cyano analogs so far. Therefore, we envisioned that enamines as Michael donors [13] could be reacted with **1a, 2a** [3,14] as the Michael acceptor. Then, such a reaction could lead to a convergent approach for constructing several new benzo[*h*]- and benzo[*f*]-chromeno [2,3-*b*] pyridine-5-one derivatives.

Prompted by these observations, the reaction of **1a, 2a** with different enamines was investigated. Thus, on being heated with ethyl 3-aminocrotonate, 4-amino-3-penten-2-one and 6-aminouracil in DMF at 80°C, the nitriles **1a, 2a** gave pyridine derivatives **3–5** (Scheme 1).

With analogy to previous reports [9,15], the mechanism of formation of the pyridine derivatives may proceed via the Michael addition of enamines to the α-β unsaturated nitrile. However, the anticipated Michael addition of e.g. ethyl 3-aminocrotonate to **1a**

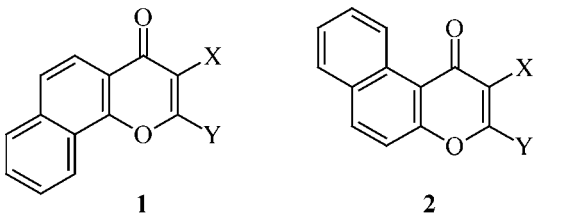
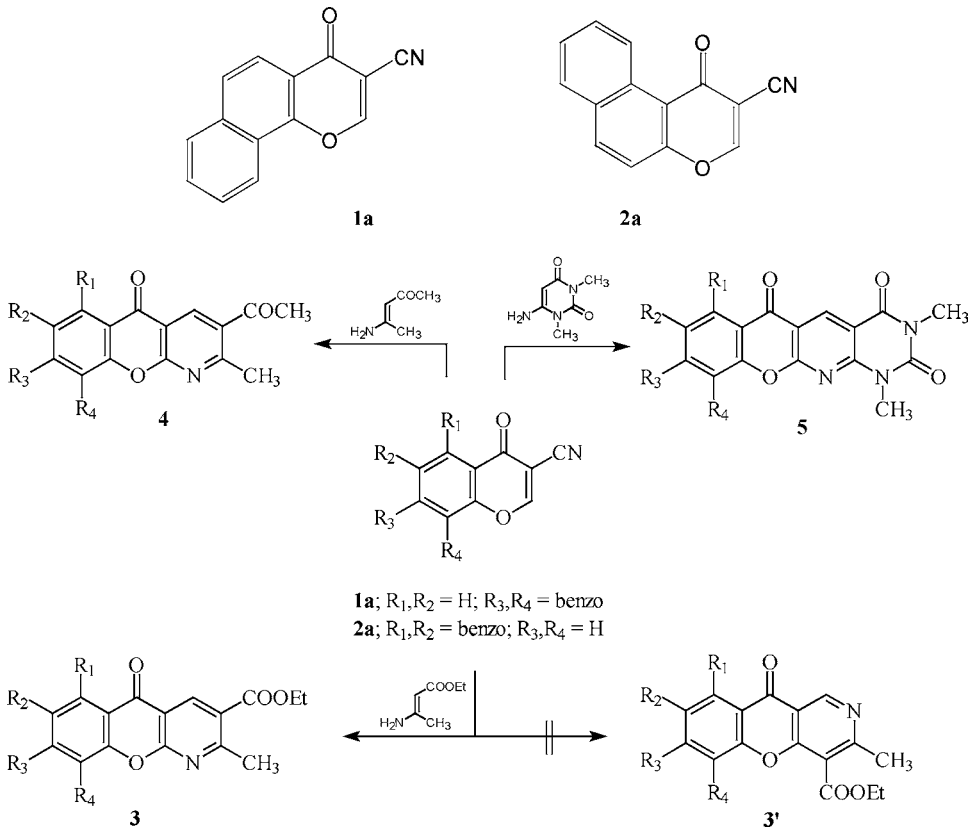


FIGURE 1

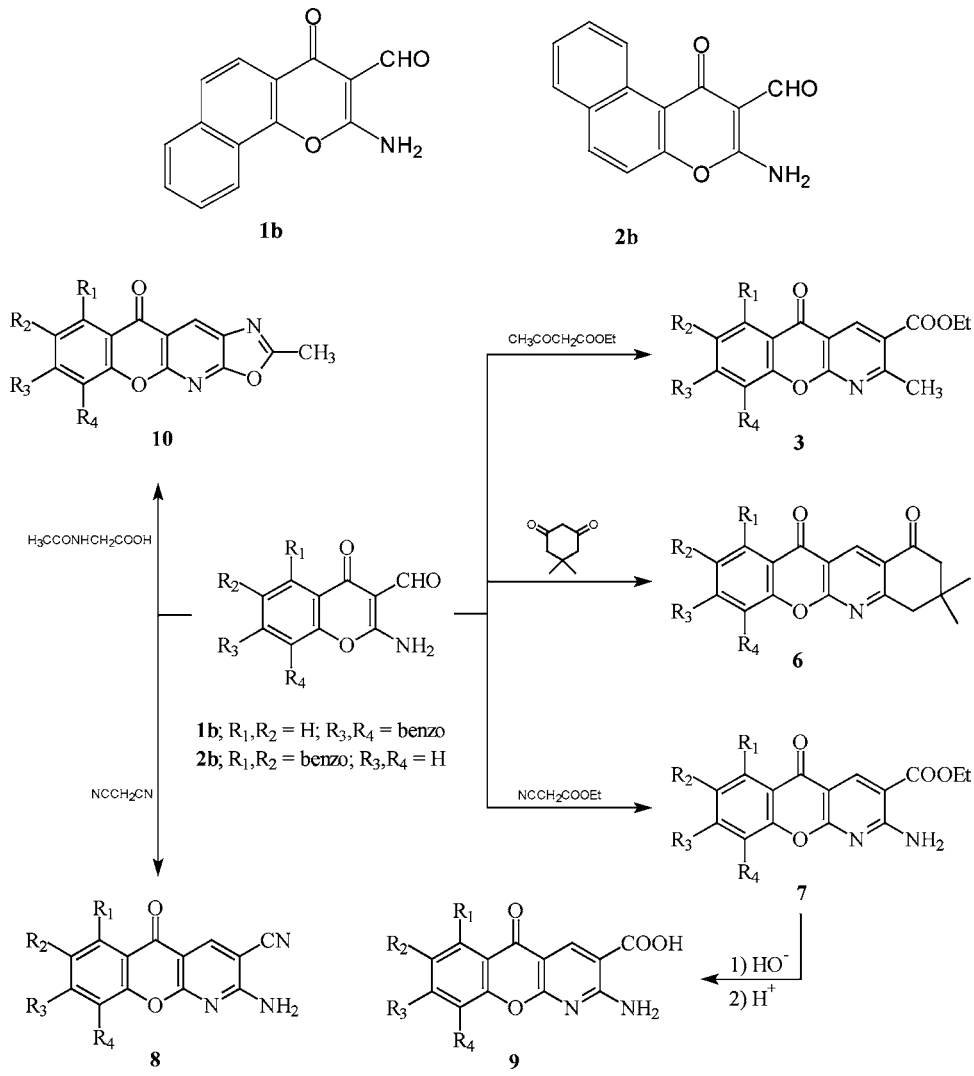
could take a different course as well; the former reacting as true Michael donor (C-nucleophile) to give compound **3** or alternatively, as N-nucleophile attacking the nitrile group that gives rise to compound **3′**. Besides to the structure elucidation of **3** via the support of spectral analysis including ^{1}H NMR, IR, and MS, the structure of compound **3** was unambiguously proved by its independent synthesis through the reaction of compound **2** with ethyl acetoacetate. The products obtained from both cyclocondensation are identical.

The second method for the preparation of pyridine compounds was achieved using amino-benzo[*h*]- and benzo[*f*]chromone-carbaldehydes **1b, 2b** [2], which was efficiently prepared from benzo[*h*]- and benzo[*f*]chromone-carbaldehydes [16] by heating their oximes in aqueous NaOH [17] in 80–83% yield. Since the compounds **1b, 2b** were thought to be valuable starting materials for heterocycles, we explored the synthesis of pyridine derivatives from **1b, 2b** by their reactions with reactive methylene compounds such as dimedone, ethyl acetoacetate, ethyl cyanoacetate, and malononitrile in ethanol–piperidine mixture. Apart from the mentioned procedure, the reaction of **1b** with ethyl cyanoacetate or malononitrile was performed exclusively by refluxing in pyridine.

Benzopyranopyridine carboxylic acid derivatives are of particular interest as they are analogs of antiallergic drugs [5]. Therefore, hydrolysis of the amino esters **7** in ethanolic sodium hydroxide afforded the desired amino acids **9** in good yield. It was possible to form an additional heterocyclic system by refluxing **1b, 2b** with acetyl glycine in acetic anhydride containing fused sodium acetate [9], which afforded the oxazole-benzopyrano pyridine derivatives **10** (see Scheme 2).



SCHEME 1



SCHEME 2

EXPERIMENTAL

Melting points are uncorrected. NMR, IR, and mass spectra were recorded using Varian XL-200 MHZ, Mattson 5000 FTIR spectrometer, and GC-MS cef-1000 Ex Shimadzu (Japan). Analytical TLC was performed on aluminum sheets (Merck, silica gel 60 F-254, thickness 0.2 mm). Solvents were distilled off before use. The nitriles **1a, 2a** were prepared according to [3].

*Synthesis of Benzo-chromeno Pyridines (***3a,b, 4a,b, 5a,b***)*

General Procedure A. A solution of **1a** or **2a** (0.5 g, 2.26 mmol) and ethyl 3-aminocrotonate (0.88 g, 6.79 mmol) or 4-amino-3-penten-2-one (0.67 g, 6.79 mmol) was heated in DMF at 80°C for 9 h. The formed precipitate was filtered off, dried, and washed with ethanol or recrystallized.

Ethyl 10-methyl-7-oxo-7H-benzo[7,8]chromeno-[2,3-b]pyridine-9-carboxylate **3a**. (Prepared from **1a** and ethyl 3-aminocrotonate). After pouring the reaction mixture on to ice/water, the formed precipitate was recrystallized from EtOH–$CHCl_3$ (1:1); Yield 60%, mp 330°C; IR: ν = 1670 (COOEt), 1650 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.25 (s, 1H), 8.85–7.65 (m, 6H, Ar-H), 4.45 (q, 2H, OCH_2—), 2.95 (s, 3H, Ar-CH_3), 1.45 (t, 3H, —CH_3). Anal. Calcd for $C_{20}H_{15}NO_4$ (333.343) C, 72.06; H, 4.54; N, 4.20%. Found: C, 72.01; H, 4.25; N, 4.05%.

Ethyl-9-methyl-12-oxo-12H-benzo[5,6]chromeno-[2,3-b]pyridine-10-carboxylate **3b**. (Prepared from

2a and ethyl 3-aminocrotonate). After pouring the reaction mixture on to ice/water, the formed precipitate was recrystallized from EtOH–$CHCl_3$ (1:1); Yield 70%, mp 170°C; IR: ν = 1669 (COOEt), 1649 (CO) cm^{-1}; ^1H NMR (DMSO): δ = 9.99 (d, 1H, Ar-H), 9.3 (s, 1H), 8.2–7.61 (m, 5H, Ar-H), 4.4 (q, 2H, O–CH_2—), 3.01 (s, 3H, Ar-CH_3), 1.49 (t, 3H, CH_3). Anal. Calcd for $C_{20}H_{15}NO_4$ (333.343) C, 72.06; H, 4.54; N, 4.20%. Found: C, 72.15; H, 4.35; N, 4.18%.

3a and **3b** were also prepared according to general procedure B via reaction of **1b**, **2b** with ethyl acetoacetate (yield 60%, 70% respectively). mp, TLC, IR, and ^1H NMR were identical with that obtained by general procedure A.

9-Acetyl-10-methyl-7H-benzo[7,8]chromeno[2,3-b]pyridine-7-one **4a**. (Prepared from **1a** and 4-amino-3-pentene-2-one). Yield 60%; mp 325°C; IR: ν = 3183, 3000 (=CH), 1748 (—$COCH_3$), 1667 (CO) cm^{-1}; ^1H NMR (DMSO): δ = 9.5 (s, 1H), 8.5–7.7 (m, 6H, Ar-H), 2.77 (s, 3H, Ar-CH_3), 2.64 (s, 3H, CH_3CO); MS: *m/z* (%): 303 (M^+, 4.8), 288 (3.07), 207 (15.8), 179 (11.6), 151 (7.49). Anal. Calcd for $C_{19}H_{13}NO_3$ (303.315): C, 75.24; H, 4.32; N, 4.62%. Found: C, 75.40; H, 4.15; N, 4.45%.

10-Acetyl-9-methyl-12H-benzo[5,6]chromeno[2,3--b]pyridine-10-carboxylate-12-one **4b**. (Prepared from **2a** and 4-amino-3-pentene-2-one). Yield 70%, mp 300°C; IR: ν = 1760 (—$COCH_3$), 1650 (CO) cm^{-1}; ^1H NMR(DMSO): δ = 9.8 (d, 1H, Ar-H), 9.5 (s, 1H), 8.7–7.4 (m, 5H, Ar-H), 2.83 (s, 3H, Ar-CH_3), 2.65 (s, 3H, CH_3CO); MS: *m/z* (%): 303 (M^+, 67.86), 288 (100), 260 (17.76). Anal. Calcd for $C_{19}H_{13}NO_3$ (303.315): C, 75.24; H, 4.32; N, 4.62%. Found: C, 75.45; H, 4.22; N, 4.53 %.

10,12-Dimethyl-9,10,11,12-tetrahydro-7H-benzo-[7′,8′]chromeno[2′,3′:2,3] pyrido[6,5-d]pyrimidine-7,8,11-trione **5a**. (Prepared from **1a** and 6-aminouracil). **5a** was prepared according to the general procedure A using an equimolar quantities of **1a** and 6-aminouracil (0.29 g, 2.26 mmol); yield 80%, mp 305°C; IR: ν = 1717 (2CO), 1665 (CO) cm^{-1}; ^1H NMR (DMSO): δ = 8.9 (s, 1H), 8.2–7.6 (m, 6H, Ar-H), 3.5 (s, 3H, N-CH_3), 3.3 (s, 3H, N-CH_3); MS: *m/z* (%): 359 (M^+, 100), 330 (24.4), 247 (44.7). Anal. Calcd for $C_{20}H_{13}N_3O_4$(359.339): C, 66.85; H, 3.65; N, 11,69%. Found: C, 66.94; H, 4.45; N, 11.34%.

9,11-Dimethyl-9,10,11,12-tetrahydro-14H-benzo-[5′,6′]chromeno[2′,3′:2,3]pyrido[6,5-d]pyrimidine-10,12,14-trione **5b**. (Prepared from **2a** and 6-aminouracil). **5b** was prepared according to the general procedure A using an equimolar quantities of **2a** and 6-aminouracil (0.29 g, 2.26 mmol); yield 70%, mp above 350°C; IR: ν = 1719 (CO), 1660 (CO) cm^{-1}; ^1H NMR (DMSO): δ = 9.54 (d, 1H, Ar-H), 9.5 (s, 1H), 8.5–7.6 (m, 5H, Ar-H), 3.5 (s, 3H, N-CH_3), 3.2 (s, 3H, N-CH_3); MS: *m/z* (%): 359 (M^+, 100), 330 (9.27), 247 (16.91). Anal. Calcd for $C_{20}H_{13}N_3O_4$ (359.339): C, 66.85; H, 3.65; N, 11.6%. Found: C, 66.91; H, 3.34; N, 11.47%.

*Synthesis of Benzo-chromeno-pyridines (***6a,b, 7a,b, 8a,b***)*

General procedure B. A mixture of 2-amino-3-formyl naphthopyrone **1b** or **2b** (0.5 g, 2.09 mmol) and the reactive methylene compounds [ethyl acetoacetate (0.027 mL, 2.09 mmol) or dimedone (0.029 g, 2.09 mmol) or ethyl cyanoacetate (0.22 mL, 2.09 mmol) or malononitrile (0.14 g, 2.09 mmol)] with drops of piperidine was refluxed in ethanol for 9 h. The formed precipitate was filtered off, dried, and recrystallized from the proper solvent.

11,11-Dimethyl-9,10,11,12-tetrahydro-7H-benzo-[7,8]chromeno[2,3-b]quinoline-7,9-dione **6a**. (Prepared from **1b** and dimedone). Recrystallization from EtOH—$CHCl_3$ (1:1); yield 60%, mp 270°C; IR: ν = 2959 (CH_3), 1690 (CO), 1600 (CO) cm^{-1}; ^1H NMR (DMSO): δ = 9.35 (s, 1H), 8.75–7.7 (m, 6H, Ar-H), 3.25 (s, 2H, H-C_{12}), 2.65 (s, 2H, —CH_2—), 1.25 (s, 6H, $2CH_3$). Anal. Calcd for $C_{22}H_{17}NO_3$ (343.380): C, 76.95; H, 4.99; N, 4.08%. Found: C, 76.74; H, 4.55; N, 4.03%.

10,10-Dimethyl-9,10,11,12-tetrahydro-14H-benzo-[5,6]chromeno[2,3-b]quinoline-12,14-dione **6b**. (Prepared from **2b** and dimedone). Recrystallization from $CHCl_3$; Yield 70%, mp 275°C; IR: ν = 2960 (CH_3), 1690 (CO), 1648 (CO) cm^{-1}; ^1H NMR (DMSO): δ = 9.98 (d, 1H, Ar-H), 9.35 (s, 1H), 8.2–7.61 (m, 5H, Ar-H), 3.16 (s, 2H, —CH_2—), 2.65 (s, 2H, —CH_2—), 1.18 (s, 6H, $2CH_3$). Anal. Calcd for $C_{22}H_{17}NO_3$ (343.380): C, 76.95; H, 4.99; N, 4.08%. Found: C, 76.81; H, 4.74; N, 4.00%.

Ethyl 9-amino-12-oxo-12H-benzo[5,6]chromeno-[2,3-b]pyridine-10-carboxylate **7b**. (Prepared from **2b** and ethyl cyanoacetate). Recrystallization from DMF; yield 70%, mp 275°C; IR: ν = 3277, 3168 (NH_2), 1670 (COOEt), 1660 (CO) cm^{-1}; MS: *m/z* (%): 334 (M^+, 100), 306 (8), 289 (22), 262 (25), 234 (8), 170 (8), 130 (5), 52 (3). Anal. Calcd for $C_{19}H_{14}N_2O_4$ (334.329): C, 68.26; 4.22; N, 8.38%. Found: C, 68.14; H, 4.20, N, 8.1%.

10-Amino-12-oxo-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile **8b**. (Prepared from **2b** and malononitrile). Recrystallization from EtOH–DMF (1:1); yield 50%, mp above 350°C; IR: $\nu = 3393$, 3318 (NH_2), 2221 (CN), 1650 (CO) cm^{-1} ; MS *m/z* (%): 287 (M^+, 100), 259 (35.4), 231 (6), 193 (5.2), 126 (5.5), 114 (9.97). Anal. Calcd for $C_{17}H_9N_3O_2$ (287.276): C, 71.08; H, 3.16; N, 14.63%. Found: C, 71.18; H, 3.05; N, 14.44%.

Ethyl 10-Amino-7-oxo-7H-benzo[7,8]chromeno-[2,3-b]pyridine-9-carboxylate **7a**. (Prepared from **1b** and ethyl cyanoacetate). **7a** was prepared according to the general procedure B using six-fold excess of ethyl cyanoacetate (1.3 mL, 12.54 mmol) in refluxing pyridine; recrystallization from EtOH–$CHCl_3$ (1:1); yield 90%, mp 295°C; IR: $\nu = 3277$–3167 (NH_2), 1699 (COOEt), 1665 (CO) cm^{-1}; ^1H NMR (DMSO): $\delta =$ 8.9 (s, 1H), 8.5 (br, 2H,NH_2), 8.2–7.75 (m, 6H, Ar-H), 4.4 (q, 2H, OCH_2—), 1.4 (t, 3H, —CH_3); MS: *m/z* (%) 334 (M^+, 100), 306 (7.3), 289 (18.58), 170 (8.02), 114 (1.91). Anal. Calcd for $C_{19}H_{14}N_2O_4$ (334.329): C, 68.26; H, 4.22; N, 8.38%. Found: C, 68.41; H, 4.15; N, 8.26%.

10-Amino-7-oxo-7H-benzo[7,8]chromeno[2,3-b]-pyridine-9-carbonitrile **8a**. (Prepared from **1b** and malononitrile). **8a** was prepared according to the general procedure B using six-fold excess of malononitrile (0.83 g, 12.54 mmol) in refluxing pyridine; recrystallization from EtOH–DMF (1:1); yield 80%, mp 325°C; IR: $\nu = 3393$, 3318 (NH_2), 2224 (CN), 1653 (CO) cm^{-1}; ^1H NMR (DMSO): $\delta = 8.87$ (s, 1H), 8.45 (d, 1H, Ar-H), 8.25 (sb, 2H, NH_2), 8.15–7.7 (m, Ar-H). Anal. Calcd for $C_{17}H_9N_3O_2$ (287.276): C, 71.08; H, 3.16; N, 14.63%. Found: C, 71.15; H.3.09; N, 14.47%.

Synthesis of Amino-benzo-chromeno-pyridine-carboxylic Acid **9a,b**

A mixture of **7a** or **7b** (1 g, 2.9 mmol) and 0.5 N NaOH (17mL) in EtOH (60 mL) was refluxed with stirring for 2.5 h. The reaction mixture was acidified with 10% N HCl. The precipitate was collected by filtration, washed with H_2O, dried, and recrystallized.

10-Amino-7-oxo-7H-benzo[7,8]chromeno[2,3-b]-pyridine-9-carboxylic Acid **9a**. (Prepared from **7a**). Recrystallization from DMF–EtOH (1:1); yield 80%, mp above 350°C; IR: $\nu = 3277$, 3167 (NH_2), 1699 (COOEt), 1655 (CO) cm^{-1}; MS: *m/z* (%): 306 (M^+, 100), 288 (25, M^+-H_2O), 262 (20, M^+-CO_2), 231 (8), 177 (5), 170 (10), 114 (5), 88.2 (4). Anal. Calcd for $C_{17}H_{10}N_2O_4$ (306.275): C, 66.67; H, 3.29; N, 9.15%. Found: C, 66.34; H, 3.16; N, 9.06%.

9-Amino-12-oxo-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carboxylic Acid **9b**. (Prepared from **7b**). Recrystallization from DMF–EtOH (1:1); yield 70%, mp above 350°C; IR: $\nu =$ 3295–3188 (NH_2), 1690 (COOH), 1650 (CO) cm^{-1}, MS: *m/z* (%): 306 (M^+,100), 288 (25, M^+-H_2O), 262 (20, M^+-CO_2), 231 (8), 177 (5). Anal. Cald for $C_{17}H_{10}N_2O_4$ (306.275): C, 66.67; H, 3.29; N, 9.15%. Found: C, 66.46; H, 3.20; N, 9.07%.

Synthesis of Benzo-chromeno-pyrido-oxazolone **10a,b**

A mixture of **1b** or **2b** (0.5 g, 2.09 mmol), *N*-acetylglycine (0.24 g, 2.09 mmol), and fused sodium acetate (0.37 g, 4.52 mmol) was refluxed in acetic anhydride (15 mL) for 3 h. The reaction mixture was poured onto ice/water; the formed precipitate was filtered off and recrystallized.

10-Methyl-7H-benzo[7′,8′]chromeno[2′,3′:2,3]-pyrido[6,5-d][1,3]oxazol-7-one **10a**. (Prepared from **1b**). Recrystallization from $CHCl_3$; yield 70%, mp 280°C; IR: $\nu = 3304$ (CH), 1635 (CO) cm^{-1}; ^1H NMR (DMSO): $\delta = 8.99$ (s, 1H), 8.81–7.76 (m, Ar-H), 2.78 (s, 3H,CH_3). Anal. Calcd for $C_{18}H_{10}N_2O_3$ (302.287): C, 71.52; H, 3.33;N, 9.27%. Found: C, 71.69; H, 3.24; N, 9.17%.

10-Methyl-13H-benzo[5′,6′]chromeno[2′,3′:2,3]-pyrido[6,5-d][1,3]oxazol-13-one **10b**. (Prepared from **2b**). Recrystallization from EtOH–$CHCl_3$ (1:1); yield 70%, mp 273°C; IR: $\nu = 3078$ (C–H), 1640 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 10.04$ (d, 1H, Ar-H), 9.03 (s, 1H), 8.21–7.62 (m, Ar-H), 2.76 (s, 3H, CH_3). Anal. Calcd for $C_{18}H_{10}N_2O$ (302.287): C, 71.52; H, 3.33;N, 9.27%. Found: C, 71.67; H, 3.15; N, 9.21%.

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