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Reaction of chromone-3-carbaldehyde with α-amino acids—syntheses of 3- and 4-(2-hydroxybenzoyl)pyrroles

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Abstract—Azomethine ylides generated from the reaction of chromone-3-carbaldehyde with α-amino acids undergo 1,5-electrocyclization reactions to afford 3- and 4-(2-hydroxybenzoyl)pyrroles. These ylides can be trapped with dipolarophiles in 1,3-dipolar cycloaddition reactions to yield chromonyl pyrrolidines. The reaction of chromone-3-carbaldehyde with methyl glycinate gives a mixture of pyrrole, pyridine, and 3-aza-9-xanthenone derivatives.

1. Introduction

Chromone-3-carbaldehyde has been extensively used in the synthesis of various heterocyclic systems since its convenient synthesis was reported in the 1970s. The synthesis and reactivity of this versatile compound have been reviewed.[1–4] Much of the synthetic utilities of this compound are derived from the reactivity of its electron-deficient centers at C-2, C-4, and formyl group.[2] Chromone-3-carbaldehyde can give access to compounds where the chromone ring is retained or to 2-hydroxybenzoyl derivatives resulting from the opening of the pyran-4-one ring.

Chromone-3-carbaldehyde has been used to prepare 1,3-dipolar compounds, namely, nitrones,[5,6] nitrile imines,[7] nitrile oxides,[8] and azomethine ylides.[9] The utility of these dipolar species in 1,3-dipolar cycloadditions has already been demonstrated. Here we describe the generation of azomethine ylides from the reaction of chromone **1** with various α-amino acids and one α-amino ester. This study allowed us to find that these dipoles give mainly 1,5-electrocyclizations, affording 3- and 4-(2-hydroxybenzoyl)pyrroles. It is known that benzoylpyrroles show antibacterial[10] and anti-inflammatory activity[11] and act as aldose reductase inhibitors.[11] In that way, the pyrrole derivatives described here are potential biologically active agents. Considering that pyrroles have found many applications in medicine and in technology,[12] novel synthesis for these type of compounds is, therefore, of interest.

Keywords: Azomethine ylides; Benzoylpyrroles; 1,5-Electrocyclizations; 1,3-Dipolar cycloadditions; Chromones.
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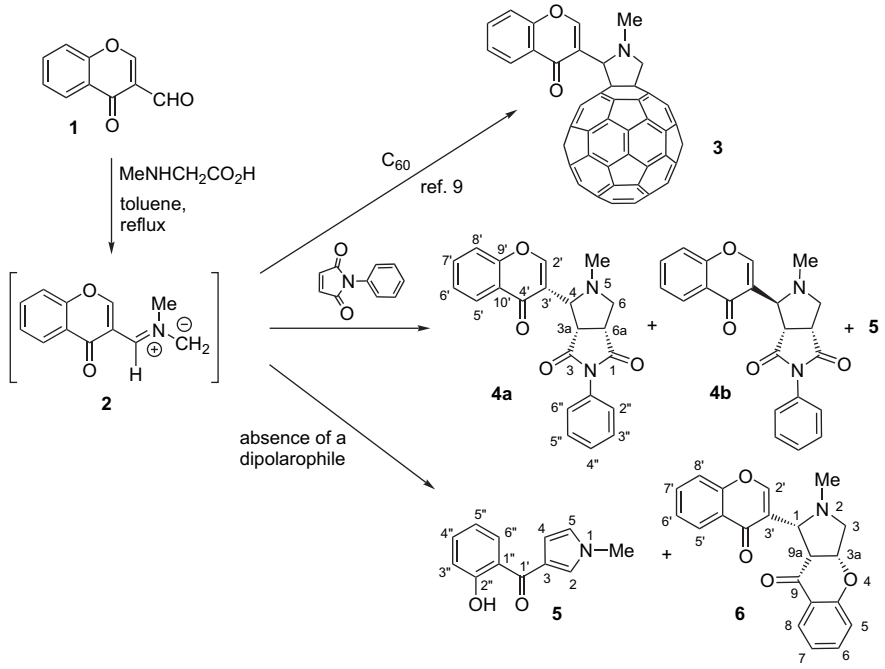
2. Results and discussion

Recently, we described the synthesis of the fullerene–chromone dyad **3** from the 1,3-dipolar cycloaddition of chromone-azomethine ylide **2** with C_{60} (Scheme 1).[9] Since the azomethine ylide **2** can be easily generated in situ from chromone-3-carbaldehyde and *N*-methylglycine, we thought that it could be a useful intermediate in the synthesis of other chromonyl pyrrolidines. We decided then to study the reaction of **2** with various dipolarophiles in order to obtain a range of novel chromonyl pyrrolidines just by changing the dipolarophile. As expected, when the azomethine ylide **2** was generated in the presence of *N*-phenylmaleimide the cycloadducts **4a** and **4b** were obtained (60% yield, as a mixture of cis/trans diastereoisomers). In this reaction, the 3-(2-hydroxybenzoyl)pyrrole **5** was also formed in 27% yield. Surprisingly, when we used dimethyl fumarate, 1,4-naphthoquinone or dimethyl acetylenedicarboxylate as dipolarophiles the expected cycloadducts were not obtained; in all cases pyrrole **5** was the isolated product. In the absence of any dipolarophile, pyrrole **5** was obtained in 80% yield just by refluxing a toluene solution of chromone **1** and *N*-methylglycine (2.5 equiv), under nitrogen atmosphere. It is well known that *N*-methylglycine reacts with aldehydes and ketones generating azomethine ylides.[13] In that way, the formation of pyrrole **5** probably involves the 1,5-electrocyclization[14] of dipole **2** followed by the opening of the pyran-4-one ring (Scheme 2).[15] The reaction of chromone **1** with *N*-methylglycine has already been described, but different experimental conditions were used. Clarke et al.[16] obtained pyrrole **5** in 72% yield by heating at reflux, for 6 h, a toluene solution of equimolar quantities of the two reagents in the presence of a catalytic amount of *p*-toluenesulfonic acid and using a Dean–Stark water trap. These

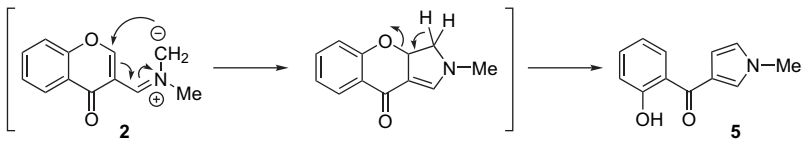


Scheme 1.

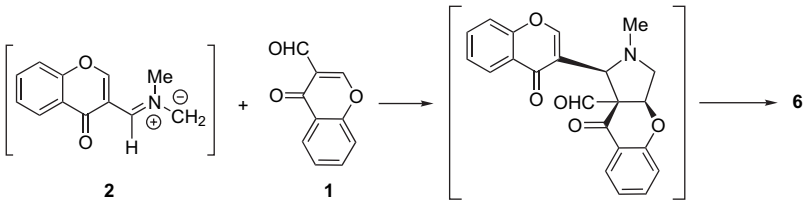
authors postulated a completely different mechanism for this reaction, suggesting that pyrrole **5** 'arises via attack of the secondary amine (with ring-opening) at the chromone 2-position. Subsequent cyclization of the resulting enamine then leads to the pyrrole-2-carboxylic acid, which is readily decarboxylated to the observed product.'[16]

We have also isolated from the reaction of chromone **1** with *N*-methylglycine a minor product which incorporates two units of chromone. This product, identified as **6** (vide infra), presumably results from the 1,3-dipolar cycloaddition of dipole **2** to another molecule of chromone **1**[17] followed by deformylation[18] of the resulting cycloadduct, as indicated in Scheme 3. The yield of compound **6** was increased to 50% by reacting chromone **1** with *N*-methylglycine in a 10:1 proportion (pyrrole **5** was obtained in 22% yield in this experiment). It is worth to note that this 'dimerization' is simultaneously regio- and stereoselective, although other two isomers of compound **6** were also isolated (ca. 3% yield each). The all-cis configuration of compound **6**, resulting from an *endo* transition state, was deduced by 2D NMR experiments (vide infra).

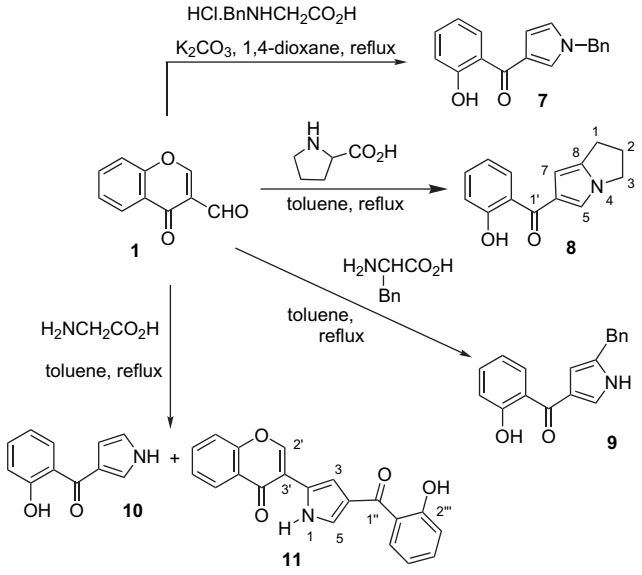
The reaction of aldehyde **1** with *N*-benzylglycine, L-proline, L-phenylalanine, and glycine was also studied in order to find if the corresponding azomethine ylides generated also undergo 1,5-electrocyclization (Scheme 4). The reaction between aldehyde **1** and *N*-benzylglycine hydrochloride (2.5 equiv) was carried out in refluxing dry 1,4-dioxane (5 h) in the presence of potassium carbonate (2.5 equiv) and afforded the *N*-benzylpyrrole **7** in 87% yield. The reaction of aldehyde **1** with L-proline or with L-phenylalanine, in refluxing toluene, afforded complex product mixtures from which the corresponding pyrroles **8** and **9** were isolated in 22% and 27% yields, respectively. The reaction between aldehyde **1** and glycine (5 equiv), in refluxing toluene (17 h), afforded pyrroles **10** and **11**[19] in 46% and 2% yields, respectively. A probable mechanism for the formation of the minor



Scheme 2.

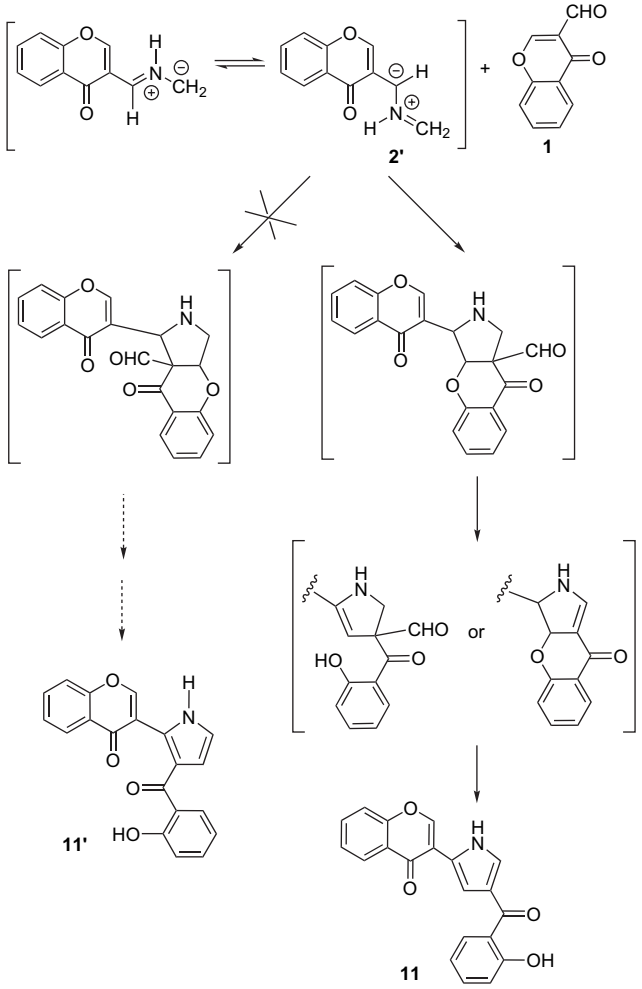


Scheme 3.



Scheme 4.

pyrrole **11** is shown in Scheme 5. The structure of **11** is unexpected since it corresponds to the inversion in the regiochemistry of the cycloaddition observed when *N*-methylglycine is used. A plausible explanation for this inversion



Scheme 5.

in the regioselectivity is the stabilization of the intermediate azomethine ylide **2′** by intramolecular hydrogen bonding; this type of stabilization is not possible in the azomethine ylide **2**.

The reaction of aldehyde **1** with ethyl glycinate, and with other α-amino esters, gives typically a mixture of pyridine and pyrrole derivatives.[16,20] We decided to re-examine the reaction of aldehyde **1** with methyl glycinate and found that the outcome is highly dependent on the reaction conditions. For instance, the reaction of **1** with methyl glycinate hydrochloride (5 equiv) and potassium carbonate (5 equiv) in refluxing toluene afforded two main products: the expected pyrrole **12** (37% yield) and the pyridine derivative **13** (6% yield) (Scheme 6).[20,21] When only 1 equiv of methyl glycinate hydrochloride and 0.5 equiv of potassium carbonate were used, pyrrole **12** was obtained in only 8% yield and compound **13** was the main product (21% yield). In this case, a new product was also isolated, which was identified as 3-aza-9-xanthenone **14** (12% yield). When these reactions were carried out in 1,4-dioxane the pyrrole **12** was obtained in much higher yield. For instance, when a mixture of **1**, methyl glycinate hydrochloride (5 equiv), and potassium carbonate (5 equiv) in dry 1,4-dioxane was refluxed for 4 h, pyrrole **12** was obtained in 54% yield. In this case, compounds **13** and **14** were not formed.

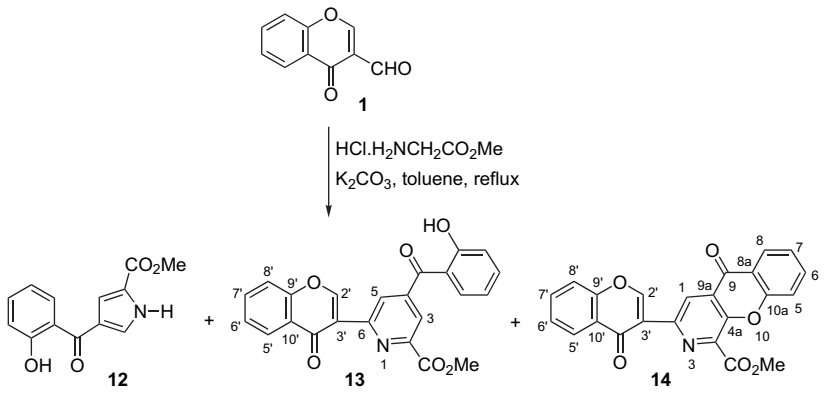
A probable mechanism for the formation of compounds **13** and **14** is indicated in Scheme 7.[22] It is possible that dihydro-3-aza-9-xanthenone **15** is a common intermediate for both compounds: isomerization with ring-opening leads to **13** while dehydrogenation affords **14**.

2.1. Structural characterization of the new compounds

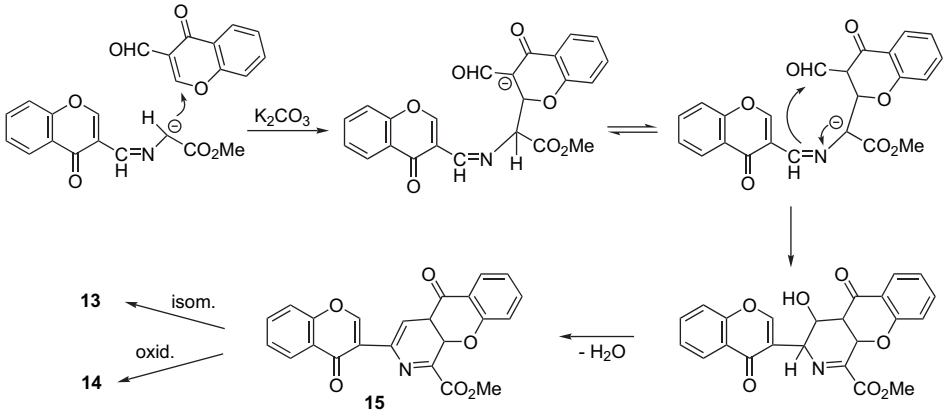
All new compounds were characterized by ^{1}H and ^{13}C NMR, MS, and elemental analysis or HRMS. As said above, compounds **5**, **11**, **12**, and a derivative of **13** were previously synthesized by other approaches.[16,21,20] Since the earlier structural characterization of these compounds was not complete, a detailed NMR characterization of these compounds was also included here.

In the ^{1}H NMR spectra of cycloadducts **4a** and **4b** (see Section 4) the resonance of the *N*-methyl group appears as a singlet at ca. δ 2.3 ppm. In the spectrum of diastereoisomer **4a**, the resonances of the two unequivalent protons H-6 appear at δ 2.71 and 3.70 ppm, respectively, as a double doublet and as a doublet. For the isomer **4b** these signals appear at δ 2.97 and 3.51 ppm, both as double doublets. In compound **4a** proton H-4 appears at δ 3.98 ppm as a doublet with J=8.4 Hz, which is consistent with a cis relationship with H-3a. For the same compound, protons H-3a and H-6a appear as double doublets ($J_{3a,4}$=8.4 Hz, $J_{3a,6a}$=7.9 Hz, $J_{6a,6}$=7.4 Hz) at δ 3.87 and 3.43 ppm, respectively. From these data it is clear that, in compound **4a**, protons H-4, H-3a, and H-6a are all co-planar (all-cis configuration). These data were corroborated by NOESY experiments. For isomer **4b** the signals corresponding to protons H-4, H-3a, and H-6a appear within multiplets, preventing the determination of coupling constants.

The resonances of the protons and carbons in the chromone moiety of compounds **4** were identified by their 2D COSY,



Scheme 6.



Scheme 7.

HSQC, and HMBC spectra, and also by comparison with our previous work.[23] The resonance of H-2′ in **4b** appears at δ 7.93 ppm as a singlet while in **4a** it appears at 7.79 ppm as a doublet, due to long-range coupling with H-4 ($J_{2',4}$=0.8 Hz). In both isomers, the resonance of H-5′ appears as a doublet of doublets at ca. δ 8.2 ppm with $J_{5',6'}$=8.0 Hz and $J_{5',7'}$=1.6 or 1.7 Hz; H-7′ appears at ca. 7.7 ppm as a double doublet of doublets (for **4a** and **4b**).

In the ^{13}C NMR spectra of compounds **4**, the resonance of the *N*-methyl group appears at δ 38–40 ppm. The signals corresponding to carbons C-4 and C-6 appear, respectively, at ca. δ 64–66 and 58–59 ppm, while the signals corresponding to C-3a and C-6a appear at ca. δ 48–50 and 44–45 ppm, respectively. The resonances of the three carbonyl groups appear at δ 175–178 ppm.

The connectivities found in the HMBC spectra of compounds **4** allowed the assignment of the quaternary carbon resonances; some of the most important connectivities for dyad **4a** are shown in Figure 1.

The ^{1}H NMR spectrum of compound **6** is similar to that of compound **4a**; the main difference is the position of the signals corresponding to protons H-1 (doublet at δ 4.42 ppm) and H-3a (multiplet centered at δ 5.1 ppm). The ^{13}C NMR spectrum of cycloadduct **6** shows, among others, peaks corresponding to five sp^3 carbons and two carbonyl carbons (δ 177.0 and 190.0 ppm). The all-cis configuration of protons H-1, H-9a, and H-3a was deduced from the NOESY spectrum. The regiochemistry of the compound was deduced from the HMBC spectrum, which shows the connectivities of H-1 with C-2′, C-3′, C-4′, and C-9a and of H-9a with C-9, C-8a, and C-1, which are only compatible with the structure depicted in Scheme 1 and Figure 2.

The ^{1}H NMR spectrum of pyrrole **5** shows two distinctive singlets: one at δ 3.74 ppm corresponding to the N–Me group, and the other at 12.22 ppm corresponding to the hydroxyl group. The resonance corresponding to the pyrrolic proton H-2 appears at δ 7.28 ppm, while H-4 and H-5 give a multiplet at 6.65–6.69 ppm. The signals corresponding to the remaining protons show the expected chemical shifts and multiplicities. The ^{13}C NMR spectrum of pyrrole **5** shows three distinctive signals: one at δ 36.7 ppm corresponding to the N–Me group, one at 162.2 ppm corresponding to C-2″ and one at 193.6 ppm corresponding to the carbonyl group. The remaining signals appear in the range δ 111.3–134.8 ppm.

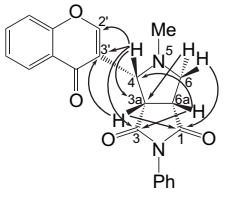


Figure 1. Main connectivities observed in the HMBC spectrum of compound **4a**.

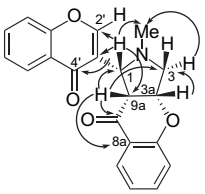


Figure 2. Main connectivities observed in the HMBC spectrum of compound **6**.

As expected, the ^{1}H NMR spectra of pyrroles **7**–**10**, and **12** show similar features to that of the spectrum of pyrrole **5**. The signal of the NH proton, for compounds **9**, **10**, and **12**, appears as a broad singlet at δ 8.47, 8.76, and 9.72 ppm, respectively.

The ^{1}H NMR spectrum of pyrrole **11** shows, simultaneously, features corresponding to a chromonyl group and to a 2-hydroxybenzoyl moiety. The resonances of protons H-3 and H-5 were identified as two doublet of doublets centered at δ 7.01 (J=2.3 and 1.6 Hz) and 7.52 ppm (J=3.0 and 1.6 Hz), respectively. The signal of the NH proton appears as a broad singlet at 11.50 ppm, which indicates that it is involved in hydrogen bonding with the chromone carbonyl group. The NOESY spectrum of this compound shows close proximity between H-2′ (8.52 ppm) and H-3, indicating that it must have the structure (and conformation) shown in Scheme 4. The broad singlet at 12.15 ppm was attributed to the 2‴-hydroxyl proton.

The ^{1}H NMR spectrum of pyridine **13** shows signals typical of the chromonyl group and of the 2-hydroxybenzoyl moiety. The resonances of protons H-2′ and H-5′ appear, respectively, as a singlet at δ 9.08 ppm and as a doublet of doublets centered at 8.32 ppm; the resonance of the hydroxyl proton appears at 11.82 ppm. It also displays double doublets (J=1.5 Hz) centered at δ 8.27 and 8.88 ppm, which were assigned, respectively, to the pyridine protons H-5 and H-3. The resonance of the methyl ester group appears at 4.06 ppm. The ^{13}C NMR spectrum shows the resonances of three carbonyl groups at 165 (CO_2Me), 176 (C-4′), and 199 ppm (4-COAr). The substituted carbons from the pyridine nucleus appear at 152.0 (C-6), 148.1 (C-4), and 146.3 (C-2) ppm; carbons C-5 and C-3 appear at 122.6 and 125.9 ppm, respectively.

The ^{1}H NMR spectrum of compound **14** is similar to that of **13**, except the absence of the signals corresponding to the hydroxyl proton and to H-3.

3. Conclusions

Chromone-3-carbaldehyde reacts with amino acids to generate chromone-azomethine ylides, which undergo 1,5-electrocyclization to yield 3- or 4-(2-hydroxybenzoyl)pyrrole. In the presence of a dipolarophile, these ylides can participate in 1,3-dipolar cycloaddition reactions to yield chromonyl pyrrolidines. The reaction of chromone-3-carbaldehyde with methyl glycinate gives a mixture of pyrrole, pyridine, and 3-aza-9-xanthenone derivatives. The regio- and stereochemistry of the products were established by 1D and 2D NMR studies.

4. Experimental section

4.1. General

Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^{1}H and ^{13}C solution NMR spectra were recorded in $CDCl_3$ solutions (unless otherwise stated), on a Bruker Avance 300 spectrometer (except compounds **11** and **14**, which were recorded on a Bruker Avance 500). TMS was used as an internal reference and the solvent is indicated in each case; the chemical shifts are expressed in δ (ppm) and the coupling constants (J) in hertz (Hz). ^{1}H assignments were made using 2D *g*COSY and NOESY (mixing time of 800 ms) experiments, while ^{13}C assignments were made on the basis of 2D *g*HSQC and *g*HMBC experiments (delay for long-range J C/H couplings were optimized for 7 Hz).

Mass spectra and HRMS were recorded on VG AutoSpec Q and M mass spectrometers using $CHCl_3$ as solvent and NBA as matrix. Elemental analyses were performed in a Leco 932 CHNS analyser. Column chromatography was carried out using silica gel (Merck, 35–70 mesh). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick).

4.1.1. 1,3-Dipolar cycloaddition of azomethine ylide 2 with *N*-phenylmaleimide. A toluene (30 mL) solution of chromone-3-carbaldehyde (**1**) (129 mg, 0.739 mmol), *N*-methylglycine (129 mg, 1.44 mmol), and *N*-phenylmaleimide (200 mg, 1.15 mmol) was refluxed for 7 h under nitrogen atmosphere. The solvent was removed under vacuum and the mixture was purified by flash chromatography (silica) using a gradient of CH_2Cl_2 to CH_2Cl_2/ethyl acetate (50:50) as an eluent. The first fraction was the unchanged *N*-phenylmaleimide and the next one was pyrrole **5** (40 mg, 27% yield). The next fraction was adduct **4a** (isomer with cis configuration), which was further purified by preparative TLC using toluene/ethyl acetate (90:10) as an eluent. Compound **4a** was crystallized from 1-chlorobutane to afford white crystals (91.3 mg, 33% yield) with mp 242–243 °C. The last fraction was adduct **4b** (isomer with trans configuration), which was crystallized from 1-chlorobutane to afford white crystals (75.3 mg, 27% yield) with mp 272–274 °C.

4.1.1.1. *rel*-(3a*S*,4*R*,6a*S*)-5-Methyl-4-(4-oxo-4*H*-chromen-3-yl)-2-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]-pyrrole-1,3-dione, 4a. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=8.25 (dd, J=8.0, 1.7 Hz, 1H, H-5′), 7.79 (d, J=0.8 Hz, 1H, H-2′), 7.65 (ddd, J=8.6, 7.0, 1.7 Hz, 1H, H-7′), 7.34–7.44 (m, 5H, H-6′,8′,3″,4″,5″), 7.18–7.21 (m, 2H, H-2″,6″), 3.98 (br d, J=8.4 Hz, 1H, H-4), 3.87 (dd, J=8.4, 7.9 Hz, 1H, H-3a), 3.70 (d, J=9.8 Hz, 1H, H-6), 3.43 (dd, J=7.9, 7.4 Hz, 1H, H-6a), 2.71 (dd, J=9.8, 7.4 Hz, 1H, H-6), 2.33 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=178.0 (C-1), 177.4 (C-4′), 174.8 (C-3), 156.4 (C-9′), 153.2 (C-2′), 133.7 (C-7′), 131.8 (C-1″), 129.1 (C-3″,5″), 128.5 (C-4″), 126.3 (C-2″,6″), 125.8 (C-5′), 125.2 (C-8′), 123.5 (C-10′), 120.4 (C-3′), 118.2 (C-6′), 63.9 (C-4), 58.9 (C-6), 48.2 (C-3a), 43.7 (C-6a), 40.2 (CH$_3$). MS (EI) m/z (%): 374 ($M^{+\bullet}$, 15.5), 359 (100), 345 (0.6), 329 (0.6), 252 (4.3), 238 (12.0), 226 (11.9), 212 (28), 200 (6.0), 186

(2.8), 172 (4.2), 159 (2.9), 141 (0.7), 128 (2.9), 121 (7.3), 114 (3.9), 106 (4.8), 91 (9.9), 84 (6.9), 77 (13.0), 65 (7.1), 57 (1.0), 51 (5.6). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; N, 7.48; H, 4.85. Found: C, 70.53; N, 7.39; H, 4.90.

4.1.1.2. *rel*-(3a*S*,4*S*,6a*S*)-5-Methyl-4-(4-oxo-4*H*-chromen-3-yl)-2-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]-pyrrole-1,3-dione, 4b. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=8.23 (dd, *J*=8.0, 1.6 Hz, 1H, H-5′), 7.93 (s, 1H, H-2′), 7.71 (ddd, *J*=8.5, 7.0, 1.6 Hz, 1H, H-7′), 7.33–7.51 (m, 7H, H-6′,8′, H–Ph), 3.82–3.88 (m, 3H, H-3a,4,6a), 3.51 (dd, *J*=9.7, 7.6 Hz, 1H, H-6), 2.97 (dd, 1H, *J*=9.7, 4.1 Hz, H-6), 2.25 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=177.9 (C-1), 177.4 (C-3), 177.2 (C-4′), 156.2 (C-9′), 155.3 (C-2′), 134.0 (C-7′), 131.9 (C-1″), 129.1 (C-3″,5″), 128.6 (C-4″), 126.5 (C-2″,6″), 126.0 (C-5′), 125.6 (C-6′), 124.3 (C-10′), 120.7 (C-3′), 118.1 (C-8′), 66.0 (C-4), 57.8 (C-6), 50.5 (C-3a), 45.4 (C-6a), 38.1 (CH_3). MS (EI) *m*/*z* (%): 374 ($M^{+\bullet}$, 15), 359 (100), 345 (0.5), 329 (0.2), 291 (0.3), 274 (0.3), 252 (1.7), 238 (5.9), 226 (6.5), 212 (14.5), 199 (9.8), 184 (1.9), 171 (7.4), 160 (3.0), 128 (2.7), 121 (4.8), 114 (3.8), 106 (2.6), 92 (4.7), 84 (16.5), 65 (3.8), 57 (0.8). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; N, 7.48; H, 4.85. Found: C, 70.58; N, 7.38; H, 4.88.

4.1.2. Reaction of chromone-3-carbaldehyde with *N*-methylglycine. The best procedure to synthesize pyrrole **5** was the following: a solution of chromone-3-carbaldehyde **1** (50.9 mg, 0.29 mmol) and *N*-methylglycine (64.6 mg, 0.73 mmol) in toluene (25 mL) was heated at reflux under N_2 for 7:30 h. Part of the solvent was removed under vacuum and the mixture was purified by flash chromatography using toluene as an eluent. The first fraction to be collected was pyrrole **5**; it was crystallized from ethanol to afford yellow crystals (46.9 mg, 80% yield) with mp 76–77 °C (lit.,[16] 83–84 °C). A minor fraction of pyrrolidine **6** was also isolated. The yield of compound **6** could be increased to 50% by reacting chromone **1** with *N*-methylglycine in a 10:1 proportion. In this case the pyrrole **5** was obtained in 22% yield. Pyrrolidine **6** was crystallized from ethanol to afford yellow crystals with mp 166–169 °C.

4.1.2.1. 3-(2-Hydroxybenzoyl)-1-methylpyrrole, 5. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=12.22 (s, 1H, 2″-OH), 7.94 (dd, *J*=8.0, 1.7 Hz, 1H, H-6″), 7.44 (ddd, *J*=8.4, 7.1, 1.7 Hz, 1H, H-4″), 7.28 (t, *J*=1.9 Hz, 1H, H-2), 7.02 (dd, *J*=8.4, 1.1 Hz, 1H, H-3″), 6.90 (ddd, *J*=8.0, 7.1, 1.1 Hz, 1H, H-5″), 6.65–6.69 (m, 2H, H-4,5), 3.74 (s, 3H, N–CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=193.6 (C=O), 162.2 (C-2″), 134.8 (C-4″), 131.7 (C-6″), 128.3 (C-2), 123.6 (C-3), 123.3 (C-5), 120.5 (C-1″), 118.4 (C-5″), 118.0 (C-3″), 111.3 (C-4), 36.7 (N–CH_3). MS (EI) *m*/*z* (%): 201 ($M^{+\bullet}$, 87), 184 (9.5), 173 (2), 159 (2), 149 (4), 131 (2), 121 (10), 115 (2), 108 (41), 104 (1.5), 100 (3.5), 92 (5), 81 (100), 65 (8), 53 (9). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; N, 6.96; H, 5.51. Found: C, 71.49; N, 6.58; H, 5.76.

4.1.2.2. *rel*-(1*R*,3a*R*,9a*R*)-2-Methyl-1-(4-oxo-4*H*-chromen-3-yl)-1,3,3a,9a-tetrahydro-1*H*-chromeno[2,3-*c*]pyrrol-9-one, 6. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=8.24 (dd, *J*=8.0, 1.7 Hz, 1H, H-5′), 7.83 (s, 1H, H-2′), 7.60 (ddd, *J*=8.5, 7.1, 1.7 Hz, 1H, H-7′), 7.56 (dd, *J*=8.0, 1.7 Hz, 1H, H-5), 7.43 (ddd, *J*=8.4, 7.0, 1.7 Hz, 1H, H-7), 7.37 (ddd, *J*=8.0, 7.1, 1.0 Hz, 1H, H-6′), 7.31 (d, *J*=8.5 Hz, 1H, H-8′), 6.97 (dd, *J*=8.4, 1.0 Hz, H-8), 6.86 (ddd, *J*=8.0, 7.0, 1.0 Hz, 1H, H-6), 5.09–5.11 (m, 1H, H-3a), 4.42 (d, *J*=10.8 Hz, 1H, H-1), 3.61 (d, *J*=10.8 Hz, 1H, H-3), 3.60 (dd, *J*=10.8, 6.2 Hz, 1H, H-9a), 2.83 (dd, *J*=10.8, 3.5 Hz, 1H, H-3), 2.39 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=190.0 (C-9), 177.0 (C-4′), 160.7 (C-4a), 156.1 (C-9′), 155.1 (C-2′), 136.2 (C-7), 133.4 (C-7′), 126.7 (C-5), 126.2 (C-5′), 125.0 (C-6′), 123.5 (C-10′), 121.5 (C-3′), 121.4 (C-6), 120.7 (C-8a), 117.9 and 117.9 (C-8′ and C-8), 79.4 (C-3a), 62.4 (C-1), 62.2 (C-3), 52.4 (C-9a), 40.6 (*C*H_3). MS (EI) *m*/*z* (%): 347 ($M^{+\bullet}$, 32), 332 (23.5), 315 (3), 304 (6), 287 (2), 252 (1.5), 238 (1.5), 226 (100), 212 (66.5), 201 (12.5), 184 (9), 171 (7), 156 (4), 149 (6.5), 131 (7), 121 (49.5), 106 (9), 92 (16), 81 (36), 69 (10), 57 (16.5). HRMS (EI) *m*/*z* calculated for $C_{21}H_{17}NO_4$ ($M^{+\bullet}$) 347.1158, found 347.1152. Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; N, 4.03; H, 4.93. Found: C, 72.96; N, 4.09; H, 4.89.

4.1.3. Reaction of chromone-3-carbaldehyde with glycine. A solution of chromone-3-carbaldehyde (98.5 mg, 0.56 mmol) and glycine (222.0 mg, 2.96 mmol) in toluene (50 mL) was refluxed for 17 h under N_2. Part of the solvent was removed under vacuum and the mixture was purified by flash chromatography using toluene as an eluent. The first fraction to be eluted was pyrrole **11**, which was crystallized from 1-chlorobutane to afford white crystals (1.7 mg, 2% yield) with mp 254–255 °C (lit.,[16] 242–243 °C). The second fraction was the pyrrole **10**, which was crystallized from ethanol to afford yellow crystals (48.7 mg, 46% yield) with mp 128–129 °C.

4.1.3.1. 3-(2-Hydroxybenzoyl)pyrrole, 10. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=12.20 (s, 1H, 2″-OH), 8.76 (br s, 1H, NH), 7.96 (dd, *J*=8.0, 1.7 Hz, 1H, H-6″), 7.44–7.50 (m, 1H, H-4″), 7.46 (t, *J*=3.3 Hz, 1H, H-2), 7.04 (dd, *J*=8.3, 1.1 Hz, 1H, H-3″), 6.91 (ddd, *J*=8.0, 7.1, 1.1 Hz, 1H, H-5″), 6.87–6.89 (m, 1H, H-5), 6.76–6.79 (m, 1H, H-4). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=194.3 (C=O), 162.3 (C-2″), 135.1 (C-4″), 131.9 (C-6″), 124.7 (C-2), 123.9 (C-3), 120.5 (C-1″), 119.3 (C-5), 118.5 (C-5″), 118.1 (C-3″), 110.8 (C-4). MS (EI) *m*/*z* (%): 187 ($M^{+\bullet}$, 100), 170 (4), 159 (2.5), 130 (6.5), 121 (50), 115 (2), 103 (5), 94 (67.5), 77 (11), 67 (76), 53 (7). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; N, 7.48; H, 4.85. Found: C, 70.34; N, 7.50; H, 4.92.

4.1.3.2. 2-(4-Oxo-4*H*-chromen-3-yl)-4-(2-hydroxybenzoyl)pyrrole, 11. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=12.15 (s, 1H, 2‴-OH), 11.50 (br s, 1H, NH), 8.52 (s, 1H, H-2′), 8.33 (dd, *J*=8.0, 1.6 Hz, 1H, H-5′), 7.99 (dd, *J*=7.8, 1.6 Hz, 1H, H-6‴), 7.75 (ddd, *J*=8.5, 7.1, 1.6 Hz, 1H, H-7′), 7.56 (d, *J*=8.5 Hz, 1H, H-8′), 7.52 (dd, *J*=3.0, 1.6 Hz, 1H, H-5), 7.47–7.51 (m, 2H, H-4‴,6′), 7.05 (dd, *J*=8.3, 0.9 Hz, 1H, H-3‴), 7.01 (dd, *J*=2.3, 1.6 Hz, 1H, H-3), 6.94 (ddd, *J*=7.8, 7.6, 0.9 Hz, 1H, H-5‴). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=194.0 (C-1″), 177.0 (C-4′), 162.3 (C-2‴), 155.8 (C-9′), 151.7 (C-2′), 135.1 (C-4‴), 134.2 (C-7′), 131.7 (C-6‴), 126.3 (C-2), 126.0 (C-5′), 125.7 (C-6′), 124.8 (C-5), 123.9 and 123.8 (C-10′ and C-4), 120.5 (C-1‴), 118.6 (C-5‴), 118.3 (C-8′), 118.2 (C-3‴), 115.3 (C-3′), 105.0 (C-3). MS (EI) *m*/*z* (%): 331 ($M^{+\bullet}$, 62.5), 303 (3.5), 238 (14), 226 (1), 211 (100), 198

(1.5), 183 (6), 172 (3), 154 (5.5), 138 (1.5), 127 (3.5), 121 (9.5), 105 (3.5), 91 (19.5), 77 (7), 65 (8). Anal. Calcd for $C_{20}H_{13}NO_4$: C, 72.50; N, 4.23; H, 3.95. Found: C, 72.50; N, 4.17; H, 4.01.

4.1.4. Reaction of chromone-3-carbaldehyde with *N*-benzylglycine. A solution of chromone-3-carbaldehyde (99.9 mg, 0.57 mmol), *N*-benzylglycine hydrochloride (296.8 mg, 1.47 mmol) and potassium carbonate (209.1 mg, 1.51 mmol) in dry 1,4-dioxane (25 mL) was refluxed for 5 h. After cooling to room temperature the reaction mixture was filtered and the solvent was removed under vacuum. The residue was dissolved in toluene and the product was purified by flash chromatography (silica) using toluene as an eluent. Evaporation of the solvent under vacuum afforded pure pyrrole **7** (138.2 mg, 87% yield) as a yellow oil.

4.1.4.1. 1-Benzyl-3-(2-hydroxybenzoyl)pyrrole, 7. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=12.20 (s, 1H, 2″-OH), 7.93 (dd, *J*=8.0, 1.7 Hz, 1H, H-6″), 7.44 (ddd, *J*=8.4, 7.1, 1.7 Hz, 1H, H-4″), 7.32–7.37 (m, 4H, H-2 and Bn-H-3,4,5), 7.16–7.19 (m, 2H, Bn-H-2,6), 7.01 (dd, *J*=8.4, 1.1 Hz, 1H, H-3″), 6.88 (ddd, *J*=8.0, 7.1, 1.1 Hz, 1H, H-5″), 6.71–6.74 (m, 2H, H-4,5), 5.12 (s, 2H, N-CH_2Ph). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=193.7 (C=O), 162.3 (C-2″), 136.2 (Bn-C-1), 134.9 (C-4″), 131.7 (C-6″), 129.0 (Bn-C-3,5), 128.3 (Bn-C-4), 127.7 (C-2), 127.2 (Bn-C-2,6), 123.8 (C-3), 122.7 (C-5), 120.5 (C-1″), 118.5 (C-5″), 118.0 (C-3″), 111.5 (C-4), 53.9 (N-*C*H_2Ph). MS (EI) *m*/*z* (%): 277 ($M^{+\bullet}$, 86), 260 (5), 186 (7), 172 (6), 157 (63), 131 (4), 121 (5), 103 (3), 91 (100), 83 (1), 77 (6), 65 (26). HRMS (EI) *m*/*z* calculated for $C_{18}H_{15}NO_2$ ($M^{+\bullet}$) 277.1103, found 277.1104.

4.1.5. Reaction of chromone-3-carbaldehyde with L-proline. A solution of chromone-3-carbaldehyde (100 mg, 0.57 mmol) and L-proline (329.6 mg, 2.86 mmol) in toluene (50 mL) was refluxed for 4 h under N_2. Part of the solvent was removed under vacuum and the mixture was purified by flash chromatography using toluene as an eluent. Pyrrole **8** (28.5 mg, 22% yield) was obtained as a yellow oil. This compound decomposes slowly at room temperature.

4.1.5.1. 6-(2-Hydroxybenzoyl)-2,3-dihydro-1*H*-pyrrolizine, 8. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=12.24 (s, 1H, 2″-OH), 7.95 (dd, *J*=8.0, 1.7 Hz, 1H, H-6″), 7.44 (ddd, *J*=8.5, 7.2, 1.7 Hz, 1H, H-4″), 7.27 (d, *J*=1.2 Hz, 1H, H-5), 7.01 (dd, *J*=8.5, 1.0 Hz, 1H, H-3″), 6.89 (ddd, *J*=8.0, 7.2, 1.0 Hz, 1H, H-5″), 6.37 (q, *J*=1.2 Hz, 1H, H-7), 4.03 (t, *J*=7.2 Hz, 2H, H-3), 2.88 (dt, *J*=7.2, 1.2 Hz, 2H, H-1), 2.55 (qui, *J*=7.2 Hz, 2H, H-2). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=193.8 (C-1′), 162.2 (C-2″), 138.7 (C-8), 134.6 (C-4″), 131.8 (C-6″), 127.7 (C-6), 121.2 (C-5), 120.7 (C-1″), 118.3 (C-5″), 117.9 (C-3″), 102.0 (C-7), 46.7 (C-3), 27.8 (C-2), 23.9 (C-1). MS (EI) *m*/*z* (%): 227 ($M^{+\bullet}$, 80.5), 210 (11), 198 (8), 186 (7.5), 170 (3.5), 159 (3.5), 147 (2.5), 134 (28), 121 (10), 115 (6), 107 (100), 93 (5.5), 81 (1), 77 (15.5), 65 (18.5). HRMS (EI) *m*/*z* calculated for $C_{14}H_{13}NO_2$ ($M^{+\bullet}$): 227.0946; found: 227.0948.

4.1.6. Reaction of chromone-3-carbaldehyde with L-phenylalanine. A solution of chromone-3-carbaldehyde (99.3 mg, 0.57 mmol) and L-phenylalanine (96.7 mg, 0.58 mmol) in toluene (25 mL) was refluxed for 3 h under N_2. Part of the solvent was removed under vacuum and the mixture was purified by flash chromatography using a gradient of CH_2Cl_2 to CH_2Cl_2/ethyl acetate as an eluent. Pyrrole **9** (43.0 mg, 27%) was obtained as yellow oil.

4.1.6.1. 2-Benzyl-4-(2-hydroxybenzoyl)pyrrole, 9. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=12.21 (s, 1H, 2″-OH), 8.47 (br s, 1H, NH), 7.94 (dd, *J*=8.0, 1.7 Hz, 1H, H-6″), 7.44 (ddd, *J*=8.4, 7.1, 1.7 Hz, 1H, H-4″), 7.21–7.34 (m, 5H, $CH_2C_6H_5$), 7.28 (dd, *J*=2.8, 1.7 Hz, 1H, H-5), 7.01 (dd, *J*=8.4, 1.1 Hz, 1H, H-3″), 6.89 (ddd, *J*=8.0, 7.1, 1.1 Hz, 1H, H-5″), 6.52 (br s, 1H, H-3), 3.99 (s, 2H, 2×H-1‴). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=194.1 (C=O), 162.2 (C-2″), 138.1 (Bn-C-1), 134.9 (C-4″), 132.6 (C-2), 131.8 (C-6″), 128.8 (Bn-C-3,5), 128.7 (Bn-C-2,6), 126.9 (Bn-C-4), 124.7 (C-5), 123.9 (C-4), 120.5 (C-1″), 118.5 (C-5″), 118.0 (C-3″), 108.5 (C-3), 33.7 (*C*H_2Ph). MS (EI) *m*/*z* (%): 277 ($M^{+\bullet}$, 100), 260 (9), 249 (4), 231 (3), 211 (1), 198 (3), 186 (22), 172 (5), 157 (92), 139 (1), 128 (11), 121 (26), 115 (7), 106 (24), 91 (29), 80 (36), 65 (65), 57 (3). HRMS (EI) *m*/*z* calculated for $C_{18}H_{15}NO_2$ ($M^{+\bullet}$) 277.1103, found 277.1103.

4.1.7. Reaction of chromone-3-carbaldehyde with methyl glycinate. A solution of methyl glycinate hydrochloride (355.3 mg, 2.83 mmol) and potassium carbonate (398.6 mg, 2.88 mmol), in toluene (60 mL), was stirred at room temperature during 15–30 min. Then chromone-3-carbaldehyde (99.9 mg, 0.57 mmol) was added and the mixture heated at reflux for 10 h under N_2 atmosphere. The reaction mixture was filtered and part of the solvent was removed under vacuum. The mixture was purified by flash chromatography using toluene as an eluent. The first fraction was pyridine **13**, which was crystallized from 1-chlorobutane to afford light yellow crystals (7 mg, 6% yield) with mp 200–202 °C. The second fraction was pyrrole **12**, which was crystallized from ethanol to afford yellow crystals (51.5 mg, 37%) with mp 149 °C (lit.,[21] 149–150 °C). Compound **14** was obtained in a similar experiment but using 1 equiv of methyl glycinate hydrochloride (72.3 mg, 0.58 mmol) and 0.5 equiv of potassium carbonate (40.7 mg, 0.29 mmol). Compound **14**, which has a lower R_f value than **12** and **13**, was crystallized from 1-chlorobutane to afford white crystals (13.6 mg, 12% yield) with mp >300 °C.

4.1.7.1. Methyl 4-(2-hydroxybenzoyl)pyrrole-2-carboxylate, 12. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=12.04 (s, 1H, 2″-OH), 9.72 (br s, 1H, NH), 7.90 (dd, *J*=8.0, 1.7 Hz, 1H, H-6″), 7.61 (dd, *J*=3.3, 1.6 Hz, 1H, H-3), 7.50 (ddd, *J*=8.4, 7.1, 1.7 Hz, 1H, H-4″), 7.37 (dd, *J*=2.4, 1.6 Hz, 1H, H-5), 7.05 (dd, *J*=8.4, 1.1 Hz, 1H, H-3″), 6.94 (ddd, *J*=8.0, 7.1, 1.1 Hz, 1H, H-5″), 3.92 (s, 3H, CO_2CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=193.6 (C-1′), 162.5 (C-2″), 161.2 (*C*O_2CH_3), 135.7 (C-4″), 131.7 (C-6″), 127.6 (C-3), 125.1 (C-2), 123.8 (C-4), 120.0 (C-1″), 118.8 (C-5″), 118.3 (C-3″), 116.5 (C-5), 52.0 (CO_2CH_3). MS (EI) *m*/*z* (%): 245 ($M^{+\bullet}$, 71.5), 212 (7), 196 (1), 186 (14), 159 (4), 152 (7), 140 (1), 130 (3), 125 (46), 120 (100), 115 (1.5), 107 (2), 92 (26), 77 (6), 65 (27), 53 (7). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; N, 5.71; H, 4.52. Found: C, 63.29; N, 5.62; H, 4.76.

4.1.7.2. Methyl 4-(2-hydroxybenzoyl)-6-(4-oxo-4*H*-chromen-3-yl)pyridine-2-carboxylate, 13. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=11.82 (s, 1H, 2″-OH), 9.08 (s, 1H, H-2′), 8.88

(d, J=1.5 Hz, 1H, H-3), 8.32 (dd, J=8.0, 1.7 Hz, 1H, H-5′), 8.27 (d, J=1.5 Hz, 1H, H-5), 7.75 (ddd, J=8.6, 7.0, 1.7 Hz, 1H, H-7′), 7.56–7.61 (m, 3H, H-4″,6″,8′), 7.49 (ddd, J=8.0, 7.0, 1.1 Hz, 1H, H-6′), 7.12 (dd, J=8.8, 1.1 Hz, 1H, H-3″), 6.96 (ddd, J=8.0, 7.1, 1.1 Hz, 1H, H-5″), 4.06 (s, 3H, CO_2CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=199.0 (C═O), 175.9 (C-4′), 164.9 (CO_2CH_3), 163.6 (C-2″), 158.4 (C-2′), 156.0 (C-9′), 152.0 (C-6), 148.1 (C-4), 146.3 (C-2), 137.6 (C-4″), 134.1 (C-7′), 133.2 (C-6″), 126.3 (C-5′), 125.9 (C-3,6′), 124.6 (C-10′), 122.6 (C-5), 121.1 (C-3′), 119.4 (C-5″), 118.8 (C-3″), 118.3 (C-8′), 118.3 (C-1″), 53.1 (CO_2CH_3). MS (EI) m/z (%): 401 ($M^{+\bullet}$, 100), 386 (15), 372 (98.5), 358 (30), 341 (23), 331 (50), 317 (82), 312 (88), 302 (5.5), 286 (9), 258 (35), 245 (8), 238 (9), 224 (19), 211 (79), 197 (55.5), 171 (12), 165 (37), 147 (19), 138 (33), 121 (70), 111 (10), 92 (37), 83 (17.5), 65 (47), 57 (39). Anal. Calcd for $C_{23}H_{15}NO_6$: C, 68.83; N, 3.49; H, 3.77. Found: C, 69.27; N, 3.49; H, 3.81.

4.1.7.3. Methyl 9-oxo-2-(4-oxo-4*H*-chromen-3-yl)-9*H*-3-azaxanthene-4-carboxylate, 14. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=9.04 (s, 1H, H-1), 8.37 (s, 1H, H-2′), 8.35 (dd, J=8.0, 1.6 Hz, 1H, H-8), 8.34 (dd, J=7.7, 1.7 Hz, 1H, H-5′), 7.78 (ddd, J=8.5, 7.3, 1.7 Hz, 1H, H-7′), 7.77 (ddd, J=8.5, 7.1, 1.6 Hz, 1H, H-6), 7.61 (dd, J=8.5, 0.9 Hz, 1H, H-8′), 7.53 (ddd, J=7.7, 7.3, 0.9 Hz, 1H, H-6′), 7.45–7.48 (m, 1H, H-7), 7.44 (d, J=8.5 Hz, 1H, H-5), 4.06 (s, 3H, CO_2CH_3). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=175.8 (C-9), 174.6 (C-4′), 164.6 (CO_2CH_3), 156.34 (C-9′), 156.29 (C-2′), 155.6 (C-10a), 152.1 (C-4a), 145.2 (C-4), 142.0 (C-2), 136.2 (C-6), 134.2 (C-7′), 126.9 (C-9a), 126.8 (C-8), 126.3 (C-5′), 125.8 (C-6′), 125.4 (C-7), 124.4 (C-10′), 122.5 (C-3′), 122.2 (C-1), 121.9 (C-8a), 118.8 (C-5), 118.3 (C-8′), 53.1 (CO_2CH_3). MS (IE) m/z (%): 399 ($M^{+\bullet}$, 37), 341 (100), 322 (4.5), 312 (1.8), 293 (1.4), 220 (0.7), 164 (4.5), 149 (1.5), 120 (7), 92 (28), 76 (2.2), 63 (7), 57 (3.6). HRMS (EI) m/z calculated for $C_{23}H_{13}NO_6$ ($M^{+\bullet}$) 399.0743, found 399.0732.

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References and notes

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