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Studies on the chemical reactivity of 1*H*-benzimidazol-2-ylacetonitrile towards some 3-substituted chromones: synthesis of some novel pyrido[1,2-*a*]benzimidazoles

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ABSTRACT

A simple and convenient synthesis of a novel series of pyrido[1,2-*a*]benzimidazoles was efficiently achieved from the condensation reactions of 1*H*-benzimidazol-2-ylacetonitrile (**1**) with some 3-substituted chromones, chromone-3-carboxylic acids, chromone-3-carboxamides, ethyl chromone-3-carboxylates and chromone-3-carbonitriles. Reaction of compound **1** with 2-aminochromone-3-carboxaldehydes produced 2-amino-3-(1*H*-benzimidazol-2-yl)chromeno[2,3-*b*]pyridines. The reaction mechanisms and spectral data were also discussed.

1. Introduction

Chromones are widely distributed in nature and are a well studied class of organic compounds.[1–4] The chemical reactivity of 3-substituted chromones towards nucleophilic reagents is widely different depending on the nature of substituents at position 3 and reaction conditions. The introduction of an electron-withdrawing group; COOH, COOEt, $CONH_2$ and CN at position 3 of the chromone system changes the reactivity of the γ-pyrone ring with respect to nucleophiles, and provides a broad synthetic potential of 3-substituted chromones.[5–11] The diversity of properties of these compounds is due to the fact that, are highly reactive geminally activated push–pull alkenes (α,β-unsaturated ketones) with a good leaving group at the β-carbon atom. 3-Substituted chromones have the ability to undergo a nucleophilic 1,4-addition at position 2 followed by further transformations related to γ-pyrone ring opening and heterocyclizations at the C-4 atom and/or at the substituent in position 3. The reaction of 1*H*-benzimidazol-2-ylacetonitrile (**1**) with some 3-formylchromones gave 4-cyano-2-(2-hydroxybenzoyl)pyrido[1,2-*a*]benzimidazoles as previously published.[12]

2. Results and discussion

The present work aimed to study the chemical behaviour of 1*H*-benzimidazol-2-ylacetonitrile (**1**) towards a variety of 3-substituted chromones. Thus, treatment of chromone-3-carboxylic acids **2a**,**b**[13] with compound **1**, in boiling ethanol containing few drops of triethylamine as a basic catalyst, afforded the novel pyrido[1,2-*a*]benzimidazole-4-carbonitriles (**3a**,**b**). The reaction proceeds via deprotonation of compound **1** to produce carbanion **A**, which underwent 1,4-Michael addition at C-2 position in carboxylic acids **2** to produce intermediates **B**. Intermediates **B** undergo retro-Michael addition with γ-pyrone ring opening, generating intermediates **C**, with concomitant decarboxylation to give α,β-unsaturated ketones **D**.[10] The latter intermediates **D** underwent intramolecular dehydration giving rise the final products **3a**,**b**; presumption through reactive intermediates **E** as illustrated in Scheme 1. The structures of compounds **3a**,**b** were further deduced from their authentic synthesis via reaction of 1*H*-benzimidazol-2-ylacetonitrile (**1**) with chromone **4a** and 6-methylchromone **4b**, respectively. The latter reactions confirm the decarboxylation of compounds **2a**,**b** during the course of reactions.[10] The structures of compounds **3a**,**b** were deduced from their elemental analysis and spectral data. The IR spectra of compounds **3a** and **3b** showed characteristic absorption bands attributed to the nitrile functions at 2231 cm^{-1}. The mass spectra of compounds **3a** and **3b** showed the molecular ion peaks, as the base peaks at *m*/*z* 285 and 299, which is coincident with the

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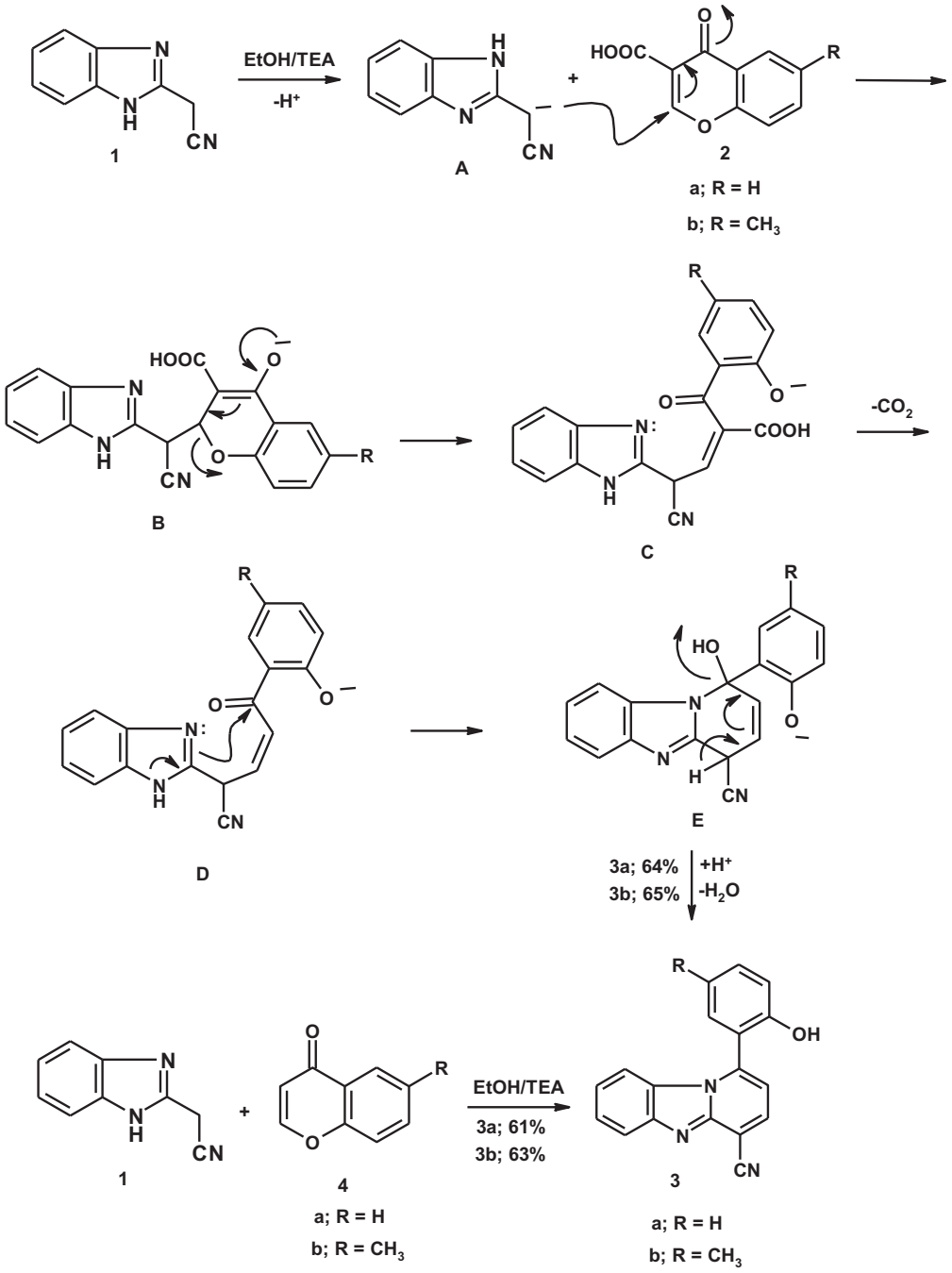
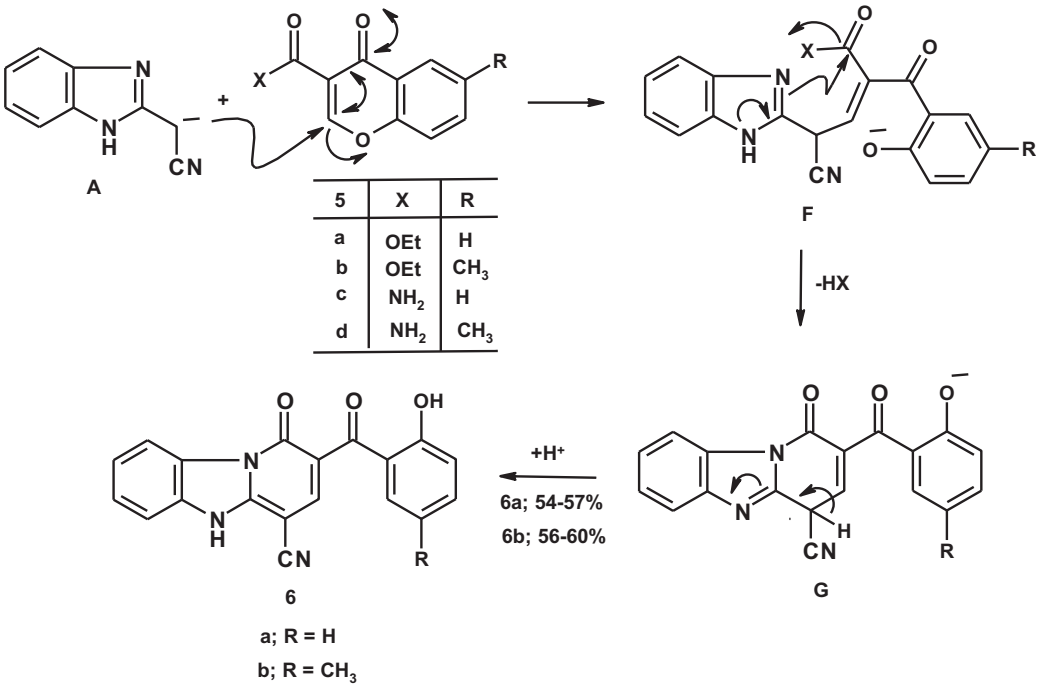


Scheme 1. Reactions of compound **1** with chromone-3-carboxylic acids **2a**,**b** and chromones **4a**,**b**.

formula weights and support the identity of the structures. Furthermore, the ^{13}C NMR spectrum of compound **3b** showed characteristic singlet signals at δ 19.9 and 114.3 ppm, assigned to the methyl and cyano carbons, respectively.

On the other hand, treating ethyl chromone-3-carboxylates **5a**,**b**[13] and chromone-3-carboxamides **5c**,**d**[8] with 1*H*-benzimidazol-2-ylacetonitrile (**1**), in boiling ethanol containing few drops of triethylamine, produced pyrido[1,2-*a*]benzimidazoles **6a**,**b**. The reactions proceed via deprotonation of compound **1**, intermediate **A**, which underwent nucleophilic attack at C-2 position with γ-pyrone ring opening of compounds **5a**–**d** to produce intermediates **F**. Cyclocondensation of the latter intermediates **F**, via loss of ethanol or ammonia molecules, afforded the target compounds **6a**,**b** as depicted in Scheme 2. The IR spectra of compounds **6a** and **6b** showed characteristic absorption bands at 2235/2231 and 1670/1680 cm^{-1}, attributed to the C≡N and $C{=}O_{pyridone}$ functions, respectively. The ^1H NMR spectra showed characteristic singlets at δ 8.78 and 9.09 ppm assigned to the H-$4_{pyridine}$ in compounds **6a** and **6b**, respectively. Furthermore, the mass spectrum of compound **6a** showed the molecular ion peak at *m*/*z* 329, which agrees with the molecular formula ($C_{19}H_{11}N_3O_3$) and supports the structure.

Next, the chemical behaviour of compound **1** towards chromone-3-carbonitriles **7a**,**b**[14] was studied under basic conditions. Thus, reaction of compound **1** with chromone-3-carbonitrile **7a**,[15] in boiling ethanol containing few drops of triethylamine, gave the novel angular heteroannulated chromone identified as chromeno[2,3:6,5]pyrido[1,2-*a*]benzimidazole-6-carbonitrile **8a**, the other expected product **9a** was ruled out on the basis of the spectral data



Scheme 2. Reactions of compound **1** with chromone derivatives **5a**–**d**.

(Scheme 3). The reaction of compound **1** with 6-methylchromone-3-carbonitrile **7b** showed different behaviour and the reaction proceeds in a different mechanism producing 2-amino-3-(1*H*-benzimidazol-2-yl)-7-methyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (**9b**) (Scheme 3). The formation of compound **9b** rather than **8b** may be attributed to the electron donating nature of the methyl group in compound **7b**, which could increase the nucleophilicity of the phenolate anion as compared with the $NH_{imidazole}$ group. Compound **9b** was obtained from the reaction of compound **1** with 2-amino-6-methylchromone-3-carboxaldehyde (**10b**)[16] under the same reaction conditions. Similarly, compound **9a** was obtained from the reaction of compound **1** with 2-aminochromone-3-carboxaldehyde (**10a**) (Scheme 3).[16,17] The IR spectrum of compound **8a** showed characteristic absorption bands at 2234 and 1657 assigned to (C≡N) and ($C{=}O_{\gamma\text{-pyrone}}$), respectively. The ^{1}H NMR spectrum of compounds **8a** showed characteristic singlet signal at δ 8.79 ppm, assigned to the H-$4_{pyridine}$. Its mass spectrum showed the molecular ion peak, as the base peak, which is coincident with the formula weight (311.30) and confirms the structure. The ^{1}H NMR spectra of compounds **9a** and **9b** showed exchangeable signals attributed to the NH_2 and NH protons, in addition to characteristic singlet signals at δ 8.44 ppm, assigned to the H-$4_{pyridine}$. The mass spectrum of compound **9b** showed the molecular ion peak, as the base peak, at *m*/*z* 342, which agrees well with the formula weight (342.35) and confirms the identity of the structure.

3. Experimental

3.1. General

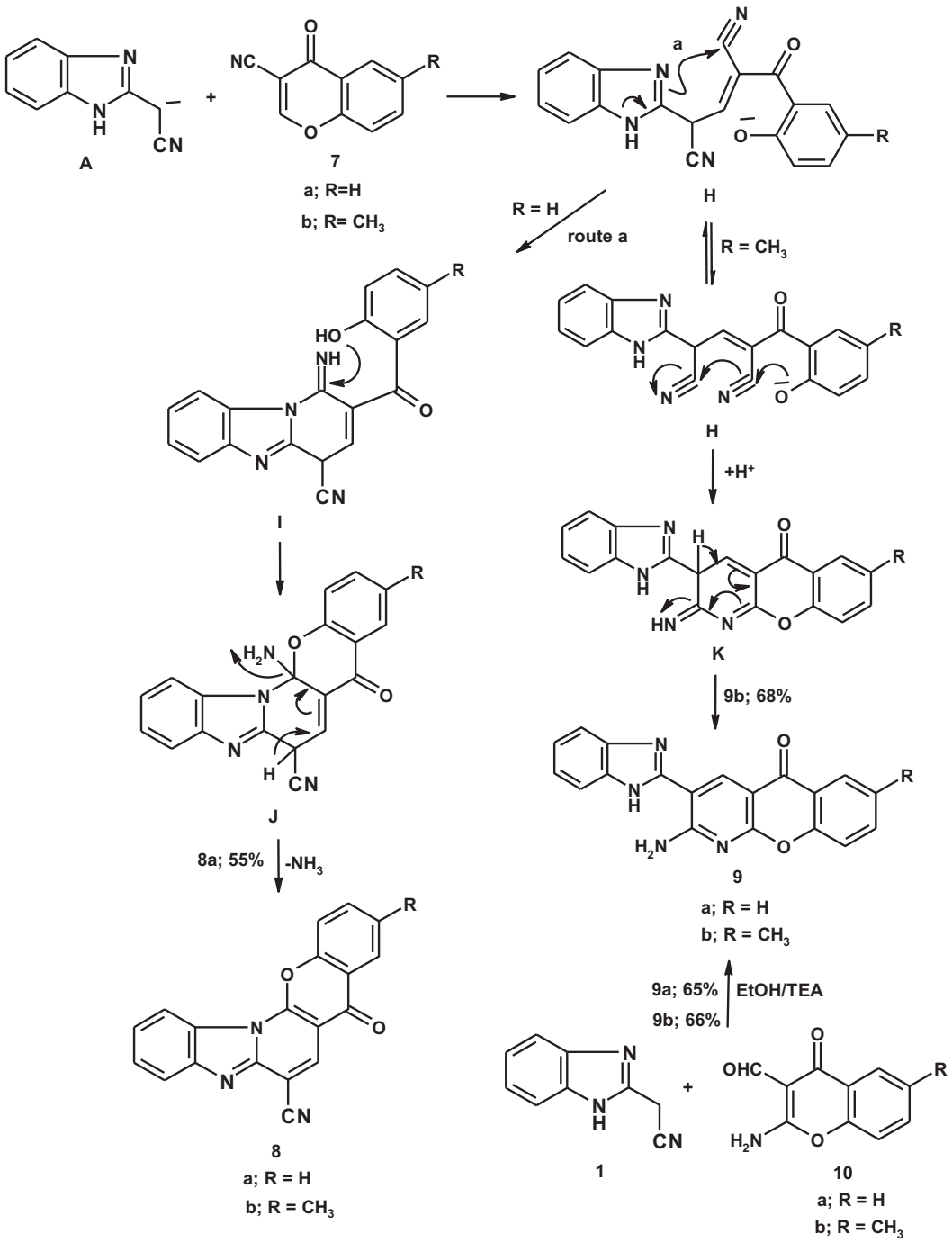
Melting points are uncorrected and were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on a Perkin–Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB spectrometers and Jeol Eca-500 MHz, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC–MS qp 1000 ex Scheimadzu instrument (70 eV). Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer.

3.2. General procedure for the reaction of 1*H*-benzimidazol-2-ylacetonitrile (1) with 3-substituted chromones

To a solution of 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute ethanol (10 mL) containing two drops of triethylamine, a solution of chromone derivatives **2**, **4**, **5**, **7** and/or **10** (2 mmol) in absolute ethanol (15 mL) was added and the reaction mixture was heated at reflux for 30 min. The yellow crystals obtained after cooling were filtered off and recrystallized from DMF to give compounds **3**, **6**, **8** and **9**, respectively.

*3.2.1. 1-(2-Hydroxyphenyl)pyrido[1,2-a]benzimidazole-4-carbonitrile (**3a**).* Yield (61–64%), mp 296 °C. IR (KBr, cm^{-1}): 3421 (OH), 3073 ($CH_{arom.}$), 2231 (C≡N), 1628 (C=N), 1609 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.71 (d, *J*=9.0 Hz, 1H, Ar–H), 6.98 (d, *J*=7.2 Hz, 1H, Ar–H), 7.10–7.17 (m, 3H, Ar–H), 7.45–7.58 (m, 3H, Ar–H), 7.92 (d, *J*=8.1 Hz, 1H, Ar–H), 8.33 (d, *J*=7.2 Hz, 1H, Ar–H), 10.20 (br s, 1H, OH exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 98.9, 111.9, 114.1, 115.8, 115.9, 119.4, 119.7, 120.2, 121.6, 126.0, 129.3, 130.1, 132.4, 137.8, 144.1, 144.3, 146.3, 155.4. MS (*m*/*z*, %): 286 (M+1, 17), 285 (M^+, 100), 268 (10), 255 (11), 149 (49), 114 (15), 102 (8), 77 (11) and 64 (12). Anal. Calcd for $C_{18}H_{11}N_3O$ (285.29): C, 75.78; H, 3.89; N, 14.73%. Found: C, 75.53; H, 3.55; N, 14.49%.

*3.2.2. 1-(2-Hydroxy-5-methylphenyl)pyrido[1,2-a]benzimidazole-4-carbonitrile (**3b**).* Yield (63–65%), mp>320 °C. IR (KBr, cm^{-1}): 3446 (OH), 3045 ($CH_{arom.}$), 2920, 2837 ($CH_{aliph.}$), 2231 (C≡N), 1629 (C=N), 1609 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 6.76 (d, *J*=9.0 Hz, 1H, Ar–H), 6.97 (t, *J*=7.5 Hz, 1H, Ar–H), 7.16 (t, *J*=7.2 Hz, 1H, Ar–H), 7.26 (s, 1H, Ar–H), 7.34 (d, 1H, *J*=7.8 Hz, Ar–H), 7.48–7.53 (m, 2H, Ar–H), 7.91 (d, *J*=8.1 Hz, 1H, Ar–H), 8.32 (d, *J*=7.2 Hz, 1H, Ar–H), 10.00 (br s, 1H, OH exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.9, 98.7, 111.8, 114.3, 115.8, 119.3, 119.6, 121.6, 126.0, 128.4, 129.3, 130.1, 132.8, 134.7, 137.8, 144.0,



Scheme 3. Reactions of compound **1** with chromone-3-carbonitriles **7a**,**b** and 2-amino-3-formylchromones **10a**,**b**.

144.5, 146.2, 153.2. MS (*m*/*z*, %): 300 (M+1, 15), 299 (M^+, 100), 282 (26), 163 (49), 91 (14), 77 (20). Anal. Calcd for $C_{19}H_{13}N_3O$ (299.33): C, 76.24; H, 4.38; N, 14.04%. Found: C, 76.03; H, 4.14; N, 13.91%.

*3.2.3. 2-(2-Hydroxybenzoyl)-1-oxo-1,5-dihydropyrido[1,2-a]benzimidazole-4-carbonitrile (**6a**).* Yield (54–57%), mp>320 °C. IR (KBr, cm^{-1}): 3354 (OH), 3174 (NH), 3056 ($CH_{arom.}$) 2235 (C≡N), 1670 (C=$O_{pyridone}$), 1630 (C=$O_{benzoyl}$), 1591 (C=C). ^1H NMR (500 MHz, DMSO-d_6): δ 6.50 (d, J=9.0 Hz, 1H, Ar–H), 7.14 (t, 1H, Ar–H), 7.22 (t, 1H, Ar–H), 7.54–7.56 (m, 3H, Ar–H), 7.58 (t, 1H, Ar–H), 7.97 (d, J=8.4 Hz, 1H, Ar–H), 8.78 (s, 1H, H-$4_{pyridine}$), 10.40 (br s, 1H, OH exchangeable with D_2O), 13.40 (br s, 1H, NH exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 98.8, 114.3, 115.3, 116.1, 118.4, 119.6, 121.0, 122.0, 126.3, 129.8, 130.2, 132.4, 137.4, 142.6, 144.6, 145.7, 155.4, 162.9, 165.8. MS (*m*/*z*, %): 329 (M^+, 2), 311 (100), 282 (10), 254 (17), 228 (5), 155 (12), 127 (19), 114 (18), 76 (11) and 64 (8). Anal. Calcd for $C_{19}H_{11}N_3O_3$ (329.31): C, 69.30; H, 3.37; N, 12.76%. Found: C, 69.51; H, 3.25; N, 12.38%.

*3.2.4. 2-[(2-Hydroxy-5-methylbenzoyl)-1-oxo-1,5-dihydropyrido[1,2-a]benzimidazole-4-carbonitrile (**6b**).* Yield (56–60%), mp>320 °C. IR (KBr, cm^{-1}): 3361 (OH), 3180 (NH), 3061 ($CH_{arom.}$), 2231 (C≡N), 1680 (C=$O_{pyridone}$), 1654 (C=$O_{benzoyl}$), 1617 (C=C). ^1H NMR (300 MHz, DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.26 (br s, 2H, Ar–H),

7.49–7.64 (m, 4H, Ar–H), 7.95 (s, 1H, Ar–H), 9.09 (s, 1H, H-4$_{pyridine}$), 10.15 (br s, 1H, OH exchangeable with D_2O), 13.22 (br s, 1H, NH exchangeable with D_2O). Anal. Calcd for $C_{20}H_{13}N_3O_3$ (343.33): C, 69.96; H, 3.82; N, 12.24%. Found: C, 69.74; H, 3.65; N, 12.35%.

*3.2.5. 8-Oxo-8H-chromeno[2,3:6,5]pyrido[1,2-a]benzimidazole-6-carbonitrile (**8a**).* Yield (55%), mp>320 °C. IR (KBr, cm^{-1}): 3066 (CH$_{arom.}$), 2234 (C≡N), 1657 (C=O$_{\gamma\text{-pyrone}}$), 1596 (C=N and C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.37 (d, J=8.6 Hz, 1H, Ar–H), 7.18 (t, J=8.6 Hz, 1H, Ar–H), 7.55 (t, J=8.0 Hz, 1H, Ar–H), 7.61 (d, J=8.6 Hz, 1H, Ar–H), 7.63 (t, J=7.4 Hz, 1H, Ar–H), 7.77 (d, J=7.4 Hz, 1H, Ar–H), 7.88 (t, J=7.4 Hz, 1H, Ar–H), 7.97 (d, J=8.6 Hz, 1H, Ar–H), 8.79 (s, 1H, H-4$_{pyridine}$). MS (m/z, %): 312 (M+1, 13), 311 (M$^+$, 21), 310 (100), 293 (13), 280 (9), 154 (11), 126 (11), 114 (9) and 77 (5). Anal. Calcd for $C_{19}H_9N_3O_2$ (311.29): C, 73.31; H, 2.91; N, 13.50%. Found: C, 73.53; H, 2.75; N, 13.36%.

*3.2.6. 2-Amino-3-(1H-benzimidazol-2-yl)-5H-chromeno[2,3-b]pyridin-5-one (**9a**).* Yield (65%), mp>320 °C. IR (KBr, cm^{-1}): 3305, 3150 (NH$_2$, NH), 3071 (CH$_{arom.}$), 1645 (C=O$_{\gamma\text{-pyrone}}$), 1629 (C=N), 1614 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.22 (t, J=8.4 Hz, 1H, Ar–H), 7.25 (t, J=8.4 Hz, 1H, Ar–H), 7.45 (t, J=7.6 Hz, 1H, Ar–H), 7.53 (t, J=6.8 Hz, 1H, Ar–H), 7.61 (d, J=7.6 Hz, 1H, Ar–H), 7.68 (t, J=8.4 Hz, 1H, Ar–H), 7.81 (t, J=7.6 Hz, 1H, Ar–H), 8.15 (d, J=7.6 Hz, 1H, Ar–H), 8.44 (s, 1H, H-4$_{pyridine}$), 9.07 (s, 1H, NH exchangeable with D_2O), 9.98 (s, 1H, NH exchangeable with D_2O), 13.36 (s, 1H, NH exchangeable with D_2O). Anal. Calcd for $C_{19}H_{12}N_4O_2$ (328.32): C, 69.51; H, 3.68; N, 17.06%. Found: C, 69.33; H, 3.61; N, 17.08%.

*3.2.7. 2-Amino-3-(1H-benzimidazol-2-yl)-7-methyl-5H-chromeno[2,3-b]pyridin-5-one (**9b**).* Yield (66–68%), mp>320 °C. IR (KBr, cm^{-1}): 3298, 3154 (NH$_2$, NH), 3061 (CH$_{arom.}$), 2913, 2837 (CH$_{aliph.}$), 1651 (C=O$_{\gamma\text{-pyrone}}$), 1633 (C=N), 1614 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, CH$_3$), 7.26–7.29 (m, 2H, Ar–H), 7.54 (t, J=8.7 Hz, 1H, Ar–H), 7.62 (d, 1H, Ar–H), 7.72 (d, 1H, Ar–H), 7.94 (s, 1H, Ar–H), 8.25 (d, 1H, Ar–H), 8.44 (s, 1H, H-4$_{pyridine}$), 9.09 (s, 1H, NH), 9.99 (s, 1H, NH), 13.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.3, 106.3, 110.6, 111.2, 111.7, 114.4, 117.8, 118.5, 120.8, 121.9, 123.2, 125.1, 126.6, 133.9, 135.1, 135.7, 142.4, 149.1, 152.6, 157.2. MS (m/z, %): 343 (M+1, 24), 342 (M$^+$, 100), 325 (41), 313 (17), 253 (5), 208 (11), 117 (6), 107 (11), 91 (8), 77 (20) and 64 (34). Anal. Calcd for $C_{20}H_{14}N_4O_2$ (342.35): C, 70.17; H, 4.12; N, 16.37%. Found: C, 69.84; H, 4.05; N, 16.15%.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.011.

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