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Synthesis of 3-aminochromenes: the Zincke reaction revisited

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ABSTRACT

3-Aminocoumarines and 2-iminochromen-3-amines were efficiently prepared from the Zincke-ring-opening reaction of the corresponding 2*H*-chromen-3-pyridinium chlorides using *N*-methylpiperazine. This methodology unravels the marked potential of pyridinium salts as protective groups for primary amines.

These scaffolds can be considered important building blocks for new novobiocin analogues and heterocyclic compounds.

1. Introduction

The chromene nucleus is present in a wide range of natural products[1] and can be considered an important scaffold in medicinal chemistry.[2] The 3-aminocoumarine core, in particular, has attracted considerable interest since this molecule can be used as an intermediate in the preparation of bioactive compounds.[3] Novobiocin, clorobiocin and coumermycin A1 (Fig. 1) are naturally occurring antibiotics bearing this core unit, isolated from several Streptomyces strains.[4] Novobiocin, an inhibitor of DNA gyrase,[5] binds to heat shock protein 90 at the C-terminal nucleotide-binding region and leads to a decrease on hsp90 client protein in various cancer cell lines.[6] Analogues have been studied as anticancer agents, inhibiting hsp90,[7] a target that has attracted the attention of both industrial and academic laboratories for cancer chemotherapeutics.

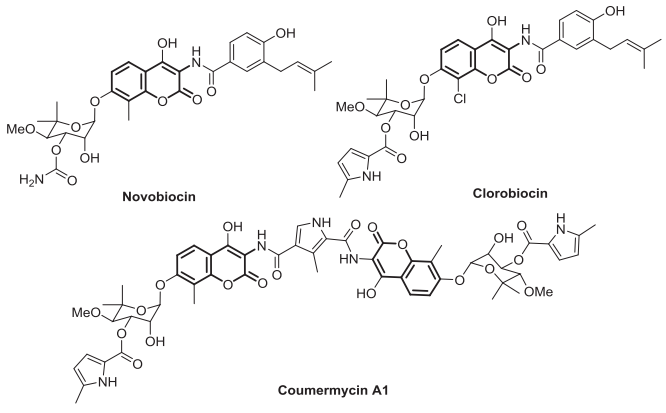

Fig. 1. Natural antibiotics bearing the 3-aminocoumarin nucleus.

A scarce number of methods are available for the preparation of 3-aminocoumarin. The first reported synthesis, by F. Linch,[8a] dates back over a century and several attempts have been made to improve this synthetic route.[7a,8b] Experimental procedures described in the literature often lead to satisfactory yields but the pathway implies multiple steps, the use of environmentally harmful reagents and solvents and several purifications steps. Furthermore only a limited selection of substituents in the aromatic ring allowed the successful isolation of the product.

2. Results and discussion

Herein, inspired by the Zincke-ring-opening of pyridinium salts, we anticipated that the pyridinium ion could be used as a protecting group for the amine function in the C_3 position of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chlorides **3** and 1-(2-oxo-2*H*-chromen-3-yl)pyridinium chlorides **4**. Compounds **3a**–**d** and **4a** were previously prepared in our group from the base-catalyzed Knoevenagel condensation of salicylaldehydes **1** and 1-(cyanomethyl) pyridinium chloride **2** (Scheme 1).[9]

Initial deprotecting assays were performed using the reaction of 2-methoxyethylamine with 1-(8-methoxy-2-oxo-2*H*-chromen-3-

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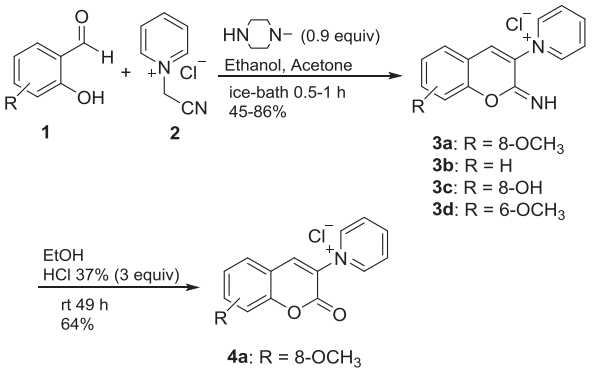
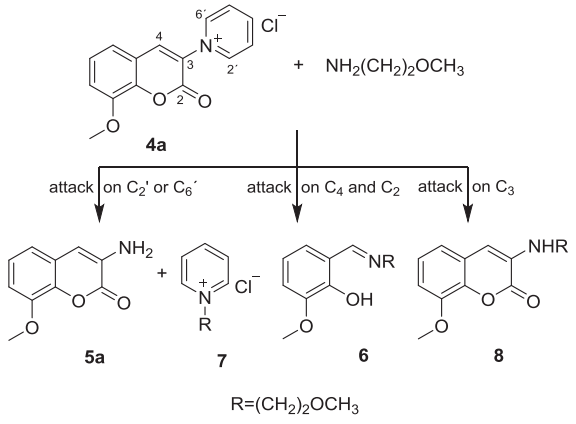


Scheme 1. Previous work: reaction of salicylaldehyde derivatives **1** with 1-(cyanomethyl)pyridinium chloride **2**.

yl)pyridinium chloride **4a**. The use of a primary amine, mimicking the conditions normally used for the Zincke reaction, was expected to release the amine unit in the 3-position of the chromene ring, upon nucleophilic attack at $C_{2'}$ and $C_{6'}$.

Compound **5a** (Scheme 2) was indeed isolated when the reagents were combined in ethanol in a 1:1 molar ratio, and the red suspension was stirred at 10 °C for 22 h. The product was isolated in a modest yield (27%) and analysis of the reaction mixture by ^{1}H NMR evidenced that the starting material **4a** and the imine **6** were also present, together with other non-identified components (Scheme 2).



Scheme 2. Reaction of 2-oxo-2*H*-chromen-3-yl-pyridinium chloride **4a** with 2-methoxyethylamine.

When the reaction was repeated at room temperature, ^{1}H NMR on the resulting oil indicated the formation of 3-aminocoumarin **5a**, accompanied by unreacted starting material **4a** and imine **6** in an equally complex mixture.

The reaction was performed in water, at 60 °C for 26 h, leading to a complex mixture. Imine **6** was the only product isolated in a modest yield, after dry flash chromatography (Scheme 2).

The reaction was also performed using 2 M equiv of the amine, although in this case chromene **4a** was contaminated with ammonium chloride (1 M equiv). Ethyl acetate and ethanol (2:1) were used as solvents and the reaction mixture was kept at 60 °C for 25 h. The solid product that precipitated after appropriate work-up, was identified as the desired product, the 3-aminocoumarin **5a** (49% yield). The mother liquor, analyzed by ^{1}H NMR after removal of the solvent in the rotary evaporator, showed that a complex mixture had also been formed.

The reaction of **4a** (contaminated with ammonium chloride) and 2-methoxyethylamine (1 M equiv) was followed by ^{1}H NMR in deuterated dimethylsulfoxide. A clean progression to chromene **5a** and pyridinium salt **7** was observed under these dilute conditions. These were the only products identified in the spectrum in a 1:1 molar ratio, after 24 h. The ammonium chloride, present as a contamination in the starting material, was also identified. This study confirmed that the reaction followed the usual pathway for the Zincke reaction: nucleophilic attack of the primary amine to $C_{2'}$ of the pyridinium salt moiety of chromene **4a** leading to ring opening followed by ring closure to generate pyridinium salt **7** incorporating the primary amine (Scheme 2).

The contamination with ammonium chloride was not affecting the reaction, as ammonia did not compete with the primary amine for nucleophilic attack.

This reaction was also repeated in the absence of solvent, using 5 M equiv of 2-methoxyethylamine. Heating the reaction mixture at 60 °C for 17 h followed by addition of water resulted in a solid product, identified as 8-methoxy-3-((2-methoxyethyl)amino)-2*H*-chromen-2-one **8** (31% yield, Scheme 2). The same product was isolated, although in a lower yield (12%), when chromene **4a** was reacted with 5 M equiv of 2-methoxyethylamine at room temperature for 1 day. This transformation may proceed through nucleophilic attack of the primary amine to the electron deficient carbon C_3, releasing pyridinium chloride.

The poor selectivity in the reaction of the primary amine with chromen-3-yl-pyridinium chloride **4** was assigned to the presence of several electron deficient carbon atoms (C_2, C_3, C_4, $C_{2'}$ and $C_{6'}$) resulting in the formation of different products by nucleophilic attack on these positions, depending basically on the reaction conditions.

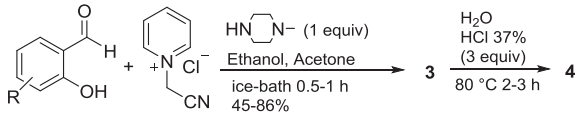
In order to overcome this lack of selectivity and improve the yield in the synthesis of the 3-aminocoumarins, a secondary amine was used. Although the Zincke reaction is generally associated with the reaction of primary amines with pyridinium salts, the reaction of chromen-3-yl-pyridinium chloride **4a** (contaminated with 0.6 M equiv of NH_4Cl) was performed with 2 M equiv of *N*-methylpiperazine in acetone, at room temperature. The formation of compound **5a** was confirmed by TLC and removal of the solvent in the rotary evaporator after ca. 20 h, followed by addition of water and ethanol, allowed the isolation of this product. A second crop was collected by flash chromatography of the mother liquor but the total yield did not exceed 39%. In an attempt to improve the yield, the reaction was repeated under the same experimental conditions but using 5 M equiv of *N*-methylpiperazine. After stirring the mixture at room temperature for 1 day, the solvent was removed and the red oil was purified by flash chromatography using ethyl acetate as eluent. 3-Aminocoumarin **5a** was isolated an excellent yield of 99% after removal of the solvent. Other substituted 1-(2-imino-2*H*-chromen-3-yl)pyridinium chlorides **3** were prepared according to our previously reported procedure[9] and further converted into the corresponding 1-(2-oxo-2*H*-chromen-3-yl)pyridinium chlorides **4**, after addition of 3 M equiv of concentrated HCl (37%) to an aqueous solution of **3** and heating for a 2–3 h (Table 1).

The optimal reaction conditions for the synthesis of 3-aminocoumarins **5** were applied to the remaining chromen-3-yl-pyridinium chlorides **4** and the desired products **5** were isolated (Scheme 3).

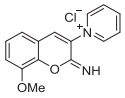
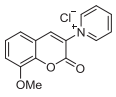
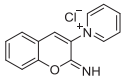
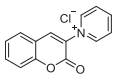
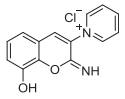
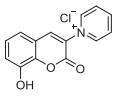
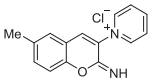
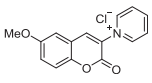
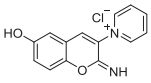
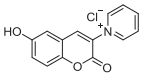
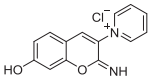
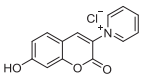
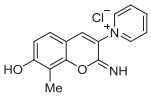
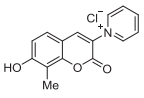
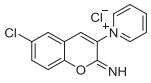
For chromenes **4c**,**e**–**g**, bearing a hydroxyl group in the aromatic ring, the reaction conditions had to be adapted due to the lower solubility of these compounds in acetone. A small amount of water and heating conditions were applied and the products were isolated in good yield (70–98%).

The successful and efficient release of the amino group by nucleophilic attack of the secondary amine to the pyridinium ion at C_3 of the chromene unit in 2-oxochromene **4**, encouraged the application of this methodology to 2-iminochromenes **3**. In general, 2-imino-2*H*-chromenes are more delicate to handle due to the presence of the NH group in the C_2 position that allows a facile intramolecular nucleophilic attack to $C_{2'}$/$C_{6'}$ of the pyridinium ion.

Table 1
Preparation of 2-imino and 2-oxo-2*H*-chromenes **3** and **4**



1a: R = 3-OCH_3 **1e**: R = 5-OH
1b: R = H **1f**: R = 4-OH
1c: R = 3-OH **1g**: R = 3-Me, 4-OH
1d: R = 5-OCH_3 **1h**: R = 5-Cl

Entry	1	2	Yield (%)	3	Yield (%)
1	**1a**		78[a]		83[a]
2	**1b**		45[a]		69
3	**1c**		86[a]		75
4	**1d**		69[a]		53
5	**1e**		78		74
6	**1f**		64		91
7	**1g**		64		94
8	**1h**		34	—	—

[a] Previously reported by our group.[9]

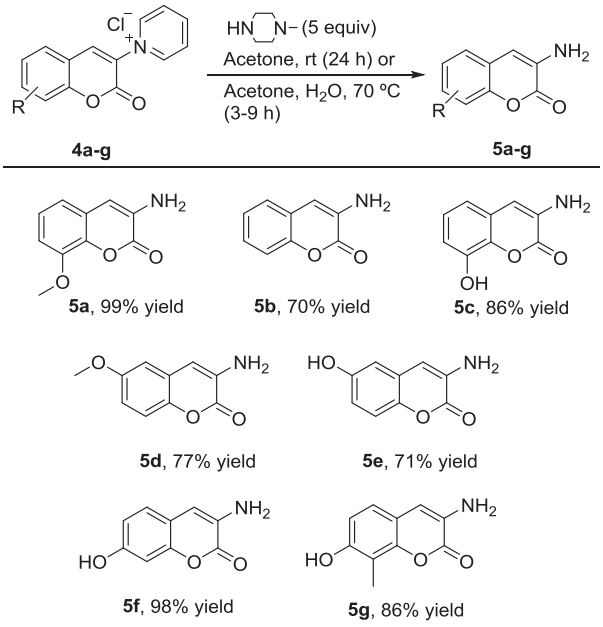
This reaction was previously observed by our group,[9] and competition with *N*-methylpiperazine was to be expected. The reaction of 2-imino-2*H*-chromen-3-yl-pyridinium chloride **3a** with 5 equiv of *N*-methylpiperazine was performed in acetone, at room temperature.

The solvent was removed in the rotary evaporator after 1 day, and analysis of the red oil by ^{1}H and ^{13}C NMR spectroscopy showed the presence of chromene **9a** and salt **10**, contaminated with *N*-methylpiperazine (Scheme 4).

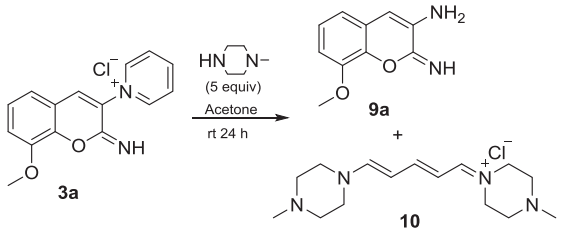
The formation of compound **10** confirmed that the Zincke reaction involves 2 equiv of the secondary amine leading to an interesting symmetrically substituted conjugated system. This salt was never isolated before although the formation of an analogous structure was reported 60 years ago. The compound was only characterized by elemental analysis and melting point data.[10]

Flash chromatography was used to isolate the pure 2-imino-2*H*-chromen-3-amine derivative **9a** (56% yield). When the same reaction was performed in acetonitrile, the desired product **9a** was isolated in a higher yield (70%). Chromene derivatives **9b**–**g** were synthesized using the reaction conditions presented in Scheme 5.

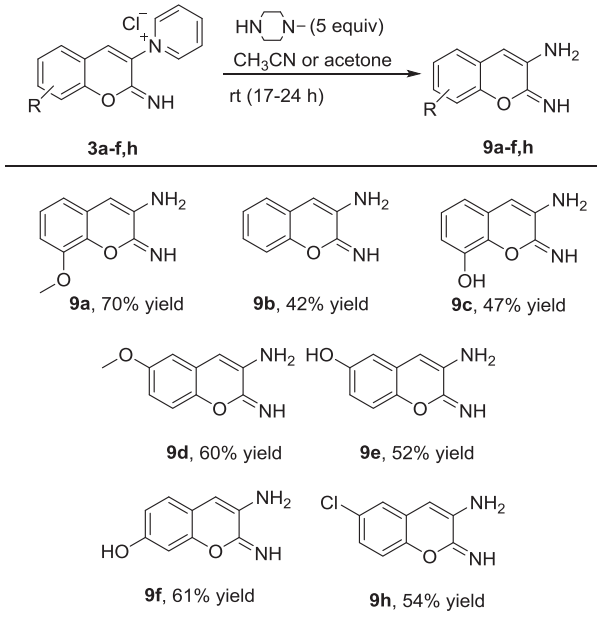
The synthesis of chromene derivatives **9c**,**e** and **f**, bearing hydroxyl groups, resulted in modest yields. Again, the poor solubility



Scheme 3. Synthesis of 3-aminocoumarin derivatives **5a**–**g**.



Scheme 4. Evolution of 2-imino-2*H*-chromene-3-yl-pyridinium chloride **3a** in the presence of *N*-methylpiperazine.



Scheme 5. Synthesis of 2-imino-2*H*-chromen-3-amines **9a**–**g**.

of the corresponding reagents **3** in acetone or acetonitrile may be the source of the problem. In this case, water could not be added to the reaction mixture in order to enhance solubility as evolution to the 2-oxo-chromene **4** was detected. Heating the reaction mixture

was also impracticable, as the 2-imino-chromenes **3** evolved to a tetracyclic product under heating conditions in the presence of base. This work was previously reported and the product results from intramolecular cyclization of the imino group to the carbon of the pyridine moiety, without ring opening.[9] The evolution of chromene derivative **3c** in the presence of *N*-methylpiperazine resulted in a suspension and in this case the solid was filtered and identified as a mixture of 2-imino-2*H*-chromen-3-amine derivative **9c** and piperazinium chloride **10**, in a 1:1 ratio, by ^{1}H NMR.

This mixture was separated by flash chromatography, and ethyl acetate allowed the isolation of chromene **9c** while a mixture of dichloromethane and methanol (12–20%) resulted in the isolation of the pure piperazinium chloride **10** as viscous orange oil. The highly conjugated structure of compound **10**, where the positive charge bounces between the two piperazine nitrogen atoms, is corroborated by the ^{1}H and ^{13}C NMR data. The linear carbon chain displays a symmetrical and alternating electron density leading to three signals in the ^{13}C NMR spectrum: $C_{1'}$ and $C_{5'}$ at δ 160.0 ppm, $C_{2'}$ and $C_{4'}$ at δ 102.5 ppm and $C_{3'}$ at δ 163.0 ppm. The associated proton coupling constant in the ^{1}H NMR spectrum, around J=12 Hz, indicates that the trans isomer is stable in DMSO, under the NMR conditions.

3. Conclusion

In conclusion, the Zincke-ring-opening reaction of chromen-3-yl-pyridinium salts induced by *N*-methylpiperazine led to a series of 3-aminochromenes in excellent yield. Preliminary studies using a primary amine (2-methoxyethylamine) resulted in poor selectivity and lower isolated yields of the product, even when different experimental conditions were assayed. The use of a secondary amine to perform the Zincke reaction may unravel a versatile perspective regarding pyridinium salts as surrogates for the amino group. The primary amine could be released by excess of *N*-methylpiperazine, at room temperature or under mild heating, and solvents, such as acetone, acetonitrile or water were well tolerated in the process. The success of this methodology, now applied to chromen-3-yl-pyridinium salts, where competition for nucleophilic attack on the chromene moiety could be a serious drawback, suggests that this may be used as a general protocol for amino group protection/deprotection. 3-Aminocoumarines **5** with different substituents in the aromatic moiety were efficiently prepared by this method, paving the way for the preparation of novobiocin analogues. Novel 2-iminochromen-3-amines **9** were also isolated and the amino/imino functionality can be considered an important building block for the new fused heterocycles incorporating the chromene moiety.

4. Experimental section

4.1. General

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded on a Varian Unity Plus at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Bruker Avance 3400 at 400 MHz for ^{1}H and 100 MHz for ^{13}C, including the ^{1}H–^{13}C correlation spectra (HMQC and HMBC). Deuterated DMSO was used as solvent. The chemical shifts are expressed in δ (ppm) and the coupling constants (J) in hertz (Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet and br, broad. IR spectra were recorded on an FT-IR Bomem MB using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography using silica gel 60 F_{254} (Merck and Macherey–Nagel). The melting points were determined on a Stuart SMP3 melting point apparatus. Elemental analyses were performed on a LECO CHNS-932 instrument or obtained from C.A.C.T.I. (Universidade de Vigo) using Carlo Erba 1108.

Compounds **2** and **5b** were synthesized in the laboratory but are commercially available. Chromene derivatives **3a**–**d** and **4a** were previously reported by our research group and synthesized according to the established experimental procedures (**3a**–**d**) or by new methodologies (**4a**).[9]

4.2. Synthesis of 1-(cyanomethyl)pyridinium chloride 2

Pyridine (0.77 g, 9.73 mmol; 800 μl) was added to a solution of a chloroacetonitrile (0.47 g, 6.22 mmol, 400 μl) in acetonitrile (1 ml) and the mixture was kept under reflux conditions. After 5 min a beige solid started to precipitate and after 10 min heating was stopped. The suspension was cooled in an ice bath for a few minutes. The beige solid was filtered and washed with acetonitrile leading to 1-(cyanomethyl)pyridinium chloride (0.82 g, 5.30 mmol, 85.2%), by ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.07 (s, 2H), 8.26 (td, J=6.9, 1.8 Hz, 2H), 8.73 (td, J=1.5, 1.2 Hz, 1H), 9.24 (d, J=6.2 Hz, 2H) ppm.

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

N-Methylpiperazine (0.90 mmol) was added to a suspension of salicylaldehyde derivative **1** (1.0 mmol) and 1-(cyanomethyl)pyridinium chloride **2** (1.0 mmol) in ethanol (0.4 ml) and acetone (1.2 ml). A red solution was obtained and stirred in an ice bath. After a few minutes a red suspension was formed and after 30–60 min the product was filtered and washed with acetone leading to 1-(2-imino-2*H*-chromen-3-yl)pyridinium chloride **3**.

*4.3.1. 1-(2-Imino-8-methoxy-2H-chromen-3-yl)pyridinium chloride **3a**.*[9] Yellow solid, 78%. ^{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.

*4.3.2. 1-(2-Imino-2H-chromen-3-yl)pyridinium chloride **3b**.*[9] Yellow solid, 45%. ^{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 Hz, 1H), 9.02 (br s, 1H), 9.32 (dt, J=5.6, 1.6 Hz, 2H) ppm.

*4.3.3. 1-(8-Hydroxy-2-imino-2H-chromen-3-yl)pyridinium chloride **3c**.*[9] Yellow solid, 86%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05 (dd, J=7.6, 1.6 Hz, 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.

*4.3.4. 1-(2-Imino-6-methoxy-2H-chromen-3-yl)pyridinium chloride **3d**.*[9] Yellow solid, 69%. ^{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.

*4.3.5. 1-(2-Imino-6-hydroxy-2H-chromen-3-yl)pyridinium chloride **3e**.* Brown solid, 78%. Mp 205–207 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1663, 1623, 1612, 1577 cm^{-1}; ^{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), 8.32 (t, J=6.8 Hz, 2H), 8.74–8.83 (m, 2H), 9.29 (dd, J=6.8, 1.2 Hz, 2H), 10.06 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.2, 116.2, 118.0, 120.4, 127.7 (2C), 131.1, 134.3, 146.2 (2C), 146.4, 147.9, 151.8, 153.9 ppm; Anal. Calcd for $C_{14}H_{11}N_2O_2Cl\cdot 0.25NH_4Cl$: C, 58.36; H, 4.17; N, 10.94. Found: C, 58.48; H, 4.47; N, 11.13.

*4.3.6. 1-(2-Imino-7-hydroxy-2H-chromen-3-yl)pyridinium chloride **3f**.* Yellow solid, 64%. Mp 207–208 °C; IR (Nujol mull) ν 3287, 3119, 1667, 1630, 1614, 1582 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.74

(s, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 7.45 (d, *J*=8.8 Hz, 1H), 8.11 (s, 1H), 8.30 (t, *J*=7.6 Hz, 2H), 8.72 (s, 1H), 8.78 (td, *J*=7.6, 1.6 Hz, 1H), 9.26 (d, *J*=7.6, Hz, 2H), 11.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.9, 109.2, 112.8, 127.4, 127.7 (2C), 130.9, 134.4, 146.3 (2C), 147.5, 151.6, 155.0, 162.6 ppm; Anal. Calcd for $C_{14}H_{11}N_2O_2Cl\cdot 0.15H_2O$: C, 60.61; H, 4.08; N, 10.10. Found: C, 60.61; H, 4.42; N, 10.09.

4.3.7. 1-(2-Imino-7-hydroxy-8-methyl-2H-chromen-3-yl)pyridinium chloride ***3g***. Orange solid, 64%. Mp 255–256 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1661, 1607, 1462 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H), 6.93 (d, *J*=8.4 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 8.08 (s, 1H), 8.29 (t, *J*=7.6 Hz, 2H), 8.72 (s, 1H), 8.78 (tt, *J*=7.6, 1.2 Hz, 1H), 9.26 (d, *J*=6.4, Hz, 2H), 11.00 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 7.9, 109.3, 110.7, 111.7, 127.0, 127.6$_7$, 127.7$_4$, 134.8, 146.3 (2C), 147.5, 152.5, 152.8, 160.5 ppm; Anal. Calcd for $C_{15}H_{13}N_2O_2Cl$: C, 55.56; H, 4.01; N, 8.64. Found: C, 55.55; H, 4.12; N, 8.71.

4.3.8. 1-(2-Imino-6-chloro-2H-chromen-3-yl)pyridinium chloride ***3h***. Beige solid, 34%. Mp 229–230 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1666, 1461 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.35 (d, *J*=9.0 Hz, 1H), 7.66 (dd, *J*=9.0, 2.7 Hz, 1H), 7.82 (d, *J*=2.7 Hz, 1H), 8.22 (s, 1H), 8.35 (t, *J*=7.8 Hz, 2H), 8.84 (tt, *J*=7.8, 1.2 Hz, 1H), 9.29 (dd, *J*=6.8, 1.2 Hz, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 117.4, 119.3, 127.9, 128.0, 128.7, 131.9, 132.6, 133.0, 146.1 (2C), 148.2, 150.9, 152.0 ppm; Anal. Calcd for $C_{14}H_{10}N_2OCl_2$: C, 57.34; H, 3.41; N, 9.56. Found: C, 57.32; H, 3.42; N, 9.66.

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

Concentrated HCl (1.8 mmol, 3 M equiv) was added to a solution of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chloride **3** (0.60 mmol) in water (3 ml) and the reaction mixture was stirred in a water bath at 80 °C. After 2–3 h the solvent was removed in the rotary evaporator and acetone was added to the crude mixture to precipitate a solid that was filtered and washed with acetone. The solid was identified as 1-(2-oxo-2*H*-cromen-3-yl)pyridinium chloride **4**, in some cases contaminated with NH_4Cl in variable ratios (calculated by ^{1}H NMR). For characterization purposes, compounds **4** were recrystallized in ethanol, whenever the presence of NH_4Cl was detected.

4.4.1. 1-(2-Oxo-8-methoxy-2H-chromen-3-yl)pyridinium chloride ***4a***.[9] Yellow solid, 83%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.98 (s, 3H), 7.43–7.51 (m, 2H), 7.55 (d, *J*=7.1, 2.4 Hz, 1H), 8.41 (td, *J*=6.3, 1.8 Hz, 2H), 8.85–8.92 (m, 2H), 9.31 (dd, *J*=7.1, 1.5 Hz, 2H) ppm.

4.4.2. 1-(2-Oxo-2H-chromen-3-yl)pyridinium chloride ***4b***. Beige solid, 69%; Mp higher than 300 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1710, 1696, 1628, 1610, 1461 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.54 (t, *J*=6.9 Hz, 1H), 7.62 (d, *J*=8.4 Hz, 1H), 7.85 (td, *J*=7.9, 1.5 Hz, 1H), 7.93 (dd, *J*=7.9, 1.2 Hz, 1H), 8.41 (t, *J*=6.6 Hz, 2H), 8.86–8.92 (m, 2H), 9.31 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.7, 117.6, 125.8, 128.0 (2C), 129.0, 130.2, 134.4, 140.8, 146.0 (2C), 148.4, 153.2, 156.5 ppm; Anal. Calcd for $C_{14}H_{10}NO_2Cl\cdot 0.1NH_4Cl\cdot 0.8H_2O$: C, 60.16; H, 4.30; N, 5.52. Found: C, 59.82; H, 4.17; N, 5.29.

4.4.3. 1-(2-Oxo-8-hydroxy-2H-chromen-3-yl)pyridinium chloride ***4c***. Yellow solid, 75%; Mp 242–244 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1718, 1618, 1572, 1463 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26–7.35 (m, 2H), 7.43 (dd, *J*=7.6, 2.4 Hz, 1H), 8.39 (td, *J*=6.3, 1.5 Hz, 2H), 8.78 (s, 1H), 8.87 (tt, *J*=7.8, 1.2 Hz, 1H), 9.28 (dd, *J*=6.6, 1.2 Hz, 2H), 10.88 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 118.5, 119.7, 120.5, 125.8, 128.0 (2C), 129.0, 141.7, 145.1, 146.0 (2C), 148.2, 156.6 ppm; Anal. Calcd for $C_{14}H_{10}NO_3Cl$: C, 60.98; H, 3.63; N, 5.08. Found: C, 60.75; H, 3.91; N, 5.13.

4.4.4. 1-(2-Oxo-6-methoxy-2H-chromen-3-yl)pyridinium chloride ***4d***. Yellow solid, 53%; Mp 275–277 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1690, 1628, 1575, 1496, 1456 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.90 (s, 3H), 7.42–7.46 (m, 2H), 7.60 (d, *J*=10.0 Hz, 1H), 8.40 (td, *J*=6.4, 1.2 Hz, 2H), 8.78 (s, 1H), 8.88 (tt, *J*=8.0, 1.2 Hz, 1H), 9.28 (dd, *J*=6.8, 1.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.0, 117.9, 118.1, 121.8, 128.0 (2C), 129.4, 140.5, 146.0, 147.6 (2C), 148.3, 156.3, 156.5 ppm; Anal. Calcd for $C_{15}H_{12}NO_3Cl\cdot 2H_2O$: C, 55.30; H, 4.92; N, 4.30. Found: C, 55.31; H, 5.01; N, 4.37.

4.4.5. 1-(2-Oxo-6-hydroxy-2H-chromen-3-yl)pyridinium chloride ***4e***. Brown solid, 74%; Mp higher than 300 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1720, 1687, 1623, 1633, 1570, 1486, 1463 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26 (d, *J*=2.7 Hz, 1H), 7.30 (dd, *J*=9.0, 2.7 Hz, 1H), 7.48 (d, *J*=9.0 Hz, 1H), 8.38 (td, *J*=7.2, 1.2 Hz, 2H), 8.76 (s, 1H), 8.86 (td, *J*=7.2, 1.2 Hz, 1H), 9.27 (dd, *J*=6.9, 1.2 Hz, 2H), 10.38 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 113.7, 117.6, 118.1, 122.4, 128.0 (2C), 129.1, 140.8, 146.0 (2C), 148.2, 154.8, 156.6 ppm; Anal. Calcd for $C_{14}H_{10}NO_3Cl$: C, 60.98; H, 3.63; N, 5.08. Found: C, 60.79; H, 3.91; N, 5.15.

4.4.6. 1-(2-Oxo-7-hydroxy-2H-chromen-3-yl)pyridinium chloride ***4f***. Yellow solid, 91%; Mp higher than 300 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1717, 1695, 1608, 1460 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.01–7.06 (m, 2H), 7.72 (d, *J*=8.4 Hz, 1H), 8.35 (td, *J*=6.8, 1.2 Hz, 2H), 8.71 (s, 1H), 8.83 (tt, *J*=7.6, 1.2 Hz, 1H), 9.25 (dd, *J*=6.8, 1.2 Hz, 2H), 11.52 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.5, 109.7, 114.8, 124.9, 127.8 (2C), 131.6, 141.2, 146.1 (2C), 147.8, 155.4, 156.8, 163.9 ppm; Anal. Calcd for $C_{14}H_{10}NO_3Cl$: C, 60.98; H, 3.63; N, 5.08. Found: C, 60.91; H, 3.72; N, 5.06.

4.4.7. 1-(2-Oxo-8-hydroxy-7-methyl-2H-chromen-3-yl)pyridinium chloride ***4g***. Yellow solid, 94%; Mp higher than 300 °C; IR (Nujol mull) ν 3600–1700 (br, fringed), 1720, 1678, 1580, 1461 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H), 7.15 (d, *J*=8.4 Hz, 1H), 7.58 (d *J*=8.4 Hz, 1H), 8.36 (td, *J*=6.6, 1.2 Hz, 2H), 8.58 (s, 1H), 8.83 (tt, *J*=7.8, 1.2 Hz, 1H), 9.25 (dd, *J*=6.8, 1.2 Hz, 2H), 11.40 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 7.92, 109.8, 111.2, 113.6, 124.6, 128.0 (2C), 128.5, 141.6, 146.1 (2C), 147.8, 153.3, 157.0, 161.8 ppm; Anal. Calcd for $C_{15}H_{12}NO_3Cl$: C, 62.17; H, 4.14; N, 4.86. Found: C, 59.99; H, 0.17; N, 4.85.

4.5. General procedure for the synthesis of 3-amino-2*H*-chromen-2-ones 5

N-Methylpiperazine (10 mmol, 5 M equiv) was added to a suspension of 1-(2-oxo-2*H*-cromen-3-yl)pyridinium chloride **4** (2 mmol, contaminated with NH_4Cl) in acetone (50 ml) and an orange/red suspension was formed and stirred at room temperature. After 2–3 h a red solution was obtained and after a further 18–24 h the solvent was removed in the rotary evaporator leading to a red oil. Flash chromatography was performed using ethyl acetate as eluent. Several crops were isolated, all containing the pure product by TLC. The crops were combined and the solvent was removed in the rotary evaporator. The solid was collected and identified as 3-amino-2*H*-chromen-2-one derivative **5**.

4.5.1. 3-Amino-8-methoxy-2H-chromen-2-one ***5a***.[11] Orange solid, 99% yield. Mp 128–129 °C; IR (Nujol mull) ν 3453, 3362, 1706, 1635, 1612, 1573, 1461 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 5.68 (s, 2H), 6.67 (s, 1H), 6.91 (dd, *J*=8.2, 1.2 Hz, 1H), 6.96 (dd, *J*=7.6, 1.2 Hz, 1H), 7.12 (t, *J*=8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-

d_6): δ 55.8, 107.7, 108.2, 116.6, 122.4, 124.4, 133.5, 136.9, 146.2, 158.3 ppm; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.81; H, 4.95; N, 7.05.

4.5.2. 3-Amino-2H-chromen-2-one ***5b***. Yellow solid, 98% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.68 (s, 2H), 6.70 (s, 1H), 7.18–7.40 (m, 3H), 7.39 (d, J=7.8 Hz, 1H) ppm.

4.5.3. 3-Amino-8-hydroxy-2H-chromen-2-one ***5c***. *N*-Methylpiperazine (0.41 g, 4.05 mmol, 458 μl, 7.2 equiv) was added to a suspension of 1-(2-oxo-8-hydroxy-2*H*-cromen-3-yl)pyridinium chloride **4c**, contaminated with NH_4Cl in a 1:1 ratio (0.19 g, 0.58 mmol) in acetone (25 ml) and water (0.5 ml). The reaction mixture was heated at 70 °C and after 4 h a red solution was obtained. The reaction mixture was heated for a further 5 h and the solvent was removed in the rotary evaporator. Flash chromatography was performed using ethyl acetate (90 ml) as eluent. The solvent was removed in the rotary evaporator and a red solid was collected and identified as 3-amino-8-hydroxy-2*H*-chromen-2-one (87.8 mg, 0.50 mmol, 86% yield). Mp 192–192 °C; IR (Nujol mull) ν 3454, 3439, 3365, 1706, 1634, 1594, 1567, 1460 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.61 (s, 2H), 6.65 (s, 1H), 6.72 (dd, J=7.8, 1.5 Hz, 1H), 6.80 (dd, J=7.8, 1.5 Hz, 1H), 6.97 (t, J=7.8 Hz, 1H), 9.85 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 108.2, 112.4, 115.1, 122.7, 124.4, 133.2, 136.6, 144.2, 158.5 ppm; Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.95; N, 7.91. Found: C, 61.15; H, 4.09; N, 7.98.

4.5.4. 3-Amino-6-methoxy-2H-chromen-2-one ***5d***.[12] Yellow solid, 93% yield. Mp 130–131 °C; IR (Nujol mull) ν 3428, 3311, 1710, 1638, 1612, 1573, 1462 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H), 5.71 (s, 2H), 6.66 (s, 1H), 6.78 (dd, J=8.8, 3.0 Hz, 1H), 6.95 (d, J=3.0 Hz, 1H), 7.18 (t, J=8.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.5, 107.5$_0$, 107.5$_4$, 112.4, 116.3, 122.5, 133.6, 142.3, 155.9, 158.7 ppm; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.83; H, 4.71; N, 7.33. Found: C, 63.19; H, 5.04; N, 7.39.

4.5.5. 3-Amino-6-hydroxy-2H-chromen-2-one ***5e***.[11] *N*-Methylpip erazine (0.29 g, 2.92 mmol, 330 μl, 7 equiv) was added to a suspension of 1-(2-oxo-6-hydroxy-2*H*-cromen-3-yl)pyridinium chloride **4e**, contaminated with NH_4Cl in a 1:1 ratio (0.14 g, 0.41 mmol) in acetone (22 ml) and water (0.5 ml). The reaction mixture was heated at 70 °C and after a few minutes a red solution was obtained. After 9 h the solvent was removed in the rotary evaporator and flash chromatography was performed using ethyl acetate (80 ml) as eluent. The solvent was removed in the rotary evaporator and an orange solid was collected and identified as 3-amino-6-hydroxy-2*H*-chromen-2-one **5e** (52.2 mg, 0.30 mmol, 71% yield). Mp 213–214 °C; IR (Nujol mull) ν 3465, 3390, 3347, 1683, 1630, 1561, 1461 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.59 (s, 2H), 6.59 (s, 1H), 6.63 (dd, J=8.8, 2.8 Hz, 1H), 6.70 (d, J=2.8 Hz, 1H), 7.08 (d, J=8.8 Hz, 1H), 9.37 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 107.7, 109.2, 113.2, 116.2, 122.4, 133.3, 141.5, 153.9, 158.8 ppm; Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.95; N, 7.91. Found: C, 61.34; H, 4.34; N, 7.83.

4.5.6. 3-Amino-7-hydroxy-2H-chromen-2-one ***5f***.[13] *N*-Methylpiperazine (0.29 g, 2.92 mmol, 330 μl, 5 equiv) was added to a suspension of 1-(2-oxo-7-hydroxy-2*H*-cromen-3-yl)pyridinium chloride **4f**, contaminated with NH_4Cl in a 1:0.7 ratio (0.18 g, 0.58 mmol) in acetone (25 ml) and water (0.5 ml). The reaction mixture was refluxed for 9 h. The solvent was removed in the rotary evaporator and flash chromatography was performed using ethyl acetate (30 ml) as eluent. The solvent was removed in the rotary evaporator, resulting in an orange solid, collected and identified as 3-amino-7-hydroxy-2*H*-chromen-2-one **5f** (0.10 g, 0.57 mmol, 98% yield). Mp 244–245 °C; IR (Nujol mull) ν 3438, 3347, 3173, 1680, 1609, 1556, 1460 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.22 (s, 2H), 6.63–6.69 (m, 3H), 7.22 (d, J=8.7 Hz, 1H), 9.80 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 101.8, 109.8, 113.0, 113.5, 125.7, 130.2, 149.3, 156.1, 159.0 ppm; Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.95; N, 7.91. Found: C, 61.31; H, 4.23; N, 8.12.

4.5.7. 3-Amino-7-hydroxy-8-methyl-2H-chromen-2-one ***5g***. *N*-Methylpiperazine (0.36 g, 3.61 mmol, 409 μl, 5 equiv) was added to a suspension of 1-(2-oxo-8-hydroxy-7-methyl-2*H*-cromen-3-yl) pyridinium chloride **4g** (0.21 g, 0.72 mmol) in acetone (30 ml) and water (0.6 ml). The reaction mixture was heated at 70 °C and after 3 h a red solution was obtained. The solvent was removed in the rotary evaporator after 19 h. Flash chromatography was performed using ethyl acetate (150 ml) as eluent. The solvent was removed in the rotary evaporator and a red solid was collected and identified as 3-amino-8-hydroxy-7methyl-2*H*-chromen-2-one **5g** (0.084 g, 0.44 mmol, 61% yield). Mp 213–214 °C; IR (Nujol mull) ν 3443, 3380, 3254, 1679, 1633, 1604, 1568, 1461 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (s, 3H), 5.17 (s, 2H), 6.68 (s, 1H), 6.73 (d, J=8.4 Hz, 1H), 7.05 (d, J=8.4 Hz, 1H), 9.71 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 8.1, 110.3, 110.5, 112.1, 113.5, 122.4, 129.8, 147.7, 154.1, 159.3 ppm; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.95; H, 4.74; N, 7.46.

4.6. General procedure for the synthesis of 2-imino-2*H*-chromen-3-amines 9

N-Methylpiperazine (1.5 mmol, 5 equiv) was added to a suspension of 1-(2-imino-2*H*-chromen-3-yl)pyridinium chloride derivatives **3** (0.30 mmol) in acetonitrile or acetone (12 ml) and a red solution/suspension was obtained and stirred at room temperature. After 17–48 h the solvent was removed in the rotary evaporator leading to a red oil. Flash chromatography was performed using ethyl acetate as eluent to separate the product and the solvent was removed in the rotary evaporator. The orange solid was collected and identified as 2-imino-2*H*-chromen-3-amine **9**.

4.6.1. 2-Imino-8-methoxy-2H-chromen-3-amine ***9a***. Orange solid, 70% yield. Mp 115–117 °C; IR (Nujol mull) ν 3422, 3291, 3235–3078 (br), 1645, 1620, 1557, 1450 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3H), 5.43 (s, 2H), 6.18 (s, 1H), 6.74–6.79 (m, 2H), 6.95 (t, J=8.1 Hz, 1H), 8.30 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.5, 100.9, 107.8, 116.3, 123.0, 123.1, 134.8, 137.2, 145.8, 153.4 ppm; Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.20; H, 5.27; N, 14.74.

4.6.2. 2-Imino-2H-chromen-3-amine ***9b***. Orange solid, 42% yield. Mp 116–118 °C; IR (Nujol mull) ν 3429, 3366–3120 (br), 1644, 1626, 1588, 1451 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.45 (s, 2H), 6.22 (s, 1H), 7.00–7.05 (m, 3H), 7.17 (d, J=8.0 Hz, 1H), 8.27 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.1, 114.2, 122.3, 123.3, 124.1, 124.4, 134.4, 148.3, 154.1 ppm; Anal. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.51; H, 5.06; N, 17.64.

4.6.3. 2-Imino-8-hydroxy-2H-chromen-3-amine ***9c*** *and 4-methyl-1-(5-(4-methylpiperazin-1-yl)penta-2,4-dien-1-ylidene)piperazin-1-ium chloride* ***10***. *N*-Methylpiperazine (0.62 g, 6.18 mmol, 700 μl, 7 equiv) was added to a suspension of 1-(2-imino-8-hydroxy-2*H*-chromen-3-yl)pyridinium chloride (0.24 g, 0.89 mmol) in acetone (40 ml) and an orange suspension was obtained and stirred at room temperature. After 2 days the yellow solid was filtered and washed with ethyl acetate, leading to a mixture of 2-imino-8-hydroxy-2*H*-chromen-3-amine and piperazinium chloride **10** (1:1 ratio), by ^{1}H NMR. Flash chromatography of the isolated mixture was performed using a mixture of DCM and MeOH 4–10% (150 ml) as eluent. The solvents of this orange

solution were removed in the rotary evaporator and the orange solid was collected and identified as 2-imino-8-hydroxy-2*H*-chromen-3-amine **9c** (52.9 mg, 0.30 mmol, 47% yield). Mp 168–170 °C; IR (Nujol mull) ν 3485–3091 (br), 1658, 1626, 1563, 1457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.36 (s, 2H), 6.16 (s, 1H), 6.59 (dd, J=7.8, 1.2 Hz, 1H), 6.61 (dd, J=7.8, 1.2 Hz, 1H), 6.80 (t, J=8.8 Hz, 1H), 8.00 (s, 1H), 9.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 108.2, 112.4, 115.1, 122.7, 124.4, 133.2, 136.5, 144.2, 158.5 ppm; Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.91. Found: C, 61.54; H, 4.52; N, 15.95.

Flash chromatography was continued using a mixture of DCM and MeOH 12–20% (150 ml) as eluent and the solvent of this orange solution was removed in the rotary evaporator. An orange oil was obtained and identified as piperazinium chloride **9c** (44.4 mg, 0.145 mmol). Silica from the flash chromatography was stirred, at room temperature, in 100 ml of a mixture of DCM and MeOH 20% for 17 h. The silica was filtered off and the solvent of the yellow solution was removed in the rotary evaporator. An orange oil was obtained and identified as a second crop of piperazinium chloride (11.2 mg, 0.04 mmol). 4-Methyl-1-(5-(4-methylpiperazin-1-yl)penta-2,4-dien-1-ylidene) piperazin-1-ium chloride **10** was isolated as an orange oil and in a total yield of 21% (0.56 g, 0.18 mmol). ^1H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 6H), 2.43–2.50 (m, 8H), 3.57 (t, J=4.8 Hz, 4H), 3.62 (t, J=4.8 Hz, 4H), 5.94 (t, J=12.0 Hz, 2H), 7.48 (t, J=12.4 Hz, 1H), 7.84 (d, J=12.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.0 (2C), 45.7 (2C), 53.4 (2C), 54.4 (2C), 102.7 (2C), 160.1 (2C), 163.1 ppm.

4.6.4. 2-Imino-6-methoxy-2H-chromen-3-amine ***9d***. Orange solid, 60% yield. Mp 136–138 °C; IR (Nujol mull) ν 3453, 3322, 3272, 1644, 1620, 1601, 1563, 1488, 1451 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 5.48 (s, 2H), 6.19 (s, 1H), 6.61 (dd, J=8.8, 2.8 Hz, 1H), 6.75 (d, J=2.8 Hz, 1H), 6.94 (d, J=8.8 Hz, 1H), 8.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.3, 101.1, 107.9, 110.6, 114.8, 123.0, 134.9, 142.6, 154.5, 155.1 ppm; Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.18; H, 5.16; N, 14.75.

4.6.5. 2-Imino-6-hydroxy-2H-chromen-3-amine ***9e***. Orange solid, 52% yield. Mp 200 °C (decomp.); IR (Nujol mull) ν 3397, 3297, 3247–3097 (br), 1638, 1607, 1563, 1488, 1457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.39 (s, 2H), 6.12 (s, 1H), 6.46 (dd, J=8.8, 2.8 Hz, 1H), 6.52 (d, J=2.8 Hz, 1H), 6.84 (d, J=8.8 Hz, 1H), 8.06 (s, 1H), 9.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.3, 109.3, 111.6, 114.7, 122.8, 134.6, 141.7, 153.0, 154.6 ppm; Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.91. Found: C, 61.36; H, 4.58; N, 15.99.

4.6.6. 2-Imino-7-hydroxy-2H-chromen-3-amine ***9f***. Orange solid, 61% yield. Mp 178 °C (decomp.); IR (Nujol mull) ν 3435, 3353–3065 (br), 1632, 1607, 1556, 1500, 1457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.03 (s, 2H), 6.18 (s, 1H), 6.45 (d, J=2.4 Hz, 1H), 6.49 (dd, J=8.4, 2.4 Hz, 1H), 6.99 (d, J=8.4 Hz, 1H), 8.08 (s, 1H), 9.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.3, 102.8, 111.1, 113.8, 124.9, 131.5, 149.4, 155.3 (2C) ppm; Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.91. Found: C, 61.37; H, 4.58; N, 16.02.

4.6.7. 2-Imino-6-hydroxy-2H-chromen-3-amine ***9g***. Orange solid, 54% yield. Mp 176–178 °C; IR (Nujol mull) ν 3441, 3322, 3285, 1644, 1626, 1588, 1557, 1469, 1457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.64 (s, 2H), 6.18 (s, 1H), 6.90–7.05 (m, 2H), 7.28 (s, 1H), 8.40 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.3, 115.7, 123.0, 123.4, 124.4, 127.1, 135.7, 146.7, 153.0 ppm; Anal. Calcd for $C_9H_7N_2OCl$: C, 55.53; H, 3.60; N, 14.40. Found: C, 55.56; H, 3.65; N, 14.51.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra of all intermediates and final products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.074.

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