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Plant Coumarins: XVII.[1] Synthesis and Transformations of 7-Hydroxy-2-oxo-2*H*-chromene-6-carboxamides

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Abstract—Umbelliferone-6-carbonyl chloride reacted with amines and α-, β-, and ω-amino acid methyl esters to afford the corresponding *N*-substituted 7-hydroxy-2-oxo-2*H*-chromene-6-carboxamides. The reaction of umbelliferone-6-carbonyl chloride with glycine gave 2-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)acetic acid which was converted into acid chloride, and the latter reacted with benzylamines and α-amino acid methyl esters to produce compounds containing a dipeptide fragment.

Keywords: coumarins, umbelliferone, amino acids, amides, peptides.

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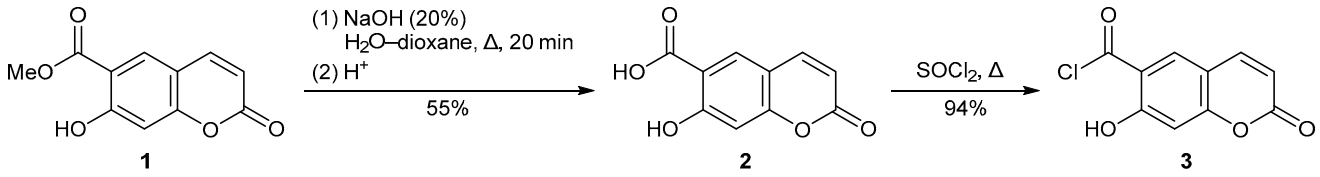
Natural and synthetic coumarins constitute an important class of biologically active compounds whose biological effect is largely determined by the nature and position of substituents present in their molecules. 6-Substituted coumarin derivatives were found to exhibit selective antitumor [2–4] and antiviral (including anti-HIV-1) activities [5–7], and some compounds of this series are selective progesterone receptor antagonists [8] and cyclin-dependent kinase [9] and monoamine oxidase inhibitors [10]. It should be noted that the presence of certain substituents in the 6-position of coumarins (such as isoprenyl group, fluorine, chlorine, hydroxytriazolyl or hydroxyisoxazolyl fragment, nitro group) increases the selectivity of their antitumor effect [2, 3, 9] and enhances the anti-HIV activity [5].

Herein, we propose a new method for the synthesis of coumarins containing a substituted carbamoyl group on C^6 starting from the natural coumarin peuruthenicin (**1**). It should be noted that a large number of peuruthenicin derivatives modified at the 7- and 8-positions were synthesized previously by palladium-catalyzed cross-coupling, amination, aminomethylation, and azide–alkyne cycloaddition reactions [1, 11–14]. Some of the synthesized compounds are promising as anticoagulants [13] and antiarrhythmic agents [14].

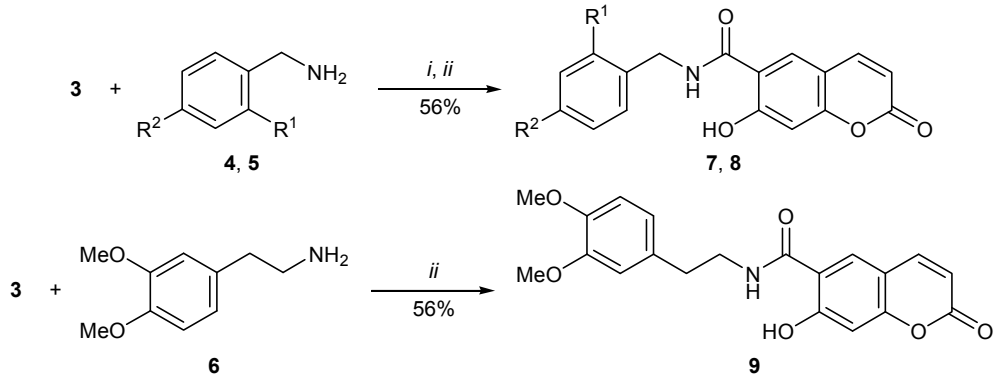
By hydrolysis of peuruthenicin (**1**) with 20% aqueous sodium hydroxide in dioxane according to modified procedure [15] we obtained umbelliferone-6-carboxylic acid (**2**) which was converted to acid chloride **3** by heating in thionyl chloride under reflux (Scheme 1). No satisfactory results were achieved under milder chlorination conditions such as treatment with oxalyl chloride in THF or the use of lesser amount of thionyl chloride. In these cases, the conversion of **2** did not exceed 50%.

Scheme 1.



[1] For communication XVI, see [1].

Scheme 2.



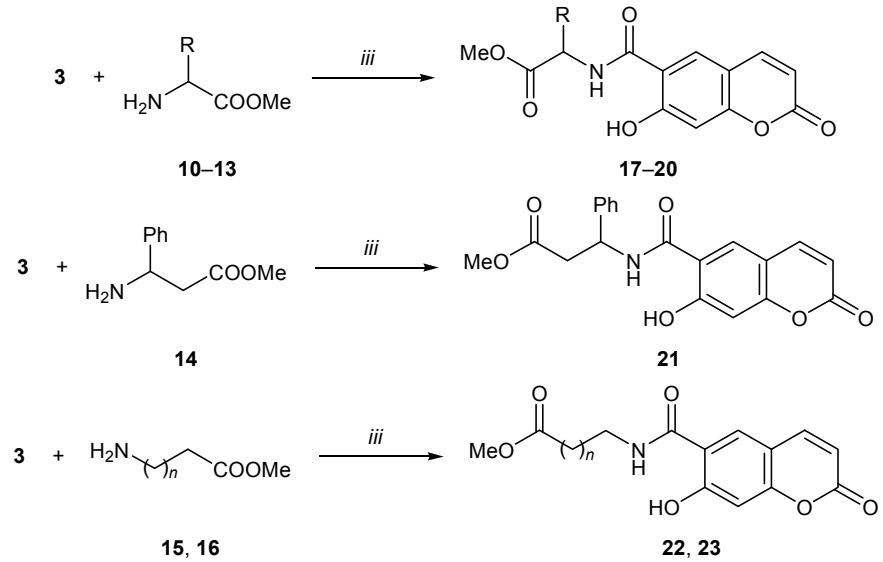
4, **7**, $R^1 = R^2 = H$; **5**, **8**, $R^1 = R^2 = OMe$; *i*: THF, Et_3N (1.3 equiv), 65°C; *ii*: benzene, Et_3N (2.3 equiv), 80°C.

Acid chloride **3** failed to react with benzylamines **4** and **5** in THF in the presence of triethylamine under the conditions reported in [16]. The use of halogenated solvents was also unsuccessful. We succeeded in obtaining *N*-benzyl amides **7**–**9** by carrying out the reaction in boiling benzene with 1.2 equiv of amine **4**–**6** and 2.3 equiv of triethylamine (Scheme 2).

A promising way for modification of peuruthenicin (**1**) is introduction of various amino acid residues into its molecule. The expected products attract interest taking into account antiviral, antibacterial, and antitumor activities of compounds containing amino acid fragments. The reactions of **3** with L-alanine, L-valine, L-methionine, and L-α-phenylalanine methyl esters **10**–**13** afforded N-substituted amino acid esters **17**–**20** in 40–60% yields (Scheme 3). Analogous reaction with β-phenylalanine methyl ester (**14**) gave 53% of **21**. The highest yields (71–75%) were obtained in the reactions of **3** with long-chain ω-amino acid methyl esters, methyl 8-aminooctanoate (**15**) and methyl 9-aminononanoate (**16**).

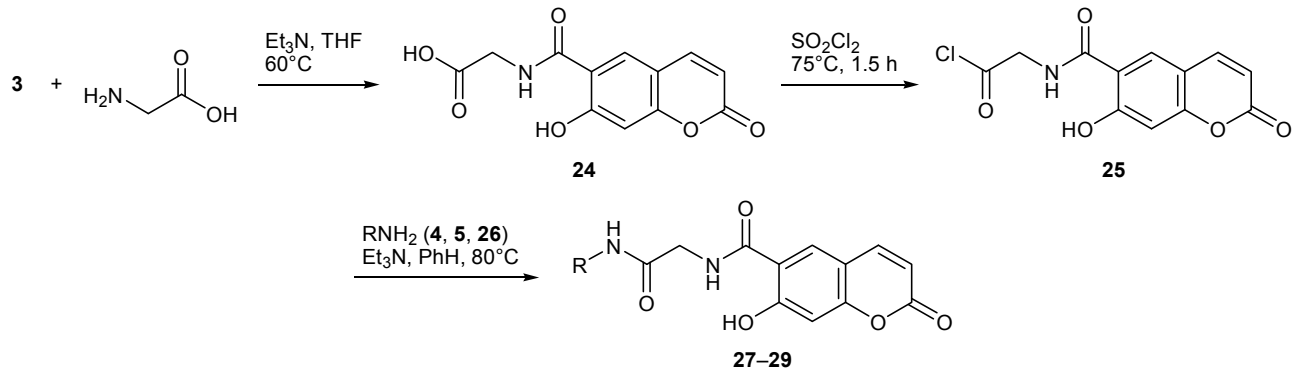
Dipeptide derivatives of natural compounds are important from the viewpoint of their potential biological activity. For example, di- and polypeptide conjugates of chitosan with glycine and alanine showed cytotoxicity both *in vitro* and *in vivo* and are promising for the design of antidiabetic agents [17]. Dipeptides derived from leucine and glycine conjugates are extensively studied as anti-CFS (chronic fatigue syndrome) agents [18]. Promising antiviral agents have been found among compounds containing several glycine residues [19]. Therefore, it seemed reasonable to

Scheme 3.



10, **17**, R = Me; **11**, **18**, R = *i*-Pr; **12**, **19**, R = $MeSCH_2CH_2$; **13**, **20**, R = $PhCH_2CH(CO_2Me)$; **15**, **22**, *n* = 7; **16**, **23**, *n* = 8.
iii: benzene, Et_3N, 80°C.

Scheme 4.



27, R= $PhCH_2$; **28**, R = 2,4-$(MeO)_2C_6H_3CH_2$; **26**, **29**, R = $MeCH_2CH(CO_2Me)$.

synthesize substituted coumarins conjugated with dipeptide fragments.

The reaction of **3** with glycine in THF in the presence of triethylamine smoothly afforded amido acid **24** (yield 86%; Scheme 4). Acid **24** was treated with thionyl chloride, and acid chloride **25** thus formed (yield 81%) was brought into reactions with benzylamines **4** and **5** and α-aminobutyric acid methyl ester (**26**) under the conditions used for the synthesis of amino acid derivatives **17**–**23**. As a result, coumarin dipeptides **27**–**29** were obtained (yield 62–75%).

The structure of the synthesized compounds was determined on the basis of their spectral data and elemental analyses. In the IR spectra of **7**–**9**, **17**–**23**, **24**, and **27**–**29**, the amide carbonyl band was located at 1626–1650 cm^{-1}, and NH and OH stretching bands were observed in the region 3285–3503 cm^{-1}. The ^1H and ^{13}C NMR spectra were fully consistent with the assigned structures, and only one set of signals from the coumarin fragment and the corresponding substituent was present.

The structure of **2** was confirmed by the X-ray diffraction data for its 1:1 solvate with DMSO (Fig. 1; one of the three crystallographically independent **2**–DMSO pairs is shown). The bond lengths in molecule **2** are similar to those in 7-hydroxy-6-methoxy-2*H*-chromen-2-one [20]. The hydroxy group is involved in intramolecular hydrogen bond with the carbonyl oxygen atom (H···O 1.85, 1.86, and 1.86 Å for the three independent molecules). Molecules **2** in crystal are linked to the solvate DMSO molecules through C(O)OH···O=SMe_2 hydrogen bonds (H···O 1.74, 1.75, 1.76 Å) and are packed in stacks via π–π interactions between the benzene rings [distance between the centroids 3.619(3), 3.679(3), 3.880(3) Å].

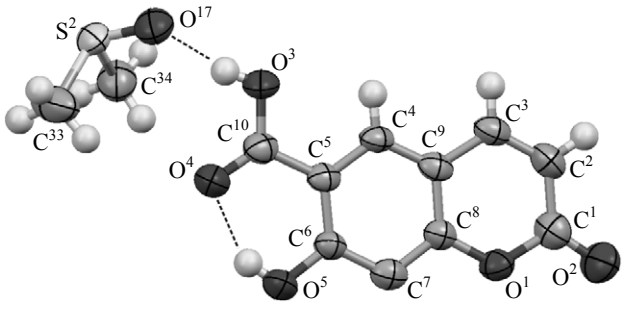


Fig. 1. Molecular structure of 7-hydroxy-2-oxo-2*H*-chromene-6-carboxylic acid (**2**, 1:1 solvate with DMSO) according to the X-ray diffraction data.

Thus, the reactions of umbelliferone-6-carbonyl chloride with amines and α-, β-, and ω-amino acid methyl esters in the presence of excess triethylamine lead to the formation of the corresponding *N*-substituted carboxamides. The obtained 6-substituted coumarins containing amide and dipeptide fragments attract interests as potential drug candidates.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ or $CDCl_3$–CD_3OD (5:1) (**24**) on Bruker AV-300 [300.13 (^1H) and 75.47 MHz (^{13}C)], AV-400 [400.13 (^1H) and 100.78 MHz (^{13}C)], and AV-600 [600.30 (^1H) and 150.96 MHz (^{13}C)] instruments (Germany). The chemical shifts were measured relative to tetramethylsilane as internal standard. The multiplicity of ^{13}C signals was determined from the *J*-modulation spectra. The IR spectra were recorded in KBr on a Bruker Vector-22 spectrometer with Fourier transform. The UV spectra were taken on an HP 8453 UV Vis spectrophotometer. The optical rotations ($[\alpha]_D$) were measured on a PolAAr 3005 polarimeter (Germany) from solutions in chloroform at room tem-

perature (23–25°C). Elemental analyses were carried out with a Carlo Erba Model 1106 CHN analyzer (Italy). The mass spectra were recorded on a Thermo Scientific DFS high-resolution mass spectrometer (USA) (electron impact, 70 eV, vaporizer temperature 270–300°C). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform and chloroform–ethanol (50:1) as eluents; spots were visualized under UV light. The products were isolated by column chromatography on silica gel (0.035–0.070 mm, Acros Organics) using chloroform and chloroform–ethanol (50:3) as eluents or by recrystallization from appropriate solvents.

Peuruthenicin (**1**) was synthesized from peucedanin (furocoumarin) according to the procedure described in [21]. Methyl esters **10**–**14** and **26** were prepared as described in [22] from the corresponding commercial amino acids (98% purity, Sigma–Aldrich, Acros Organics). 8-Aminocaprylic and 9-aminopelargonic acid hydrochlorides were synthesized from azelaic and sebacic acids, respectively, according to [23]. The solvents (THF, benzene) and triethylamine were purified by standard methods and were distilled in a stream of argon just before use. Amines **4**–**6** (Alfa Aesar) were used without further purification.

The X-ray diffraction data for compound **2** (solvate with DMSO) were obtained at 297 K on a Bruker KAPPA APEX-II diffractometer [CCD detector, graphite monochromator, λ(Mo K_α) 0.71073 Å; φ,ω-scanning]. A single crystal of **2** (1:1 solvate with DMSO) was obtained by slow evaporation of its solution in DMSO. A correction for absorption was applied empirically using SADABS. The structure was solved by the direct method and was refined in anisotropic approximation for non-hydrogen atoms using SHELXTL software package. Hydrogen atoms were placed in geometrically calculated positions which were refined in isotropic approximation according to the riding model. Triclinic crystal system, space group *P*-1; $C_{10}H_6O_5 \cdot C_2H_6SO$; unit cell parameters: a = 9.8317(16), b = 14.153(3), c = 14.642(2) Å; α = 94.164(6), β = 103.756(5), γ = 97.066(6)°; V = 1952.9(6) Å^3; Z = 6; d_{calc} = 1.450 g/cm^3; μ = 0.268 mm^{-1}. Total of 12184 reflection intensities were measured in the range 2θ < 50°, including 6847 independent reflections (R_{int} = 0.0554). Final divergence factors: wR_2 = 0.1992, R = 0.1144 for all independent reflections; R = 0.0620 for 3446 reflections with $F > 4\sigma(F)$; goodness of fit S = 0.901. The X-ray diffraction data were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1896497) [24].

7-Hydroxy-2-oxo-2*H*-chromene-6-carboxylic acid (2). Peuruthenicin (**1**), 1.0 g (4.5 mmol), was dissolved in 200 mL of dioxane, 400 mL of 20% aqueous sodium hydroxide was added, and the mixture was refluxed for 20 min. The resulting solution was cooled to 10°C, acidified to pH 3–4 by adding 70 mL of 10% sulfuric acid, and extracted with chloroform (3×15 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue was recrystallized from ethanol and dried under reduced pressure. Yield 0.514 g (55%). mp 248–250°C (decomp.); published data [15]: mp 258°C (decomp.). IR spectrum, ν, cm^{-1}: 3504, 3394, 3066, 2849, 2702, 2472, 1705, 1678, 1628, 1597, 1579, 1392, 1294, 1242, 1147, 1119, 916, 862, 810, 760, 727, 633. UV spectrum (EtOH), λ_{max}, nm (logε): 208 (3.69), 224 (3.58), 238 (3.56), 305 (3.32), 330 (3.50). ^{1}H NMR spectrum, δ, ppm: 6.14 d (1H, 4-H, J = 9.4 Hz), 6.70 s (1H, 8-H), 7.59 d (1H, 3-H, J = 9.4 Hz), 7.96 s (1H, 5-H), 11.25 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 95.83 (C^{4a}), 103.27 (C^8), 110.97 (C^6), 111.74 (C^3), 131.30 (C^4), 144.52 (C^5), 157.37 (C^{8a}), 161.79 (C^7), 164.51 (C^2), 173.13 (C=O).

7-Hydroxy-2-oxo-2*H*-chromene-6-carbonyl chloride (3). *a*. Thionyl chloride, 0.282 mL (3.92 mmol), was added to a solution of 100 mg (0.49 mmol) of acid **2** in 20 mL of anhydrous benzene, and the mixture was refluxed for 24 h. The solvent and excess thionyl chloride were removed under reduced pressure to leave 85 mg (84%) of **3** which was used in further syntheses without additional purification.

b. A solution of 100 mg (0.49 mmol) of acid **2** in 2 mL of thionyl chloride was refluxed for 1.5 h. The mixture was evaporated under reduced pressure to obtain 96 mg (88%) of **3** as a solid residue which was used without further purification. ^{1}H NMR spectrum, δ, ppm: 6.34 d (1H, 4-H, J = 9.4 Hz), 6.88 s (1H, 8-H), 7.70 d (1H, 3-H, J = 9.4 Hz), 8.26 s (1H, 5-H), 9.98 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 105.10 (C^8), 112.92 (C^6), 114.62 (C^{4a}), 114.96 (C^3), 135.00 (C^4), 142.55 (C^5), 158.90 (C^{8a}), 160.23 (C^2), 163.42 (C^7), 172.39 (C=O). Found, %: C 53.52; H 2.26; Cl 15.75. $C_{10}H_5ClO_4$. Calculated, %: C 53.48; H 2.24; Cl 15.78.

Reaction of acid chloride 3 with amines 4–6 and amino acid methyl esters 10–16 (*general procedure*). *a*. Compound **3**, 0.1 g (0.45 mmol), was dissolved in 7.5 mL of anhydrous methylene chloride, 0.074 mL (0.54 mmol) of anhydrous triethylamine and

1.03 mmol of the corresponding amino compound were added, and the mixture was refluxed for 20 h. After cooling, the solvent was evaporated, the residue was treated with a mixture of water and methylene chloride, and the organic layer was separated, dried over $MgSO_4$, and evaporated.

b. Compound **3**, 0.1 g (0.45 mmol), was dissolved in 7.5 mL of anhydrous benzene, 0.074 mL (0.54 mmol) of anhydrous triethylamine and 1.03 mmol of the corresponding amino compound were added, and the mixture was refluxed for 20 h. After cooling, the solvent was evaporated, the residue was treated with a mixture of water and methylene chloride, and the organic layer was separated, dried over $MgSO_4$, and evaporated.

c. Compound **3**, 0.1 g (0.45 mmol), was dissolved in 7.5 mL of anhydrous benzene, 0.31 mL (2.23 mmol) of anhydrous triethylamine and 0.54 mmol of the corresponding amino compound (amino esters **15** and **16** were used as hydrochlorides) were added, and the mixture was refluxed for 20 h. After cooling, the solvent was evaporated, the residue was treated with a mixture of water and methylene chloride, and the organic layer was separated, dried over $MgSO_4$, and evaporated, and the residue was ground with diethyl ether.

d. Compound **3**, 0.1 g (0.45 mmol), was dissolved in 7.5 mL of anhydrous THF, 0.31 mL (2.23 mmol) of anhydrous triethylamine and 0.54 mmol of the corresponding amino compound were added, and the mixture was refluxed for 48 h. After cooling, the solvent was evaporated, the residue was treated with a mixture of water and methylene chloride, and the organic layer was separated, dried over $MgSO_4$, and evaporated.

***N*-Benzyl-7-hydroxy-2-oxo-2*H*-chromene-6-carboxamide (7)** Yield 0.101 g (77%, method *c*), mp 115°C (decomp., from Et_2O). IR spectrum, ν, cm^{-1}: 3398, 3066, 3032, 2920, 2850, 1741, 1649, 1569, 1392, 1300, 1238, 1144, 823, 752, 698. UV spectrum (EtOH), λ_{max}, nm (logε): 201 (3.79), 204 (3.79), 206 (3.65), 223 (3.43), 244 (3.24), 329 (3.07), 372 (3.45). ^{1}H NMR spectrum, δ, ppm: 4.56 s (2H, CH_2), 6.10 d (1H, 4-H, *J* = 9.4 Hz), 6.67 s (1H, 8-H), 7.23 m (2H, *o*-H), 7.25 m (1H, *p*-H), 7.28 m (2H, *m*-H), 7.55 d (1H, 3-H, *J* = 9.4 Hz), 7.91 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 43.31 (CH_2), 104.73 (C^8), 110.70 (C^6), 112.21 (C^3), 114.05 (C^{4a}), 120.49 (C^5), 127.33 (C^p), 127.56 (C^o), 128.49 (C^m), 137.71 (C^i), 143.65 (C^4), 157.40 (C^{8a}), 159.33 (C^2), 161.00 (C–OH), 164.73 (C=O), 167.76 (C^7). Found, %: C 69.24; H 4.52; N 4.68. $C_{17}H_{13}NO_4$. Calculated, %: C 69.15; H 4.44; N 4.74.

***N*-(2,4-Dimethoxybenzyl)-7-hydroxy-2-oxo-2*H*-chromene-6-carboxamide (8).** Yield 0.106 g (67%, method *c*), mp 197–200°C (from Et_2O). IR spectrum, ν, cm^{-1}: 3384, 3082, 3064, 2944, 2921, 2846, 2515, 1747, 1656, 1626, 1589, 1567, 1510, 1392, 1292, 1243, 1211, 1155, 1134, 1114, 1037, 831. UV spectrum (EtOH), λ_{max}, nm (logε): 225 (3.55), 278 (3.79), 283 (3.53), 327 (3.22), 373 (2.91). ^{1}H NMR spectrum, δ, ppm: 3.69 s (3H, OCH_3), 3.75 s (3H, OCH_3), 4.44 s (2H, CH_2), 6.12 d (1H, 4-H, *J* = 9.7 Hz), 6.34 d.d (1H, 5′-H, *J* = 8.2, 2.0 Hz), 6.37 d (1H, 3′-H, *J* = 2.0 Hz), 6.69 s (1H, 8-H), 7.13 d (1H, 6′-H, *J* = 8.2 Hz), 7.58 d (1H, 3-H, *J* = 9.7 Hz), 7.83 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 38.72 (CH_2), 55.19 (OMe), 55.21 (OMe), 98.45 (C^8), 103.94 ($C^{8'}$), 104.34 ($C^{6'}$), 111.28 (C^{4a}), 112.70 (C^6), 114.21 (C^3), 117.98 (C^5), 128.54 ($C^{4'}$), 130.08 ($C^{5'}$), 143.87 (C^4), 157.15 (C^{8a}), 158.37 (C^2), 160.44 ($C^{7'}$), 161.20 ($C^{9'}$), 163.06 (C=O), 166.85 (C^7), 167.16 (C=O). Mass spectrum: *m*/z 355.1044 $[M]^+$. Found, %: C 64.27; H 4.62; N 3.96. $C_{19}H_{17}NO_6$. Calculated, %: C 64.22; H 4.82; N 3.94. *M* 355.1050.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-7-hydroxy-2-oxo-2*H*-chromene-6-carboxamide (9).** Yield 0.092 g (56%, method *c*), yellow viscous oily material. IR spectrum, ν, cm^{-1}: 3377, 2953, 2922, 2850, 1739, 1650, 1602, 1572, 1516, 1463, 1390, 1305, 1261, 1234, 1143, 1025, 906, 823, 259. UV spectrum (EtOH), λ_{max}, nm (logε): 225 (3.61), 286 (3.78), 328 (3.36), 372 (3.07). ^{1}H NMR spectrum, δ, ppm: 2.88 t (2H, $NCH_2C\mathbf{H}_2$, *J* = 8.8 Hz), 3.70 m (2H, NCH_2, *J* = 8.8 Hz), 3.82 s (3H, OCH_3), 3.84 s (3H, OCH_3), 6.17 d (1H, 3-H, *J* = 9.4 Hz), 6.73 s (1H, 8-H), 6.74–6.89 m (3H, 2′-H, 5′-H, 6′-H) 7.34 s (1H, 5-H), 7.51 d (1H, 4-H, *J* = 9.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 34.97 ($NCH_2\mathbf{C}H_2$), 41.02 (NCH_2), 55.87 (2C, OMe), 105.41 (C^8), 111.03 (C^{4a}), 111.47 ($C^{7'}$), 111.94 ($C^{10'}$), 112.96 (C^3), 113.41 (C^6), 120.69 ($C^{6'}$), 126.23 (C^5), 130.87 ($C^{5'}$), 142.97 (C^4), 147.89 ($C^{8'}$), 149.14 ($C^{9'}$), 157.81 (C^{8a}), 161.64 (C^2), 165.05 (C=O), 168.63 (C^7). Found, %: C 65.22; H 5.32; N 3.65. $C_{20}H_{19}NO_6$. Calculated, %: C 65.03; H 5.18; N 3.79.

Methyl 2-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)propanoate (17). Yield 0.067 g (46%, method *c*), mp 168°C (decomp., from Et_2O), $[\alpha]_D^{28.5}$ = 6.15° (*c* = 1.00). IR spectrum, ν, cm^{-1}: 3386, 3351, 3060, 2952, 2921, 1741, 1650, 1571, 1390, 1309, 1215, 1147, 1111, 825. UV spectrum (EtOH), λ_{max}, nm (logε): 225 (3.77), 242 (3.53), 327 (3.42), 371 (3.12). ^{1}H NMR spectrum, δ, ppm: 1.54 d (3H, CH_3, *J* = 7.2 Hz), 3.71 s (3H, OCH_3), 4.75 d.d (1H, CH, *J* = 6.5,

7.2 Hz), 6.25 d (1H, 4-H, J = 9.4 Hz), 6.79 s (1H, 8-H), 7.58 d (1H, 3-H, J = 9.4 Hz), 7.64 s (1H, 5-H), 8.35 d (1H, NH, J = 6.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.21 (CH_3), 48.41 (OCH_3), 52.90 (CH), 105.42 (C^8), 111.40 (C^{4a}), 111.67 (C^6), 113.89 (C^3), 126.38 (C^5), 142.82 (C^4), 158.02 (C^{8a}), 160.18 (C^2), 164.70 (C=O), 168.35 (C^7), 173.43 (**C**OOMe). Found, %: C 57.89; H 4.60; N 4.73. $C_{14}H_{13}NO_6$. Calculated, %: C 57.73; H 4.50; N 4.81.

Methyl 2-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)-3-methylbutanoate (18). Yield 0.06 g (40%, method *c*), mp 168°C, $[\alpha]_D^{28.5}$ = +3.18° (*c* = 1.05). IR spectrum, ν, cm^{-1}: 3344, 3066, 2952, 2919, 1743, 1620, 1600, 1565, 1538, 1496, 1388, 1307, 1282, 1147, 1103, 987, 825. UV spectrum ($CHCl_3$), λ_{max}, nm (logε): 247 (4.78), 307 (4.24), 330 (4.52), 343 (4.44). ^{1}H NMR spectrum, δ, ppm: 0.85 d (6H, CH_3, J = 7.0 Hz), 3.50 m (1H, 3′-H), 3.68 s (3H, OCH_3), 5.09 d.d (1H, 2′-H, J = 7.0, 6.4 Hz), 6.26 d (1H, 3-H, J = 9.4 Hz), 6.86 s (1H, 8-H), 7.59 d (1H, 4-H, J = 9.4 Hz), 8.00 s (1H, 5-H), 8.67 d (1H, NH, J = 6.4 Hz), 11.17 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 22.60 (CH_3), 23.42 (CH_3), 29.68 ($C^{3'}$), 52.76 (OCH_3), 60.02 ($C^{2'}$), 104.81 (C^8), 109.96 (C^{4a}), 111.13 (C^6), 111.91 (C^3), 126.99 (C^4), 142.97 (C^5), 158.87 (C^{8a}), 160.43 (C^2), 161.83 (C=O), 164.23 (C^7), 169.43 (**C**OOMe). Found, %: C 60.80; H 5.94; N 4.40. $C_{16}H_{17}NO_6$. Calculated, %: C 60.18; H 5.37; N 4.39.

Methyl 2-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)-4-(methylsulfanyl)butanoate (19). Yield 0.104 g (60%, method *c*), yellow oil, $[\alpha]_D^{28.5}$ = +13.34° (*c* = 1.00). IR spectrum, ν, cm^{-1}: 3344, 3062, 2952, 2920, 2850, 1739, 1648, 1600, 1568, 1548, 1439, 1388, 1307, 1230, 1147, 1103, 912, 825, 752. UV spectrum (EtOH), λ_{max}, nm (logε): 247 (4.84), 306 (4.27), 330 (4.14). ^{1}H NMR spectrum, δ, ppm: 2.08 s (3H, SCH_3), 2.14 m (2H, CHC**H**$_2$), 2.58 t (2H, SCH_2, J = 8.4 Hz), 3.79 s (3H, OCH_3), 4.90 t (1H, CH), 6.19 d (1H, 3-H, J = 9.5 Hz), 6.71 s (1H, 8-H), 7.56 d (1H, 4-H, J = 9.5 Hz), 7.77 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 15.47 (SCH_3), 30.21 (SCH_2), 30.73 (CH**C**H$_2$), 51.86 (OCH_3), 52.90 (CH), 105.23 (C^8), 111.37 (C^{4a}), 111.71 (C^6), 113.69 (C^3), 126.90 (C^4), 143.03 (C^5), 157.92 (C^{8a}), 160.25 (C^2), 164.49 (C=O), 168.61 (C^7), 172.49 (**C**OOMe). Mass spectrum: m/z 351.0772 $[M]^+$. Found, %: C 54.86; H 4.94; N 3.87; S 9.02. $C_{16}H_{17}NO_6S$. Calculated, %: C 54.69; H 4.88; N 3.99; S 9.12. M 351.0771.

Methyl 2-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)-3-phenylpropanoate (20). Yield 0.057 g (55%, method *c*), yellow oil, $[\alpha]_D^{28.5}$ = +7.12° (*c* = 1.00). IR spectrum, ν, cm^{-1}: 3369, 3062, 3029, 2919, 2850, 1743, 1648, 1619, 1600, 1571, 1540, 1388, 1217, 1147, 1101, 823, 700. UV spectrum (EtOH), λ_{max}, nm (logε): 201 (4.57), 205 (4.32), 225 (4.67), 243 (4.21), 327 (4.18), 375 (3.84). ^{1}H NMR spectrum, δ, ppm: 3.01–3.24 m (2H, CH_2), 3.71 s (3H, OCH_3), 4.95 m (1H, CH), 6.13 d (1H, 3-H, J = 9.4 Hz), 6.72 s (1H, 8-H), 7.15–7.24 m (3H, *o*-H, *p*-H), 7.32–7.40 m (2H, *m*-H), 7.42 s (1H, 5-H), 7.43 d (1H, 4-H, J = 9.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 37.57 (CH_2), 52.64 (OCH_3), 53.37 (CH), 105.32 (C^8), 111.32 (C^{4a}), 111.72 (C^6), 113.72 (C^3), 126.35 (C^4), 127.32 (C^p), 128.65 (C^o), 129.13 (C^m), 135.29 (C^i), 142.77 (C^5), 157.96 (C^{8a}), 160.05 (C^2), 164.51 (C=O), 168.11 (**C**OOMe), 171.77 (C^7). Mass spectrum: m/z 367.1053 $[M]^+$. Found, %: C 65.68; H 4.73; N 3.75. $C_{20}H_{17}NO_6$. Calculated, %: C 65.39; H 4.66; N 3.81. M 367.1050.

Methyl 3-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)-3-phenylpropanoate (21). Yield 0.095 g (53%, method *c*), mp 94°C (decomp., from Et_2O). IR spectrum, ν, cm^{-1}: 3435, 3336, 3060, 3033, 2951, 2850, 1737, 1621, 1600, 1533, 1436, 1390, 1296, 1238, 1213, 1168, 1116, 910, 700. UV spectrum (EtOH), λ_{max}, nm (logε): 206 (4.75), 223 (4.45), 328 (4.29), 372 (4.03). ^{1}H NMR spectrum, δ, ppm: 2.65 m and 2.97 m (1H each, CH_2), 3.61 s (3H, OCH_3), 5.58 m (1H, CH), 6.18 d (1H, 4-H, J = 9.4 Hz), 6.75 s (1H, 8-H), 7.22–7.30 m (3H, *o*-H, *p*-H), 7.41–7.48 m (2H, *m*-H), 7.61 d (1H, 3-H, J = 9.4 Hz), 7.89 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 39.76 (CH_2), 49.79 (CH), 51.99 (OCH_3), 104.76 (C^8), 111.23 (C^{4a}), 112.93 (C^6), 113.38 (C^3), 126.13 (C^o), 128.12 (C^4), 128.17 (C^p), 128.72 (C^m), 143.61 (C^5), 147.22 (C^i), 157.50 (C^{8a}), 160.89 (C^2), 163.92 (C=O), 167.21 (C^7), 171.93 (**C**OOMe). Found, %: C 65.48; H 4.73; N 3.77. $C_{20}H_{17}NO_6$. Calculated, %: C 65.39; H 4.66; N 3.81.

Methyl 8-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)octanoate (22). Yield 0.132 g (75%, method *c*), viscous oily material. IR spectrum, ν, cm^{-1}: 3409, 3380, 3055, 2925, 2854, 1736, 1708, 1653, 1622, 1570, 1437, 1390, 1311, 1246, 1145, 916, 854, 837, 825. UV spectrum (EtOH), λ_{max}, nm (logε): 245 (3.72), 307 (3.34), 331 (3.20). ^{1}H NMR spectrum, δ, ppm: 1.33 m (6H, CH_2), 1.59 m (4H, CH_2), 2.28 t (2H, $COCH_2$), 3.43 t (2H, NHC**H**$_2$), 3.64 s (3H, OCH_3), 6.22 d (1H, 3-H, J = 9.4 Hz), 6.83 s (1H, 8-H), 7.59 d (1H, 4-H, J = 9.4 Hz), 7.65 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 24.63 ($C^{6'}$), 26.57 ($C^{3'}$), 28.73 ($C^{5'}$), 28.87 ($C^{4'}$), 29.22 ($C^{2'}$), 33.93 ($C^{7'}$), 39.82 ($C^{1'}$), 51.53

(OCH_3), 105.36 (C^8), 111.15 (C^{4a}), 112.45 (C^6), 113.55 (C^3), 126.19 (C^4), 143.03 (C^5), 157.74 (C^{8a}), 160.38 (C^2), 164.82 (C=O), 168.72 (C^7), 174.34 (**C**OOMe). Found, %: C 63.29; H 6.52; N 3.77. $C_{19}H_{23}NO_6$. Calculated, %: C 63.15; H 6.42; N 3.88.

Methyl 9-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)nonanoate (23). Yield 0.130 g (71%, method *c*), mp 78°C (from Et_2O). IR spectrum, ν, cm^{-1}: 3409, 3380, 3055, 2925, 2854, 1736, 1708, 1653, 1622, 1570, 1437, 1390, 1311, 1246, 1145, 916, 854, 837, 825. UV spectrum (EtOH), λ_{max}, nm (logε): 245 (3.72), 307 (3.34), 331 (3.20). ^{1}H NMR spectrum, δ, ppm: 1.27 m (8H, CH_2), 1.59 m (4H, CH_2), 2.28 t (2H, $COCH_2$), 3.43 t (2H, NHC**H**$_2$), 3.64 s (3H, OCH_3), 6.20 d (1H, 3-H, *J* = 9.4 Hz), 6.81 s (1H, 8-H), 7.59 s (1H, 5-H), 7.65 d (1H, 4-H, *J* = 9.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 24.72 ($C^{6'}$), 26.72 ($C^{3'}$), 28.64 ($C^{5'}$), 28.84 ($C^{4'}$), 29.20 ($C^{2'}$), 33.92 ($C^{7'}$), 39.84 ($C^{1'}$), 51.37 (OCH_3), 105.17 (C^8), 111.09 (C^{4a}), 112.51 (C^6), 113.37 (C^3), 126.26 (C^4), 143.06 (C^5), 157.63 (C^{8a}), 160.37 (C^2), 164.72 (C=O), 168.64 (C^7), 174.29 (**C**OOMe). Found, %: C 63.29; H 6.52; N 3.77. $C_{19}H_{23}NO_6$. Calculated, %: C 63.15; H 6.42; N 3.88.

2-(7-Hydroxy-2-oxo-2*H*-chromene-6-carboxamido)acetic acid (24). Yield 0.101 g (86%, method *d*), mp 208°C (from Et_2O). IR spectrum, ν, cm^{-1}: 3386, 3163, 3058, 3008, 2965, 2919, 2699, 1742, 1626, 1601, 1577, 1492, 1391, 1298, 1222, 1190, 1147, 1103, 1076, 1042, 904, 828. UV spectrum (EtOH), λ_{max}, nm (logε): 205 (4.38), 224 (4.29), 243 (4.33), 326 (4.15). ^{1}H NMR spectrum, δ, ppm: 3.97 s (2H, CH_2), 6.05 d (1H, 3-H, *J* = 9.6 Hz), 6.65 s (1H, 8-H), 7.59 d (1H, 4-H, *J* = 9.6 Hz), 7.93 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 40.96 (CH_2), 103.88 (C^8), 111.49 (C^{4a}), 112.63 (C^6), 113.98 (C^3), 129.49 (C^4), 144.05 (C^5), 161.22 (C^{8a}), 162.10 (C^2), 167.28 (C=O), 167.30 (C^7), 171.46 (COOH). Found, %: C 55.01; H 3.64; N 5.13. $C_{12}H_9NO_6$. Calculated, %: C 54.76; H 3.45; N 5.32.

2-(7-Hydroxy-2-oxo-2*H*-chromene-6-carboxamido)acetyl chloride (25). A solution of 0.15 g (0.49 mmol) of acid **24** in 2 mL of thionyl chloride was refluxed for 1.5 h. Excess thionyl chloride was removed under reduced pressure to leave 0.13 g (81%) of acid chloride **25** as amorphous powder. ^{1}H NMR spectrum, δ, ppm: 4.23 s (2H, CH_2), 6.31 d (1H, 3-H, *J* = 9.4 Hz), 6.91 s (1H, 8-H), 7.85 d (1H, 4-H, *J* = 9.4 Hz), 8.19 s (1H, 5-H), 9.97 (2H, NH, OH). ^{13}C NMR spectrum, δ_C, ppm: 50.10 (CH_2), 95.65 (C^8), 111.49 (C^{4a}), 112.63 (C^6), 113.89 (C^3), 129.49 (C^4), 144.05 (C^5), 157.07 (C^{8a}), 161.22 (C^2), 162.04 (C^7), 162.10 (C=O), 169.66 (COCl). Found, %: C 48.22; H 2.18; Cl 12.12; N 4.56. $C_{12}H_8ClNO_6$. Calculated, %: C 48.42; H 2.71; Cl 11.91; N 4.71.

***N*-[2-(Benzylamino)-2-oxoethyl]-7-hydroxy-2-oxo-2*H*-chromene-6-carboxamide (27)** was synthesized according to method *c* from 0.1 g (0.35 mmol) of **25** and 0.046 mL (0.42 mmol) of **4**. Yield 0.081 g (66%), yellow viscous oil. IR spectrum, ν, cm^{-1}: 3445, 3348, 2917, 2849, 2599, 2489, 1753, 1737, 1645, 1612, 1601, 1496, 1480, 1418, 1388, 1320, 1299, 1287, 1146, 1134, 1096, 1028, 908, 826, 748, 741. UV spectrum ($CHCl_3$), λ_{max}, nm (logε): 202 (4.48), 237 (4.25), 300 (3.85), 327 (3.97). ^{1}H NMR spectrum, δ, ppm: 3.73 s (2H, CH_2), 4.01 s (2H, CH_2), 6.09 d (1H, 3-H, *J* = 9.8 Hz), 6.59 m and 7.00 m (5H, Ph), 6.69 s (1H, 8-H), 7.57 d (1H, 4-H, *J* = 9.8 Hz), 7.93 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 42.92 (CH_2), 51.85 (CH_2), 95.77 (C^8), 111.43 (C^{4a}), 112.76 (C^6), 113.73 (C^3), 115.85, 119.36 (C^4), 121.10, 128.93, 131.14, 143.93 (C^5), 157.08 (C^{8a}), 158.20 (C^2), 161.05 (C^7), 161.99 (C=O), 169.91 (C=O). Found, %: C 65.16; H 4.21; N 8.08. $C_{19}H_{16}N_2O_5$. Calculated, %: C 64.77; H 4.58; N 7.95.

***N*-[2-(2,4-Dimethoxybenzylamino)-2-oxoethyl]-7-hydroxy-2-oxo-2*H*-chromene-6-carboxamide (28)** was synthesized according to method *c* from 0.1 g (0.35 mmol) of **25** and 0.063 mL (0.42 mmol) of **5**. Yield 0.089 g (62%), yellow viscous oil. IR spectrum, ν, cm^{-1}: 3372, 3285, 2993, 2953, 2918, 2849, 1736, 1628, 1591, 1510, 1464, 1456, 1391, 1287, 1209, 1159, 1141, 1030, 831. UV spectrum ($CHCl_3$), λ_{max}, nm (logε): 204 (4.56), 227 (4.19), 283 (3.64), 329 (3.81), 372 (3.35). ^{1}H NMR spectrum, δ, ppm: 3.71 s and 3.73 s (3H each, OCH_3), 3.99 m (2H, CH_2), 4.14 m (2H, CH_2), 6.09 d (1H, 3-H, *J* = 9.4 Hz), 6.29 br.s (2H, H_{arom}), 6.37 d (1H, H_{arom}, *J* = 9.1 Hz), 6.65 s (1H, 8-H), 7.57 d (1H, 4-H, *J* = 9.4 Hz), 7.92 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 44.84 (CH_2), 51.86 (CH_2), 67.92 (OMe), 68.50 (OMe), 96.05 (C^8), 98.38 (C_{arom}), 104.65 (C_{arom}), 110.00 (C^{4a}), 111.81 (C^6), 113.84 (C^3), 114.91 (C_{arom}), 120.04 (C^4), 131.30 (C_{arom}), 143.16 (C^5), 159.03 (C^{8a}), 159.52 (C_{arom}), 160.16 (C_{arom}), 164.74 (C^2), 167.78 (C^7), 168.93 (C=O), 171.09 (C=O). Found, %: C 60.89; H 4.25; N 6.62. $C_{21}H_{20}N_2O_7$. Calculated, %: C 61.16; H 4.89; N 6.79.

Methyl 2-[2-(7-hydroxy-2-oxo-2*H*-chromene-6-carboxamido)acetamido]butanoate (29) was synthesized according to method *c* from 0.1 g (0.35 mmol) of **25** and 0.048 g (0.42 mmol) of methyl 2-aminobutanoate (**26**). Yield 0.095 g (75%), mp 114°C (from Et_2O). IR spectrum, ν, cm^{-1}: 3503, 3399, 3247, 3065,

2956, 2919, 2850, 1741, 1678, 1627, 1599, 1579, 1491, 1460, 1391, 1294, 1211, 1145, 1118, 1105, 1076, 912, 827. UV spectrum ($CHCl_3$), λ_{max}, nm ($\log\varepsilon$): 205 (4.32), 242 (4.21), 324 (4.06), 349 (3.7). ^{1}H NMR spectrum, δ, ppm: 1.85 m (3H, CH_3), 2.25–2.48 m (2H, CH_2), 3.74 (3H, OCH_3), 4.34 m (3H, CH_2, CH), 6.25 d (1H, 3-H, J = 9.6 Hz), 6.85 s (1H, 8-H), 7.61 d (1H, 4-H, J = 9.6 Hz), 8.05 s (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 21.83 (CH_3), 25.24 (CH_2), 44.53 (CH_2), 54.79 (OMe), 56.15 (CH), 104.33 (C^8), 109.69 (C^{4a}), 111.61 (C^6), 113.53 (C^3), 131.06 (C^4), 142.86 (C^5), 158.64 (C^{8a}), 159.91 (C^2), 163.38 (C^7), 164.42 (C=O), 170.78 (C=O), 177.49 (**C**OOMe). Found, %: C 55.94; H 5.45; N 7.87. $C_{17}H_{18}N_2O_7$. Calculated, %: C 56.35; H 5.01; N 7.73.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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24. The X-ray diffraction data for compound **2** are available at *www.ccdc.cam.ac.uk/data_request/cif*