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ORIGINAL PAPER

An efficient multicomponent transformation of alkyl isocyanides, dialkyl acetylenedicarboxylates, and 2,4-dihydroxybenzophenones or 2,4-dihydroxyacetophenones into 2-amino-4*H*-chromene derivatives

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Abstract The addition of 2,4-dihydroxybenzophenones or 2,4-dihydroxyacetophenones to dialkyl acetylenedicarboxylates under neutral conditions in the presence of alkyl isocyanides leads to 2-amino-4*H*-chromene derivatives in high yields.

Keywords Dialkyl acetylenedicarboxylates · 2,4-Dihydroxybenzophenone · Alkyl isocyanides · 2,4-Dihydroxyacetophenone · 2-Amino-4*H*-chromene · Three component reaction

Introduction

The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry [1–4]. The MCR strategy offers significant advantages over conventional linear-type synthesis because of its flexible, convergent, and atom-efficient nature [5, 6].

The chromene moiety is often an important structural component in both biologically active and natural alkaloids, flavonoids, tocopherols, and anthocyanins [7–12]. Moreover, in recent years functionally substituted chromenes have played an ever increasing role in synthetic approaches towards promising compounds in biomedicinal chemistry [13–16]. Substituted 4*H*-chromenes are a new class of anti-cancer compounds [17]. Recently, Huang and coworkers [18, 19] reported that 4*H*-chromene derivatives bind to Bcl-2 protein and induce apoptosis in the tumor cells. Many studies have been published on the synthesis of the chromene ring system yet [20, 21]. 2-Amino-4*H*-chromenes have been of interest because of their biological activities, but few methods have been reported for their synthesis [22].

As part of our current studies [23–25] on the development of new routes to heterocyclic systems, we have recently reported the synthesis of a novel class of coumarin derivatives [25] using the reaction of dihydroxybenzophenones or dihydroxyacetophenones with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine as a nucleophile. Now, we wish to report an efficient synthesis of a novel class of 4*H*-chromenes using alkyl isocyanides as nucleophiles. Thus, a three-component reaction of 2,4-dihydroxybenzophenones or 2,4-dihydroxyacetophenones with dialkyl acetylenedicarboxylates in the presence of alkyl isocyanides proceeds spontaneously at room temperature in dichloromethane, and produces dialkyl 6-benzoyl(or acetyl)-2-(alkyl amino)-5-hydroxy-4*H*-chromene-3,4-dicarboxylates **4** and dialkyl 6-acetyl-2-(alkylamino)-7-hydroxy-4*H*-chromene-3,4-dicarboxylates **5** in fairly good yields (Scheme 1; Table 1).

Results and discussion

The structures of the products **4** and **5** were determined on the basis of their elemental analyses, mass spectra, ^{1}H and ^{13}C NMR, and IR spectroscopic data. The ^{1}H NMR spectrum of **4a** contained four singlets identified as acetyl ($\delta = 2.57$ ppm), two methoxy ($\delta = 3.69$ and 3.85 ppm), and methine ($\delta = 4.95$ ppm) protons. On addition of a drop of D_2O to a solution of compound **4a** in $CDCl_3$ the

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Scheme 1

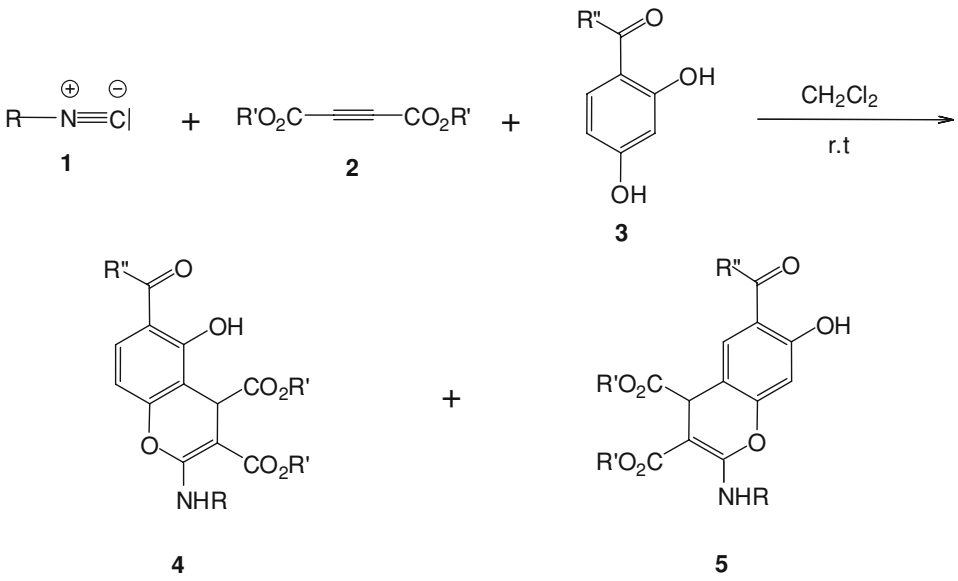


Table 1 Yields of compounds **4** and **5**

4, **5**	R	R′	R″	Yield (%)	
				4	**5**
a	Cyclohexyl	Me	Me	90	–
b	Cyclohexyl	Et	Me	65	30
c	Cyclohexyl	*t*-Bu	Me	60	35
d	Cyclohexyl	Me	Ph	88	–
e	Cyclohexyl	Et	Ph	90	–
f	Cyclohexyl	*t*-Bu	Ph	93	–
g	*t*-Bu	Me	Me	–	85
h	*t*-Bu	Et	Me	10	75
i	*t*-Bu	*t*-Bu	Me	15	70
j	*t*-Bu	Me	Ph	87	–
k	*t*-Bu	Et	Ph	88	–
l	*t*-Bu	*t*-Bu	Ph	95	–

NH signal ($\delta = 8.66$ ppm) disappeared. Also, a single peak was observed at ($\delta = 13.03$ ppm) that was assigned to the remaining hydroxy proton. This proton has been deshielded because of intramolecular hydrogen bonding with the neighboring carbonyl compounds.

Interestingly, when 2,4-dihydroxybenzophenone was used as OH-acid, only product **4** was formed regioselectively. The regiochemistry of the cyclization was confirmed by observation of an AX pattern corresponding to the aromatic protons of **4d** which were displayed at $\delta = 6.59$ and 7.54 ppm ($^3J = 8.9$ Hz). ^{1}H NMR spectroscopy was also used to distinguish structures **4** from **5**. For example, the ^{1}H NMR spectrum of **4b** displayed an AX pattern for the aromatic protons, whereas that for compound **5b** exhibited two single lines at $\delta = 6.64$ and 7.62 ppm. The proton decoupled ^{13}C NMR spectrum of **4a** contained 21 distinct resonance signals in agreement with the proposed structure. The presence of oxo and amino groups at one end of the double bond leads to polarization of the olefinic system. The α-carbon atom of this polarized system appears at $\delta = 161.4$ ppm, and the β-carbon at $\delta = 71.4$ ppm. Similar chemical shifts have been observed for the polarized carbon–carbon double bonds in 2-alkylamino-4*H*-benzo[*h*]chromene derivatives [26]. The carbonyl groups of **4a** appear at $\delta = 169.6$, 173.5, and 203.1 ppm for ester and keto groups, respectively.

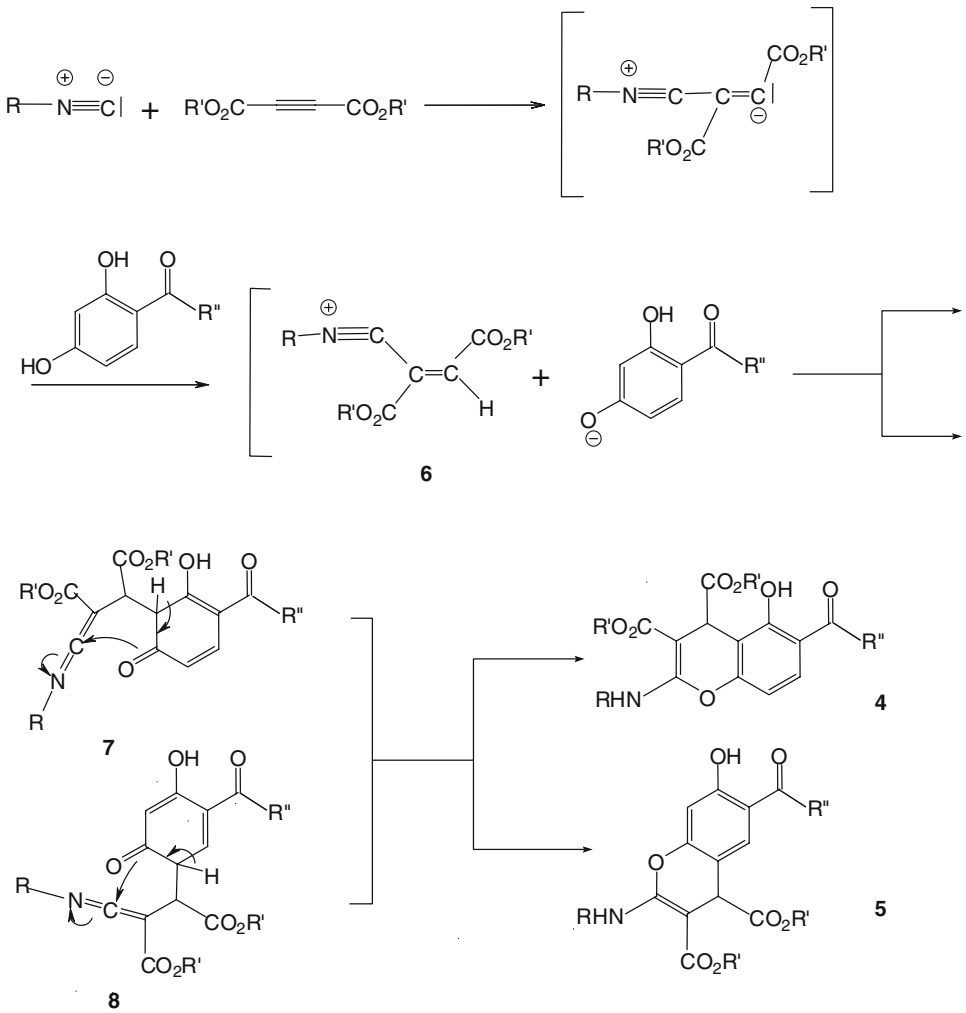
A possible mechanism for the formation of products **4** and **5** is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides [4, 27, 28], it is reasonable to assume that compounds **4** and **5** resulted from nucleophilic addition of alkyl isocyanides to the acetylenic esters and subsequent protonation of the 1:1 adduct by the OH-acid. Then, the resulting positively charged ion **6** is attacked by the anion of the OH-acid from the *ortho* positions relative to the strong activating group forming ketenimines **7** and **8**. These addition products may tautomerize and then cyclize under the reaction conditions employed to produce **4** and **5**.

In conclusion, we have found a three component synthetic method for preparation of some 4*H*-chromenes. The method has the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were

Scheme 2



performed using a Heraeus CHN–O-Rapid analyzer and the results agreed favorably with calculated values. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DRX-500 Avance instrument with $CDCl_3$ as solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an electron energy of 70 eV. Alkyl isocyanides, dialkyl acetylenedicarboxylate, and 2,4-dihydroxybenzophenones and 2,4-dihydroxyacetophenones were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

To a magnetically stirred solution of a 2,4-dihydroxybenzophenone or 2,4-dihydroxyacetophenone (2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) in 10 cm^3 CH_2Cl_2 was added dropwise at room temperature over 10 min alkyl isocyanide (2 mmol). The reaction mixture was stirred for 24 h. The solvent was then removed under reduced pressure and the residue was separated by column chromatography (silica gel, Merck 230–400 mesh) using *n*-hexane–ethyl acetate (70:30) as eluent.

Dimethyl 6-acetyl-2-(cyclohexylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4a**, $C_{21}H_{25}NO_7$)

Yellow powder, yield 90%; m.p. 98–100 °C; IR (KBr): $\bar{\nu}$ = 1,625 and 1,770 (C=O), 3,360–3,460 (OH) cm^{-1}; MS: *m/z* (%) = 403 (M^+, 4), 344 (100), 277 (65), 230 (68); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.25–2.02 (10 H, m, 5 CH_2), 2.57 (3 H, s, CH_3), 3.69 and 3.85 (6 H, 2s, 2 OMe), 3.85 (1 H, m, CHN), 4.95 (1 H, s, CH), 6.62 (1 H, d, ^{3}J = 8.9 Hz, CH), 7.66 (1 H, d, ^{3}J = 8.9 Hz, CH), 8.66 (1 H, d, ^{3}J = 6.0 Hz, NH), 13.03 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 24.4, 25.4, 26.4, 33.50, 33.8 (5 CH_2), 25.5 (CH_3), 35.4 (CH), 49.8 (CHN), 52.3, 53.4 (2 OCH_3), 71.4 (*C*=C–N), 107.4, 130.8 (2 CH), 110.4,

116.1, 155.1, 160.0 (4 C), 161.4 (C=*C*–N), 169.6, 173.5 (2 C=O, ester), 203.1 (C=O, ketone) ppm.

Diethyl 6-acetyl-2-(cyclohexylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4b**, $C_{23}H_{29}NO_7$)
Yellow powder, yield 65%; m.p. 140–143 °C; IR (KBr): $\bar{\nu}$ = 1,625 and 1,770 (C=O), 3,300–3,450 (OH) cm^{-1}; MS: *m/z* (%) = 432 (M^++1, 32), 358 (100), 276 (75), 230 (60); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.21 and 1.29 (6 H, 2 t, ^3J = 7.1 Hz, 2 CH_3), 1.37–2.02 (10 H, m, 5 CH_2), 2.59 (3 H, s, CH_3), 3.79 (1 H, m, CHN), 3.74–3.80 (1 H, m, CHN), 3.92–4.05 (2 H, 2 dq, ABX_3 System, ^3J = 7.2 Hz, ^2J = 10.7 Hz, $OCH_AH_BCH_3$), 4.08–4.20 (2 H, 2 dq, ABX_3 System, ^3J = 7.2 Hz, ^2J = 10.7 Hz, $OCH_AH_BCH_3$), 4.93 (1 H, s, CH), 6.60 (1 H, d, ^3J = 8.8 Hz, CH), 7.67 (1 H, d, ^3J = 8.8 Hz, CH), 8.68 (1 H, d, ^3J = 6.4 Hz, NH), 13.05 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.1, 14.5 (2 CH_3), 24.4, 25.4, 26.4, 33.5, 33.8 (5 CH_2), 25.4 (CH_3), 35.6 (CH), 49.8 (CHN), 59.4, 60.9 (2 OCH_2), 71.5 (*C*=C–N), 107.4, 130.7 (2 CH), 110.4, 116.0, 155.2, 159.8 (4 C), 161.5 (C=*C*–N), 169.3, 173.3 (2 C=O, ester), 203.1 (C=O, ketone) ppm.

Di-tert-butyl 6-acetyl-2-(cyclohexylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4c**, $C_{27}H_{37}NO_7$)
Yellow powder, yield 60%; m.p. 122–125 °C; IR (KBr): $\bar{\nu}$ = 1,656 and 1,735 (C=O), 3,370–3,450 (OH) cm^{-1}; MS: *m/z* (%) = 487 (M^+, 1), 330 (100), 230 (65), 386 (65), 57 (81); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.24–1.77 (10 H, m, 5 CH_2), 1.39 and 1.52 (18 H, 2s, 2 *t*-Bu), 2.58 (3 H, s, CH_3), 3.71 (1 H, m, CHN), 4.43 (1 H, s, CH), 6.57 (1 H, d, ^3J = 8.8 Hz, CH), 7.62 (1 H, d, ^3J = 8.8 Hz, CH), 8.57 (1 H, d, ^3J = 6.4 Hz, NH), 13.02 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 24.7, 25.5, 26.4, 33.7, 34.1 (5 CH_2), 25.6 (CH_3), 28.0, 28.6 (6 CH_3), 37.1 (CH), 50.0 (CHN), 73.1 (*C*=C–N), 79.2, 80.4 (2 C), 107.3, 130.5 (2 CH), 111.1, 115.8, 155.4, 159.6 (4 C), 161.5 (C=*C*–N), 169.0, 172.7 (2 C=O, ester), 203.2 (C=O, ketone) ppm.

Dimethyl 6-benzoyl-2-(cyclohexylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4d**, $C_{26}H_{27}NO_7$)
Yellow powder, yield 88%; m.p. 128–130 °C; IR (KBr): $\bar{\nu}$ = 3,261 (NH), 1,750 and 1,674 (C=O) cm^{-1}; MS: *m/z* (%) = 466 (M^+, 3), 406 (100), 324 (18), 292 (16), 214 (16); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.26–2.02 (10 H, m, 5 CH_2), 3.68 and 3.76 (6 H, 2s, 2 CH_3), 3.77–3.82 (1 H, m, CHN), 5.03 (1 H, s, CH), 6.59 (1 H, d, ^3J = 8.9 Hz, CH), 7.48–7.66 (5 H, m, 5 CH), 7.54 (1 H, d, ^3J = 8.9 Hz, CH), 8.68 (1 H, d, ^3J = 6.5 Hz, NH), 12.93 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 24.4, 24.5, 25.5, 33.5, 33.9 (5 CH_2), 35.6 (CH), 49.9 (CHN), 51.0, 52.4 (2 OCH_3), 71.5 (*C*=C–N), 107.2, 128.4, 129.0, 131.9, 137.8 (5 CH), 110.5, 115.5, 133.8, 155.2, 160.1 (5 C), 162.4 (C=C–N), 169.6, 173.6 (2 C=O, ester), 200.5 (C=O, ketone) ppm.

Diethyl 6-benzoyl-2-(cyclohexylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4e**, $C_{28}H_{31}NO_7$)
Yellow powder, yield 90%; m.p. 97–99 °C; IR (KBr): $\bar{\nu}$ = 3,282 (NH), 1,750 and 1,660 (C=O) cm^{-1}; MS: *m/z* (%) = 509.6 (M^+, 2), 437.5 (100), 412.4 (58), 365.5 (76), 324.4 (20), 214 (23); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.26 and 1.28 (6 H, 2 t, ^3J = 7.1 Hz, 2 CH_3), 1.29–2.03 (10 H, m, 5 CH_2), 3.74–3.80 (1 H, m, CHN), 3.95–4.11 (2 H, 2 dq, ABX_3 System, ^3J = 7.2 Hz, ^2J = 10.7 Hz, $OCH_AH_BCH_3$), 4.14–4.30 (2 H, 2 dq, ABX_3 System, ^3J = 7.2 Hz, ^2J = 10.7 Hz, $OCH_AH_BCH_3$), 4.95 (1 H, s, CH), 6.59 (1 H, d, ^3J = 8.9 Hz, CH), 7.47–7.66 (5 H, m, 5 CH), 7.60 (1 H, d, ^3J = 8.9 Hz, CH), 8.74 (1 H, br, NH), 12.91 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.2, 14.6 (2 CH_3), 24.5, 24.6, 25.6, 33.6, 33.9 (5 CH_2), 36.5 (CH), 49.9 (CHN), 59.8, 60.2 (2 OCH_2), 71.8 (*C*=C–N), 107.1, 128.4, 129.1, 131.9, 137.9 (5 CH), 110.3, 115.4, 133.7, 155.0, 161.0 (5 C), 162.4 (C=*C*–N), 169.3, 173.0 (2 C=O, ester), 200.5 (C=O, ketone) ppm.

Di-tert-butyl 6-benzoyl-2-(cyclohexylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4f**, $C_{32}H_{39}NO_7$)
Yellow powder, yield 93%; m.p. 138–140 °C; IR (KBr): $\bar{\nu}$ = 3,259 (NH), 1,727 and 1,661 (C=O) cm^{-1}; MS: *m/z* (%) = 565.7 (M^+, 28), 510 (16), 466 (68), 409 (100), 214 (19); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.29–2.04 (10 H, m, 5 CH_2), 1.44 and 1.55 (18 H, 2s, 2 *t*-Bu), 3.73–3.76 (1 H, m, CHN), 4.85 (1 H, s, CH), 6.56 (1 H, d, ^3J = 8.9 Hz, CH), 7.48–7.66 (5 H, m, 5 CH), 7.61 (1 H, d, ^3J = 8.9 Hz, CH), 8.59 (1 H, d, ^3J = 6.5 Hz, NH), 12.90 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.6, 33.7, 34.1 (5 CH_2), 28.1, 28.7 (6 CH_3), 37.2 (CH), 50.1 (CHN), 73.2 (*C*=C–N), 79.2, 80.6 (2 $OCMe_3$), 107.2, 128.4, 129.0, 131.8, 137.9 (5 CH), 111.4, 115.2, 133.5, 155.5, 159.7 (5 C), 162.5 (C=*C*–N), 169.1, 172.8 (2 C=O, ester), 200.5 (C=O, ketone) ppm.

Diethyl 6-acetyl-2-(tert-butylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4h**, $C_{21}H_{27}NO_7$)
White powder, yield 10%; m.p. 127–129 °C; IR (KBr): $\bar{\nu}$ = 1,670 and 1,750 (C=O), 3,350–3,450 (OH) cm^{-1}; MS: *m/z* (%) = 405 (M^+, 5), 346 (45), 276 (70), 230 (75), 57 (100); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.20 and 1.29 (6 H, 2 t, ^3J = 7.1 Hz, 2 CH_3), 1.45 (9 H, s, *t*-Bu), 2.58 (3 H, s, CH_3), 3.97–4.13 (2 H, 2 dq, ABX_3 System, ^3J = 7.2 Hz, ^2J = 10.7 Hz, $OCH_AH_BCH_3$), 4.14–4.28 (2 H, 2 dq, ABX_3 System, ^3J = 7.2 Hz, ^2J = 10.7 Hz, $OCH_AH_BCH_3$), 4.94 (1 H, s, CH), 6.61 (1 H, d, ^3J = 8.9 Hz, CH), 7.65 (1 H, d, ^3J = 8.9 Hz, CH), 8.81 (1 H, s, NH), 13.05 (1 H, s, OH) ppm; ^{13}C NMR

(125.77 MHz, $CDCl_3$): $\delta = 14.1$, 14.6 (2 CH_3), 26.4 (CH_3), 30.6 (3 CH_3), 35.5 (CH), 52.6 (*C*Me_3), 59.5, 60.9 (2 OCH_2), 72.4 (*C*=C–N), 107.2, 130.9 (2 CH), 110.5, 116.1, 155.0, 161.3 (4 C), 161.5 (C=*C*–N), 169.3, 173.2 (2 C=O, ester), 203.2 (C=O, ketone) ppm.

Di-tert-butyl 6-acetyl-2-(tert-butylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4i**, $C_{25}H_{35}NO_7$)
White powder, yield 15%; m.p. 163–166 °C; IR (KBr): $\bar{\nu} = 1{,}675$, 1,719 (C=O), 3,400–3,450 (OH) cm^{-1}; MS: *m*/*z* (%) = 462 (M^++1, 27), 360 (76), 304 (100), 248 (82), 57 (78); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.39$, 1.45, 1.52 (27 H, 3s, 3 *t*-Bu), 2.57 (3 H, s, CH), 4.78 (1 H, s, CH), 6.59 (1 H, d, $^3J = 8.9$ Hz, CH), 7.64 (1 H, d, $^3J = 8.9$ Hz, CH), 8.73 (1 H, s, NH), 13.02 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 26.5$ (CH_3), 28.0, 28.6, 30.7 (9 CH_3), 37.0 (CH), 52.3 (*C*Me_3), 74.0 (*C*=C–N), 79.3, 80.5 (2 *C*Me_3), 107.2, 130.7 (2 CH), 111.2, 116.0, 155.2, 161.0 (4 C), 161.6 (C=*C*–N), 169.1, 172.6 (2 C = O, ester), 203.2 (C = O, ketone) ppm.

Dimethyl 6-benzoyl-2-(tert-butylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4j**, $C_{24}H_{25}NO_7$)
Yellow powder, yield 87%; m.p. 130–132 °C; IR (KBr): $\bar{\nu} = 3{,}261$ (NH), 1,739, 1,671 (C=O) cm^{-1}; MS: *m*/*z* (%) = 455.5 (M^+, 3), 397 (100), 339 (73), 277 (24), 214 (21); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.47$ (9 H, s, *t*-Bu), 3.68, 3.75 (6 H, 2s, 2 OCH_3), 5.05 (1 H, s, CH), 6.61 (1 H, d, $^3J = 8.9$ Hz, CH), 7.48–7.66 (5 H, m, 5 CH), 7.55 (1 H, d, $^3J = 8.9$ Hz, CH), 8.82 (1 H, s, NH), 12.91 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 30.6$ (3 CH_3), 35.4 (CH), 51.1, 52.4 (2 OCH_3), 52.7 (*C*Me_3), 72.4 (*C*=C–N), 107.0, 128.4, 129.0, 131.9, 137.8 (5 CH), 110.7, 115.6, 133.9, 155.0, 161.5 (5 C), 162.4 (C=*C*–N), 169.7, 173.4 (2 C=O, ester), 200.5 (C=O, ketone) ppm.

Diethyl 6-benzoyl-2-(tert-butylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4k**, $C_{26}H_{29}NO_7$)
Yellow powder, yield 88%; m.p. 97–99 °C; IR (KBr): $\bar{\nu} = 3{,}271$ (NH), 1,729, 1,669 (C=O) cm^{-1}; MS: *m*/*z* (%) = 483.6 (M^+, 2), 394 (100), 338 (80), 310 (6), 292 (30), 214 (29); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.24$, 1.26 (6 H, 2 t, $^3J = 7.1$ Hz, 2 CH_3), 1.47 (9 H, s, *t*-Bu), 3.98–4.11 (2 H, 2 dq, ABX_3 System, $^3J = 7.2$ Hz, $^2J = 10.7$ Hz, $OCH_AH_BCH_3$), 4.12–4.24 (2 H, 2 dq, ABX_3 System, $^3J = 7.2$ Hz, $^2J = 10.7$ Hz, $OCH_AH_BCH_3$), 5.03 (1 H, s, CH), 6.60 (1 H, d, $^3J = 8.9$ Hz, CH), 7.48–7.66 (5 H, m, 5 CH), 7.65 (1 H, d, $^3J = 8.9$ Hz, CH), 8.84 (1 H, s, NH), 12.93 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 14.2$, 14.6 (2 CH_3), 30.6 (3 CH_3), 35.6 (CH), 52.6 (*C*Me_3), 59.5, 60.0 (2 OCH_2), 72.5 (*C*=C–N), 107.0, 128.4, 129.0, 131.9, 137.8 (5 CH), 110.8, 115.5, 133.8, 155.1, 161.3 (5 C), 162.5 (C=*C*–N), 169.4, 173.3 (2 C=O, ester), 200.5 (C=O, ketone) ppm.

Di-tert-butyl 6-benzoyl-2-(tert-butylamino)-5-hydroxy-4H-chromene-3,4-dicarboxylate (**4l**, $C_{30}H_{37}NO_7$)
Yellow powder, yield 95%; m.p. 143–145 °C; IR (KBr): $\bar{\nu} = 3{,}262$ (NH), 1,726, 1,663 (C=O) cm^{-1}; MS: *m*/*z* (%) = 539.7 (M^+, 35), 422 (75), 366 (100), 310 (34), 292 (25), 214 (23); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.43$, 1.46, 1.54 (27 H, 3s, 3 *t*-Bu), 4.86 (1 H, s, CH), 6.57 (1 H, d, $^3J = 8.9$ Hz, CH), 7.47–7.66 (5 H, m, 5 CH), 7.61 (1 H, d, $^3J = 8.9$ Hz, CH), 8.75 (1 H, s, NH), 12.88 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 28.1$, 28.6, 30.7 (9 CH_3), 37.2 (CH), 52.4 (*C*Me_3), 74.2 (*C*=C–N), 79.4, 80.6 (2 O*C*Me_3), 107.0, 128.4, 129.0, 131.8, 137.9 (5 CH), 111.5, 115.3, 133.6, 155.3, 161.1 (5 C), 162.5 (C=*C*–N), 169.1, 172.6 (2 C=O, ester), 200.5 (C=O, ketone) ppm.

Diethyl 6-acetyl-2-(cyclohexylamino)-7-hydroxy-4H-chromene-3,4-dicarboxylate (**5b**, $C_{23}H_{29}NO_7$)
White powder, yield 30%; m.p. 140–143 °C; IR (KBr): $\bar{\nu} = 1{,}625$, 1,770 (C=O), 3,350–3,480 (OH) cm^{-1}; MS: *m*/*z* (%) = 432 (M^++1, 35), 358 (100), 276 (72), 230 (55); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.20$, 1.28 (6 H, 2 t, $^3J = 7.1$ Hz, 2 CH_3), 1.33–2.02 (10 H, m, 5 CH_2), 2.58 (3 H, s, CH_3), 3.79 (1 H, m, CHN), 3.97–4.12 (2 H, 2 dq, ABX_3 System, $^3J = 7.2$ Hz, $^2J = 10.7$ Hz, $OCH_AH_BCH_3$), 4.14–4.27 (2 H, 2 dq, ABX_3 System, $^3J = 7.2$ Hz, $^2J = 10.7$ Hz, $OCH_AH_BCH_3$), 4.53 (1 H, s, CH), 6.64, 7.62 (2 H, 2s, 2 CH), 8.60 (1 H, d, $^3J = 6.3$ Hz, NH), 12.65 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 14.0$, 14.7 (2 CH_3), 24.4, 25.4, 26.5, 33.7, 33.9 (5 CH_2), 25.5 (CH_3), 38.6 (CH), 49.7 (CHN), 59.3, 60.9 (2 OCH_2), 72.8 (*C*=C–N), 104.8, 130.7 (2 CH), 110.5, 115.3, 155.2, 159.6 (4 C), 161.5 (C=*C*–N), 169.2, 174.3 (2 C=O, ester), 203.2 (C=O, ketone) ppm.

Di-tert-butyl 6-acetyl-2-(cyclohexylamino)-7-hydroxy-4H-chromene-3,4-dicarboxylate (**5c**, $C_{27}H_{37}NO_7$)
White powder, yield 35%; m.p. 102–104 °C; IR (KBr): $\bar{\nu} = 1{,}671$, 1,750 (C=O), 3,300–3,450 (OH) cm^{-1}; MS: *m*/*z* (%) = 487 (M^+, 1), 330 (100), 230 (79), 386 (90), 57 (33); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.25$–2.03 (10 H, m, 5 CH_2), 1.42, 1.49 (18 H, 2s, 2 *t*-Bu), 2.59 (3 H, s, CH_3), 3.71 (1 H, m, CHN), 4.43 (1 H, s, CH), 6.58, 7.85 (2 H, 2s, 2 CH), 8.57 (1 H, br, NH), 12.32 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 24.7$, 25.5, 26.5, 33.7, 34.1 (5 CH_2), 25.4 (CH_3), 27.9, 28.5 (6 CH_3), 41.7 (CH), 49.9 (CHN), 72.2 (*C*=C–N), 79.2, 80.6 (2 C), 104.7, 131.6 (2 CH), 111.9, 116.9, 154.7, 159.0 (4 C), 162.9 (C=*C*–N), 169.0, 172.5 (2 C=O, ester), 203.0 (C=O, ketone) ppm.

Dimethyl 6-acetyl-2-(tert-butylamino)-7-hydroxy-4H-chromene-3,4-dicarboxylate (**5g**, $C_{19}H_{23}NO_7$)
Yellow powder, yield 85%; m.p. 105–110 °C; IR (KBr): $\bar{\nu} = 1{,}690$, 1,750 (C=O), 3,400–3,450 (OH) cm^{-1}; MS: *m*/*z* (%) = 377 (M^+, 7), 318 (43), 262 (70), 230 (43), 57 (100);

^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.47$ (9 H, s, *t*-Bu), 2.61 (3 H, s, CH_3), 3.66, 3.70 (6 H, 2s, 2 OMe), 4.64 (1 H, s, CH), 6.63, 7.81 (2 H, 2s, 2 CH), 8.80 (1 H, s, NH), 12.40 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 26.0$ (CH_3), 30.0 (3 CH_3), 39.7 (CH), 50.4, 51.9 (2 OCH_3), 52.2 (*C*Me_3), 71.1 (*C*=C–N), 104.2, 131.2 (2 CH), 110.8, 116.8, 153.8, 160.3 (4 C), 162.7 (C=*C*–N), 169.0, 173.1 (2 C=O, ester), 202.6 (C=O, ketone) ppm.

Diethyl 6-acetyl-2-(tert-butylamino)-7-hydroxy-4H-chromene-3,4-dicarboxylate (**5h**, $C_{21}H_{27}NO_7$)
Yellow powder, yield 75%; m.p. 148–151 °C; IR (KBr): $\bar{\nu} = 1{,}672$, 1,734 (C=O), 3,350–3,400 (OH) cm^{-1}; MS: *m*/*z* (%) = 405 (M^+, 2), 346 (40), 276 (65), 230 (75), 57 (100); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.22$, 1.26 (6 H, 2 t, $^3J = 7.1$ Hz, 2 CH_3), 1.46 (9 H, s, *t*-Bu), 2.60 (3 H, s, CH_3), 3.98–4.10 (2 H, 2 dq, ABX_3 System, $^3J = 7.2$ Hz, $^2J = 10.7$ Hz, $OCH_AH_BCH_3$), 4.14–4.25 (2 H, 2 dq, ABX_3 System, $^3J = 7.2$ Hz, $^2J = 10.7$ Hz, $OCH_AH_BCH_3$), 4.62 (1 H, s, CH), 6.63, 7.84 (2 H, 2s, 2 CH), 8.81 (1 H, s, NH), 12.37 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 14.2$, 14.5 (2 CH_3), 26.6 (CH_3), 30.6 (3 CH_3), 40.3 (CH), 52.6 (*C*Me_3), 59.5, 61.1 (2 OCH_2), 71.6 (*C*=C–N), 104.7, 131.8 (2 CH), 111.3, 117.2, 154.3, 160.7 (4 C), 163.2 (C=*C*–N), 169.2, 173.3 (2 C=O, ester), 203.2 (C=O, ketone) ppm.

Di-tert-butyl 6-acetyl-2-(tert-butylamino)-7-hydroxy-4H-chromene-3,4-dicarboxylate (**5i**, $C_{25}H_{35}NO_7$)
Yellow powder, yield 80%; m.p. 156–159 °C; IR (KBr): $\bar{\nu} = 1{,}672$, 1,730 (C=O), 3,350–3,450 (OH) cm^{-1}; MS: *m*/*z* (%) = 462 (M^++1, 58), 360 (87), 304 (100), 248 (67), 57 (97); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.41$, 1.46, 1.49 (27 H, 3s, 3 *t*-Bu), 2.61 (3 H, s, CH_3), 4.43 (1 H, s, CH), 6.61, 7.84 (2 H, 2s, 2 CH), 8.78 (1 H, s, NH), 12.35 (1 H, s, OH) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 26.5$ (CH_3), 28.0, 28.6, 30.7 (9 CH_3), 41.7 (CH), 52.4 (*C*Me_3), 73.0 (*C*=C–N), 79.3, 80.6 (2 *C*Me_3), 104.6, 131.7 (2 CH), 112.0, 116.9, 154.5, 160.4 (4 C), 163.0 (C=*C*–N), 169.0, 172.5 (2 C=O, ester), 203.1 (C=O, ketone) ppm.

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