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Synthesis, spectroscopic characterization and X-ray structure of novel 7-methoxy-4-oxo-*N*-phenyl-4*H*-chromene-2-carboxamides

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HIGHLIGHTS

- Novel 7-substitued chromone carboxamides have been synthesized.
- The structural characterization was performed by FTIR, NMR and X-ray.
- The data provide a better understanding of the structure–activity (A_3AR) relationships.

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ABSTRACT

The chromone scaffold has been found to be an important tool in the drug discovery process through its relevant pharmacological activities. Chromone carboxamide derivatives synthesized within our group have shown noteworthy results as inhibitors of monoamino oxidase-B and as ligands for adesonine receptors. Specifically, chromone-2-carboxamide has been shown to be a privileged structure for the development of selective A_3 adenosine receptor ligands. In this work two novel substituted 4-oxo-*N*-phenyl-*4H*-chromene-2-carboxamides have been synthesized and a complete structural characterization was performed using Fourier Transform Infrared Spectroscopy, one-dimensional and two-dimensional Nuclear Magnetic Resonance techniques and Mass Spectroscopy. Finally, the molecular and supramolecular structures were determined by X-ray analysis. The X-ray crystallographic analysis describes in detail the molecular conformation and supramolecular structure of a hemihydrate of 7-methoxy-4-oxo-N-phenyl-4H-chromene-2-carboxamide.

The data acquired from this study add valuable information to our chromone database. The unambiguous identification of the compounds will support the understanding of the structure–activity relationships of these compounds.

1. Introduction

Chromones have a 4*H*-1-benzopyran-4-one nucleus and are an important class of oxygenated heterocycles. They have emerged as a fruitful tool for the discovery of novel biologically active compounds and so they have been engaged in diverse medicinal chemistry programs [1–5].

The chromone moiety is synthetically versatile and represents a useful building block, the Claisen condensation, Baker–Venkatamaran rearrangement and Vilsmeier–Haack reaction being the most recognized methods used for chromone core construction. [6,7] This type of compounds have also a great significance in organic synthesis due to their reactivity towards nucleophiles that allow the synthesis of a wide variety of heterocycles.

Recently our research group reported chromone derivatives as suitable lead compounds for the development of novel monoamino oxidase B (MAO-B) inhibitors [3,8–10] and adenosine receptor ligands [4,11–14]. The results obtained so far reveal the importance of chromone-2-carboxamide as a template for the development of selective A_3 adenosine receptor ligands (A_3AR) [13]. The A_3 adenosine receptors are under scrutiny in relation to potential therapeutic approaches for treating inflammatory and neurodegenerative diseases, asthma and cardiac ischaemia [15]. Therefore, in our project new chromone-2-carboxamide derivatives **4** and **5** were synthesized following the procedure presented in Scheme 1, in order to carry out a structure–activity (A_3AR) relationship study.

This work presents the synthesis of two novel chromone carboxamide derivatives (Scheme 1), their identification by Fourier Transform Infrared Spectroscopy (FTIR), 1D and 2D Nuclear Magnetic Resonance (NMR) techniques and Electron Impact Mass Spectrometry (EIMS) as well as a detailed X-ray structure charac-

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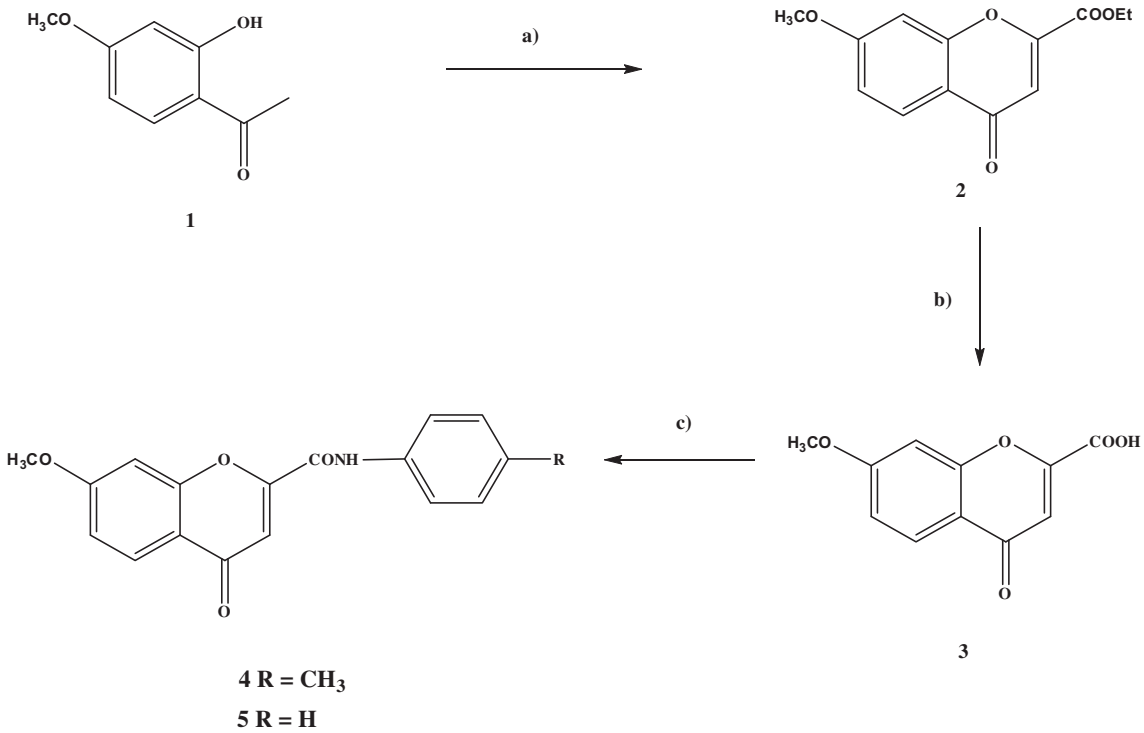


Scheme 1. Synthesis of 7-methoxy-4-oxo-*N*-phenyl-*4H*-chromene-2-carboxamides Reagents and conditions: (a) $C_2H_5OCOCOOC_2H_5$, EtONa/EtOH, HCl, EtOH, (b) $NaHCO_3$ and (c) $POCl_3$, NH_2-Ph-R.

terization. The characterization of those compounds is of the utmost importance as it allows data extrapolation, speeding up the structure–activity studies of the medicinal chemistry program.

2. Experimental

2.1. Materials

Chemicals were purchased from Sigma–Aldrich Química S.A. (Sintra, Portugal). All the solvents were *pro analysis* grade and used without additional purification.

Thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F254 (Merck) with layer thickness of 0.2 mm. For analytical control the following systems were used: ethyl acetate/dichloromethane and dichloromethane/methanol in diverse proportions. The spots were visualized under UV detection (254 and 366 nm). Flash chromatography was performed using silica gel 60, 0.040–0.063 mm (Merck, Lisbon, Portugal).

2.2. Synthesis

2.2.1. Synthesis of ethyl 7-methoxy-4-oxo-4H-chromene-2-carboxylate (*2*)

To a solution of 2′-hydroxy-4′-methoxyacetophenone (12 mmol) in sodium ethoxide (21% in ethanol, 10 mL) diethyloxalate (28 mmol, 5 mL) was added. The reaction was refluxed for 1 h. After reaction, concentrated HCl was added dropwise until the reaction was acidic and a white precipitate was formed. The product was filtered and the yellow solution concentrated. The slurry obtained was extracted with CH_2Cl_2 (3 × 50 mL), washed with water, dried over Na_2SO_4 and evaporated [16]. The light yellow solid was filtered and purified by recrystallization (CH_2Cl_2/n-hexane); Yield = 72%.

^{1}H NMR: δ = 1.35 (3H, *t*, *J* = 6.8, $COOCH_2\underline{CH_3}$); 3.93 (3H, *s*, OCH_3); 4.40 (2H, *d*, *J* = 7.2, $COO\underline{CH_2}CH_3$) 6.89 (1H, *s*, H(3)); 7.11 (1H, *dd*, *J* = 9.2; 2.4, H(6)); 7.23 (1H, *d*, *J* = 2.4, H(8)); 7.95 (1H, *d*, *J* = 9.2, H(5)).

^{13}C NMR: δ = 14.4 $COOCH_2\underline{C}H_3$; 56.8 OCH_3; 63.1 $COO\underline{C}H_2CH_3$; 101.5 C(8); 114.4 C(6); 116.2 C(3); 118.1 C(4a); 126.8 C(5); 157.8 C(8a); 160.5 C(2); 161.4 $\underline{C}OOCH_2CH_3$); 165.1 C(7); 176.8 C(4).

EIMS (m/z): 248 ($M^{+\cdot}$, 100), 220 (32), 203 (10), 192 (49), 177 (25), 148 (16), 119 (27).

2.2.2. Synthesis of 7-methoxy-4-oxo-4H-chromene-2-carboxylic acid (*3*)

The chromone (**2**) was dissolved in a solution of $NaHCO_3$ (5 mL, 20% in H_2O) and heated at 80 °C for 3 h. After cooling, the solution was acidified (concentrated HCl) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water, dried over Na_2SO_4, and evaporated [17]. The product was filtered and purified by recrystallization (CH_2Cl_2/n-hexane); Yield = 62%.

^{1}H NMR: δ = 3.93 (3H, *s*, OCH_3); 6.86 (1H, *s*, H(3)); 7.11 (1H, *dd*, *J* = 9.2; 2.4, H(6)); 7.22 (1H, *d*, *J* = 2.4, H(8)); 7.95 (1H, *d*, *J* = 9.2, H(5)).

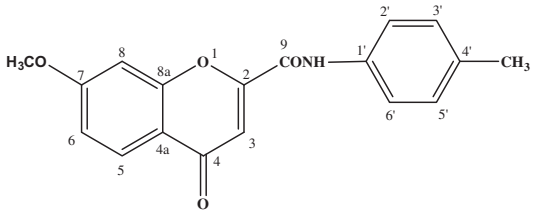
^{13}C NMR: δ = 56.7 OCH_3; 101.5 C(8); 114.1 C(6); 116.0 C(3); 118.1 C(4a); 126.8 C(5); 153.4 C(8a); 157.9 C(2); 161.9 COOH; 165.0 C(7); 177.1 C(4).

EIMS (m/z): 221 (13), 220 ($M^{+\cdot}$, 99), 192 (62), 191 (11), 177 (64), 176 (10), 149 (10), 122 (22), 107 (16), 63 (14).

2.2.3. Synthesis of 7-methoxy-4-oxo-N-p-tolyl-4H-chromene-2-carboxamide (*4*) and 7-methoxy-4-oxo-N-phenyl-4H-chromene-2-carboxamide (*5*)

To a solution of chromone-2-carboxylic acid (1.1 mmol) in DMF (1.5 mL), phosphoryl trichloride ($POCl_3$) (1 mmol) was added. The mixture was stirred at room temperature for 30 min, with the formation *in situ* of the corresponding acyl chloride. Then, the corresponding aromatic amine (1.1 mmol) was added. The system was heated 160 °C for 5 min in a microwave apparatus. After, the mixtures were poured in a beaker and water was added (20 mL).

Table 1
^{1}H and ^{13}C chemical shifts and HMBC correlations for compound **4**.

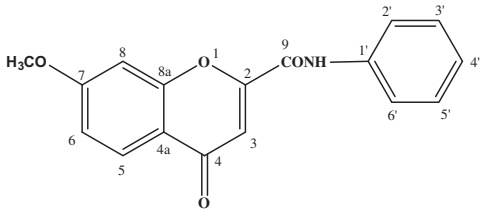


Compound 4

	^{1}H[a]	^{13}C	HMBC[b]
2	–	157.47	–
3	6.89(s)	111.05	C4a, C5, C9, C2, C4
4	–	176.37	–
4a	–	117.56	–
5	7.98(d, 8.8)	126.37	C8, C6, C8a, C7, C4
6	7.13(dd. RQ 8.8, 2.4)	115.40	C8, C4a, C8a, C7
7	–	164.29	–
8	7.30(d, 2.4)	101.09	C6, C4a, C8a, C7
8a	–	157.01	–
9	–	155.38	–
1′	–	134.98	–
2′	7.68(d, 8.4)	121.02	C3′, C5′, C4′, C1′, C6′
3′	7.22(d, 8.4)	129.20	C2′, C6′, C4′, C5′
4′	–	134.07	–
5′	7.22(d, 8.4)	129.20	C2′, C6′, C4′, C5′, C3′
6′	7.68(d, 8.4)	121.02	C3′, C5′, C4′, C1′, C2′
OCH_3	3.95(s)	56.14	C7, C8
NH	10.60(s)	–	C2, C2′,C6′
CH_3	2,31(s)	20.52	C2′, C6′, C3′, C5′, C4′

[a] Chemical shifts δ in ppm (multiplicity, J in Hz).
[b] Carbons coupled to the corresponding H atom.

Table 2
^{1}H and ^{13}C chemical shifts and HMBC correlations for compound **5**.



Compound 5

	^{1}H[a]	^{13}C	HMBC[b]
2	–	158.16	–
3	6.89(s)	111.64	C4a, C5, C9, C2, C4
4	–	176.84	–
4a	–	118.05	–
5	7.98(d, 8.8)	126.85	C8, C6, C8a, C7, C4
6	7.13(dd, RQ 8.8, 2.4)	115.89	C8, C4a, C8a, C7
7	–	164.78	–
8	7.30(d, 2.4)	101.57	C6, C4a, C8a, C7
8a	–	157.49	–
9	–	155.76	–
1′	–	137.99	–
2′	7.80(dd, 8.6, 1.1)	121.57	C3′, C5′, C4′, C1′, C6′
3′	7.43(dd, 8.6, 7.6)	129.29	C2′, C6′, C4′, C5′, C1′
4′	7.21(m)	125.40	C2′, C6′, C3′, C5′
5′	7.43(dd, 8.6, 7.6)	129.29	C2′, C6′, C4′, C5′, C3′
6′	7.80(dd, 8.6, 1.1)	121.57	C3′, C5′, C4′, C1′, C2′
OCH_3	3.95(s)	56.52	C7, C8
NH	10.66(s)	–	C2, C2′,C6′
CH_3	–	–	–

[a] Chemical shifts δ in ppm (multiplicity, J in Hz).
[b] Carbons coupled to the corresponding H atom.

The formed solids were filtered and purified by recrystallization [9,18].

Table 3
Details of data acquisition, structural solution and refinement for compound (**5**).

Crystal data	Compound **5**
Chemical formula	$2(C_{17}H_{12}NO_4)\cdot H_2O$
M_r	304.29
Crystal system, space group	Monoclinic, $C2/c$
Temperature (K)	100
a, b, c (Å)	13.1865 (10), 8.173 (6), 26.602 (19)
β (°)	96.644 (12)
V (Å^3)	2848 (3)
Z	8
$F(000)$	1272
Radiation type	Mo Kα
μ (mm^{-1})	0.10
Crystal shape	Plate
Colour	Colourless
Crystal size (mm)	0.21 × 0.15 × 0.05
Data collection	
Diffractometer	Rigaku Saturn724+(2 × 2 bin mode) diffractometer
Radiation source	Rotating anode
Monochromator	Confocal
Absorption correction	Multi-scan *CrystalClear*-SM Expert 2.0 r13 (Rigaku, 2011)
T_{min}, T_{max}	0.979, 0.995
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	13494, 3230, 3011
R_{int}	0.107
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.649
Range of h, k, l	$h = -13 \rightarrow 17$, $k = -10 \rightarrow 10$, $l = -33 \rightarrow 34$
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.094, 0.266, 1.19
No. of reflections	3230
No. of parameters	205
No. of restraints	0
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1329P)^2 + 5.9064P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e·Å^{-3})	0.58, −0.58

7-Methoxy-4-oxo-*N*-*p*-tolyl-*4H*-chromene-2-carboxamide (4): Yield 78%; ^{1}H and ^{13}C NMR data (Table 1).

EIMS (m/z): 295 (49), 294 ($M^{+\cdot}$, 99), 266 (11), 172 (13), 151 (13), 119 (56), 118(11).

7-Methoxy-4-oxo-*N*-phenyl-*4H*-chromene-2-carboxamide (5): Yield 74%; ^{1}H and ^{13}C NMR data (Table 2).

EIMS (m/z): 310 (15), 309 (74), 308 ($M^{+\cdot}$, 99), 292 (12), 280 (10), 186 (14), 151 (13), 131 (17), 119 (59), 107 (12), 106 (33), 77 (15).

2.3. Measurements and characterization

2.3.1. Apparatus

Microwave-assisted synthesis was performed in a Biotage® Initiator Microwave Synthesizer.

Infrared absorption spectra were recorded on a Bruker Tensor 27 FTIR using a single reflection ATR accessory with a germanium crystal. Approximately 1 mg from each sample was mixed with 100 mg potassium bromide (KBr) powder. After mixing, the powder was pressed into a ½-inch diameter pellet and compacted.

^{1}H and ^{13}C NMR spectra of samples (approximately 10% solutions in DMSO-d_6), were recorded, at room temperature in 5 mm outside diameter (o.d.) tubes. Tetramethylsilane (TMS) was used as internal standard, chemical shifts are expressed in ppm (δ) and J in Hz. One-dimensional ^{13}C NMR was recorded on a Bruker AMX 400 NMR spectrometer operating at 125.77 MHz, typically with a 30° pulse flip angle, a pulse repetition time of 4.8 s, and a spectral width of 31 250 Hz with 32 K data points. For the DEPT se-

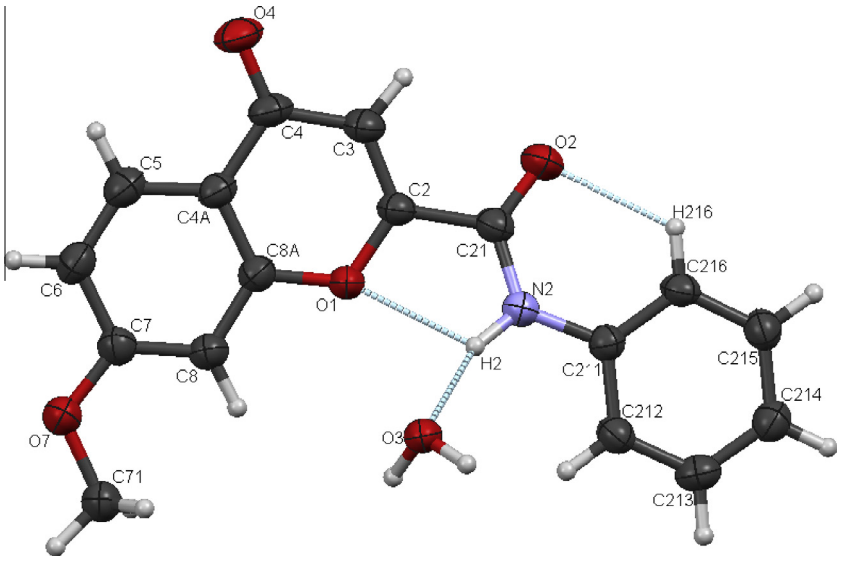


Fig. 1. A view of the asymmetric unit of **5** with the atom numbering scheme. Displacement ellipsoids are drawn at the 70% probability level. The dashed bonds show the intramolecular hydrogen bonds and the hydrogen bond between N2 and the water molecule.

Table 4
Selected hydrogen-bond and short contact parameters for **5**.

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
N2—H2···O1	1.00	2.21	2.669 (3)	106
N2—H2···O3	1.00	1.99	2.945 (3)	160
O3—H3A···O4^{i}	0.98	1.80	2.771 (3)	173
C216—H216···O2	0.95	2.26	2.873 (4)	121
C71—H71A···O2^{ii}	0.98	2.38	3.345 (4)	170
C213—H213···O2^{i}	0.95	2.55	3.420 (4)	153

Symmetry code(s): (i) $x, y+1, z$; (ii) $-x+1/2, y+1/2, -z+1/2$.

quence, the width of the 90° pulse for ^{13}C was 4 μs, and that of the 90° pulse for ^{1}H was 9.5 μs; the delay $2J_{C,H}^{-1}$ was set to 3.5 ms. ^{1}H-detected, one-bond HMQC spectra were recorded on a Bruker AMX 500 spectrometer using pulse sequence that allowed gradient selection (Bruker programs INV4GS and INVGSLPLRND). Spectra were collected in the t_1 domain in 256 experiments with 2 K data points and spectral widths of 5050 and 27 669 Hz in the F_2 (^{1}H) and F_1 (^{13}C) dimensions, respectively. The relaxation delay D_1 was set to 2 s. The data were processed using sine-bell weighting functions in both dimensions.

Electron impact mass spectra (EIMS) were carried out on a VG AutoSpec Fison, Ipswich, United Kingdom) instrument; the data are reported as *m*/*z* (percentage of relative intensity of the most important fragments).

2.3.2. Single crystal X-ray data collection, structure solution and refinement

X-ray quality crystals of 7-methoxy-4-oxo-*N*-phenyl-*4H*-chromene-2-carboxamide, **5,** were grown from an aqueous methanolic solution (1%) at room temperature and by slow isothermal evaporation and crystallised as a hemihydrate. Crystallographic data were collected on a Rigaku Saturn724+, AFC12 Kappa 3 circle diffractometer. The structure was solved using the following computer programs *SHELXS* [19], *OSCAIL* [20], *SHELXS97* [19], *PLATON* [21], *MERCURY* [22]. Detailed crystal data and structural refinement parameters are summarized in Table 3.

The water oxygen, O3, sits on the centre of symmetry at (0,*y*,1/4). H atoms were treated as riding atoms with C---H(aromatic), 0.95 Å, with U_{iso} = 1.2*U*eq(C). C---H(methyl) 0.98Å with U_{iso} = 1.5-*U*eq(C). The H attached to amido N atom and those attached to the water oxygen were allowed to ride at positions derived from a difference map and their positions and those of the methyl H atoms were checked on a final difference Fourier map.

The complete set of structural parameters in CIF format is available as an Electronic Supplementary Publication from the Cambridge Crystallographic Data Centre (CCDC 939914).

3. Results and discussion

3.1. Chemistry

Chromone carboxamides (**4** and **5**) were synthesized by the three-step synthetic strategy described in Scheme 1. The chromone (**2**) was obtained by a Claisen condensation using 2′-hydroxy-4′-methoxyacetophenone (**1**) and diethyloxalate in the presence of sodium ethoxide. The 1,3-dioxophenoxy intermediate formed in the reaction was cyclized *in situ* under acidic conditions. The subsequent hydrolysis of the ethyl chromone-2-carboxylate (**2**), under base catalysis, gave the intended chromone carboxylic acid (**3)** that was used as starting material for the synthesis of chromones **4** and **5**. The microwave assisted amidation reactions, previously described by our research group [18], were carried out by a condensation reaction, in the presence of $POCl_3$, of the chromone carboxylic acid and the corresponding aromatic amine via formation *in situ* of an acyl chloride intermediate.

3.2. FTIR functional characterization

From the infrared spectra of the 2-carboxamide chromone derivatives a characteristic band correspondent to the N—H *str* (*stretching*) at 3356 cm^{-1} and 2359–2341 cm^{-1} was observed for compounds **4** and **5**, respectively. In addition, a N—H *bending* vibration representative of the amide group is also detected (1645 cm^{-1} and 1647 cm^{-1} for compounds **4** and **5,** respectively). Finally, the carbonyl group is confirmed by a C=O *str* band showing at 1682 cm^{-1} for 2-carboxamide **4** and 1702 cm^{-1} for 2-carboxamide **5**. The C—N bond is similarly present in the spectra with vibrations of 1157 cm^{-1} and 1016 cm^{-1} for compounds **4** and **5** respectively.

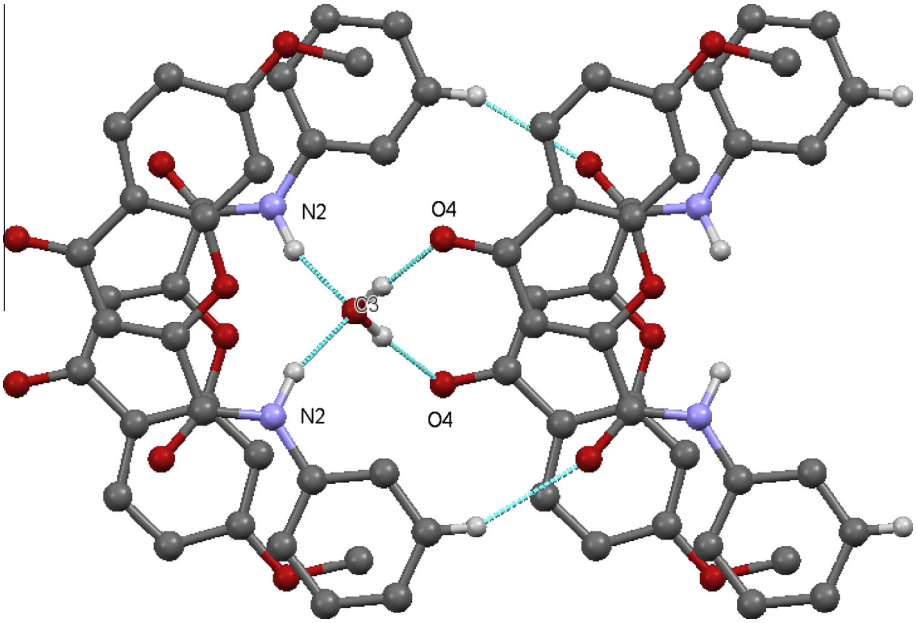


Fig. 2. Part of the crystal structure of **5** showing the hydrogen bonding around the water molecule viewed down the *a*-axis, 2a. The π…π stacking of the pyran rings is also shown. Hydrogen bonds are indicated by blue dashed lines. Hydrogen atoms not involved in the hydrogen bonding have been omitted for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

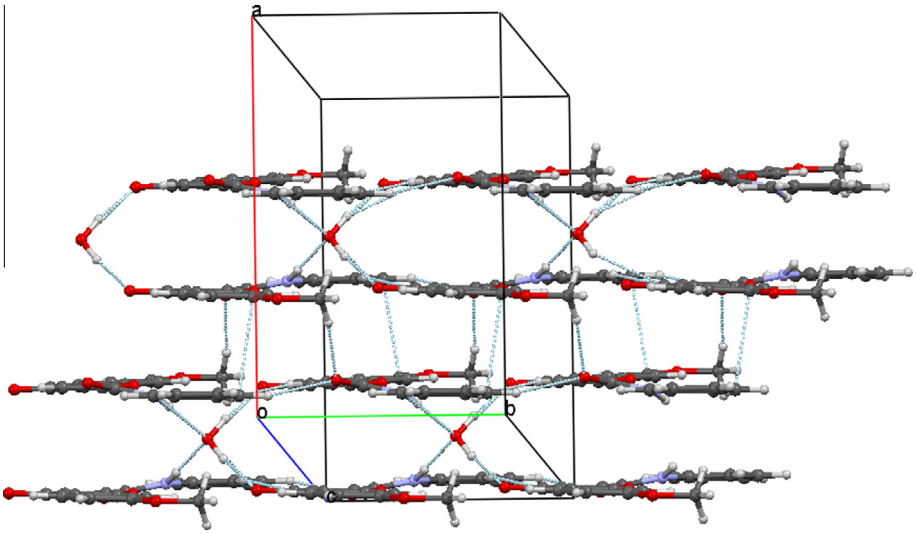


Fig. 3. Part of the crystal structure of **5** showing the chain formed by molecules linked by the water molecules running parallel to the *b*-axis. Adjacent chains are linked by a weak C—H(methyl)…O hydrogen bond. Hydrogen bonds are indicated by blue dashed lines. Hydrogen atoms not involved in the hydrogen bonding have been omitted for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The FTIR data confirmed the formation of the amide functional group generated in the amidation reaction of chromone carboxylic acid (**3**).

3.3. NMR characterization

^{1}H and ^{13}C NMR data are shown in Tables 1 and 2. Unambiguous assignments for all NMR signals were attained through the combined information of one-dimensional (1D) and homonuclear and heteronuclear two dimensional (2D) NMR techniques experiments, namely COSY, HSQC and HMBC. The protons H-3, H-5, H-6 and H-8 of chromone carboxamide (**4**) (Scheme 1) were easily assigned by their chemical shifts (δ), multiplicity and coupling constants and COSY experiments. Furthermore, the direct correlation (HSQC) between the protons and their direct attached carbons led to a straightforward identification of C-3, C-5, C-6 and C-8. Based on the same assumptions, the protons of methoxyl and methyl groups were assigned at δ of 3.95 and 2.31 ppm, respectively. The corresponding carbons were allocated at δ = 56.14 and at 20.52 ppm, respectively. These values were also confirmed by HSQC data. A long distance correlation (HMBC) between the methoxyl protons and the quaternary carbon at δ = 164.29 ppm was observed, which was assigned as C-7. The C4a and C8a quaternary carbons were assigned based on the HMBC correlations depicted in Table 1. The quaternary carbon at δ = 134.07 ppm was assigned as C-4′, essentially based on its long range interaction with the CH_3 protons.

The unequivocal assignment of C-1′ at 134.98 ppm was also performed by HMBC. The long range correlation between H-3 and the carbon at 155.38 ppm led to its identification as C-9. The two signals at δ = 7.68 and 7.22 ppm present on the ^{1}H NMR were attributed to the exocyclic ring protons H-2′/H6′ and H-3′/H-5′, respectively, in accordance with their multiplicity, integration and the long range interaction (Table 1). The HSQC experiments provide assignment of the carbons: the signal at 121.02 was attributed to the equivalent carbons C-2′/C-6′ and the signal at 129.04 ppm to the carbons C-3′/C-5′.

The structural characterization of chromone carboxamide **5** (Scheme 1) was performed using the same NMR techniques that allow the assignment of the protons and carbons of the chromone carboxamide structure (2, 3, 4, 4a, 5, 6, 7, 8, 8a and 9). The major differences found in the 1D and 2D NMR data of chromones **4** and **5** are in accordance with their structures. In fact, no signal corresponding to the CH_3 function in the ^{1}H NMR spectra of compound **5** was detected. In line with this, a new multiplet appears at δ = 7.13 ppm that was ascribed to H-4′. HMBC correlations allow to assign the quaternary carbon at δ = 137.99 ppm as C-4′. Finally, the analysis of the HSQC led to the conclusion that C-4′ appears at a δ = 125.40 ppm.

3.4. X-ray structural characterization

3.4.1. Molecular dimensions and conformation

Compound **5** crystallized in the monoclinic space group C2/c as a hemihydrate. The crystallization was carried out in methanol. The ORTEP diagram for **5** together with the adopted numbering scheme is shown in Fig. 1. The X-ray structure of **4** has been already published [23] and the data will be only used for comparative discussion purpose. The molecule is made up of two aromatic rings, a chromone ring and a benzyl ring connected by an amide residue. The bond lengths between atoms of the amide residue are within the average values obtained for phenylamides [23].

The configuration of the molecule is thus given by the C—N rotamer of the amide that defines the position of the aromatic rings with respect to one other: the molecule shows an anti-rotamer configuration in which the oxygen atom of the amide is *trans* related with oxygen atom O2 of the chromone ring, allowing for the establishment of an intramolecular hydrogen bond, N2—H2···O1 (geometric parameters given in Table 4), forming a S(5) pseudo-ring [24]. The nitrogen atom N2 also acts as a donor to the oxygen atom O3 of the water molecule linking the crystallization solvent to the chromone. In addition, there is a weak hydrogen bond linking the benzyl ring with the carboxamide O2 atom, C(*ortho*)—H···O2 forming a pseudo S6 ring [24]. Compound **4** also exhibits an intramolecular hydrogen bond between N2 and O1 as well as the C216—H216···O2 weak contact [23].

The dihedral angle between the best planes of the chromone and the benzyl ring for **5** is 3.71(10)° but the clockwise torsions of the aromatic rings around the N2—C211 and C2—C21 axis, for the benzyl and the chromone rings respectively, are significantly higher [the C3—C2—C21—O2 and the C21—N2—C211—C216 torsion angles are of −11.9(4) and 11.5(4)°, respectively] showing that the rings are not co-planar but they lie on nearly parallel planes. Compound **5** is more planar than compound **4**, in which the dihedral angle between mean planes made between the chromone and the benzyl ring atoms is 11.05(5)°.

3.4.2. Supramolecular structure

Considering the type of the donor/acceptor pair as well as the direction of the interaction [21], [26–27], it can be considered that the supramolecular structure of compound **5** is governed by two strong classical O—H…O, N—H…O hydrogen bond interactions and by one weak C—H…O interaction. These dipole-dipole interactions are directional and can vary in strength depending on the type of donor and acceptor involved on the interaction.

The geometric parameters for those interactions are given in Table 4. The N2—H2···O3 (within the selected asymmetric unit) and the N—H at $(-x, y, 1/2 - z)$ act as hydrogen donors to the water molecule at (0, *y*, 1/4) which in turn acts as hydrogen donor via O3—H3···O4 $(x, 1 + y, z)$ and via the water generated by the two-fold axis at $(0, y, 0.1/4)$, on which the water atom sits, to O4 at $(-x, 1 + y, ½ + z)$, Fig. 2. This forms a sandwich type chain structure which runs parallel to the *b*-axis, Fig. 3. Adjacent chains are linked by a weak C—H(methyl) interaction to atom O2 at $(-x + 1/2, y + 1/2, -z + 1/2)$, Fig. 3.

This structure is reinforced by the weak C213—H213···O2 $(x, 1 + y, z)$ interaction. Within this chain the pyran rings of the 2-fold related molecules are π…π stacked above each other with a centroid to centroid distance of 3.872(3)Å, a perpendicular distance between of 3.5074(10)Å and a slippage of 1.640 Å, Fig. 2.

In **4,** which is not hydrated, the molecules are linked into chains by a hydrogen bond between the amino H and the 4-oxo oxygen atom reinforced by weak C—H…O interactions. C—H…π and π…π stacking are also present, [23].

4. Conclusion

The chromone 2-carboxamide derivatives 4 and 5 were obtained in moderate to high yields by either classic or microwave reactions.

The combination of 1D, 2D and EIRS NMR techniques allowed for full NMR ^{1}H and ^{13}C signal assignments. The compounds were also characterized by Infrared spectroscopy and XRD.

The X-ray analysis shows the interplay between intramolecular hydrogen and intermolecular hydrogen bonding in the molecular conformation, factors which may influence drug effectiveness. The data acquired from this study make a valuable addition to our chromone database which will help the unambiguous identification of the compounds in our arsenal of chromone compounds thus providing a better understanding of the structure–activity relationships of these compounds.

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