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Selective synthesis of some imidazopyridine-fused chromones

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ABSTRACT

A fused heterocyclic scaffold combining the imidazo[1,2-*a*]pyridine with a substituted chromone was synthesized in a one-pot procedure. The reaction proceeds by intramolecular cyclization of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chloride in ethanol and in the presence of DABCO. A detailed study of the experimental conditions allowed a clear understanding of the reaction pathway.

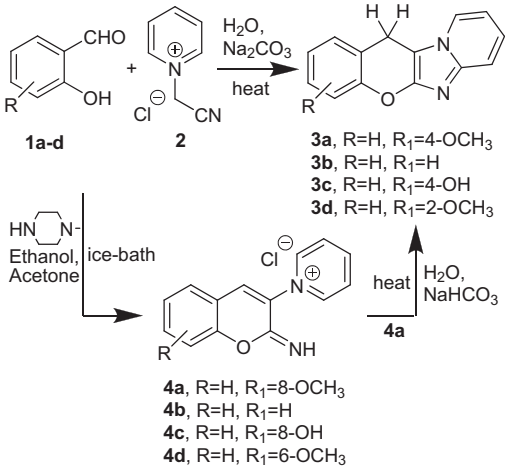
1. Introduction

The flavone ring is a common feature in a number of natural products, namely quercetin, luteolin, apigenin, tangeritin and chrysin, recognized for their antioxidant activity and are widely marketed as nutraceuticals.[1] Numerous positive health effects are associated with flavonoid intake and diverse pharmacological properties have been assigned to these small molecules.[2] Synthetic derivatives incorporating the chromone scaffold have been also reported as anti-HIV agents,[3] calpain inhibitors,[4] inhibitors of NO production,[5] MAO-B inhibitors,[6] anti-inflammatory agents,[7] antibacterial agents,[8] interleukin-5 inhibitors[9] and anticancer agents.[10a–c]

Different synthetic methods are reported in the literature for the formation of chromone derivatives.[2–11] The most frequent synthetic approach uses 2-hydroxyacetophenone as the starting material for aldol condensation, followed by intramolecular cyclization.[3a,5,9,10b] In general, different chemical transformations are performed from an aromatic ring where a carbonyl substituent and a hydroxyl group are present in adjacent positions.

2. Results and discussion

Recent work on the reaction of salicylaldehyde derivative **1** and pyridinium chloride **2** in aqueous sodium carbonate solution, evidenced that this was a new and convenient method to prepare chromeno-imidazo[1,2-*a*]pyridines **3a**–**d** (Scheme 1). The reaction proceeded through the 2-iminochromene **4**, isolated when the reagents were combined in ethanol and acetone, using *N*-methylpiperazine as base.[12]



Scheme 1. Synthetic route for chromeno-imidazo[1,2-*a*]pyridine **3a**–**d** and 1-(2-imino-2*H*-chromen-3-yl)pyridinium chlorides **4a**–**d**.

When 3-methoxysalicylaldehyde **1a** and 1-(cyanomethyl)pyridinium chloride **2** were combined in aqueous sodium carbonate solution, in the presence of 1 M equiv of *N*-methylpiperazine, the

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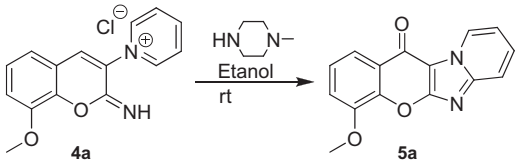
chromone derivative **5** (Table 1) was identified for the first time. Compound **3a** was the major product of this reaction, but a minute amount of compound **5** was detected in the NMR spectrum of the solid isolated after dry flash chromatography.

Table 1
Evolution of compound **4a** in ethanol and in the presence of *N*-methylpiperazine

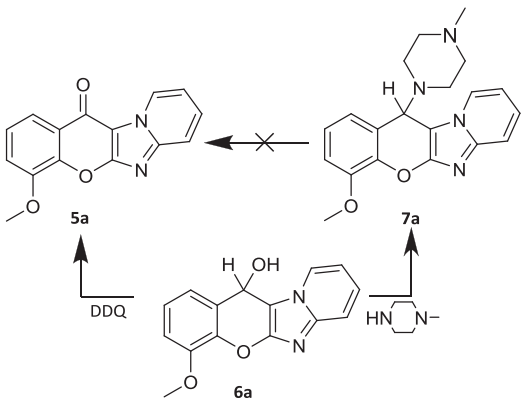


Entry	Base equiv	Reaction conditions	Product, yield
1	1	**4a** 0.6 M in ethanol, 10 °C, 1.5 h	**5a**+**6a**[a]
2	1.1	**4a** 0.6 M in ethanol, 10 °C, 18.5 h	**5a**,[b] 11%
3	1.2	1. **4a** 0.6 M in ethanol, rt, 26 min 2. Mother liquor, rt, 24 h	1. **5a**+**3a**[c] 2. **5a**,[d] 11%
4	1	**4a** 0.6 M in ethanol, 40 °C, 25 min	**5a**, 10%
5	2	**4a** 0.025 M in ethanol, reflux, 2 h 40 min	**5a**+**3a**[e]
6	2	**4a** 0.025 M in ethanol, rt, 3 h	**5a**, 24%
7	3	**4a** 0.025 M in ethanol, rt, 3 h	**5a**, 23%
8	5	**4a** 0.025 M in ethanol, rt, 5 h	**5a**, 29%

[a] Molar ratio (1.3:1), by ^{1}H NMR.
[b] Slightly contaminated with **6a** and **3a** by ^{1}H NMR.
[c] Molar ratio (1:3), by ^{1}H NMR.
[d] Slightly contaminated with **3a** by ^{1}H NMR.
[e] Molar ratio (2.2:1), by ^{1}H NMR.

Considering that the formation of **5** was induced by the presence of amine and that the 2-iminochromene **4** was the common precursor for both products **3** and **5**, a set of experiments was designed in order to optimize the isolated yield of this novel product **5**. Studies were performed on the evolution of compound **4a** in ethanol and *N*-methylpiperazine, under different experimental conditions (Table 1).

The addition of 1 M equiv (or a slight excess) of base to a 0.6 M solution of **4a** in ethanol led to the isolation of **5a** in 10–11% yield when the reaction was performed at 10 °C for 18.5 h (entry 2), at room temperature for 24 h (entry 3) or at 40 °C for 25 min (entry 4). The formation of compound **3a** was a competitive reaction at room temperature or under reflux conditions (entries 3 and 5). At 10 °C, when the product was isolated after 1.5 h, a new structure, identified as **6a** (Scheme 2), was present in the mixture (entry 1).



Scheme 2. Evolution studies by ^{1}H NMR of a solid mixture containing compounds **5a** and **6a**.

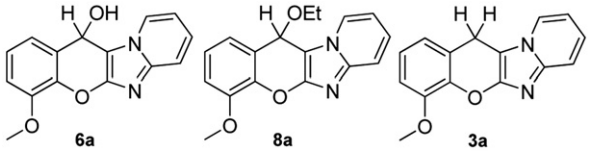
When a dilute solution of **4a** in ethanol was combined with an increasing amount of *N*-methylpiperazine, at room temperature (entries 6–8) the isolated yield of compound **5a** increased to 23–29%. The use of 5 equiv of amine (entry 8) led to the formation of a new side-product, identified as **7a** (Scheme 2).

To understand the poor isolated yield of 12*H*-chromeno [2′,3′:4,5]imidazo[1,2-*a*]pyridin-12-one **5a** and the formation of compounds **6a** and **7a**, a 1:1 mixture of compounds **5a** and **6a** was solubilized in DMSO-d_6 and the ^{1}H NMR spectrum was registered at regular intervals. No evolution was detected after 24 h at 20 °C. When a slight excess of *N*-methylpiperazine was added, the formation of compound **7a** was immediately observed and the solution was kept at room temperature (Scheme 2). The ^{1}H NMR spectrum recorded after 17 days showed a 1:1 mixture of **5a** and **7a**, confirming that, in DMSO solution, the hydroxyl group of compound **6a** was completely replaced by the amine. The formation of compound **5a**, expected to occur from oxidation of **6a**, was not detected. This transformation is faster the presence of an oxidizing agent. This was evident when a 1.2:2 mixture of compounds **5a** and **6a** in DMSO-d_6 was combined with a slight excess of DDQ and the evolution was followed by ^{1}H NMR. After 1 month at room temperature the molar ratio of **5a**/**6a** was 2.5:1, evidencing a slow evolution process (Scheme 2).

A detailed study on the effect of solvent, temperature, concentration of *N*-methylpiperazine and/or starting material (**4a**) was carried out using water, ethanol/water, DMSO, dicloromethane, acetonitrile or acetone. ^{1}H NMR of each product mixture revealed the formation of compound **5a** in a complex reaction mixture. Compound **5a** was isolated as a pure product from acetonitrile, water, or ethanol/water, but the yield never exceeded 20%.

The competitive formation of **7a** was considered a major drawback in the synthesis of **5a**, and the reaction was performed in ethanol, using sodium carbonate as base (Table 2). The use of 1 M equiv of inorganic base led to the formation of **3a** as the major product together with **6a** and **8a** (entry 1). When 5 M equiv of base were added, the formation of **5a** was detected by ^{1}H NMR of the oil obtained after removal of the excess of solid $Na_2CO_3 \cdot H_2O$, followed by removal of the solvent in the rotary evaporator. The product mixture included **6a** as the major component and also **8a** (entry 2). In this case, nucleophilic attack by ethanol was a competing process, leading to the new product.

Table 2
Products identified upon evolution of compound **4a** in ethanol (0.025 M) and in the presence of $Na_2CO_3 \cdot 10H_2O$

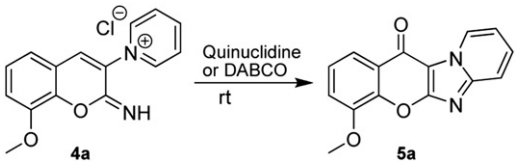


Entry	Base equiv	Reaction conditions	Identified products
1	1	rt, 21 min	Oil: **6a**+**8a**+**3a** (1:1:2.5), slightly contaminated with **5a**[a]
2	5	rt, 3 h 15 min	Oil: **5a**+**6a**+**8a** (1.7:2.6:1)[a]

[a] ^{1}H NMR of the oil obtained after elimination of the solvent in the rotary evaporator.

To overcome the problems associated with the use of *N*-methylpiperazine or sodium carbonate in ethanol, tertiary amines were selected as catalysts for the intramolecular cyclization of **4a** (Table 3). The use of quinuclidine (2–2.7 molar ratio) in ethanol or ethanol/H_2O (40:1) led to the isolation of **5a** in 17% yield (entries 1 and 3). Isopropanol, a bulkier alcohol, was expected to reduce the competitive formation of the **8a** analogue. A complex reaction mixture was formed where **5a** was not identified (entry 2). In THF or dichloromethane/H_2O (80:1), the solid product was always contaminated with **3a** (entries 4 and 5). DABCO proved to be a convenient catalyst for the formation of compound **5a** in ethanol and increasing the amount of base enhanced the isolated yield of **5a** (entries 6–8).

Table 3
Evolution of compound **4a** in different solvents (0.025 M) and in the presence of tertiary amines

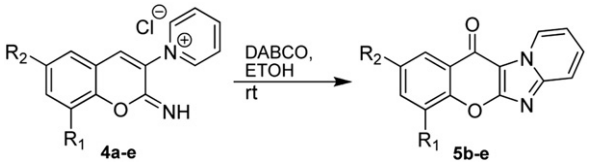


Entry	Base equiv	Reaction conditions	Product, yield
1	Quinuclidine 2 equiv	Ethanol, rt, 3 h	**5a**, 17%[a]
2	Quinuclidine 2.1 equiv	Isopropyl alcohol, rt, 6.5 h	Complex mixture
3	Quinuclidine 2.2 equiv	Ethanol+H_2O (40:1), rt, 21 h	**5a**, 17%
4	Quinuclidine 2.5 equiv	1. THF, rt, 20 h 2. 50 °C, 7 days	**5a**+**3a** (2:1)
5	Quinuclidine 2.7 equiv	1. DCM+H_2O (80:1), rt, 17 h	**5a**+**6a**+**3a** (32:1:10)
6	DABCO 2.5 equiv	Ethanol, rt, 18 h	**5a**, 41%[b]
7	DABCO 5.7 equiv	Ethanol, rt, 16 h	**5a**, 49%
8	DABCO 10 equiv	Ethanol, rt, 16 h	**5a**, 63%[c]

[a] After elimination of the solvent in the mother liquor, the oil was identified as a mixture of **5a**, **6a** and **8a** (1.2:1:1.8), by ^{1}H NMR.
[b] After elimination of the solvent in the mother liquor, the oil was identified as a mixture of **5a**, **4a** and **8a** (5:1.2:1), by ^{1}H NMR.
[c] Yield after combining the first and second crop; the second crop was isolated from the mother liquor after staying for 3 days at 0 °C.

The experimental conditions selected for the synthesis of 12*H*-chromeno[2′,3′:4,5]imidazo[1,2-*a*]pyridin-12-one **5** included the use of DABCO (10–15 M equiv) in ethanol, at room temperature. Compound **5a** was isolated in 63% yield (Table 3, entry 8) and compounds **5b**–**e** were isolated in 49–62% yield after 15–23 h at room temperature (Table 4).

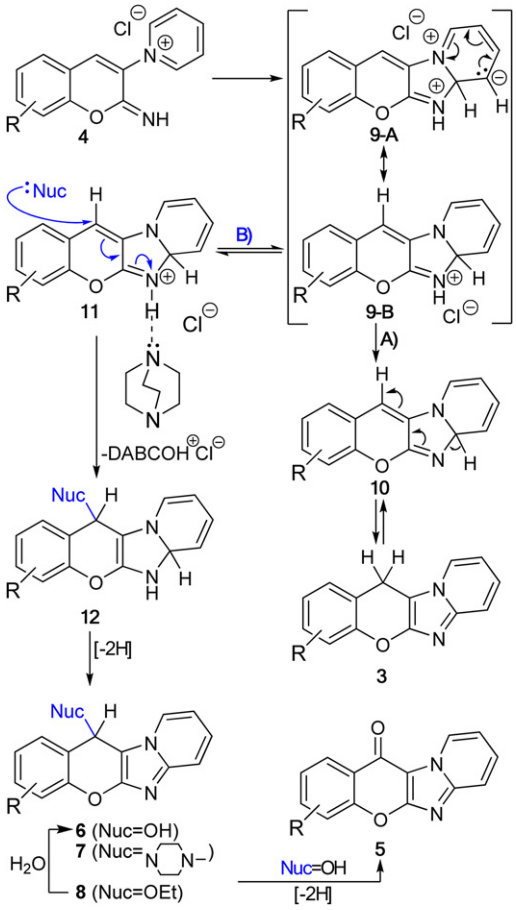
Table 4
Synthesis of 12*H*-chromeno[2′,3′:4,5]imidazo[1,2-*a*]pyridin-12-one derivatives **5b**–**e**, using ethanol and DABCO



Entry	Compd **4**	R_1, R_2	DABCO equiv	Reaction conditions	Product, yield
1	**4b**	H, H	15 equiv	rt, 15 h	**5b**, 49%
2	**4c**	OH, H	10 equiv	rt, 16 h	**5c**, 62%[a]
3	**4d**	H, OCH_3	10 equiv	rt, 18 h	**5d**, 57%[a]
4	**4e**	H, OH	10 equiv	rt, 22.5 h	**5e**, 50%

[a] Yield after combining the first and second crop; the second crop was isolated from the mother liquor after 3/4 days at 0 °C.

A mechanistic proposal for the formation of compounds **5**, **6**, **7** and **8** is presented in Scheme 3. Intramolecular cyclization evolving the imine nitrogen and C_2 of the pyridinium salt **4** was considered a fast, initial step. In aqueous solution and Na_2CO_3 as base, the chloride anion can be promptly solvated and stabilized in solution. Water acts as an excellent proton-donor and proton-acceptor, facilitating a fast tautomeric equilibrium that leads to product **3**. In ethanol and with an organic tertiary base, either a tighter ionic pair (**9B**) is formed or the amine, a stronger base than chloride ion, stabilizes the acidic proton on the imidazole nitrogen (**11**) enabling nucleophilic attack to C_{12}, activated through conjugation with the stabilized immonium salt.



Scheme 3. Proposed reaction mechanism for the formation of compound **5**.

Traces of water in ethanol, ethanol itself or a secondary amine, in this case *N*-methylpiperazine used as catalyst, can behave as nucleophiles. Compound **8a** slowly evolved to **6a** according to evidence by ^{1}H NMR on a mixture of **6a** and **8a** in DMSO-d_6, with traces of water. According to this study, formation of **6a** was complete after 2 days at room temperature. This was not the case for compound **7a**, where substitution of the amine by the hydroxyl group did not occur when a mixture of **6a** and **7a** was followed by ^{1}H NMR, under similar experimental conditions.

Compound **6** oxidizes to the isolated product **5** that precipitates from the reaction mixture, a situation that can also favour the evolution.

3. Conclusions

In summary, this work describes a simple one-pot synthesis of 12*H*-chromeno[2′,3′:4,5]imidazo[1,2-*a*]pyridin-12-one **5** from intramolecular cyclization of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chloride **4** in DABCO and ethanol. The product, a fused heterocyclic system combining the chromone and imidazo[1,2-*a*]pyridine moieties was isolated in good yield by simple filtration of the reaction mixture.

A detailed study of the reaction conditions that contribute to the preferential formation of this novel product allowed the

identification of interesting side products **6**, **7** and **8**. These compounds were formed by nucleophilic attack by water, ethanol or *N*-methylpiperazine to the postulated reaction intermediate.

4. Experimental section

4.1. General

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded at room temperature or 60 °C (**5b**), on a Varian Unity Plus (^{1}H: 300 MHz, ^{13}C: 75 MHz) or Bruker Avance 3400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), including the ^{1}H–^{13}C correlation spectra (HMQC and HMBC) and deuterated DMSO was used as solvent. The coupling constants, *J*, are reported in hertz (Hz). IR spectra were recorded on an FT-IR Bomem MB 104 using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were measured at CACTI services, University of Vigo, Spain, with a mass spectrometer Bruker apex-Qe. Elemental analyses were performed on a LECO CHNS-932 instrument.

4.2. General procedure for the synthesis of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chlorides 4

1-(Cyanomethyl)pyridinium chloride **2** (150.0 mg, 1.0 mmol) was added to a yellow solution of salicylaldehyde **1** (1.0 mmol) and 1-methylpiperazine (101 μL, 0.90 mmol) in EtOH/acetone (0.4 mL:1.2 mL). The reaction mixture was stirred in an ice bath (30 min–1 h). A solid started to precipitate after 15–20 min. The solid was filtered and washed with acetone leading to the pure product **4**. The synthesis of compounds **4a**–**d** was previously reported.[12]

*4.2.1. 1-(2-Imino-8-methoxy-2H-chromen-3-yl)pyridinium chloride (**4a**).* Yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.91 (s, 3H), 7.21 (dd, *J*=7.8, 2.1 Hz, 1H), 7.27 (t, *J*=7.8 Hz, 1H), 7.36 (dd, *J*=7.8, 1.8 Hz, 1H), 8.23 (s, 1H), 8.34 (td, *J*=7.5, 0.9 Hz, 2H), 8.82 (td, *J*=7.5, 1.8 Hz, 1H), 9.12 (s, 1H), 9.30 (dd, *J*=6.8, 1.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.2, 115.8, 118.2, 120.8, 124.5, 127.8 (2C), 131.1, 134.3, 142.4, 146.1 (2C), 146.2, 148.0, 151.0 ppm.

*4.2.2. 1-(2-Imino-2H-chromen-3-yl)pyridinium chloride (**4b**).* Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30–7.35 (m, 2H), 7.63 (td, *J*=7.6, 1.6 Hz, 1H), 7.68 (dd, *J*=7.6, 1.6 Hz 1H), 8.28 (s, 1H), 8.35 (td, *J*=6.4, 1.6 Hz, 2H), 8.83 (tt, *J*=7.6, 1.6, 1H), 9.02 (br s, 1H), 9.32 (dt, *J*=5.6, 1.6, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.4, 117.6, 124.5, 127.8 (2C), 129.8, 130.9, 133.2, 134.2, 146.1 (2C), 148.0, 151.5, 153.2 ppm.

*4.2.3. 1-(8-Hydroxy-2-imino-2H-chromen-3-yl)pyridinium chloride (**4c**).* Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05 (dd, *J*=7.6, 1.6, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 7.27 (dd, *J*=8.0, 1.6 Hz 1H), 8.19 (s, 1H), 8.33 (td, *J*=6.4, 1.6 Hz, 2H), 8.82 (tt, *J*=7.6, 1.6 Hz, 1H), 8.87 (s, 1H), 9.30 (dt, *J*=6.0, 1.6 Hz, 2H), 10.59 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 118.4, 119.4, 119.7, 124.3, 127.7 (2C), 130.9, 134.6, 141.6, 144.6, 146.2 (2C), 147.9, 151.5 ppm.

*4.2.4. 1-(2-Imino-6-methoxy-2H-chromen-3-yl)pyridinium chloride (**4d**).* Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3H), 7.21 (dd, *J*=9.0, 2.8 Hz, 1H), 7.24 (d, *J*=2.8 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 8.21 (s, 1H), 8.34 (td, *J*=6.6, 1.6 Hz, 2H), 8.83 (tt, *J*=7.6, 1.6 Hz, 1H), 8.91 (s, 1H), 9.31 (dd, *J*=6.8, 1.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.8, 112.7, 116.5, 118.1, 119.6, 127.8 (2C), 131.3, 134.1, 146.1 (2C), 147.5, 148.0, 151.8, 155.4 ppm.

*4.2.5. 1-(6-Hydroxy-2-imino-2H-chromen-3-yl)pyridinium chloride (**4e**).* Brown solid (31.0 mg, 72%). Mp 205–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05–7.10 (m, 2H), 7.14 (d, *J*=8.8 Hz, 1H), 8.16 (s, 1H), 8.74–8.83 (m, 2H), 8.32 (t, *J*=6.8 Hz, 2H), 9.29 (dd, *J*=6.8, 1.2 Hz, 2H), 10.09 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.2, 116.2, 117.9, 120.4, 127.7 (2C), 131.1, 134.3, 146.3, 146.2 (2C), 147.9, 151.8, 153.9 ppm. IR (Nujol mull): ν 3500–1700 (broad, fringed), 1663, 1623, 1612, 1577, 1487, 1464 cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_2O_2Cl.0{\cdot}25NH_4Cl$: C, 58.36; H, 4.17; N, 10.94, found: C, 58.48; H, 4.57; N, 11.13.

4.3. General procedure for the synthesis of 12*H*-chromeno [2′,3′:4,5]imidazo[1,2-*a*]pyridin-12-ones 5

DABCO (10–15 M equiv) was added to an orange solution of the corresponding 1-(2-imino-2*H*-chromen-3-yl)pyridinium chloride **4** (0.40 mmol) in ethanol (17 mL). The reaction mixture was stirred at room temperature. A solid started to precipitate after a few hours and after 16–22.5 h the suspension was cooled in an ice bath for a few minutes. The solid was filtered and washed with ethanol leading to the pure product **5**.

*4.3.1. 4-Methoxy-12H-chromeno[2′,3′:4,5]imidazo-[1,2-a]pyridin-12-one (**5a**).* Cream solid (55.0 mg, 63%). Mp 281–283. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 3H), 7.40 (dd, *J*=6.8, 1.2 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.51 (dd, *J*=8.0, 1.6 Hz, 1H), 7.80 (dd, *J*=7.6, 1.6 Hz, 1H), 7.89 (dt, *J*=8.8, 1.2 Hz, 1H), 7.83 (td, *J*=7.0, 1.6 Hz, 1H), 9.32 (dt, *J*=6,8, 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.3, 106.8, 115.0, 115.4, 115.9, 116.4, 124.2, 124.4, 128.3, 131.8, 143.8, 144.6, 148.5, 160.3, 166.8 ppm. IR (Nujol mull): ν 1650, 1588, 1537, 1485, 1466 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O_3.0.4H_2O$: C, 65.89; H, 3.95; N, 10.25, found: C, 65.70; H, 4.18; N, 10.54.

*4.3.2. 12H-Chromeno[2′,3′:4,5]imidazo[1,2-a]pyridin-12-one (**5b**).* Cream solid (44.0 mg, 49%). Mp 292–294. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.38 (td, *J*=6.9, 1.5 Hz, 1H), 7.54 (td, *J*=7.4, 1.5 Hz, 1H), 7.70–7.90 (m, 4H), 8.26 (dd, *J*=8.1, 1.2 Hz, 1H), 9.33 (dt, *J*=6.6, 1.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 106.7, 114.8, 116.2, 118.0, 123.2, 124.4, 125.1, 128.1, 131.6, 133.4, 144.5, 153.8, 160.4, 166.7 ppm. IR (Nujol mull): ν 1654, 1636, 1609, 1555, 1536, 1519, 1463, 1455 cm^{-1}. Anal. Calcd for $C_{14}H_8N_2O_2$: C, 71.19; H, 3.39; N, 11.86, found: C, 70.84; H, 3.65; N, 11.95.

*4.3.3. 4-Hydroxy-12H-chromeno[2′,3′:4,5]imidazo-[1,2-a]pyridin-12-one (**5c**).* Compound **5c** was prepared following the general procedure, but in this case the mother liquor was kept at 0 °C for 4 days. A yellow solid precipitated and was filtered and washed with ethanol leading to a second crop of the pure product **5c**. Yellow solid (54.0 mg, 62%). Mp higher than 300. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28–7.32 (m, 2H), 7.38 (td, *J*=6.8, 1.2 Hz, 1H), 7.62–7.69 (m, 1H), 7.82 (dd, *J*=7.2, 1.2 Hz, 1H), 7.88 (dt, *J*=8.8, 1.2 Hz, 1H), 9.32 (dt, *J*=6.4, 1.2 Hz, 1H), 10.50 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 106.8, 111.4, 114.7, 115.0, 116.4, 124.5, 124.6, 128.3, 131.8, 143.4, 144.7, 146.7, 160.4, 167.2 ppm. IR (Nujol mull): ν 3500–3200 (broad), 1645, 1595, 1534, 1517, 1486, 1465 cm^{-1}. Anal. Calcd for $C_{14}H_8N_2O_3.0.1H_2O$: C, 66.19; H, 3.23; N, 11.03, found: C, 66.18; H, 3.56; N, 10.88.

*4.3.4. 2-Methoxy-12H-chromeno[2′,3′:4,5]imidazo-[1,2-a]pyridin-12-one (**5d**).* Compound **5c** was prepared following the general procedure, but in this case the mother liquor was kept at 0 °C for 3 days. The cream solid that precipitated was filtered and washed with ethanol leading to a second crop of the pure product **5d**.

Cream solid (49.0 mg, 57%). Mp 219–221. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.88 (s, 3H), 7.35–7.43 (m, 2H), 7.62 (d, J=3.2 Hz, 1H), 7.75 (d, J=9.2 Hz, 1H), 7.82 (td, J=7.0, 1.2 Hz, 1H), 7.87 (d, J=8.8 Hz, 1H), 9.31 (d, J=6.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.8, 106.2, 106.6, 115.0, 116.4, 119.7, 212.8, 124.0, 128.3, 131.9, 144.7, 148.3, 156.0, 160.6, 166.6 ppm. IR (Nujol mull): ν 1658, 1645, 1613, 1588, 1540, 1520, 1465 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O_3.0.1H_2O$: C, 67.21; H, 3.81; N, 10.46, found: C, 67.25; H, 3.92; N, 10.38.

*4.3.5. 2-Hydroxy-12H-chromeno[2′,3′:4,5]imidazo-[1,2-a]pyridin-12-one (**5e**).* Light brown solid (52.0 mg, 50%). Mp higher than 300. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (dd, J=9.3, 3.0 Hz, 1H), 7.35 (td, J=6.9, 1.8 Hz, 1H), 7.52 (d, J=3.0 Hz, 1H), 7.62 (d, J=9.0 Hz, 1H), 7.75–7.86 (m, 2H), 9.29 (d, J=6.3 Hz, 1H), 9.96 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 106.5, 108.7, 114.8, 116.3, 119.4, 121.9, 124.1, 128.3, 131.8, 144.6, 147.3, 154.3, 160.6, 166.8 ppm. IR (Nujol mull): ν 3500–3000 (broad), 1647, 1611, 1548, 1536, 1514, 1459 cm^{-1}. Anal. Calcd for $C_{14}H_8N_2O_3$: C, 66.67; H, 3.18; N, 11.11, found: C, 66.62; H, 3.32; N, 11.12.

4.4. 4-Methoxy-12*H*-chromeno[2′,3′:4,5]imidazo[1,2-*a*] pyridin-12-ol 6a

Triethylamine (1 M equiv) was added to an orange suspension of 1-(2-imino-8-methoxy-2*H*-chromen-3-yl)pyridinium chloride **4a** (94.4 mg, 0.33 mmol) in ethanol (0.55 mL). The reaction mixture was stirred at 10 °C. After 1.5 h the suspension was cooled in an ice bath for a few minutes. The yellow solid was filtered and washed with ethanol leading to a mixture of compounds **5a** and **6a** (17.1 mg) in a 1.3:1 ratio, by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6) signals for **6a**, after excluding the peaks for **5a**: δ 3.89 (s, 3H), 6.02 (d, J=8.4 Hz, 1H), 6.27 (d, J=8.0 Hz, 1H), 7.06 (td, J=6.8, 1.2 Hz, 1H), 7.10 (dd, J=7.8, 2.0 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.24 (dd, J=8.0, 1.6 Hz, 1H), 7.37 (td, J=6.8, 1.2 Hz, 1H), 7.58 (dt, J=9.2, 0.8 Hz, 1H), 8.45 (dt, J=6.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 58.6, 102.3, 111.2, 112.2, 115.8, 121.8, 123.3, 124.8, 125.2, 125.3, 140.0, 140.7, 147.8, 151.3 ppm; HRMS (ESI, [M−1]$^-$) calcd for $C_{15}H_{11}N_2O_4$ 267.07703, found 267.07642.

4.5. 4-Methoxy-12-(4-methylpiperazin-1-yl)-12*H*-chromeno [2′,3′:4,5]imidazo[1,2-*a*]pyridine 7a

One drop of *N*-methylpiperazine was added to an NMR tube containing a mixture of compound **5a** and **6a** in a 1.3:1 ratio (by ^{1}H NMR) in DMSO-d_6 (650 μL). The evolution of this mixture was followed at room temperature as compound **6a** evolved to compound **7a**. After 17 days the solution in the NMR tube was identified as a mixture of compounds **5a** and **7a** in a 1.3:1 ratio by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6) signals for **7a**, after excluding the peaks for **5a**: δ 5.74 (s, 1H), 2.11 (m, 8H), 2.02 (s, 3H), 7.01–7.06 (m, 2H), 7.16 (t, J=8.0 Hz, 1H), 7.10 (dd, J=8.2, 2.0 Hz, 1H), 3.88 (s, 3H), 7.54 (dt, J=8.8, 1.2 Hz), 7.34 (td, J=8.8, 1.2 Hz, 1H), 7.01–7.06 (m, 2H), 8.43 (dt, J=6.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 47.8, 45.6, 55.1, 55.5, 55.8, 99.2, 111.3, 111.9, 115.7, 119.5, 121.8, 122.8, 125.0, 125.5, 140.7, 141.8, 148.1, 153.4 ppm.

4.6. 2-Methoxy-12-(4-methylpiperazin-1-yl)-12*H*-chromeno [2′,3′:4,5]imidazo[1,2-*a*]pyridine 7b

N-Methylpiperazine (5 M equiv) was added to an orange solution of 1-(2-imino-6-methoxy-2*H*-chromen-3-yl)pyridinium chloride **4d** (13.0 mg, 0.46 mmol) in ethanol (18 mL). The reaction mixture was stirred at room temperature. A solid started to precipitate after 1 h and after 4 h the suspension was cooled in an ice bath for a few minutes. The cream solid was filtered and washed with ethanol leading to the pure product **5d** (24.2 mg). The mother liquor was kept at 0 °C for 24 h and a solid started to precipitate and was filtered and washed with ethanol leading to a second crop of the pure product **5d** (9.1 mg, total yield: 27%). The solvent of the resulting mother liquor was evaporated in the rotary evaporator and the red oil was kept at 0 °C for 24 h. A yellow solid precipitated and was filtered and washed with ethanol leading to product **7b** (16.0 mg), contaminated with *N*-methylpiperazine. Since compound **7b** was not pure, it was only characterized by ^{1}H and ^{13}C NMR. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H), 2.44 (t, J=4.8 Hz, 4H), 2.96 (t, J=5.2 Hz, 4H), 3.79 (s, 3H), 5.71 (s, 1H), 6.98 (dd, J=9.6, 3.2 Hz, 1H), 7.01–7.05 (m, 2H), 7.25 (t, J=8.8 Hz, 4H), 7.34 (td, J=7.8, 1.2 Hz, 1H), 7.53 (dt, J=9.2, 1.2 Hz, 1H), 8.42 (dt, J=6.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.2, 45.6, 52.0, 55.5, 55.6, 98.8, 111.9, 114.4, 115.0, 115.6, 118.0, 119.4, 124.9, 125.5, 140.8, 146.3, 153.8, 154.7 ppm; HRMS (ESI, M$^+$+1) calcd for $C_{20}H_{23}N_4O_2$ 351.18229, found 351.18232.

4.7. 12-Ethoxy-4-methoxy-12*H*-chromeno[2′,3′:4,5]imidazo-[1,2-*a*]pyridine 8a

Sodium carbonate (4.9 M equiv) was added to an orange solution of 1-(2-imino-8-methoxy-2*H*-chromen-3-yl)pyridinium chloride **4a** (87.0 mg, 0.30 mmol) in ethanol (12 mL). The suspension was stirred at room temperature. After 3 h and 15 min the suspension was cooled in an ice bath for a few minutes. The solid was filtered and washed with ethanol and identified as Na_2CO_3 by ^{1}H NMR. The mother liquor was concentrated in the rotary evaporator and the resulting yellow oil was identified as a mixture of compound **5a**, **6a** and **8a** in a 1.7:2.6:1 ratio, by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6) signals for **8a**, after excluding the peaks for **5a** and **6a**: δ 0.89 (t, J=8.0 Hz, 3H), 2.98 (qd; J=9.2, 7.2 Hz, CH_AH_B), 3.01 (qd; J=9.2, 7.2 Hz, CH_AH_B), 3.90 (s, 3H), 6.49 (s, 1H), 7.13–7.26 (m, 3H)[a], 7.40–7.44 (m, 1H)[a], 7.06–7.09 (m, 1H)[a], 7.61 (dt, J=9.2, 1.2 Hz, 1H), 8.44 (dt, J=6.8, 1.2 Hz, 1H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.3, 55.8, 58.4, 65.8, 99.0, 111.9, 112.7, 115.9, 120.8, 121.2, 123.7, 125.2, 126.0, 141.1, 141.4, 148.0, 151.2 ppm. ([a]under the signal for compound **5a** and **6a**); HRMS (ESI, M$^+$+1) calcd for $C_{17}H_{17}N_2O_3$ 297.12401, found 297.12405.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.09.054.

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