Synthesis and Characterization of New 3-Acyl-7-hydroxy-6,8-substituted-coumarin and 3-Acyl-7-benzyloxy-6,8-substituted-coumarin Derivatives

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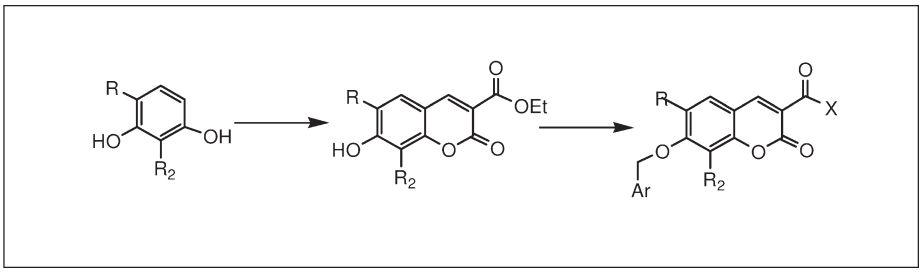

A new series of 3-acyl-6,7,8-substituted coumarin derivatives has been synthesized in high yields (79–99%) and characterized by means of elemental analysis, mass spectrometry, IR, and ^{1}H NMR spectroscopy. We examined with particular attention the presence of an acyl group at position 3 (ethyl ester, carboxylic acid, and acyl chloride), and of a hydroxyl group at position 7 or a functionalized one like benzyloxy or phthalimido. The hydroxyl group has been modified by an etherification in presence of crown ether with substituted benzyl bromide or chloride to evaluate the influence on chemical characteristics and lipophilicity of coumarin nucleus. Halogens (Cl, Br) and methyl group were introduced in position 6 and 8 of the coumarin ring, respectively, in order to study their effect on reaction feasibility. Some of these 3-acyl derivatives have been recently assayed as MAO inhibitors and as intermediates (i.e. reactive chloride derivative) to design new anti-*Helicobacter pylori* agents.

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INTRODUCTION

Coumarins, (2*H*)-1-benzopyran-2-ones, represent a common type of phytochemicals, frequently encountered in plants of the *Apiaceae*, *Rutaceae*, *Fabaceae*, and *Hyppocastanaceae* [1]. Interest in this scaffold arose from the identification of both natural or synthetic pharmacologically active derivatives, which have been found to be useful in photochemotherapy, antitumor [2], and anti-HIV [3] therapy, and as stimulants for central nervous system, antibacterials, antioxidants [4], anti-inflammatory [5], anticoagulants, and dyes according to the nature and the substitution pattern. In particular we recently demonstrated that 3-acyl and 3-carboxyamido coumarins could be considered good lead compounds as reversible and effective human monoamine oxidase (hMAO) inhibitors [6,7].

The interesting biological properties of coumarins made these compounds very attractive for organic synthesis. There are many developed methods of coumarins synthesis, e.g. Pechman reaction, Perkin reaction, Knoevenagel condensation, and many others [1]. However, it is important to highlight that all the reported procedures have some disadvantages, as they lack generality and efficiency making the development of new reliable high-yielding methods for the synthesis of coumarins an important matter. For these reasons, we synthesized many molecules based on the coumarin ring system by utilizing classic and innovative synthetic techniques such as carbon suboxide [8] and microwave [9].

In particular, microwave irradiation usually accelerates some chemical transformations and offers numerous benefits for performing solventless procedures (green chemistry) and improving reaction yields, especially in heterocyclic chemistry [10].

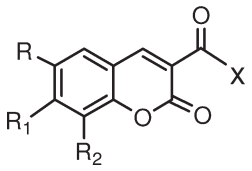
Hence, in this article, we report on synthesis and characterization by spectral data, such as IR, ^{1}H NMR, and mass spectroscopy of coumarin analogues bearing an acyl function (ethyl ester, carboxylic acid, and acyl chloride) at position 3, halogens (Cl, Br) at position 6, different unsubstituted or substituted benzyloxy moieties at position 7, and methyl group at position 8 (Table 1).

RESULTS AND DISCUSSION

Coumarin derivatives were synthesized starting from substituted salicylic aldehydes according to the pathway reported in Scheme 1.

Table 1

Structure and CLogP (ChemDraw Ultra 8.0) of synthesized coumarin derivatives.



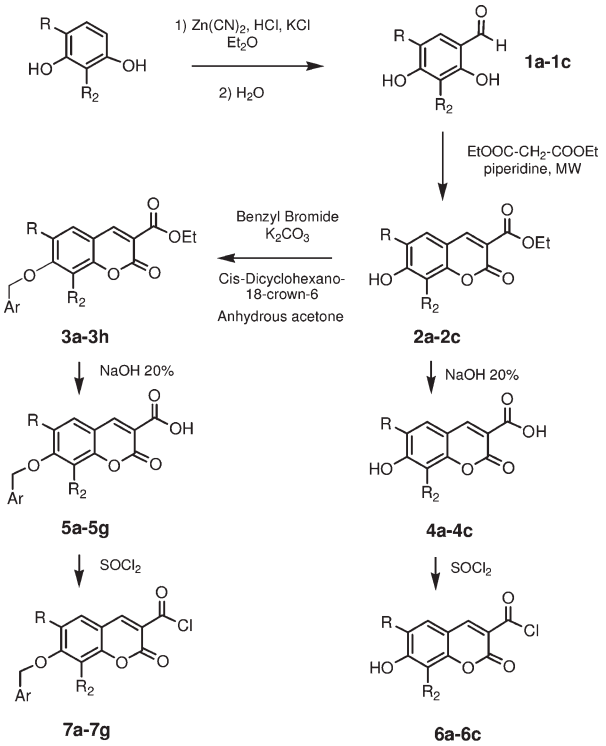
Comp	R	R_1	R_2	X	ClogP	*m/z*
3a	Cl	CH_2Ph	H	OEt	4.52	358.77
3b	Br	OCH_2Ph	H	OEt	4.67	403.22
3c	H	OCH_2Ph	CH_3	OEt	4.53	338.35
3d	H	OCH_2(2-Cl-Ph)	H	OEt	4.74	358.77
3e	H	OCH_2(4-F-Ph)	H	OEt	4.17	342.31
3f	H	OCH_2(4-Cl-Ph)	H	OEt	4.74	358.77
3g	H	OCH_2(4-NO_2-Ph)	H	OEt	3.77	369.32
3h	H	OCH_2phtalimido	H	OEt	3.15	393.35
5a	Cl	OCH_2Ph	H	OH	3.80	330.71
5b	Br	OCH_2Ph	H	OH	3.95	375.17
5c	H	OCH_2Ph	CH_3	OH	3.81	310.30
5d	H	OCH_2(2-Cl-Ph)	H	OH	4.02	330.72
5e	H	OCH_2(4-F-Ph)	H	OH	3.45	314.26
5f	H	OCH_2(4-Cl-Ph)	H	OH	4.02	330.72
5g	H	OCH_2(4-NO_2-Ph)	H	OH	3.05	341.27
6a	Cl	OH	H	Cl	1.46	259.04
6b	Br	OH	H	Cl	1.66	303.49
6c	H	OH	CH_3	Cl	1.49	238.32
7a	Cl	OCH_2Ph	H	Cl	3.43	349.16
7b	Br	OCH_2Ph	H	Cl	3.58	393.61
7c	H	OCH_2Ph	CH_3	Cl	3.43	328.74
7d	H	OCH_2(2-Cl-Ph)	H	Cl	3.65	349.16
7e	H	OCH_2(4-F-Ph)	H	Cl	3.08	332.71
7f	H	OCH_2(4-Cl-Ph)	H	Cl	3.65	349.16
7g	H	OCH_2(4-NO_2-Ph)	H	Cl	2.68	359.72

The corresponding salicylic aldehydes were obtained by a Gattermann aromatic formylation starting from 2- or 4-substituted resorcinol in a strongly acidic environment (**1a**–**1c**). Ethyl esters of (2*H*)-1-benzopyran-2-one-3-carboxylic acids (**2a**–**2c**), were easily obtained by a Knoevenagel cyclization in 15–20 min (80°C) under microwave irradiation with an automatic single-mode reactor. All reactions were performed solventless in vials of 10 mL, confirming that the focused microwave irradiation was a very effective technique for accelerating thermal organic reactions and limiting solvent wasting, not being affected by substituents. These compounds, bearing a hydroxyl group at position 7, were subsequently functionalized by benzylation in the presence of *N*,*N*′-dicyclohexyl-18-crown-6-ether, which by chelating potassium ion facilitated the nucleophilic attack to improve the yields of the related compounds (**3a**–**3h**). Alkaline hydrolysis with 10% sodium hydroxide gave carboxylic acid compounds (**4a**–**4c** and **5a**–**5f**), which were treated with thionyl chloride at reflux to yield the desired and reactive acyl chloride derivatives (**6a**–**6c** and **7a**–**7g**). In general this synthetic procedure allowed us to obtain the desired compounds in high yields and simplify reaction work up, limiting the presence of by-products.

The compounds, correctly analyzed for their molecular formula, showed in the IR spectrum strong bands at 1695–1720 cm^{-1} due to the presence of a δ-lactone C=O and eventually a carbonyl group, and characteristic bands at 1655, 1615, 1575, and 1500 cm^{-1} (double bonds in the aromatic ring).

The lipophilicity (ClogP) of this coumarin scaffold has been calculated with the suitable algorithm for each molecule by using ChemDraw Ultra 8.0. because of its importance in modulating biological activity and pharmacodynamic profile of the molecules [11]. As expected, the introduction of a benzyloxy group at position 7 of the coumarin ring deeply affects this parameter. All compounds, and above all compound **5g**, which was insoluble in common organic solvents (dimethyl

Scheme 1. General synthetic pattern of coumarin derivatives.



EXPERIMENTAL

Starting materials and reagents were obtained from commercial suppliers and were used without purification. Melting points (mp) were determined by the capillary method on an FP62 apparatus (Mettler-Toledo) and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer using DMSO-d_6 as solvent. Chemical shifts are expressed as δ units (ppm) relative to TMS. Coupling constants *J* are expressed in hertz (Hz). Elemental analyses for C, H, and N were determined with a PerkinElmer 240 B microanalyzer and the analytical results were within ±0.4% of the theoretical values for all compounds. All reactions were monitored by TLC performed on 0.2 mm thick silica gel plates (60 F_{254} Merck). Preparative flash column chromatography was carried out on silica gel (230–400 mesh, G60 Merck). Organic solutions were dried over anhydrous sodium sulphate. Concentration and evaporation of the solvent after reaction or extraction was carried out on a rotary evaporator (Büchi Rotavapor) operating at reduced pressure. IR spectra were registered on a PerkinElmer FTIR Spectrometer Spectrum 1000 in potassium bromide. Mass spectra (EI) were obtained with a Fisons QMD 1000 mass spectrometer (70 ev, 200 μA, ion source temperature 200°C). The samples were introduced directly into the ion source. Compounds **2a**–**2c**, synthesized with the microwave method, were obtained with a Biotage Initiator^{TM} 2.0.

The synthesis of some compounds (**1a**–**1c**, **2a**–**2c**, and **4a**–**4c**) has been previously described and was performed with slight changes. Their analytical and spectral data were in full agreement with those reported in the literature.

sulfoxide, chloroform, and acetone), have been characterized by mass spectral studies. In the mass spectra the fragment ion at *m*/*z* (%) = 173 (90) corresponding to the 3-acyl coumarin structure was always the most abundant observed. The fragmentation pattern of derivative **5g** was described in Figure 1. This compound showed the fragment at *m*/*z* (%) 341 (10), which likely represented the molecular ion. In fact, the base peak, referred to the 4′-nitro-benzyl fragment, was always present at 134 (100). In addition the mass spectrum revealed ion suggestive at *m*/*z* 297 (5), 250 (5), and 205 (20) because of the loss of COOH, CO_2, and NO_2.

In this article, we have synthesized, by using readily available and inexpensive reagents, and fully characterized a new series of heterocyclic derivatives (3-acyl-6,7,8-substituted coumarins), which could reveal their potentials as versatile biodynamic agents. The most important results of our approach are the optimization of the yields and of the reaction times using microwave irradiation. In addition, lower amount of solvent was used and a better workup was obtained. The introduction of a substituted benzyloxy group at position 7 could influence not only the physical–chemical properties, but also their biological activity. Halogens (Cl, Br) and methyl group were introduced in position 6 and 8 of the coumarin ring, respectively, to study their effect on reaction feasibility.

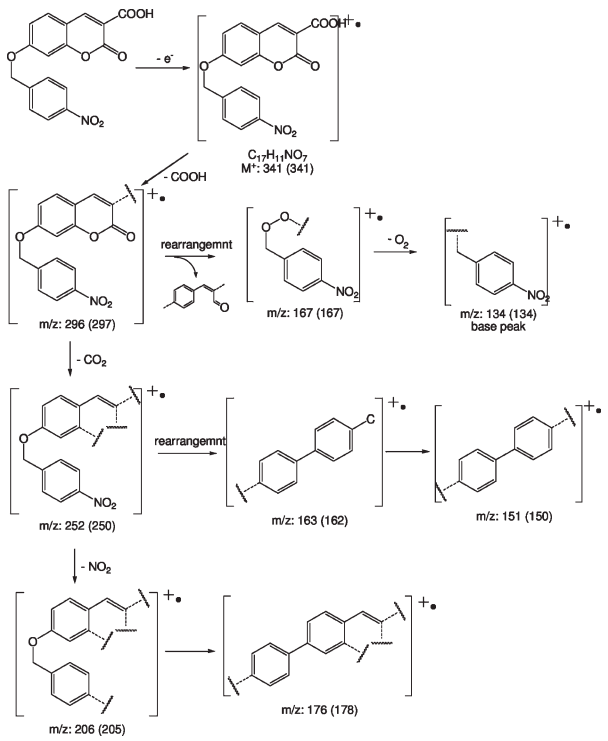


Figure 1. The fragmentation pattern of derivative **5g**.

General procedure for the synthesis of coumarin derivatives 1a–1c. The substituted salicylic aldehydes were prepared in a 500 mL bottle, fitted with a mechanical stirrer, a reflux water condenser and an inlet tube, with wide mouth to prevent clogging from the precipitate. Resorcinol derivatives (1 mmol), zinc cyanide (2 mmol), and potassium chloride (0.3 mmol) were suspended in anhydrous diethyl ether (40 mL). Gaseous HCl was bubbled inside the bottle and then water was added to hydrolyze the immine product into aldehyde. The zinc chloride, which was produced at the same time, acted as an effective condensing agent.

General procedure for the synthesis of coumarin derivatives 2a–2c. The starting ethyl ester of coumarin-3-carboxylic acid was prepared by Knoevenagel reaction between diethyl malonate (1 mmol) and the appropriate salicylic aldehyde (1 mmol) with catalytic amounts of piperidine (0.5 mL) in a 10 mL vial suitable for an automatic single-mode microwave reactor (2.45 GHz high-frequency microwaves, power range 0–300 W). The mixture was prestirred for 30 sec and then heated by microwave irradiation for 15–20 min at 80°C (irradiation power reaches its maximum at the beginning of reaction, then it decreases to lower and quite constant values). The internal vial temperature was controlled by an IR sensor. After cooling with pressurized air, the reaction mixture was poured onto ice, filtered, and dried under vacuum.

General procedure for the synthesis of coumarin derivatives 3a–3h. The etherification at position 7 was performed by adding suitable benzyl bromide (1 mmol) and potassium carbonate (1 mmol) in dry acetone (50 mL) for 48 h at room temperature, using *N*,*N*′-dicyclohexyl-18-crown-6-ether (1 mmol) as a chelating agent. The resulting reaction mixture was filtered and the crude product was purified by chromatography.

Ethyl 7-(benzyloxy)-6-chloro-2-oxo-2H-chromene-3-carboxylate (3a). 85% yield; mp 211–212°C; ^{1}H NMR (DMSO-d_6) δ 1.27–1.29 (t, 3H, CH_3), 4.29–4.31 (q, 2H, CH_2), 5.31 (s, 2H, OCH_2Ar), 7.30 (s, 1H, C_8H-chrom.), 7.31–7.50 (m, 5H, Ar), 8.18 (s, 1H, C_5H-chrom.), 8.68 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{19}H_{15}ClO_5$: C, 63.61; H, 4.21. Found: C, 63.63; H, 4.22.

Ethyl 7-(benzyloxy)-6-bromo-2-oxo-2H-chromene-3-carboxylate (3b). 87% yield; mp 215–216°C; ^{1}H NMR (DMSO-d_6) δ 1.30–1.32 (t, 3H, CH_3), 4.32–4.34 (q, 2H, CH_2), 5.40 (s, 2H, OCH_2Ar), 7.19 (s, 1H, C_8H-chrom.), 7.21–7.49 (m, 5H, Ar), 8.10 (s, 1H, C_5H-chrom.), 8.60 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{19}H_{15}BrO_5$: C, 56.59; H, 3.75. Found: C, 56.57; H, 3.76.

Ethyl 7-(benzyloxy)-8-methyl-2-oxo-2H-chromene-3-carboxylate (3c). 89% yield; mp 154–155°C; ^{1}H NMR (DMSO-d_6) δ 1.27–1.29 (t, 3H, CH_3), 2.20 (s, 3H, $ArCH_3$), 4.22–4.27 (q, 2H, CH_2), 5.31 (s, 2H, OCH_2Ar), 7.39 (s, 1H, C_8H-chrom.), 7.40–7.45 (m, 5H, Ar), 7.46 (s, 1H, C_5H-chrom.), 8.72 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.01; H, 5.37.

Ethyl 7-(2-chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3d). 79% yield; mp 126–127°C; ^{1}H NMR (DMSO-d_6) 1.28–1.30 (t, 3H, CH_3), 4.29–4.31 (q, 2H, CH_2), 5.44 (s, 2H, OCH_2Ar), 7.19 (s, 1H, C_8H-chrom.), 7.21–7.22 (m, 1H, C_6H-chrom.), 7.23–7.27 (m, 4H, Ar), 7.28–7.29 (m, 1H, C_5H-chrom.), 8.70 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{19}H_{15}ClO_5$: C, 63.61; H, 4.21. Found: C, 63.63; H, 4.22.

Ethyl 7-(4-fluorobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3e). 87% yield; mp 159–160 °C; ^{1}H NMR (DMSO-d_6) 1.29 (t, 3H, CH_3), 4.33 (q, 2H, CH_2), 5.23 (s, 2H, OCH_2Ar), 7.15 (s, 1H, C_8H-chrom.), 7.26–7.28 (m, 1H, C_6H-chrom.), 7.61–7.65 (m, 2H, C_3H-Ar and C_5H-Ar), 7.72–7.74 (m, 1H, C_5H-chrom.), 7.89–7.92 (m, 2H, C_2H-Ar and C_6H-Ar), 8.85 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{19}H_{15}FO_5$: C, 66.66; H, 4.42. Found: C, 66.68; H, 4.43.

Ethyl 7-(4-chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3f). 79% yield; mp 160–161°C; ^{1}H NMR (DMSO-d_6) 1.28 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 5.26 (s, 2H, OCH_2Ar), 7.19 (s, 1H, C_8H-chrom.), 7.25–7.28 (m, 1H, C_6H-chrom.), 7.31–7.36 (m, 2H, C_3H-Ar and C_5H-Ar), 7.41–7.43 (m, 1H, C_5H-chrom.), 7.54–7.58 (m, 2H, C_2H-Ar and C_6H-Ar), 8.80 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{19}H_{15}ClO_5$: C, 63.61; H, 4.21. Found: C, 63.63; H, 4.22.

Ethyl 7-(4-nitrobenzyloxy)-2-oxo-2H-chromene-3-carboxylate (3g). 87% yield; mp 210–211°C; ^{1}H NMR (DMSO-d_6) 1.29 (t, 3H, CH_3), 4.33 (q, 2H, CH_2), 5.45 (s, 2H, OCH_2Ar), 7.26 (s, 1H, C_8H-chrom.), 7.30–7.32 (m, 1H, C_6H-chrom.), 7.41–7.44 (m, 2H, C_2H-Ar and C_6H-Ar), 7.51–7.53 (m, 1H, C_5H-chrom.), 8.26–8.30 (m, 2H, C_3H-Ar and C_5H-Ar), 8.83 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.09; N, 3.79. Found: C, 61.77; H, 4.10; N, 3.80.

Ethyl 7-[(1,3-dioxoisoindolin-2-yl)methoxy]-2-oxo-2H-chromene-3-carboxylate (3h). 98% yield; mp 284–285°C; ^{1}H NMR (DMSO-d_6) 1.27–1.31 (t, 3H, CH_3), 4.26-4.28 (q, 2H, CH_2), 5.73 (s, 2H, OCH_2Ar), 7.29 (s, 1H, C_8H-chrom.), 7.33–7.35 (m, 1H, C_6H-chrom.), 7.49–7.51 (m, 1H, C_5H-chrom.), 7.86–7.92 (m, 4H, Ar), 8.73 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{21}H_{15}NO_7$: C, 64.12; H, 3.84; N, 3.56. Found: C, 64.10; H, 3.83; N, 3.57.

General procedure for the synthesis of coumarin derivatives 4a–4c and 5a–5g. All ethyl ester derivatives were dissolved in NaOH 10% (50 mL) and added of HCl 3*N* (50 mL). The resulting suspension was filtered and dried under vacuum.

7-(Benzyloxy)-6-chloro-2-oxo-2H-chromen-3-carboxylic acid (5a). 87% yield; mp 233–234°C; ^{1}H NMR (DMSO-d_6) δ 5.34 (s, 2H, OCH_2Ar), 7.41 (s, 1H, C_8H-chrom.), 7.43–7.48 (m, 5H, Ar), 8.18 (s, 1H, C_5H-chrom.), 8.43 (s, 1H, C_4H-chrom.), 13.24 (bs, 1H, COOH, D_2O exch.). Anal. Calcd. for $C_{17}H_{11}ClO_5$: C, 61.74; H, 3.35. Found: C, 61.76; H, 3.36.

7-(Benzyloxy)-6-bromo-2-oxo-2H-chromene-3-carboxylic acid (5b). 92% yield; mp 255–256°C; ^{1}H NMR (DMSO-d_6) δ 5.30 (s, 2H, OCH_2Ar), 7.30 (s, 1H, C_8H-chrom.), 7.41–7.47 (m, 5H, Ar), 8.20 (s, 1H, C_5*H*-chrom.), 8.59 (s, 1H, C_4H-chrom.), 13.15 (bs, 1H, COOH, D_2O exch.). Anal. Calcd. for $C_{17}H_{11}BrO_5$: C, 54.42; H, 2.96. Found: C, 54.44; H, 2.95.

7-(Benzyloxy)-8-methyl-2-oxo-2H-chromene-3-carboxylic acid (5c). 90% yield; mp 204–205°C; ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H, $ArCH_3$), 5.28 (s, 2H, OCH_2Ar), 7.21 (s, 1H, C_8H-chrom.), 7.47–7.53 (m, 5H, Ar), 7.77 (s, 1H, C_5H-chrom.), 8.70 (s, 1H, C_4H-chrom.), 12.98 (bs, 1H, COOH, D_2O exch.). Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.69; H, 4.54.

7-(2-Chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5d). 92% yield; mp 218–219°C; ^{1}H NMR (DMSO-d_6) 5.32 (s, 2H, OCH_2Ar), 7.12 (s, 1H, C_8H-chrom.), 7.13–7.15 (m, 1H, Ar) 7.40–7.41 (m, 1H, C_6H-chrom.), 7.42–7.44 (m, 1H, Ar), 7.65–7.67 (m, 1H, Ar), 7.77–7.79 (m, 1H, Ar), 7.85–7.86 (m, 1H, C_5H-chrom.), 8.72 (s, 1H, C_4H-chrom.), 13.12 (bs, 1H,

COOH, D_2O exch.). Anal. Calcd. for $C_{17}H_{11}ClO_5$: C, 61.74; H, 3.35. Found: C, 61.72; H, 3.36.

7-(4-Fluorobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5e). 91% yield; mp 228–229°C; ^{1}H NMR (DMSO-d_6) 5.33 (s, 2H, OCH_2Ar), 7.12 (s, 1H, C_8H-chrom.), 7.25–7.27 (m, 1H, C_6H-chrom.), 7.37–7.40 (m, 2H, C_3H-Ar and C_5H-Ar), 7.53–7.56 (m, 2H, C_2H-Ar and C_6H-Ar), 7.82–7.84 (m, 1H, C_5H-chrom.), 8.85 (s, 1H, C_4H-chrom.), 13.02 (s, 1H, COOH, D_2O exch.). Anal. Calcd. for $C_{17}H_{11}FO_5$: C, 64.97; H, 3.53. Found: C, 64.98; H, 3.54.

7-(4-Chlorobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5f). 93% yield; mp 251–252°C; ^{1}H NMR (DMSO-d_6) 5.26 (s, 2H, OCH_2Ar), 7.07 (s, 1H, C_8H-chrom.), 7.09–7.12 (m, 1H, C_6H-chrom.), 7.47–7.53 (m, 4H, Ar), 7.84–7.86 (m, 1H, C_5H-chrom.), 8.72 (s, 1H, C_4H-chrom.), 13.12 (bs, 1H, COOH, D_2O exch.). Anal. Calcd. for $C_{17}H_{11}ClO_5$: C, 61.74; H, 3.35. Found: C, 61.75; H, 3.34.

7-(4-Nitrobenzyloxy)-2-oxo-2H-chromene-3-carboxylic acid (5g). 89% yield; mp 281–282°C. Insoluble in DMSO, chloroform, and acetone. ms: *m*/*z* 134 (100), 205 (20), 250 (5), 297 (5), 341 (10). Anal. Calcd. for $C_{17}H_{11}NO_7$: C, 59.83; H, 3.25; N, 4.10. Found: C, 59.84; H, 3.26; N, 4.09.

General procedure for the synthesis of coumarin derivatives 6a–6c and 7a–7g. Carboxylic acid derivatives were refluxed under magnetic stirring with thionyl chloride (40 mL) for 3 h to give the desired compound. The obtained solutions were added with hexane and the resulting suspensions were then filtered and dried under vacuum.

6-Chloro-7-hydroxy-2-oxo-2H-chromene-3-carbonyl chloride (6a). 95% yield; mp >300°C; ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 1H, C_8H-chrom.), 7.99 (s, 1H, C_5H-chrom.), 8.62 (s, 1H, C_4H-chrom.), 11.96 (bs, 1H, OH, D_2O exch.). Anal. Calcd. for $C_{10}H_4Cl_2O_4$: C, 46.37; H, 1.56. Found: C, 46.39; H, 1.57.

6-Bromo-7-hydroxy-2-oxo-2H-chromene-3-carbonyl chloride (6b). 91% yield; mp >300°C; ^{1}H NMR (DMSO-d_6) δ 6.87 (s, 1H, C_8H-chrom.), 8.11 (s, 1H, C_5H-chrom.), 8.63 (s, 1H, C_4H-chrom.), 11.92 (bs, 1H, OH, D_2O exch.). Anal. Calcd. for $C_{10}H_4BrClO_4$: C, 39.57; H, 1.33. Found: C, 39.55; H, 1.32.

7-Hydroxy-8-methyl-2-oxo-2H-chromene-3-carbonyl chloride (6c). 87% yield; mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H, $ArCH_3$), 6.96–6.98 (m, 1H, C_6H-chrom.), 7.58–7.60 (m, 1H, C_5H-chrom.), 8.69 (s, 1H, C_8H-chrom.). Anal. Calcd. for $C_{11}H_7ClO_4$: C, 55.37; H, 2.96. Found: C, 55.39; H, 2.95.

7-(Benzyloxy)-6-chloro-2-oxo-2H-chromene-3-carbonyl chloride (7a). 95% yield; mp 214–215°C; ^{1}H NMR (DMSO-d_6) δ 5.34 (s, 2H, OCH_2Ar), 7.41 (s, 1H, C_8H-chrom.), 7.43–7.48 (m, 5H, Ar), 8.18 (s, 1H, C_5H-chrom.), 8.43 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: C, 58.48; H, 2.89. Found: C, 58.50; H, 2.90.

7-(Benzyloxy)-6-bromo-2-oxo-2H-chromene-3-carbonyl chloride (7b). 85% yield; mp 214–215°C; ^{1}H NMR (DMSO-d_6) δ 5.30 (s, 2H, OCH_2Ar), 7.30 (s, 1H, C_8H-chrom.), 7.41–7.47 (m, 5H, Ar), 8.20 (s, 1H, C_5H-chrom.), 8.60 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{17}H_{10}BrClO_4$: C, 51.87; H, 2.56. Found: C, 51.89; H, 2.57.

7-(2-Chlorobenzyloxy)-2-oxo-2H-chromene-3-carbonyl chloride (7d). 91% yield; mp 171–172°C; ^{1}H NMR (DMSO-d_6) δ 5.29 (s, 2H, $ArCH_2$), 7.18 (s, 1H, C_8H-chrom.), 7.19–7.21 (m, 1H, Ar), 7.40–7.41 (m, 1H, C_6H-chrom.), 7.42–7.44 (m, 1H, Ar), 7.50–7.53 (m, 1H, Ar), 7.59–7.61 (m, 1H, Ar), 7.85–7.86 (m, 1H, C_5H-chrom.), 8.73 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: C, 58.48; H, 2.89. Found: C, 58.50; H, 2.90.

7-(4-Nitrobenzyloxy)-2-oxo-2H-chromene-3-carbonyl chloride (7g). 79% yield; mp 220–221°C; ^{1}H NMR (DMSO-d_6) δ 5.45 (s, 2H, $ArCH_2$), 7.20 (s, 1H, C_8H-chrom.), 7.33–7.35 (m, 1H, C_6H-chrom.), 7.49–7.52 (m, 2H, C_2H-Ar and C_6H-Ar), 7.95–7.97 (m, 1H, C_5H-chrom.), 8.25–8.29 (m, 2H, C_3H-Ar and C_5H-Ar), 8.81 (s, 1H, C_4H-chrom.). Anal. Calcd. for $C_{17}H_{10}ClNO_6$: C, 56.76; H, 2.80. Found: C, 56.74; H, 2.79.

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