Electrocatalytic chain transformation of salicylaldehyde and CH acids into substituted 4*H*-chromenes

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Electrochemically initiated catalytic chain transformation of salicylaldehydes and CH acids containing the cyano group in an ethanolic solution in an undivided cell produced substituted 4*H*-chromenes in 85—95% yields.

Key words: electrocatalysis, electrosynthesis, salicylaldehyde, CH acids, 4*H*-chromenes.

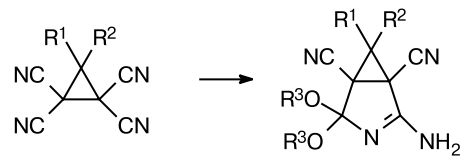
Chromene derivatives are important representatives of biologically active natural compounds such as alkaloids, flavonoids, tocopherol, and anthocyanins.[1—6] In the last few years, functionalized chromenes have found increasingly frequent use in biomedicinal chemistry.[7—10] For example, 4*H*-chromenes containing the cyano group (especially (4*H*-chromen-4-yl)malononitriles) are employed for treatment of inflammatory arthritis and some kinds of cancers. It has also been found that (4*H*-chromen-4-yl)malononitriles hinder the mutagen-activated protein MK-2 and suppress the tumor factor TNFα in U937 cells.[11] Cancer is treated with substituted alkyl (4*H*-chromen-4-yl)cyanoacetates, a novel class of small molecules which can bind the protein Bcl-2 and excite the apoptosis of tumor cells.[12,13]

Condensation of salicylaldehyde with active methylene compounds in the presence of ammonium acetate, pyridine, or piperidine normally gives coumarins[14—19] or coumarin imines, which subsequently undergo hydrolysis to coumarins.[16] It has been, however, reported that 4*H*-chromen-4-yl derivatives can be obtained from salicylaldehydes and alkyl cyanoacetates with ammonium acetate,[20] alumina,[21] or zirconium phosphate[22] as a catalyst. In the reaction catalyzed by ammonium acetate, temperature control to within 5—10 °C is required to ensure the selectivity of the process; the yield of the final product is 40—80% (see Ref. 20). Solid-state catalysis on alumina partly simplifies the synthesis of 4*H*-chromene derivatives, their yields being 50—85% (see Ref. 21). The highest yields of 4*H*-chromenes (70—95%) were achieved with catalysts based on zirconium phosphate; however, this process is long enough (2—15 h) and requires the temperature to be maintained at 60 °C (see Ref. 22).

Alumina-catalyzed reactions of salicylaldehydes with malononitrile give the corresponding (2-amino-3-cyano-4*H*-chromen-4-yl)malononitriles in 64% yields (see Ref. 21). In acetic acid in the presence of piperidine, the yield of the product reaches 90%, but the reaction time is extended to 24 h (see Ref. 23). Thus, it follows from the literature data that the reactions of salicylaldehydes with malononitrile or alkyl cyanoacetate are sensitive to the reaction conditions and that the known procedures either provide insufficiently low yields of the final product or are characterized by a long reaction time. That is why the development of novel, highly efficient methods for the synthesis of 4*H*-chromenes is still of current interest.

An intensive development of the electrochemistry of organic compounds in the last few decades have made electrosynthesis competitive in modern organic chemistry,[24,25] which allows, in some cases, unique transformations of organic compounds. With our investigations, we have discovered a novel type of electrochemical processes, *viz.*, an electrocatalytic chain transformation initiated by catalytic amounts of a base electrogenerated in an undivided cell. The first example was the electrocatalytic chain cyclization of tetracyanocyclopropanes into substituted 4,4-dialkoxy-2-amino-1,5-dicyano-3-azabicyclo-[3.1.0]hex-2-enes in the presence of alkoxy anions generated at the cathode[26] (Scheme 1).

Scheme 1



Reagents and conditions: electrolysis, 0.05—0.10 *F* mol^{-1}, R^{3}OH.

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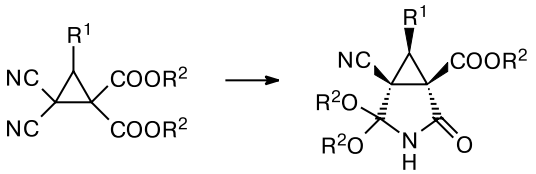
Later, we have obtained 6-substituted alkyl (1*R**,5*R**,6*R**)-4,4-dialkoxy-5-cyano-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylates from 3-substituted alkyl 2,2-dicyanocyclopropane-1,1-dicarboxylates *via* electrocatalytic chain transformation[27] (Scheme 2).

Scheme 2



Reagents and conditions: electrolysis, 0.2 $F\,mol^{-1}$, R^2OH.

Here, we employed the electrocatalytic chain method for the synthesis of 4*H*-chromenes **3a—p** under mild conditions by the coelectrolysis of salicylaldehydes **1a—f** and CH acids **2a—c** (Scheme 3). The room-temperature reaction in an undivided cell was completed over 15—30 min in an ethanolic solution in the presence of NaBr as an electrolyte (for preliminary communication, see Refs 28, 29).

To estimate the synthetic potential of this reaction and find optimum reaction conditions, first we studied transformations of unsubstituted salicylaldehyde (**1a**) with two equivalents of malononitrile (**2a**) and methyl cyanoacetate (**2b**) into 4*H*-chromenes **3a** and **3g**, respectively, under different conditions (Table 1).

Table 1. Electrocatalytic transformations of salicylaldehyde (**1a**) and malononitrile (**2a**) or methyl cyanoacetate (**2b**) into 4*H*-chromene **3**[a]

CH acid	τ[b] /min	i[c] /mA cm^{-2}	Solvent	Q[d] /$F\,mol^{-1}$	Yield (%)[e]
2a	15	50	EtOH	0.23	**3a**, 75
2a	15	25	EtOH	0.12	**3a**, 80
2a	15	10	EtOH	0.05	**3a**, 85
2a	15	5	EtOH	0.02	**3a**, 78
2a	15	10	MeOH	0.05	**3a**, 69
2a	15	10	PrOH	0.05	**3a**, 95
2b	30	50	EtOH	0.47	**3g**, 68
2b	30	25	EtOH	0.23	**3g**, 75
2b	30	10	EtOH	0.09	**3g**, 95
2b	30	5	EtOH	0.05	**3g**, 79

[a] Reagents and conditions: salicylaldehyde (**1a**) (10 mmol), CH acid **2** (20 mmol), NaBr (1 mmol), ethanol (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C.

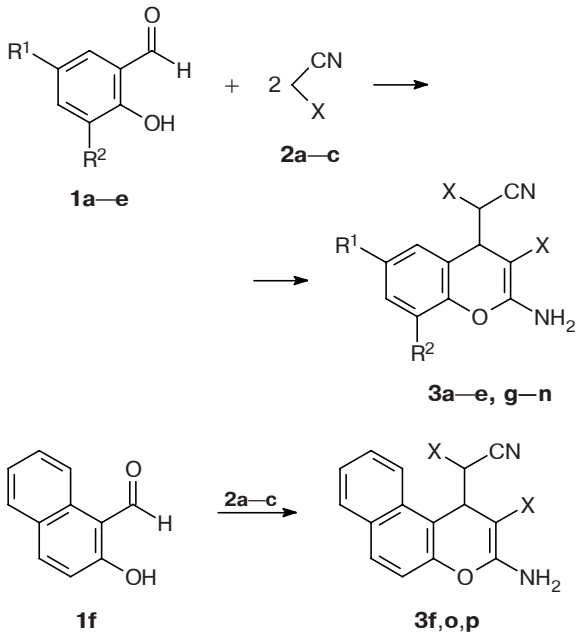
[b] Reaction time.

[c] Current density.

[d] Quantity of electricity.

[e] Yield with respect to the isolated product. For **3a**, m.p. 151—152 °C (*cf.* Ref. 21: m.p. 150—153 °C); for **3g**, m.p. 121—123 °C (*cf.* Ref. 21: m.p. 120—122 °C), the ratio of its diastereomers is 2 : 1 (NMR data).

Scheme 3



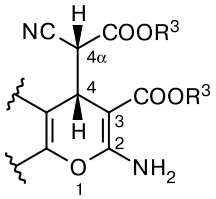
Reagents and conditions: electrolysis, ROH, NaBr.

1	R^1	R^2	**2**	X	**3**	R^1	R^2	X
a	H	H	**a**	CN	**g**	H	H	COOMe
b	Br	H	**b**	COOMe	**h**	H	H	COOEt
c	NO_2	H	**c**	COOEt	**i**	Br	H	COOMe
d	H	OMe			**j**	Br	H	COOEt
e	Br	OMe			**k**	NO_2	H	COOMe
					l	NO_2	H	COOEt
3	R^1	R^2	X		**m**	H	OMe	COOMe
a	H	H	CN		**n**	H	OMe	COOEt
b	Br	H	CN					
c	NO_2	H	CN		**3**	X		
d	H	OMe	CN		**f**	CN		
e	Br	OMe	CN		**o**	COOMe		
					p	COOEt		

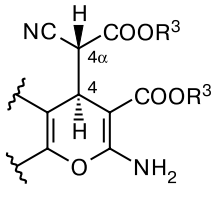
The highest yields of 4*H*-chromenes **3a** and **3g** (95%) were achieved at the current density j = 10 mA cm^{-2}; the quantity of electricity Q required for the electrolysis was 0.05 F mol^{-1} in the case of malononitrile and 0.09 F mol^{-1} in the case of methyl cyanoacetate. At j = 50 mA cm^{-2}, the yield was somewhat lower, probably because of undesired electrode processes resulting in oligomerization of the starting CH acids under these conditions. 4*H*-Chromene **3a** precipitated directly from the reaction mixture at the end of the reaction. The electrolysis of salicylaldehyde and malononitrile in PrOH provided the highest yield of 4*H*-chromene **3a** isolated by simple filtration of the precipitate formed after the completion of the electrolysis.

Coelectrolysis of substituted salicylaldehydes **1b—f** and two equivalents of CH acids **2a—c** were carried out under the optimum reaction conditions (j = 10 mA cm^{-2}, Q = 0.05—0.09 $F\,mol^{-1}$) (Table 2). The yields of 4*H*-chromenes **3b—p** were 83—95%.

According to ^{1}H and ^{13}C NMR data, 4*H*-chromenes **3h—p** are mixtures of two diastereomers, one of them being dominant (see Table 2). From thermodynamic considerations, the major isomer should have the 4α*R**,4*S**-configuration.



4α*R**,4*S**



4α*R**,4*R**

Based on the results obtained, as well as on previous data for the mechanisms of the electrocatalytic chain cyclization of tetracyanocyclopropanes[26] and 3-substituted alkyl 2,2-dicyanocyclopropane-1,1-dicarboxylates,[27] we proposed a mechanism for the electrocatalytic chain transformations of salicylaldehydes and CH acids into 4*H*-chromenes (Scheme 4). The cathodic reaction produces an alkoxide anion that deprotonates the CH acid in solution. The resulting anion of the CH acid enters into the Knoevenagel condensation with salicylaldehyde, with elimination of the OH anion.[30] Subsequent steps involve intramolecular cyclization of the condensation product and addition of a second molecule of the CH acid, giving 4*H*-chromene **3**. The regenerated anion of the CH acid reacts with another salicylaldehyde molecule, thus opening the next cycle of the catalytic chain process. Therefore, the formation of only one alkoxide anion at the cathode is theoretically sufficient for the complete conversion of salicylaldehyde and a CH acid into the corresponding 4*H*-chromene.

Scheme 4

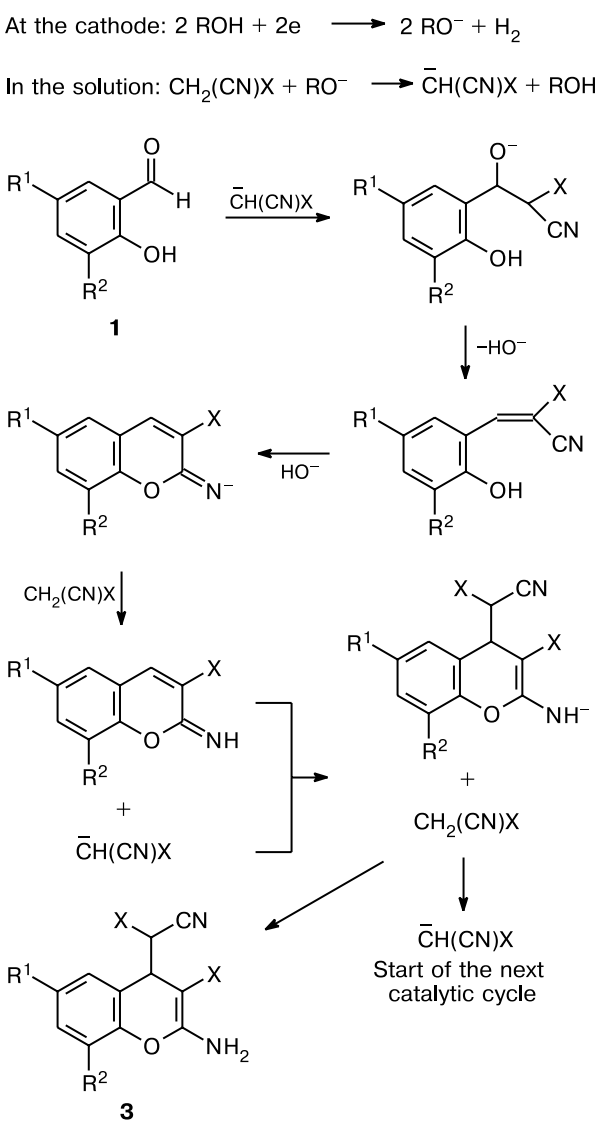


Table 2. Electrocatalytic transformations of substituted salicylaldehydes **1a—f** and CH acids **2a—c** into 4*H*-chromenes **3a—p** [a]

Aldehyde	CH acid	Yield[b] (%)	Ratio of diastereomers[c]	M.p./°C[d]
1a	**2a**	**3a**, 95	—	151—152 (150—153)[21]
1b	**2a**	**3b**, 85	—	160—161
1c	**2a**	**3c**, 93	—	169—170
1d	**2a**	**3d**, 95	—	173—174 (173)[21]
1e	**2a**	**3e**, 86	—	166—167
1f	**2a**	**3f**, 91	—	159—160 (160)[21]
1a	**2c**	**3h**, 91	2 : 1	141—143 (142—143)[20]
1b	**2b**	**3i**, 93	3 : 2	126—127
1b	**2c**	**3j**, 88	2 : 1	107—108 (104—105)[20]
1c	**2b**	**3k**, 85	3 : 2	155—156 (156)[22]
1c	**2c**	**3l**, 87	5 : 2	134—135
1e	**2b**	**3m**, 84	2 : 1	156—157 (150—153)[21]
1e	**2c**	**3n**, 89	2 : 1	125—126 (126—127)[20]
1f	**2b**	**3o**, 85	7 : 2	150—152
1f	**2c**	**3p**, 83	2 : 1	127—128

[a] Reagents and conditions: salicylaldehyde **1** (10 mmol), CH acid **2** (20 mmol), NaBr (1 mmol), ethanol (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C.

[b] Yield with respect to the isolated product.

[c] According to NMR spectroscopic data.

[d] The literature data are given in parentheses.

To sum up, functionalized 4*H*-chromenes can be obtained in high yields by direct transformation of salicylaldehydes and CH acids containing the cyano group in a simple electrocatalytic system under mild conditions. The advantages of the electrocatalytic chain process we proposed include the short reaction time, simple equipment, an undivided cell, inexpensive starting reagents, and a simple procedure for isolation of the final products.

Experimental

Melting points were determined on a Gallenkamp instrument (Sanyo). NMR spectra were recorded on Bruker WM-250 (250 (^{1}H) and 63 MHz (^{13}C)) and Bruker AC-200 instruments (200 (^{1}H) and 50 MHz (^{13}C)) in DMSO-d_6. Chemical shifts are given on the δ scale with reference to $SiMe_4$. IR spectra were recorded on a Specord M82 FTIR spectrometer (KBr pellets) with the Soft Spectra software. Mass spectra (EI, 70 eV) were recorded on a Finnigan MAT INCOS 50 mass spectrometer (direct inlet probe).

The starting reagents (salicylaldehyde, substituted salicylaldehydes, malononitrile, and methyl and ethyl cyanoacetates) were purchased from Aldrich and Acros.

4*H*-Chromenes 3 (general procedure). A solution of salicylaldehyde **1** (10 mmol), CH acid **2** (20 mmol), and NaBr (1 mmol) in PrOH or EtOH (20 mL) were subjected to room-temperature electrolysis in a stirred undivided cell fitted with a graphite anode and an iron cathode (electrode surface area 5 cm^2) at a constant current density of 10 mA cm^{-2}. The quantity of electricity passed through the cell was 0.05 *F* mol^{-1} for malononitrile **2a** and 0.09 *F* mol^{-1} for alkyl cyanoacetates **2b,c**. After the electrolysis was completed, the precipitates of 4*H*-chromenes **3a—e,f** were filtered off, washed with cooled 85% EtOH, and dried in air. 4*H*-Chromenes **3d—n,o,p** were isolated by evaporation of the solution to dryness and crystallized from 85% EtOH.

(2-Amino-3-cyano-4*H*-chromen-4-yl)malononitrile (3a), m.p. 151—152 °C (*cf.* Ref. 21: m.p. 150—153 °C). ^{1}H NMR, δ: 4.59 (d, 1 H, *J* = 3.8 Hz); 5.08 (d, 1 H, *J* = 3.8 Hz); 7.14 (d, 1 H, *J* = 8.2 Hz); 7.27 (t, 1 H, J_1 = 7.5 Hz, J_2 = 7.5 Hz); 7.38—7.53 (m, 4 H).

(2-Amino-6-bromo-3-cyano-4*H*-chromen-4-yl)malononitrile (3b), m.p. 160—161 °C. Found (%): C, 49.43; H, 2.14; Br, 25.46; N, 17.70. $C_{13}H_7BrN_4O$. Calculated (%): C, 49.55; H, 2.24; Br, 25.36; N, 17.78. ^{1}H NMR, δ: 4.65 (d, 1 H, *J* = 3.8 Hz); 5.15 (d, 1 H, *J* = 3.8 Hz); 7.12 (d, 1 H, *J* = 8.7 Hz); 7.55—7.65 (m, 3 H); 7.73 (s, 1 H). ^{13}C NMR, δ: 32.3, 36.7, 48.5, 112.6, 112.8, 116.3, 118.5, 119.0, 120.3, 131.3, 132.8, 149.0, 163.2. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 315 $[M]^+$, (0.2), 248 (27), 221 (18), 170 (6), 143 (8), 114 (49), 88 (17), 66 (100), 50 (24), 38 (48). IR (KBr), ν/cm^{-1}: 3460, 3348, 2884, 2196, 1596, 1480, 1428, 1268, 1228, 1036.

(2-Amino-3-cyano-6-nitro-4*H*-chromen-4-yl)malononitrile (3c), m.p. 169—170 °C. Found (%): C, 55.43; H, 2.61; N, 24.80. $C_{13}H_7N_5O_3$. Calculated (%): C, 55.52; H, 2.51; N, 24.90. ^{1}H NMR, δ: 4.80 (d, 1 H, *J* = 3.8 Hz); 5.22 (d, 1 H, *J* = 3.8 Hz); 7.40 (d, 1 H, *J* = 9.0 Hz); 7.78 (s, 2 H); 8.29 (d, 1 H, *J* = 9.0 Hz); 8.51 (s, 1 H). ^{13}C NMR, δ: 32.3, 36.7, 48.6, 112.5, 112.7, 117.8, 118.6, 119.2, 125.1, 125.7, 143.8, 154.0, 162.6. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 281 $[M]^+$ (0.1), 215 (34), 185 (7), 158 (8), 142 (3), 114 (38), 88 (15), 66 (100), 50 (16), 38 (46). IR (KBr), ν/cm^{-1}: 3408, 3320, 2904, 2204, 1612, 1528, 1424, 1264, 1240, 1029.

(2-Amino-3-cyano-8-methoxy-4*H*-chromen-4-yl)malononitrile (3d), m.p. 173—174 °C (*cf.* Ref. 21: m.p. 173 °C). ^{1}H NMR, δ: 3.85 (s, 3 H); 4.55 (d, 1 H, *J* = 3.9 Hz); 5.05 (d, 1 H, *J* = 3.9 Hz); 7.02 (d, 1 H, *J* = 7.3 Hz); 7.10—7.25 (m, 2 H); 7.48 (s, 2 H).

(2-Amino-6-bromo-3-cyano-8-methoxy-4*H*-chromen-4-yl)-malononitrile (3e), m.p. 166—167 °C. Found (%): C, 48.64; H, 2.70; Br, 23.21; N, 16.16. $C_{14}H_9BrN_4O_2$. Calculated (%): C, 48.72; H, 2.63; Br, 23.15; N, 16.23. ^{1}H NMR, δ: 3.85 (s, 3 H); 4.56 (d, 1 H, *J* = 3.8 Hz); 5.09 (d, 1 H, *J* = 3.8 Hz); 7.23 (s, 1 H); 7.30 (s, 1 H); 7.57 (s, 2 H). ^{13}C NMR, δ: 32.2, 36.8, 48.5, 56.4, 112.7, 112.8, 115.8, 116.2, 119.0, 120.5, 122.0, 138.6, 148.0, 163.1. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 345 $[M]^+$ (0.1), 278 (97), 235 (11), 184 (17), 156 (9), 128 (31), 114 (6), 101 (27), 66 (100), 50 (31), 38 (41). IR (KBr), ν/cm^{-1}: 3436, 3336, 2908, 2196, 1596, 1528, 1432, 1268, 1220, 1092.

(3-Amino-2-cyano-1*H*-benzo[*f*]chromen-4-yl)malononitrile (3f), m.p. 159—160 °C (*cf.* Ref. 21: m.p. 160 °C). ^{1}H NMR, δ: 5.03 (d, 1 H, *J* = 3.6 Hz); 5.30 (d, 1 H, *J* = 3.6 Hz); 7.33 (d, 1 H, *J* = 8.9 Hz); 7.50—7.75 (m, 4 H); 7.96—8.05 (m, 2 H); 8.30 (d, 1 H, *J* = 8.3 Hz).

Methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (3g), m.p. 121—123 °C (*cf.* Ref. 21: m.p. 120—122 °C). Major diastereomer. ^{1}H NMR, δ: 3.79 (s, 3 H, OMe); 3.81 (s, 3 H, OMe); 4.00 (d, 1 H, CH, *J* = 3.8 Hz); 4.71 (d, 1 H, CH, *J* = 3.8 Hz); 7.05—7.91 (m, 6 H, Ar and NH_2). ^{13}C NMR, δ: 36.3, 46.9, 50.8, 53.1, 71.2, 116.1, 116.3, 120.3, 124.6, 128.0, 129.4, 150.1, 162.6, 165.7, 167.7. Minor diastereomer. ^{1}H NMR, δ: 3.68 (s, 3 H, OMe); 3.77 (s, 3 H, OMe); 3.95 (d, 1 H, CH, *J* = 3.5 Hz); 4.62 (d, 1 H, CH, *J* = 3.5 Hz); 7.05—7.91 (m, 6 H, Ar and NH_2). ^{13}C NMR, δ: 36.7, 47.3, 50.6, 52.9, 70.4, 115.8, 116.2, 121.7, 124.8, 128.1, 129.1, 150.0, 162.8, 165.5, 167.9.

Ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (3h), m.p. 141—143 °C (*cf.* Ref. 20: m.p. 142—143 °C). Major diastereomer. ^{1}H NMR, δ: 1.17 (t, 3 H, Me, *J* = 7.3 Hz); 1.25 (t, 3 H, Me, *J* = 7.3 Hz); 3.98—4.22 (m, 4 H, 2 OCH_2); 4.33 (d, 1 H, CH, *J* = 3.7 Hz); 4.59 (d, 1 H, CH, *J* = 3.7 Hz); 7.02—7.45 (m, 4 H, Ar); 7.80 (s, 2 H, NH_2). ^{13}C NMR, δ: 13.8, 14.4, 36.4, 47.1, 59.2, 62.2, 71.4, 116.1, 116.2, 120.4, 124.6, 128.1, 129.4, 150.1, 162.6, 165.2, 167.3. Minor diastereomer. ^{1}H NMR, δ: 1.11 (t, 3 H, Me, *J* = 7.4 Hz); 1.22 (t, 3 H, Me, *J* = 7.4 Hz); 3.97—4.22 (m, 5 H, 2 OCH_2 and CH); 4.54 (d, 1 H, CH, *J* = 3.7 Hz); 7.02—7.45 (m, 4 H, Ar); 7.80 (s, 2 H, NH_2). ^{13}C NMR, δ: 13.6, 14.3, 36.7, 46.4, 59.1, 61.9, 71.2, 115.8, 116.7, 121.5, 124.7, 128.7, 129.1, 149.9, 162.7, 165.0, 167.6.

Methyl 2-amino-6-bromo-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (3i), m.p. 159—160 °C. Found (%): C, 47.13; H, 3.53; Br, 20.81; N, 7.19. $C_{15}H_{13}BrN_2O_5$. Calculated (%): C, 47.26; H, 3.44; Br, 20.96; N, 7.35. IR (KBr), ν/cm^{-1}: 3428, 3312, 2956, 2252, 1744, 1688, 1524, 1436, 1232, 1024. Major diastereomer. ^{1}H NMR, δ: 3.65 (s, 3 H, OMe); 3.72 (s, 3 H, OMe); 4.40 (d, 1 H, CH, *J* = 3.6 Hz); 4.52 (d, 1 H, CH, *J* = 3.6 Hz); 7.08 (d, 1 H, Ar, *J* = 8.7 Hz); 7.18 (s, 1 H, Ar); 7.57 (d, 1 H, Ar, *J* = 8.7 Hz); 7.91 (s, 2 H, NH_2). ^{13}C NMR, δ: 36.0, 46.8, 50.9, 53.1, 70.7, 115.9, 116.2, 118.4, 124.2, 130.6, 132.2, 149.4, 162.2, 165.6, 167.5. Minor diastereomer. ^{1}H NMR, δ: 3.57 (s, 3 H, OMe); 3.62 (s, 3 H, OMe); 4.26 (d, 1 H, CH, *J* = 3.0 Hz); 4.55 (d, 1 H, CH, *J* = 3.0 Hz); 7.05 (d, 1 H, Ar, *J* = 8.5 Hz); 7.52 (d, 1 H, Ar, *J* = 8.5 Hz); 7.62 (s, 1 H, Ar); 7.89 (s, 2 H, NH_2). ^{13}C NMR, δ: 36.3, 47.0, 50.8, 53.0, 69.9, 116.0, 116.1, 118.1, 122.9, 131.4, 132.0, 149.3, 162.5, 165.4, 167.7.

Ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (3j), m.p. 107—108 °C (*cf.* Ref. 20: m.p. 104—105 °C). Major diastereomer. ^{1}H NMR, δ: 1.18 (t, 3 H, Me, *J* = 7.3 Hz); 1.22 (t, 3 H, Me, *J* = 7.3 Hz); 4.02—4.23 (m, 4 H, two OCH_2); 4.37 (d, 1 H, CH, *J* = 3.8 Hz); 4.54 (d, 1 H, CH, *J* = 3.8 Hz); 7.08 (d, 1 H, Ar, *J* = 8.6 Hz); 7.20 (s, 1 H, Ar); 7.55 (d, 1 H, Ar, *J* = 8.6 Hz); 7.84 (s, 2 H, NH_2). Minor diastereomer. ^{1}H NMR, δ: 1.12 (t, 3 H, Me, *J* = 7.3 Hz); 1.24 (t, 3 H, Me, *J* = 7.3 Hz); 4.02—4.23 (m, 5 H, two OCH_2 and CH); 4.53 (d, 1 H, CH, *J* = 3.0 Hz); 7.02 (d, 1 H, Ar, *J* = 8.4 Hz); 7.55 (d, 1 H, Ar, *J* = 8.4 Hz); 7.62 (s, 1 H, Ar); 7.89 (s, 2 H, NH_2).

Methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-6-nitro-4*H*-chromene-3-carboxylate (3k), m.p. 155—156 °C (*cf.* Ref. 22:

m.p. 156 °C). Major diastereomer. ^{1}H NMR, δ: 3.70 (s, 3 H, OMe); 3.75 (s, 3 H, OMe); 4.48 (d, 1 H, CH, *J* = 3.7 Hz); 4.67 (d, 1 H, CH, *J* = 3.7 Hz); 7.33 (d, 1 H, Ar, *J* = 8.9 Hz); 7.91 (s, 3 H, Ar and NH_2); 8.20 (d, 1 H, Ar, *J* = 8.9 Hz). ^{13}C NMR, δ: 36.1, 46.6, 50.9, 53.2, 70.5, 115.8, 117.4, 121.6, 124.1, 125.1, 143.4, 154.5, 161.5, 165.4, 167.2. Minor diastereomer. ^{1}H NMR, δ: 3.65 (s, 3 H, OMe); 3.78 (s, 3 H, OMe); 4.32 (d, 1 H, CH, *J* = 3.7 Hz); 4.65 (d, 1 H, CH, *J* = 3.7 Hz); 7.30 (d, 1 H, Ar, *J* = 8.9 Hz); 7.91 (s, 3 H, Ar and NH_2); 8.25 (d, 1 H, Ar, *J* = 8.9 Hz). ^{13}C NMR, δ: 36.0, 46.6, 50.8, 53.0, 69.9, 115.9, 117.5, 122.9, 124.1, 124.9, 143.7, 154.3, 161.7, 165.2, 167.4.

Ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-6-nitro-4*H*-chromene-3-carboxylate (3l), m.p. 134—135 °C. Found (%): C, 54.26; H, 4.62; N, 11.07. $C_{17}H_{17}N_3O_7$. Calculated (%): C, 54.40; H, 4.57; N, 11.20. IR (KBr), ν/cm^{-1}: 3428, 3316, 2992, 2260, 1740, 1692, 1520, 1472, 1228, 1040. Major diastereomer. ^{1}H NMR, δ: 1.23 (t, 3 H, Me, *J* = 7.3 Hz); 1.28 (t, 3 H, Me, *J* = 7.3 Hz); 4.05—4.27 (m, 4 H, two OCH_2); 4.47 (d, 1 H, CH, *J* = 3.7 Hz); 4.75 (d, 1 H, CH, *J* = 3.7 Hz); 7.39 (d, 1 H, Ar, *J* = 9.1 Hz); 7.93 (s, 2 H, NH_2); 8.02 (s, 1 H, Ar); 8.28 (d, 1 H, Ar, *J* = 9.1 Hz). ^{13}C NMR, δ: 13.8, 14.2, 36.0, 46.9, 59.5, 62.5, 70.7, 116.0, 117.6, 121.8, 124.2, 125.3, 143.4, 154.6, 161.5, 165.0, 166.9. Minor diastereomer. ^{1}H NMR, δ: 1.07 (t, 3 H, Me, *J* = 7.3 Hz); 1.16 (t, 3 H, Me, *J* = 7.3 Hz); 4.05—4.27 (m, 4 H, two OCH_2); 4.33 (d, 1 H, CH, *J* = 3.0 Hz); 4.74 (d, 1 H, CH, *J* = 3.0 Hz); 7.34 (d, 1 H, Ar, *J* = 8.5 Hz); 7.91 (s, 2 H, NH_2); 8.26 (d, 1 H, Ar, *J* = 8.5 Hz); 8.41 (s, 1 H, Ar); ^{13}C NMR, δ: 13.6, 14.3, 35.8, 45.9, 59.4, 62.2, 70.5, 116.3, 117.3, 122.8, 124.9, 125.1, 143.6, 154.5, 161.6, 164.8, 167.2.

Methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-8-methoxy-4*H*-chromene-3-carboxylate (3m), m.p. 156—157 °C (*cf.* Ref. 21: m.p. 150—153 °C). Major diastereomer. ^{1}H NMR, δ: 3.67 (s, 3 H, OMe); 3.71 (s, 3 H, OMe); 3.81 (s, 3 H, OMe); 4.38 (d, 1 H, CH, *J* = 3.8 Hz); 4.50 (d, 1 H, CH, *J* = 3.8 Hz); 6.56 (d, 1 H, Ar *J* = 8.8 Hz); 7.00—7.18 (m, 2 H, Ar); 7.88 (s, 2 H, NH_2). ^{13}C NMR, δ: 36.4, 46.9, 50.8, 53.0, 55.7, 71.0, 112.1, 116.1, 118.9, 121.1, 124.5, 139.4, 147.2, 162.6, 165.6, 167.7. Minor diastereomer. ^{1}H NMR, δ: 3.57 (s, 3 H, OMe); 3.65 (s, 3 H, OMe); 3.80 (s, 3 H, OMe); 4.14 (d, 1 H, CH, *J* = 3.7 Hz); 4.51 (d, 1 H, CH, *J* = 3.7 Hz); 6.91 (d, 1 H, Ar, *J* = 8.8 Hz); 7.00—7.18 (m, 2 H, Ar); 7.90 (s, 2 H, NH_2). ^{13}C NMR, δ: 36.8, 47.3, 50.7, 52.9, 55.8, 70.3, 111.8, 116.2, 119.6, 122.7, 124.7, 139.3, 147.0, 162.8, 165.5, 167.9.

Ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-8-methoxy-4*H*-chromene-3-carboxylate (3n), m.p. 125—126 °C (*cf.* Ref. 20: m.p. 126—127 °C). Major diastereomer. ^{1}H NMR, δ: 1.17 (t, 3 H, Me, *J* = 7.3 Hz); 1.20 (t, 3 H, Me, *J* = 7.3 Hz); 3.81 (s, 3 H, OMe); 3.98—4.21 (m, 4 H, 2 OCH_2); 4.30 (d, 1 H, CH, *J* = 3.7 Hz); 4.52 (d, 1 H, CH, *J* = 3.7 Hz); 6.59 (d, 1 H, Ar, *J* = 8.6 Hz); 7.00—7.18 (m, 2 H, Ar); 7.85 (s, 2 H, NH_2). ^{13}C NMR, δ: 13.8, 14.3, 36.5, 47.0, 55.7, 59.2, 62.1, 71.2, 112.0, 116.2, 119.0, 121.2, 124.4, 139.4, 147.2, 162.6, 165.1, 167.4. Minor diastereomer. ^{1}H NMR, δ: 1.10 (t, 3 H, Me, *J* = 7.3 Hz); 1.21 (t, 3 H, Me, *J* = 7.3 Hz); 3.81 (s, 3 H, OMe); 3.98—4.21 (m, 5 H, 2 OCH_2 and CH); 4.50 (d, 1 H, CH, *J* = 3.7 Hz); 6.93 (d, 1 H, Ar, *J* = 8.8 Hz); 7.00—7.18 (m, 2 H, Ar); 7.85 (s, 2 H, NH_2). ^{13}C NMR, δ: 13.5, 14.2, 36.7, 46.4, 55.7, 59.1, 61.9, 71.1, 111.7, 116.6, 119.6, 122.3, 124.5, 139.2, 147.0, 162.5, 165.0, 167.5.

Methyl 3-amino-1-(1-cyano-2-methoxy-2-oxoethyl)-1*H*-benzo[*f*]chromene-2-carboxylate (3o), m.p. 150—152 °C. Found (%): C, 64.61; H, 4.53; N, 7.81. $C_{19}H_{16}N_2O_5$. Calculated (%): C, 64.77; H, 4.58; N, 7.95. IR (KBr), ν/cm^{-1}: 3468, 3316, 2956, 2252, 1744, 1684, 1520, 1444, 1220, 1080. Major diastereomer. ^{1}H NMR, δ: 3.64 (s, 3 H, OMe); 3.82 (s, 3 H, OMe); 4.23 (d, 1 H, CH, *J* = 2.0 Hz); 5.20 (d, 1 H, CH, *J* = 2.0 Hz); 7.35 (d, 1 H, Ar, *J* = 9.2 Hz); 7.52—8.08 (m, 7 H, Ar, NH_2). ^{13}C NMR, δ: 33.7, 46.8, 50.9, 53.2, 70.3, 114.5, 116.0, 116.6, 121.5, 125.4, 128.2, 129.3, 130.1, 130.3, 130.9, 148.0, 162.9, 165.9, 168.0. Minor diastereomer. ^{1}H NMR, δ: 3.47 (s, 3 H, OMe); 3.75 (s, 3 H, OMe); 4.31 (d, 1 H, CH, *J* = 3.7 Hz); 5.24 (d, 1 H, CH, *J* = 3.7 Hz); 7.52—8.08 (m, 8 H, Ar, NH_2). ^{13}C NMR, δ: 33.2, 46.1, 50.8, 52.9, 72.3, 114.0, 116.4, 116.7, 122.1, 125.2, 127.4, 128.9, 130.2, 130.4, 130.6, 148.8, 162.8, 165.7, 167.7.

Ethyl 3-amino-1-(1-cyano-2-ethoxy-2-oxoethyl)-1*H*-benzo[*f*]chromene-2-carboxylate (3p), m.p. 127—128 °C. Found (%): C, 66.19; H, 5.37; N, 7.18. $C_{21}H_{20}N_2O_5$. Calculated (%): C, 66.31; H, 5.30; N, 7.36. IR (KBr), ν/cm^{-1}: 3456, 3328, 2976, 2256, 1740, 1676, 1516, 1464, 1228, 1076. Major diastereomer. ^{1}H NMR, δ: 1.26 (t, 3 H, Me, *J* = 7.3 Hz); 1.29 (t, 3 H, Me, *J* = 7.3 Hz); 3.85—4.28 (m, 5 H, 2 OCH_2 and CH); 5.22 (d, 1 H, CH, *J* = 1.8 Hz); 7.34 (d, 1 H, Ar, *J* = 9.2 Hz); 7.50—8.10 (m, 7 H, Ar and NH_2). ^{13}C NMR, δ: 13.9, 14.4, 33.5, 46.7, 59.2, 62.1, 71.0, 114.8, 116.1, 116.6, 121.6, 125.3, 128.1, 128.9, 129.1, 130.1, 130.9, 147.9, 162.8, 165.3, 167.6. Minor diastereomer. ^{1}H NMR, δ: 0.99 (t, 3 H, Me, *J* = 7.3 Hz); 1.34 (t, 3 H, Me, *J* = 7.3 Hz); 3.85—4.28 (m, 5 H, 2 OCH_2 and CH); 5.25 (d, 1 H, CH, *J* = 3.7 Hz); 7.50—8.10 (m, 8 H, Ar and NH_2). ^{13}C NMR, δ: 13.3, 14.3, 33.2, 46.2, 59.3, 62.0, 72.3, 114.1, 116.5, 116.7, 122.1, 125.1, 127.3, 128.8, 129.3, 130.0, 130.6, 148.7, 162.6, 165.2, 167.4.

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