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Synthesis of 2-(alkylamino)-5-{alkyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylates using a multi-component reaction in water

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ABSTRACT

A simple synthesis of 2-(alkylamino)-5-{alkyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylates via a one-pot multi-component reaction is described. The reactive 1:1 zwitterionic intermediate generated from the addition of isocyanides to dialkyl acetylenedicarboxylates was trapped at room temperature by coumarin-3-carboxylic acids prepared in situ from a 2-hydroxy aromatic aldehyde and Meldrum's acid to afford the title compounds in good to excellent yields.

1. Introduction

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features, such as atom economy, straightforward reaction design and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] MCRs leading to interesting heterocyclic scaffolds are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area.[1j,k]

Furans, benzofurans, and their reduced forms are important core structures in many biologically active natural products. Moreover, they are useful building blocks in the total synthesis of natural products and pharmaceuticals.[2–5] Many naturally occurring furans have exhibited considerable biological activities, such as antitumor and cytotoxic properties,[6] as well as antimicrobial,[7] antispasmodic,[8] and several other potentially useful activities.[9,10] In addition, furans are also present in commercially important products, such as agrochemical bioregulators, essential oils, cosmetics, dyes, photosensitizers, flavoring and fragrance compounds.[10,11] This broad range of applications has made the development of new and efficient furan synthesis very valuable. Consequently, a variety of furan syntheses have been reported in the literature. Although a lot of strategies can be found for the synthesis of furans, convergent synthetic methods from simple and readily available starting materials without using transition-metal catalysis are still rare.[1g,2a,12–14]

Coumarinyl compounds have been extensively used in medicinal chemistry. Some examples have been shown to be highly potent human β-secretase inhibitors and are used in the treatment of Alzheimer's disease. Most of the synthetic medicines containing a coumarin, are prepared by the reaction between coumarin-3-carboxylic acids and amines.[15]

2. Results and discussion

As part of our current studies on the development of new efficient strategies for the preparation of interesting bioactive molecules and drug cores,[16] herein, we present a new synthetic method for the construction of 5-amido coumarinyl 2-aminofurans via a one-pot, isocyanide-based MCR involving commercially available starting materials. Thus, a mixture of salicylaldehyde **1a**, Meldrum's acid **2**, *tert*-butyl isocyanide **3a** (2 equiv) and dimethyl

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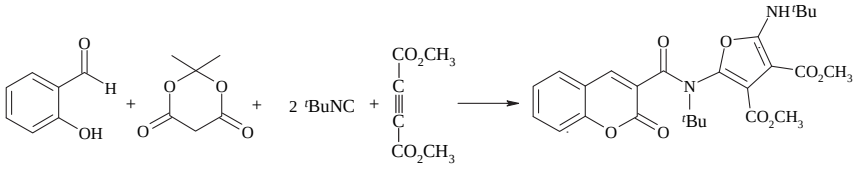
acetylenedicarboxylate (DMAD, **4a**) afforded dimethyl 2-(*tert*-butylamino)-5-{*tert*-butyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate **5a** (Scheme 1).



1a **2** **3a** **4a** **5a**

Scheme 1.

The reaction was carried out in some solvents under similar conditions at ambient temperature. As disclosed in Table 1, the maximum yield was observed in water (entry 1).

Table 1
Solvent effect in the multi-component synthesis of **5a**

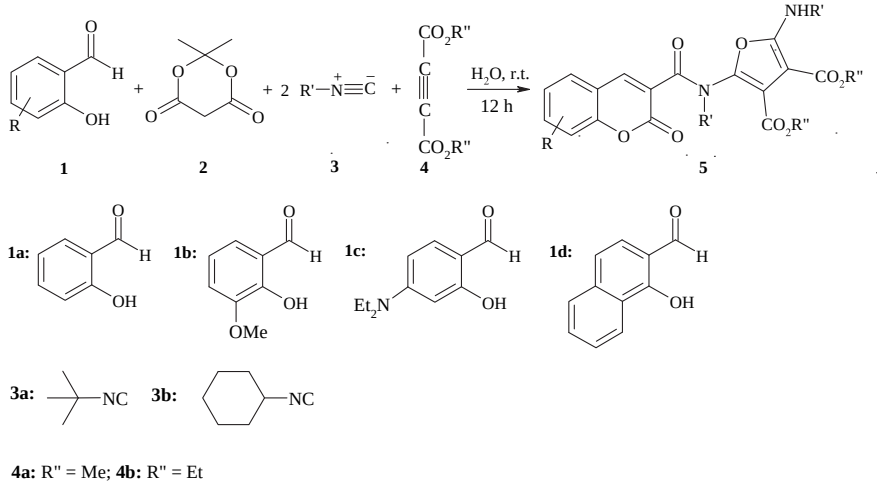
Entry	Solvent	Time h	Yield of **5a** (%)
1	H_2O	12	87
2	CH_2Cl_2	12	70
3	$CHCl_3$	12	60
4	EtOH	12	68

In order to show the generality and scope of this new protocol, we used various 2-hydroxy aromatic aldehydes, dialkyl acetylenedicarboxylates, and isocyanides in water. The results are summarized in Scheme 2 and Table 2.

water and an acetone molecule. The ^{1}H NMR spectrum of **5a** exhibited five single sharp lines readily recognized as arising from the two *tert*-butyl (δ=1.43 and 1.49 ppm) groups, two methoxy (δ=3.63 and 3.80 ppm) groups, and the coumarin vinylic H atom (δ=7.68 ppm). A fairly sharp singlet was seen for the amine NH group (δ=6.84 ppm) along with the characteristic signals with appropriate chemical shifts and coupling constants for the four aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 22 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section.

The ^{1}H and ^{13}C NMR spectra of compounds **5b**–**j** were similar to those of **5a**, except for the *N*-alkyl groups, ester functions and coumarin moieties, which exhibited characteristic signals with appropriate chemical shifts and coupling constants (see the Experimental section).

A mechanistic rationalization for this reaction is provided in Scheme 3. At first, the 2-hydroxy aromatic aldehydes **1** condense with Meldrum's acid **2** to produce intermediates **6**, which are readily converted in to coumarin-3-carboxylic acids **7** via an addition reaction and subsequent acetone elimination. Next, the



1 **2** **3** **4** **5**

Scheme 2.

All the reactions were complete within 12 h. The ^{1}H NMR spectroscopic analysis of the reaction mixtures clearly indicated the formation of the corresponding 5-amido coumarinyl 2-aminofurans **5a**–**j** in good to excellent yields.

The structures of the isolated products **5a**–**j** were deduced on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **5a** displayed the molecular ion (M^+) peak at m/z=498, which was consistent with the 1:1:2:1 adduct of salicylaldehyde, Meldrum's acid, *tert*-butyl isocyanide, and dimethyl acetylenedicarboxylate with the loss of water and an acetone molecule. The ^{1}H NMR spectrum of **5a** exhibited five single sharp lines readily recognized as arising from the two *tert*-butyl (δ=1.43 and 1.49 ppm) groups, two methoxy (δ=3.63 and 3.80 ppm) groups, and the coumarin vinylic H atom (δ=7.68 ppm). A fairly sharp singlet was seen for the amine NH group (δ=6.84 ppm) along with the characteristic signals with appropriate chemical shifts and coupling constants for the four aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 22 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section.

The ^{1}H and ^{13}C NMR spectra of compounds **5b**–**j** were similar to those of **5a**, except for the *N*-alkyl groups, ester functions and coumarin moieties, which exhibited characteristic signals with appropriate chemical shifts and coupling constants (see the Experimental section).

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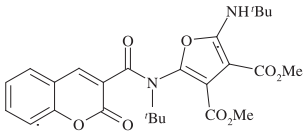
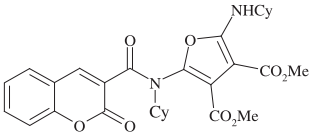
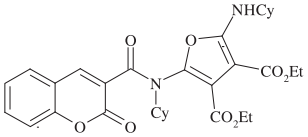
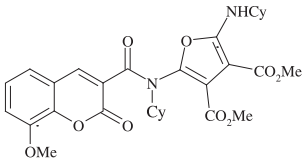
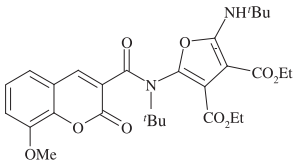
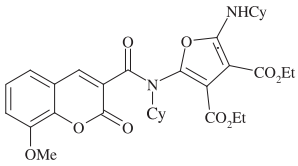
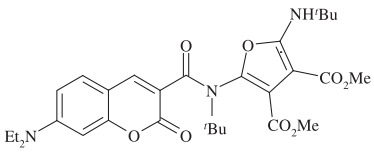
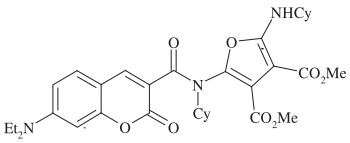
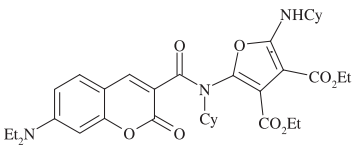
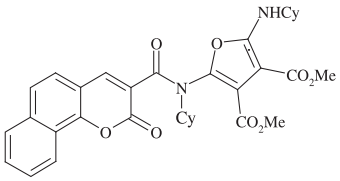
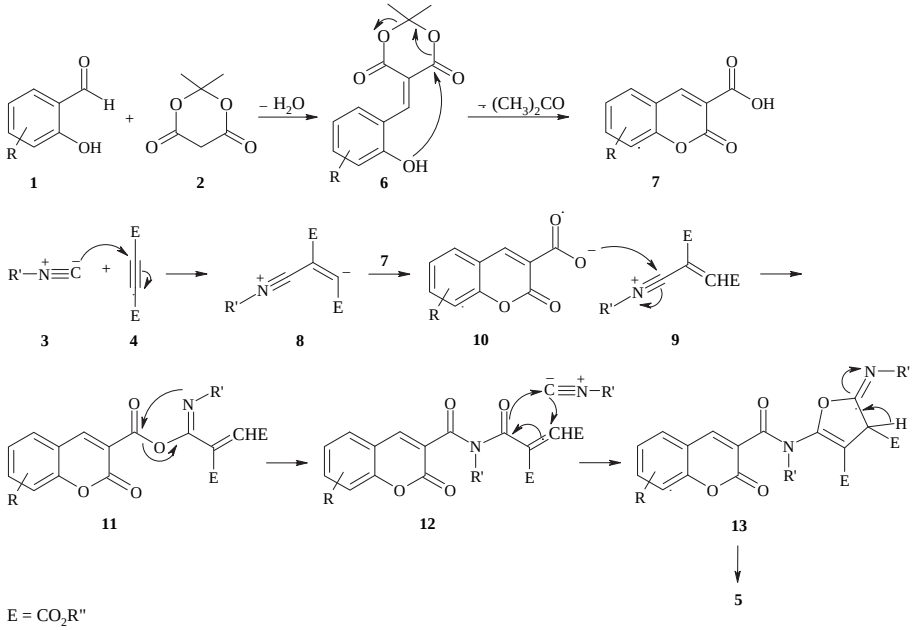
Table 2
Synthesis of 5-amido coumarinyl 2-aminofurans **5a–j**

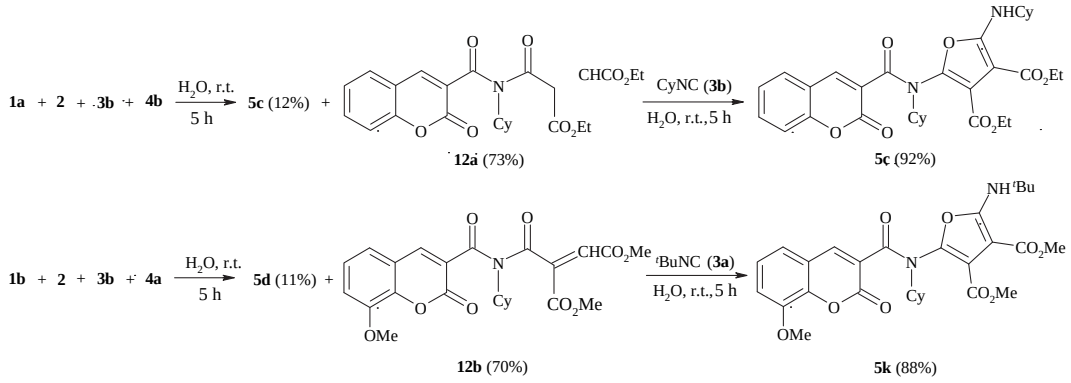
Product	Structure	Yield %	Product	Structure	Yield %
5a		87	**5b**		85
5c		89	**5d**		88
5e		85	**5f**		87
5g		90	**5 h**		92
5i		96	**5j**		83

When the reactions were performed using equivalent ratios of a 2-hydroxy aromatic aldehyde (**1a** or **1b**), Meldrum's acid **2**, cyclohexyl isocyanide **3b** and, an acetylenic ester (**4b** or **4a**) under the same reaction conditions, after 5 h, TLC and ^{1}H NMR spectroscopic analysis of the reaction mixtures clearly indicated the formation of corresponding furans **5c** and **5d** in 12 and 11% yields, in addition to other products **12a** and **12b** as the major one in 73 and 70% yields, respectively. The structures of the isolated 2-({cyclohexyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}carbonyl)-2-butenedioates **12a** and **12b** were deduced by ^{1}H and ^{13}C NMR



Scheme 3.

spectroscopy and also by elemental analysis (see the Experimental section). Addition of a second equivalent of an isocyanide **3b** or **3a** to the isolated butenedioates **12a** and **12b** and subsequent cycloaddition of the added isocyanide with **12** afforded the corresponding furans **5c** and **5k** in 92 and 88% yields, respectively (Scheme 4).



Scheme 4.

3. Conclusion

In summary, we have developed a simple, convergent and highly efficient one-pot protocol for the synthesis of 5-amido coumarinyl 2-aminofuran derivatives, which are of potential chemical, synthetic and pharmacological interest, based on a new multi-component reaction. Considering the availability of the starting materials, the simple one-pot procedure, high yield of the products, high flexibility with respect to the substitution pattern at all positions and the robust nature of this chemical process, provides a very straightforward route to construct variously substituted furans without any activation or modification. The simplicity of the present procedure makes it a viable alternative to the complex multi-step approaches for the synthesis of bioactive furans.

4. Experimental

4.1. General

Dimethyl- and diethyl-acetylenedicarboxylates, *tert*-butyl- and cyclohexyl-isocyanides, salicylaldehyde, 2-hydroxy-3-methoxybenzaldehyde, 4-(diethylamino)-2-hydroxybenzaldehyde and 1-hydroxy-2-naphthaldehyde, and Meldrum's acid were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with Bruker DRX-500 AVANCE (at 500.1 and 125.8 MHz), Bruker DRX-300 (at 300.1 and 75.5 MHz), and Bruker DPX-250 (at 250.1 and 62.9 MHz) spectrometers with TMS as an internal standard. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

4.2. General procedure for the preparation of compound 5a–j, exemplified with 5a

A mixture of salicylaldehyde (0.122 g, 1 mmol) and Meldrum's acid (0.144 g, 1 mmol) in H_2O (5 mL) was magnetically stirred at 25 °C for 20 min. After nearly complete conversion to coumarin-3-carboxylic acid, as was indicated by TLC monitoring, *tert*-butyl isocyanide (0.166 g, 2 mmol), was added to the reaction mixture. Then dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) was added at room temperature over 5 min. The reaction mixture was then allowed to stir for 12 h. Next, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography using *n*-hexane–EtOAc (3:1) as eluent. The solvent was removed and the product was obtained.

*4.2.1. Dimethyl 2-(tert-butylamino)-5-{tert-butyl[(2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5a**).* Pale yellow crystals, mp 198–199 °C, yield: 0.434 g, 87%. IR (KBr) (ν_{max}/cm^{-1}): 3338 (NH), 1719, 1670, and 1603 (C=O), 1475, 1366, 1340, 1275, 1247, 1209, 1090, 1043, 958, 924, 873, 788, 757. EI-MS, *m*/*z* (%): 498 (M^+, 4), 442 (28), 386 (23), 354 (13), 269 (8), 213 (35), 173 (100), 148 (8), 138 (9), 101 (11), 89 (12), 57 (27). Anal. Calcd for $C_{26}H_{30}N_2O_8$ (498.53): C, 62.64; H, 6.07; N, 5.62. Found: C, 62.5; H, 6.2; N, 5.5%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.68 (1H, s, CH), 7.49 (1H, td, J=2.0, 8.1 Hz, CH), 7.38 (1H, dd, J=8.1, 1.0 Hz, CH), 7.25–7.19 (2H, m, 2CH), 6.84 (1H, s, NH), 3.80 and 3.63 (6H, 2s, 2OCH_3), 1.49 and 1.43 [18H, 2s, 2C(CH_3)$_3$]. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 166.0, 164.9, 162.9, 159.5, 157.2, and 153.9 (4C=O and 2NO*C*=C), 140.3 (CH), 137.9 (C), 132.3 and 128.2 (2CH), 126.4 (C), 124.6 (CH), 118.1 (C), 116.8 (CH), 115.2 (C), 85.7 (NOC=*C*), 61.8 and 52.7 [2*C*(CH_3)$_3$], 52.1 and 51.0 (2OCH_3), 29.7 and 27.9 [2C(*C*H_3)$_3$].

*4.2.2. Dimethyl 2-(cyclohexylamino)-5-{cyclohexyl[(2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5b**).* Pale yellow crystals, mp 171–172 °C, yield: 0.468 g, 85%. IR (KBr) (ν_{max}/cm^{-1}): 3344 (NH), 1721, 1656, and 1605 (C=O), 1469, 1447, 1369, 1354, 1274, 1225, 1093, 1050, 972, 930, 888, 725, 680. EI-MS, *m*/*z* (%): 550 (M^+, 36), 519 (12), 468 (9), 410 (15), 377 (56), 295 (100), 197 (12), 173 (89), 83 (37), 55 (69). Anal. Calcd for $C_{30}H_{34}N_2O_8$ (550.61) C, 65.44; H, 6.22; N, 5.09. Found: C, 65.4; H, 6.4; N, 4.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.87 (1H, s, CH), 7.51 (1H, t, J=7.6 Hz, CH), 7.42 (1H, d, J=7.5 Hz, CH), 7.26–7.23 (2H, m, 2CH), 6.58 (1H, d, J=7.6 Hz, NH), 4.50–4.43 (1H, m, NCH), 3.69 and 3.64 (6H, 2s, 2OCH_3), 3.63–3.55 (1H, m, NCH), 1.98–1.02 [20H, m, 2CH(*C*H_2)$_5$]. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 165.3, 164.7, 162.8, 159.7, 157.1, and 154.1 (4C=O and 2NOC=C), 142.6 (CH), 136.7 (C), 132.6 and 128.5 (2CH), 125.0 (C), 124.6 (CH), 118.1 (C), 116.8 (CH), 114.8 (C), 85.3 (NOC=*C*), 55.9 (NCH), 52.0 (OCH_3), 51.6 (NCH), 51.0 (OCH_3), 33.4 (CH_2), 31.6 and 30.2 (2br, 2CH_2), 25.7, 25.4, 25.3, and 24.4 (4CH_2).

*4.2.3. Diethyl 2-(cyclohexylamino)-5-{cyclohexyl[(2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5c**).* Pale yellow

crystals, mp 170–171 °C, yield: 0.515 g, 89%. IR (KBr) (ν_{max}/cm^{-1}): 3346 (NH), 1734, 1703, 1646, 1604 (C=O), 1469, 1416, 1361, 1320, 1285, 1225, 1155, 1096, 1062, 928, 894, 858, 750, 711. EI-MS, *m*/*z* (%): 578 (M^+, 54), 496 (9), 450 (8), 423 (13), 405 (35), 377 (24), 323 (100), 295 (31), 173 (97), 83 (32), 67 (42), 55 (84). Anal. Calcd for $C_{32}H_{38}N_2O_8$ (578.66): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.4; H, 6.6; N, 4.8%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.94 (1H, s, CH), 7.54 (1H, dd, *J*=8.1, 1.5 Hz, CH), 7.45 (1H, d, *J*=8.1 Hz, CH), 7.27 (1H, d, *J*=8.1 Hz, CH), 7.26 (1H, t, *J*=7.5 Hz, CH), 6.60 (1H, d, *J*=7.8 Hz, NH), 4.49–4.42 (1H, m, NCH), 4.30–4.00 (4H, m, 2OCH$_2$), 3.62–3.57 (1H, m, NCH), 2.11–1.01 [6H, 2t (1.22 and 1.19), *J*=7.1 Hz, 2CH$_2$C*H*$_3$; and 20H, m, 2CH(C*H*$_2$)$_5$]. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 165.4, 164.4, 162.8, 159.7, 157.2, and 154.1 (4C=O and 2NO*C*=C), 142.7 (CH), 136.2 (C), 132.5 and 128.5 (2CH), 125.1 (C), 124.6 (CH), 118.3 (C), 116.8 (CH), 115.2 (C), 85.5 (NOC=*C*), 61.3 and 59.7 (2OCH$_2$), 57.0 and 51.5 (2NCH), 33.4 (CH$_2$), 31.5 and 30.4 (2br, 2CH$_2$), 25.7, 25.5, 25.4, and 24.4 (4CH$_2$), 14.3 and 14.0 (2CH$_3$).

*4.2.4. Dimethyl 2-(cyclohexylamino)-5-{cyclohexyl[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5d**).* Pale yellow crystals, mp 190 °C, yield: 0.511 g, 88%. IR (KBr) (ν_{max}/cm^{-1}): 3345 (NH), 1724, 1651, and 1606 (C=O), 1473, 1443, 1364, 1325, 1228, 1147, 1099, 1055, 976, 932, 887, 843, 784, 730, 687. EI-MS, *m*/*z* (%): 580 (M^+, 28), 513 (5), 439 (8), 407 (16), 367 (9), 325 (18), 231 (12), 97 (16), 82 (47), 67 (100), 58 (97). Anal. Calcd for $C_{31}H_{36}N_2O_9$ (580.63): C, 64.13; H, 6.25; N, 4.82. Found: C, 64.3; H, 6.3; N, 4.7%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.86 (1H, s, CH), 7.18 (1H, dd, *J*=8.1, 7.9 Hz, CH), 7.07 (1H, d, *J*=8.1 Hz, CH), 7.00 (1H, d, *J*=7.9 Hz, CH), 6.60 (1H, d, *J*=7.8 Hz, NH), 4.52–4.44 (1H, m, NCH), 3.94, 3.71, and 3.66 (9H, 3s, 3OCH$_3$), 3.63–3.55 (1H, m, NCH), 2.04–1.27 [20H, m, 2CH(C*H*$_2$)$_5$]. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 165.4, 164.7, 162.8, 159.7, 156.5, 147.1, and 143.9 (4C=O, C–O, and 2NOC=C), 143.0 (CH), 136.9 and 125.4 (2C), 124.4 and 119.8 (2CH), 118.8 and 114.7 (2C), 114.5 (CH), 85.2 (NOC=*C*), 57.0 (NCH), 56.3 and 52.0 (2OCH$_3$), 51.5 (NCH), 51.0 (OCH$_3$), 33.5 (CH$_2$), 31.6 and 30.1 (2br, 2CH$_2$), 25.7, 25.5, 25.4, and 24.5 (4CH$_2$).

*4.2.5. Diethyl 2-(tert-butylamino)-5-{tert-butyl[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5e**).* Pale yellow crystals, mp 207–208 °C, yield: 0.473 g, 85%. IR (KBr) (ν_{max}/cm^{-1}): 3325 (NH), 1730, 1685, 1652, 1615 (C=O), 1573, 1508, 1486, 1450, 1414, 1355, 1277, 1231, 1126, 1094, 893, 750, 712. EI-MS, *m*/*z* (%): 556 (M^+, 9), 500 (25), 444 (16), 398 (20), 297 (9), 210 (8), 203 (100), 89 (8), 57 (38). Anal. Calcd for $C_{29}H_{36}N_2O_9$ (556.61): C, 62.58; H, 6.52; N, 5.03. Found: C, 62.6; H, 6.5; N, 5.0%. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 7.72 (1H, s, CH), 7.17 (1H, dd, *J*=8.0, 7.7 Hz, CH), 7.05 (1H, dd, *J*=8.0, 1.2 Hz, CH), 6.97 (1H, dd, *J*=7.5, 1.3 Hz, CH), 6.84 (1H, br s, NH), 4.34 and 4.19 (2H, 2dq, *AB*X$_3$ system, ^2J=10.8 Hz and ^3J=7.0 Hz, OC*H*$_A$*H*$_B$CH$_3$), 4.17 and 4.08 (2H, 2dq, *AB*X$_3$ system, ^2J=10.8 Hz and ^3J=7.0 Hz, OC*H*$_A$*H*$_B$CH$_3$), 3.93 (3H, s, OCH$_3$), 1.51 and 1.44 [18H, 2s, 2C(CH$_3$)$_3$], 1.30 and 1.22 (6H, 2t, *J*=7.0 Hz, 2CH$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 166.1, 164.6, 162.8, 159.4, 156.7, 147.1, and 143.6 (4C=O, C–O, and 2NOC=C), 140.6 (CH), 137.3 and 126.6 (2C), 124.4 and 119.6 (2CH), 118.7 (C), 115.3 (C), 114.1 (CH), 85.9 (NOC=*C*), 61.7 [*C*(CH$_3$)$_3$], 61.4 and 59.7 (2OCH$_2$), 56.2 (OCH$_3$), 52.6 [*C*(CH$_3$)$_3$], 29.7 and 27.9 [2C(*C*H$_3$)$_3$], 14.3 and 14.1 (2CH$_3$).

*4.2.6. Diethyl 2-(cyclohexylamino)-5-{cyclohexyl[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5f**).* Pale yellow crystals, mp 186–187 °C, yield: 0.529 g, 87%. IR (KBr) (ν_{max}/cm^{-1}): 3350 (NH), 1723, 1643, and 16.09 (C=O), 1473, 1359, 1319, 1224, 1097, 1062, 973, 928, 884, 780, 730, 693. EI-MS, *m*/*z* (%): 608 (M^+, 9), 405 (16), 368 (8), 323 (43), 249 (27), 220 (20), 203 (50), 167 (19), 140 (22), 83 (32), 57 (66), 45 (100). Anal. Calcd for $C_{33}H_{40}N_2O_9$ (608.69): C, 65.12; H, 6.62; N, 4.60. Found: C, 64.9; H, 6.7; N, 4.8%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.92 (1H, s, CH), 7.17 (1H, t, *J*=7.7 Hz, CH), 7.08 (1H, d, *J*=7.9 Hz, CH), 7.02 (1H, d, *J*=7.6 Hz, CH), 6.59 (1H, d, *J*=7.4 Hz, NH), 4.50–4.30 (1H, m, NCH), 4.25–4.00 (4H, m, 2OCH$_2$), 3.93 (3H, s, OCH$_3$), 3.55–3.49 (1H, m, NCH), 2.00–1.05 [6H, 2t (1.21 and 1.17), *J*=7.1 Hz, 2OCH$_2$C*H*$_3$; and 20H, m, 2CH(C*H*$_2$)$_5$]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.4, 164.4, 162.7, 159.6, 156.5, 147.0, and 143.8 (4C=O, C–O, and 2NOC=C), 143.2 (CH), 136.3 and 125.3 (C), 124.4 and 119.8 (2CH), 118.8 and 115.0 (2C), 114.3 (CH), 85.4 (NOC=*C*), 61.3 and 59.6 (2OCH$_2$), 56.9 (NCH), 56.2 (OCH$_3$), 51.4 (NCH), 33.4 (CH$_2$), 31.8 and 30.4 (2br, 2CH$_2$), 25.6, 25.4, and 24.4 (3CH$_2$), 14.3 and 14.0 (2CH$_3$).

*4.2.7. Dimethyl 2-(tert-butylamino)-5-(tert-butyl{[7-(diethylamino)-2-oxo-2H-chromen-3-yl]carbonyl}amino)-3,4-furandicarboxylate (**5g**).* Pale yellow crystals, mp 204–205 °C, yield: 0.513 g, 90%. IR (KBr) (ν_{max}/cm^{-1}): 3348 (NH), 1726, 1674, and 16.44 (C=O), 1589, 1513, 1478, 1418, 1348, 1210, 1131, 1090, 1046, 952, 885, 840, 778. EI-MS, *m*/*z* (%): 569 (M^+, 7), 513 (18), 269 (18), 244 (100), 213 (10), 160 (6), 57 (10). Anal. Calcd for $C_{30}H_{39}N_3O_8$ (569.66): C, 63.25; H, 6.90; N, 7.38. Found: C, 63.3; H, 6.9; N, 7.3%. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.56 (1H, s, CH), 7.14 (1H, d, *J*=8.7 Hz, CH), 6.89 (1H, s, NH), 6.51 (1H, d, *J*=8.7 Hz, CH), 6.40 (1H, s, CH), 3.82 and 3.67 (6H, 2s, 2OCH$_3$), 3.39 [4H, q, *J*=7.1 Hz, N(C*H*$_2$CH$_3$)$_2$], 1.49 and 1.45 [18H, 2s, 2C(CH$_3$)$_3$], 1.19 [6H, t, *J*=7.1 Hz, N(CH$_2$C*H*$_3$)$_2$]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.3, 165.2, 162.9, 159.5, 158.3, 156.8, and 151.2 (4C=O, C, and 2NOC=C), 141.5 (CH), 139.0 (C), 129.3 (CH), 118.6 and 114.2 (2C), 108.9 (CH), 107.2 (C), 97.2 (CH), 85.7 (NOC=*C*), 61.4 and 52.6 [2*C*(CH$_3$)$_3$], 52.0 and 51.0 (2OCH$_3$), 44.8 [N(*C*H$_2$CH$_3$)$_2$], 29.8 and 28.0 [2C(*C*H$_3$)$_3$], 12.4 [N(CH$_2$*C*H$_3$)$_2$].

*4.2.8. Dimethyl 2-(cyclohexylamino)-5-(cyclohexyl{[7-(diethylamino)-2-oxo-2H-chromen-3-yl]carbonyl}amino)-3,4-furandicarboxylate (**5h**).* Pale yellow crystals, mp 208–209 °C, yield: 0.571 g, 92%. IR (KBr) (ν_{max}/cm^{-1}): 3310 (NH), 1727, 1678, and 1624 (C=O), 1585, 1511, 1445, 1351, 1232, 1134, 1075, 891, 778, 711, 663. EI-MS, *m*/*z* (%): 621 (M^+, 19), 496 (3), 377 (13), 295 (31), 244 (83), 213 (8), 181 (10), 97 (13), 82 (58), 67 (100), 54 (76). Anal. Calcd for $C_{34}H_{43}N_3O_8$ (621.73): C, 65.68; H, 6.97; N, 6.76. Found: C, 65.6; H, 7.1; N, 6.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.75 (1H, s, CH), 7.18 (1H, d, *J*=8.9 Hz, CH), 6.63 (1H, d, *J*=7.9 Hz, NH), 6.53 (1H, dd, *J*=8.9, 2.4 Hz, CH,), 6.41 (1H, d, *J*=2.4 Hz, CH), 4.53–4.48 (1H, m, NCH), 3.69 and 3.67 (6H, 2s, 2OCH$_3$), 3.66–3.59 (1H, m, NCH), 3.40 [4H, q, *J*=7.1 Hz, N(C*H*$_2$CH$_3$)$_2$], 2.06–1.03 {[6H, t (1.20), *J*=7.1 Hz, N(CH$_2$C*H*$_3$)$_2$]; and 20H, m, 2CH(C*H*$_2$)$_5$}. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 166.5, 165.0, 162.8, 159.7, 158.3, 157.1, and 151.6 (4C=O, C, and 2NOC=C), 143.9 (CH), 138.1 (C), 129.7 (CH), 116.9 and 113.8 (2C), 109.0 (CH), 107.6 (C), 97.2 (CH), 85.2 (NOC=*C*), 56.8 (NCH), 51.9 (OCH$_3$), 51.5 (NCH), 50.9 (OCH$_3$), 44.9 [N(*C*H$_2$CH$_3$)$_2$], 33.5 (CH$_2$), 31.6 and 30.4 (2br, 2CH$_2$), 25.8, 25.5, and 24.5 (3CH$_2$), 12.5 [N(CH$_2$*C*H$_3$)$_2$].

*4.2.9. Diethyl 2-(cyclohexylamino)-5-(cyclohexyl{[7-(diethylamino)-2-oxo-2H-chromen-3-yl]carbonyl}amino)-3,4-furandicarboxylate (**5i**).* Pale yellow crystals, mp 202–203 °C, yield: 0.624 g, 96%. IR (KBr) (ν_{max}/cm^{-1}): 3366 (NH), 1713 and 1642 (C=O), 1593, 1515, 1459, 1416, 1356, 1231, 1136, 1067, 891, 826, 781, 709. EI-MS, *m*/*z* (%): 649 (M^+, 13), 405 (19), 368 (9), 323 (40), 295 (12), 244 (80), 82 (48), 67 (100), 54 (65). Anal. Calcd for $C_{36}H_{47}N_3O_8$ (649.78): C, 66.54; H, 7.29; N, 6.47. Found: C, 66.5; H, 7.2; N, 6.5%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.00 (1H, s, CH), 7.19 (1H, d, *J*=8.9 Hz, CH), 6.59 (1H, d, *J*=8.0 Hz, NH), 6.52 (1H, dd, *J*=8.9, 2.4 Hz, CH), 6.39 (1H, d, *J*=2.4 Hz, CH), 4.44–4.37 (1H, m, NCH), 4.24–3.97 (4H, m, 2OCH$_2$), 3.65–3.55 (1H, m, NCH), 3.38 [4H, q, *J*=7.1 Hz, N(C*H*$_2$CH$_3$)$_2$], 2.05–1.02 {[3H, t (1.21), *J*=7.2 Hz, OCH$_2$C*H*$_3$]; [6H, t (1.18), *J*=7.1 Hz, N(CH$_2$C*H*$_3$)$_2$]; [3H, t (1.15), *J*=7.1 Hz, OCH$_2$C*H*$_3$]; and 20H, m, 2CH(C*H*$_2$)$_5$}. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 166.5, 164.6, 162.8, 159.6, 158.2, 157.1, and 151.5 (4C=O, C, and 2NOC=C), 144.0 (CH), 137.5 (C), 129.7 (CH), 117.0 and 114.2 (2C), 109.0 (CH), 107.6 (C), 97.2 (CH), 85.5 (NOC=*C*),

61.1 and 59.5 ($2OCH_2$), 56.8 and 51.4 (2NCH), 44.9 [$N(CH_2CH_3)_2$], 33.5 (CH_2), 31.7 and 30.4 (2br, $2CH_2$), 25.8, 25.5, and 24.5 ($3CH_2$), 14.3 and 14.0 ($2OCH_2CH_3$), 12.4 [$N(CH_2CH_3)_2$].

*4.2.10. Dimethyl 2-(cyclohexylamino)-5-{cyclohexyl[(2-oxo-2H-benzo[h]chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5j**).* Pale yellow crystals, mp 222 °C, yield: 0.498 g, 83%. IR (KBr) (ν_{max}/cm^{-1}): 3367 (NH), 1729 and 16.62 (C=O), 1596, 1516, 1444, 1393, 1360, 1313, 1214, 1147, 1096, 1070, 923, 819, 783, 749, 717, 679. EI-MS, *m*/*z* (%): 600 (M^+, 12), 377 (47), 295 (100), 223 (65), 263 (5), 181 (35), 139 (37), 83 (16), 55 (41). Anal. Calcd for $C_{34}H_{36}N_2O_8$ (600.67): C, 67.99; H, 6.04; N, 4.66. Found: C, 68.2; H, 6.3; N, 4.4%. ^1H NMR (300.1 MHz, $CDCl_3$): δ 8.70 (1H, s, CH), 8.22 (1H, d, *J*=8.4 Hz, CH), 8.01 (1H, d, *J*=9.0 Hz, CH), 7.91 (1H, d, *J*=8.0 Hz, CH), 7.69 (1H, dd, *J*=7.7, 7.2 Hz, CH), 7.58 (1H, dd, *J*=7.7, 7.2 Hz, CH), 7.41 (1H, d, *J*=9.0 Hz, CH), 6.60 (1H, d, *J*=7.9 Hz, NH), 4.59–4.50 (1H, m, NCH), 3.69–3.60 [6H, 2*s* (3.68 and 3.62), $2OCH_3$; and 1H, m, NCH], 2.15–1.10 [20H, m, $2CH(CH_2)_5$]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.7, 164.7, 162.9, 159.7, 157.3, and 154.3 (4C=O and 2NO*C*=C), 138.8 (CH), 136.9 (C), 134.1 (CH), 130.3 and 129.3 (2C), 129.0, 128.5, and 126.2 (3CH), 123.6 (C), 121.3 and 116.7 (2CH), 114.7 and 112.4 (2C), 85.2 (NOC=*C*), 57.0 (NCH), 52.1 (OCH_3), 51.6 (NCH), 50.9 (OCH_3), 33.6, 33.5, 31.6, and 30.3 (4br, $4CH_2$), 25.7 (CH_2), 25.4 (br, CH_2), 24.5 (CH_2).

4.3. General procedure for the preparation of compound 12a and 12b, exemplified with 12a

A mixture of salicylaldehyde (0.122 g, 1 mmol) and Meldrum's acid (0.144 g, 1 mmol) in H_2O (5 mL) was magnetically stirred at 25 °C for 20 min. After nearly complete conversion to coumarin-3-carboxylic acid, cycloyl isocyanide (0.109 g, 1 mmol) was added to the reaction mixture. Then diethyl acetylenedicarboxylate (0.170 g, 1 mmol) was added at room temperature over 5 min. The reaction mixture was then allowed to stir for 5 h. Next, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography using *n*-hexane–EtOAc (3:1) as eluent. The solvent was removed and the product was obtained.

*4.3.1. Diethyl 2-({cyclohexyl[(2-oxo-2H-chromen-3-yl)carbonyl]amino}carbonyl)-2-butenedioate (**12a**).* Pale yellow crystals, mp 166–167 °C, yield: 0.34 g, 73%. Anal. Calcd for $C_{25}H_{27}NO_8$ (469.49): C, 63.96; H, 5.80; N, 2.98. Found: C, 63.8; H, 5.9; N, 2.8%. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.83 (1H, s, CH), 7.59 (1H, dd, *J*=8.1, 7.6 Hz, CH), 7.51 (1H, d, *J*=7.6 Hz, CH), 7.32 (1H, d, *J*=8.1 Hz, CH), 7.30 (1H, t, *J*=7.6 Hz, CH), 6.64 (1H, s, C=CH), 4.23 (2H, q, *J*=7.1 Hz, OCH_2), 4.15–4.03 (2H, m, OCH_2), 3.93–3.84 (1H, m, NCH), 2.30–1.15 [6H, 2t (1.26 and 1.19), *J*=7.1 Hz, $2OCH_2CH_3$; and 10H, m, $CH(CH_2)_5$]. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 167.7, 165.9, 164.0, 162.3, 157.0, and 154.4 (5C=O and C–O), 142.0 (C), 141.9, 133.5, 129.0, and 127.2 (4CH), 125.1 (C), 125.0 (CH), 117.7 (C), 116.9 (CH), 62.5 and 61.7 ($2OCH_2$), 60.3 (NCH), 29.1, 26.5, and 25.2 ($3CH_2$), 14.0 and 13.8 ($2CH_3$).

*4.3.2. Dimethyl 2-({cyclohexyl[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]amino}carbonyl)-2-butenedioate (**12b**).* Pale yellow crystals, mp 180–181 °C, yield: 0.33 g, 70%. Anal. Calcd for $C_{24}H_{25}NO_9$ (471.46): C, 61.14; H, 5.34; N, 2.97. Found: C, 61.1; H, 5.3; N, 3.0%. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.83 (1H, s, CH), 7.24 (1H, dd, *J*=8.1, 7.8 Hz, CH), 7.15 (1H, d, *J*=8.1 Hz, CH), 7.09 (1H, d, *J*=7.8 Hz, CH), 6.64 (1H, s, C=CH), 3.96 (3H, s, OCH_3), 3.94–3.84 (1H, m, NCH), 3.78 and 3.68 (6H, 2s, $2OCH_3$), 2.32–1.19 [10H, m, $CH(CH_2)_5$]. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 168.0, 165.8, 164.4, 162.8, 156.5, 147.3, and 144.1 (5C=O and 2C–O), 142.7 (CH), 141.7 (C), 126.4 (CH), 125.3 (C), 125.0 and 120.2 (2CH), 118.3 (C), 115.4 (CH), 60.5 (NCH), 56.4, 53.0, and 52.5 ($3OCH_3$), 29.1, 26.5, and 25.2 ($3CH_2$).

4.4. Procedure for the preparation of compound 5k

A mixture of **12b** (0.236 g, 0.5 mmol) and *tert*-butyl isocyanide (0.041 g, 0.5 mmol) in H_2O (3 mL) was magnetically stirred at 25 °C for 5 h. Next, the aqueous phase was extracted with CH_2Cl_2 (2×5 mL) and the combined organic layers dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography using *n*-hexane–EtOAc (3:1) as eluent. The solvent was removed and the product was obtained.

*4.4.1. Dimethyl 2-(tert-butylamino)-5-{cyclohexyl[(8-methoxy-2-oxo-2H-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate (**5k**).* Pale yellow crystals, mp 218 °C, yield: 0.244 g, 88%. IR (KBr) (ν_{max}/cm^{-1}): 3313 (NH), 1721, 16.78, 1638, 1603 (C=O), 1472, 1441, 1402, 1362, 1323, 1253, 1215, 1065, 973, 882, 776, 728, 688. EI-MS, *m*/*z* (%): 554 (M^+, 20), 416 (7), 351 (50), 295 (9), 269 (50), 256 (12), 213 (100), 203 (98), 181 (43), 138 (16), 55 (32). Anal. Calcd for $C_{29}H_{34}N_2O_9$ (554.60): C, 62.81; H, 6.18; N, 5.05. Found: C, 62.8; H, 6.2; N, 5.0%. ^1H NMR (250.1 MHz, $CDCl_3$): δ 7.85 (1H, s, CH), 7.19 (1H, dd, *J*=8.0, 7.5 Hz, CH), 7.07 (1H, d, *J*=7.5 Hz, CH), 7.00 (1H, d, *J*=8.0 Hz, CH), 6.92 (1H, s, NH), 4.53–4.44 (1H, m, NCH), 3.93, 3.73, and 3.66 (9H, 3s, $3OCH_3$), 2.17–1.01 [9H, s, $C(CH_3)_3$; and 10H, m, $CH(CH_2)_5$]. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 165.4, 164.9, 162.8, 159.9, 156.5, 147.0, and 143.7 (4C=O, C–O, and 2NO*C*=C), 142.8 (CH), 136.8 and 125.2 (2C), 124.4 and 119.7 (2CH), 118.6 and 114.5 (2C), 114.4 (CH), 85.7 (NOC=*C*), 56.7 [$C(CH_3)_3$], 56.2 (OCH_3), 52.7 (NCH), 52.1 and 51.0 ($2OCH_3$), 31.7 and 30.0 ($2CH_2$), 29.8 [$C(CH_3)_3$], 25.8, 25.5, and 25.3 ($3CH_2$).

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Supplementary data

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References and notes

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