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Synthesis and characterisation of new 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides as potential adenosine receptor ligands

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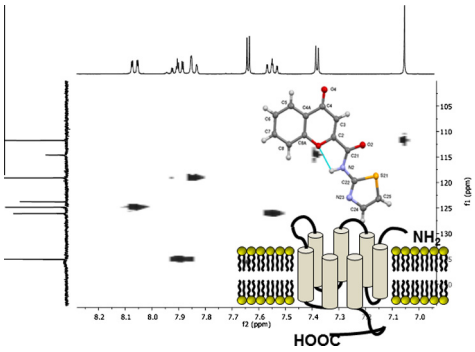
HIGHLIGHTS

- Chromones as potential adenosine receptor ligands.
- Novel 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides were synthesized.
- Compounds were characterised by NMR spectroscopy and X-ray crystallography.

GRAPHICAL ABSTRACT



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ABSTRACT

Chromones are 4*H*-benzopyran-4-one heterocycles that have been thoroughly studied due to their interesting biological activities. Thiazole based compounds have been used in therapeutics as antimicrobial, antiviral and as antifungal agents for a long time but, in the past decades, they have been identified as potent and selective ligands for adenosine receptor. In continuation of our project related to the syntheses of pharmacologically important heterocycles, a new series of chromone–thiazole hybrids have been designed as potential ligands for human adenosine receptors. In this context, new 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides were synthesized from chromone-2-carboxylic acid by two different amidation methods. The development of dissimilar synthetic approaches provided the possibility of working with diverse reaction conditions, namely with conventional heating and/or microwave irradiation. The structure of the compounds has been established on the basis of NMR and MS spectroscopy and X-ray crystallography. Relevant data related to the molecular geometry and conformation of the chromone–thiazole hybrids has been acquired which can be of the utmost importance to understand ligand–receptor binding.

Introduction

Chromones are compounds based on 4*H*-benzopyran-4-one and they form a large class of natural and synthetic heterocyclic compounds that have been studied due to their interesting biological activities [1]. Numerous biological effects (*e.g.*, enzyme inhibition properties, anti-inflammatory, anticancer, antimicrobial and antioxidant activities) [1,2] have been ascribed to this benzo-γ-pyrone nucleus in popular medicine leading to an interest in their therapeutic application. Recently, the chromone scaffold has been

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used for development of new MAO-B inhibitors [3–6] as well as a model ligand structure for adenosine receptors [7,8]. Thiazoles also act as ligands towards a great variety of biological substrates, and this being so they are very interesting functional groups for application in medicinal chemistry. Thiazoles are used in therapeutics as antimicrobial, antiviral and as antifungal agents but, in the past decades, they have been investigated for other pharmacological activities *e.g.*, anti-allergic [9], anti-hypertension [10], pain treatment [11] and for controlling schizophrenia [12] symptoms. A comprehensive review of the biological properties and uses of thiazoles derivatives, before 2005, has been recently published [13,14]. Since that time thiazoles have been assayed as agents for controlling inflammation [15] and they have been, like chromones, identified as potent and selective ligands for adenosine receptors [16]. Thus, in continuation of our project on synthesis of pharmacologically important heterocycles, a new series of chromone–thiazole hybrids have been designed as ligands for human adenosine receptors. This work reports the synthesis and structural characterisation of some chromone–thiazole hybrids that are depicted in Fig. 1.

Experimental

Materials, methods and apparatus

Chromone-2-carboxylic acid, aniline derivatives, phosphorus (V) oxychloride, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), *N,N*-diisopropylethylamine (DIPEA), dimethylformamide (DMF) and its derivatives were purchased from Sigma–Aldrich Química S.A. (Sintra, Portugal). All other reagents and solvents were *pro analysis* grade and were acquired from Merck (Lisbon, Portugal) 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/petroleum ether, ethyl acetate/methanol, chloroform/methanol in several proportions. The spots were visualised under UV detection (254 and 366 nm) and iodine vapour. Flash chromatography Microwave-assisted synthesis was performed in a Biotage® Initiator Microwave Synthesizer.

Synthesis

*Synthesis of 4-oxo-N-(thiazol-2-yl)-4H-chromene-2-carboxamide (**1**)*

To a solution of chromone-2-carboxylic acid (1 g, 5.26 mmol) in DMF (12 mL) at 4 °C was added *N,N*-diethylpropan-2-amine (0.92 ml, 5.26 mmol) and a solution of PyBOP (2.73 mg, 5.26 mmol) in CH_2Cl_2 (12 mL). The mixture was kept in an ice bath and stirred for half hour. After this period thiazol-2-amine (526 mg, 5.26 mmol) was added and the mixture was allowed to then warm up to room temperature. The reaction was kept with stirring by 4 h. The solution was diluted with water and the formed precipitate was filtered and washed with water and MeOH. 4-Oxo-*N*-(thiazol-2-yl)-4*H*-chromene-2-carboxamide was obtained as a white powder (Yield: 55%). **^{1}H NMR (DMSO):** δ = 7.05 (1H, *s*, H(3)), 7.38 (1H, *d*, *J* = 3.7 Hz, H(3′)), 7.55 (1H, *ddd*, *J* = 8.1, 7.0, 1.2 Hz, H(6)), 7.64 (1H, *d*, *J* = 3.7 Hz, H(4′)), 7.84 (1H, *dd*, *J* = 8.5, 0.8 Hz, H(8)), 7.90 (1H, *ddd*, *J* = 8.6, 7.0, 1.7 Hz, H(7)), 8.06 (1H, *dd*, *J* = 8.0, 1.3 Hz, H(5)), 13.32 (1H, *bs*, NH). **^{13}C NMR (DMSO):** δ = 111.8 (C3), 114.6 (C3′), 119.1 (C8), 123.8 (C4a), 124.9 (C5), 126.1 (C6), 135.1 (C7, C4′), 155.3 (C2, C8a, CONH), 159.5 (C1′) 177.4 (C4). **MS/EI *m/z*:** 272.1 ($M^{+\cdot}$, 58), 244 (18), 216 (13), 173 (49), 145 (30), 89 (100).

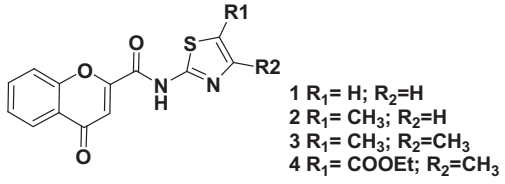


Fig. 1. Chemical structure of the 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides.

*Synthesis of N-(5-methylthiazol-2-yl)-4-oxo-4H-chromene-2-carboxamide (**2**)*

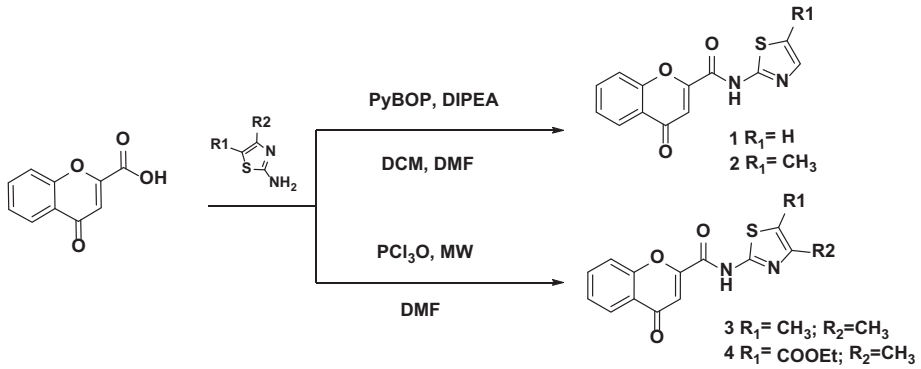
To a solution of the chromone-2-carboxylic acid (1 g, 5.26 mm) in DMF (12 mL) at 4 °C was added a solution of PyBOP (2.73 mg, 5.26 mmol) in CH_2Cl_2 (12 mL). The mixture was kept in an ice bath and stirred for half hour. After this period 5-methylthiazol-2-amine (599 mg, 5.26 mmol) was added and the mixture was allowed to warm up to room temperature. The reaction was kept with stirring by 4 h. The solution was diluted with water and the formed precipitate formed was filtered and washed with water and MeOH. *N*-(5-methylthiazol-2-yl)-4-oxo-4*H*-chromene-2-carboxamide was obtained as a white powder (Yield: 48%). **^{1}H NMR ($CDCl_3$):** δ = 2.39 (3H, *d*, *J* = 1.1 Hz, CH_3), 7.04 (1H, *s*, H(3)), 7.32 (1H, *q*, *J* = 1.1 Hz, H(4′)), 7.56 (1H, *ddd*, *J* = 8.1, 7.2, 1.1 Hz, H(6)), 7.83 (1H, *d*, *J* = 7.9 Hz, H(8)), 7.91 (1H, *ddd*, *J* = 8.6, 7.1, 1.7 Hz, H(7)), 8.07 (1H, *dd*, *J* = 8.0, 1.4 Hz, H(5)), 13.18 (1H, *bs*, NH). **^{13}C NMR ($CDCl_3$):** δ = 11.4 (CH_3), 111.7 (C3), 119.1 (C8, C3′), 123.8 (C4a), 124.9 (C5), 126.1 (C6), 135.1 (C7, C4′), 155.4 (C1′, C2, C8a, CONH), 177.4 (C4). **MS/EI *m/z*:** 288 ($M^{+\cdot}$, 53), 286 (86), 258 (72), 230 (62), 230 (62), 173 (95), 145 (82), 68 (100).

*Synthesis of N-(4,5-dimethylthiazol-2-yl)-4-oxo-4H-chromene-2-carboxamide (**3**)*

To a solution of chromone-2-carboxylic acid (0.5 g, 2.63 mmol) in DMF (4 mL), $POCl_3$ (241 μl, 2.6 mmol) was added. The mixture was stirred at room temperature for 30 min, with *in situ* formation of the corresponding acyl chloride. Then *N,N*-diethylpropan-2-amine (459 μl, 2.63 mmol) and 4,5-dimethylthiazol-2-amine hydrochloride (433 mg, 2.63 mmol) were added. The system was heated 120 °C for 5 min in a microwave apparatus. After, the mixture was diluted with dichloromethane (20 mL), washed with H_2O (2 × 10 mL) and with saturated $NaHCO_3$ solution (2 × 10 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (50% AcOEt/n-hexane). *N*-(4,5-dimethylthiazol-2-yl)-4-oxo-4*H*-chromene-2-carboxamide as a yellow powder (Yield 40%). **^{1}H NMR ($CDCl_3$):** δ = 2.26 (3H, *s*, CH_3). 2.35 (3H, *s*, CH_3), 7.27 (1H, *s*, H(3)), 7.44 (1H, *d*, *J* = 8.4 Hz, H(8)), 7.49 (1H, *ddd*, *J* = 8.0, 7.2, 1.0 Hz, H(6)), 7.76 (1H, *ddd*, *J* = 8.7, 7.2, 1.7 Hz, H(7)), 8.23 (1H, *dd*, *J* = 8.0, 1.5 Hz, H(5)). **^{13}C NMR ($CDCl_3$):** δ = 11.0 (CH_3), 14.3 (CH_3), 113.3 (C3), 118.0 (C8), 122.0 (C3′), 124.4 (C4a), 126.2 (C5), 126.3 (C6), 134.9 (C7), 142.0 (C4′), 153.3 (C8a), 156.2 (C1′), 157.0 (C2, CONH) , 177.6 (C4). **MS/EI *m/z*:** 300 ($M^{+\cdot}$, 100), 272 (17), 199 (27), 163 (31), 139 (76), 101 (41).

*Synthesis of ethyl 4-methyl-2-(4-oxo-4H-chromene-2-carboxamido)-thiazol-5-carboxylate (**4**)*

To a solution of chromone-2-carboxylic acid (0.5 g, 2.6 mmol) in DMF (4 mL), $POCl_3$ (241 μl, 2.6 mmol) was added. The mixture was stirred at room temperature for 30 min, with *in situ* formation the corresponding acyl chloride. Then ethyl 2-amino-4-methylthiazol-5-carboxylate (490 mg, 2.6 mmol) was added. The system was heated 120 °C for 5 min in a microwave apparatus. After, the mixture was diluted with dichloromethane (20 mL), washed with H_2O



Scheme 1. Synthesis of 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides.

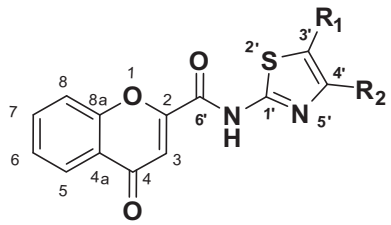


Fig. 2. Numbering of 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamide core.

(2 × 10 mL) and with saturated $NaHCO_3$ solution (2 × 10 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by crystallization in methanol/n-hexane. The ethyl 4-methyl-2-(4-oxo-4*H*-chromene-2-carboxamido)thiazole-5-carboxylate was obtained as a yellow powder (Yield 43%). **^{1}H NMR ($CDCl_3$):** 1.39 (3H, *t*, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 2.70 (3H, *s*, $\underline{CH_3}$), 4.35 (2H, *q*, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 7.32 (1H, *s*, H(3)), 7.58–7.46 (2H, m, H(8), H(6)), 7.80 (1H, *ddd*, *J* = 8.7, 7.2, 1.7 Hz, H(7)), 8.25 (1H, *dd*, *J* = 8.0, 1.6 Hz, H(5)), 10.22 (1H, *bs*, NH). **^{13}C NMR ($CDCl_3$):** δ = 14.3 ($CH_2\underline{CH_3}$), 17.0 ($\underline{CH_3}$), 61.2 ($\underline{CH_2}CH_3$), 113.9 (C3), 117.7 (C3′), 118.0 (C8), 124.4 (C4a), 126.3 (C5), 126.6 (C6), 135.2 (C7), 152.2 (C4′), 155.1 (C8a), 156.2 (C1′), 157.3 (C2), 157.9 (CONH), 162.2 ($\underline{C}OOCH_2CH_3$), 177.4 (C4). **MS/EI *m/z*:** 357.9 ($M^{+\cdot}$, 100), 173 (98), 150 (49), 89 (96).

Measurements and characterisation

Spectroscopy

The IR spectra were acquired in a Nicolet 6700 FT-IR spectrometer using potassium bromide disk. NMR was recorded on a Bruker AMX 400 NMR spectrometer. NMR spectra 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. Electron impact mass spectra (EIMS) were carried out on a VG AutoSpec, (Fisons, Ipswich, United Kingdom) instrument; the data are reported as *m*/*z* (percentage of relative intensity of the most important fragments).

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

The crystals for diffractometry of compounds **1**–**3** were grown at room temperature by slow vaporisation of CH_2Cl_2/*n*-hexane (1:1) solutions of the compounds, while **4** was crystallised from a methanol/*n*-hexane (1:1) solution.

Crystallographic data were collected on a Rigaku Saturn724+, AFC12 Kappa 3 circle diffractometer. The structure was solved using the following computer programs: CrystalClear SM Expert 2.0 r13, Rigaku Corporation, Tokyo, Japan, *SHELXS*, *SHELXL* [17], *OSCAIL* [18], *PLATON* [19], *MERCURY* [20], *ShelxLe* [21]. Detailed crystal data and structural refinement parameters are summarised in Table 1 of supplementary information. Compounds **1**, **2** and **4** crystallised in spacegroup P21/c while **3** crystallised in the monoclinic C2/c space group.

Hydrogen atoms were refined as riding atoms with C—H(aromatic), 0.95 Å N—H, 0.88 Å with *U*iso = 1.2*U*eq(C) and C—H(methyl), 0.98 Å, with *U*iso = 1.5*U*eq(C). The H atoms attached to the N_2 atom and the methyl group were checked on a final difference Fourier map.

In **3** the highest difference map peaks are associated with the S atom. These crystals were very thin plates and although the R_{int} value was 0.057 the refinement gave high *R* and weighted *R* values, Table 1 supplementary information, as a result of the measurement a large number of very weak reflections. The crystals for **4** were very small; accordingly, many high angle reflections were weak. This resulted in a data set with a high R_{int} value.

Gaseous phase quantum chemical calculations

Ab initio geometry optimisations for four gas-phase conformers of compound **1** (-*anti* rotamer conformations A1 and A2, as set in Fig. 10, with the nitrogen atoms of the amide and thiazole ring -*trans* related and -*cis* related) were performed using density functional theory. The quantum chemical calculations were performed at the B3LYP exchange correlation functional, which combines the hybrid exchange functional of Becke [22] with the gradient-correlation functional of Lee et al. [23] and the split-valence polarised

Table 1
^{1}H MNR data of the 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides.

Compounds	H3	H5	H6	H7	H8	R1	R2	NH
1	7.05 (*s*)	8.06 (*dd*)	7.55 (*ddd*)	7.90 (*ddd*)	7.84 (*dd*)	7.38 (*d*) H	7.64 (*d*) H	13.32 (*bs*)
2	7.04 (*s*)	8.07 (*dd*)	7.56 (*ddd*)	7.91 (*ddd*)	7.83 (*dd*)	2.39 (*d*) CH_3	7.32 (*q*) H	13.18 (*bs*)
3	7.27 (*s*)	8.23 (*dd*)	7.49 (*ddd*)	7.76 (*ddd*)	7.44 (*dd*)	2.35 (*s*) CH_3	2.26 (*s*) CH_3	–
4	7.32 (*s*)	8.25 (*dd*)	7.58–7.46 (*m*)	7.76 (*ddd*)	7.58–7.46 (*m*)	1.39 (*t*) $COOCH_2\underline{CH_3}$ 4.35 (*q*) $COO\underline{CH_2}CH_3$	2.70 (*s*) CH_3	10.22 (*bs*)

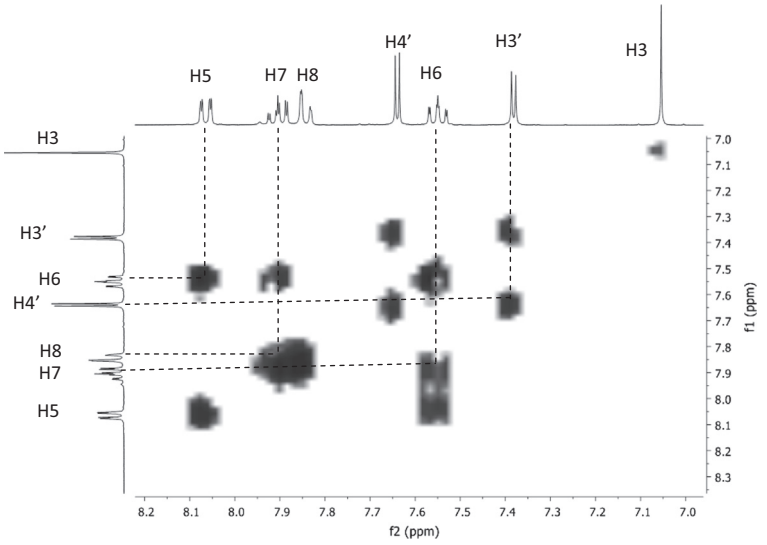


Fig. 3. $^{1}H—^{1}H$ COSY spectrum of compound **1**.

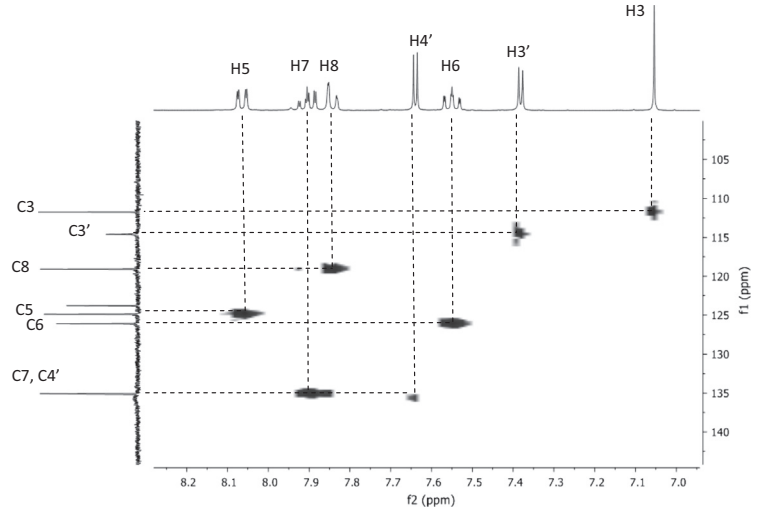


Fig. 4. $^{1}H—^{13}C$ HSQC spectrum of compound **1**.

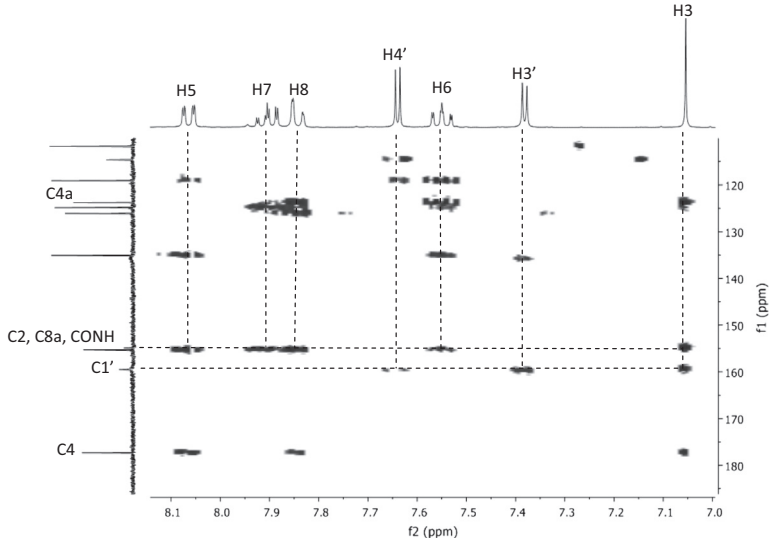


Fig. 5. $^{1}H—^{13}C$ HMBC spectrum of compound **1**.

Table 2
^{13}C MNR data of the 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides.

Compounds	C2	C3	C4	C4a	C5	C6	C7	C8	C8a	C1′	C3′	C4′	R1	R2	CONH
1	155.3	111.8	177.4	123.8	124.9	126.2	135.1	119.1	155.3	159.5	114.7	135.1	–	–	155.3
2	155.4	111.7	177.4	123.8	124.9	126.5	135.1	119.1	155.4	155.4	119.1	135.1	11.4 CH_3	–	155.4
3	157.0	113.3	177.6	124.4	126.2	126.3	134.9	118.0	153.3	156.2	122.0	142.0	11.0 CH_3	14.3 CH_3	157.0
4	157.3	113.9	177.4	124.4	126.3	126.6	135.2	118.0	155.1	156.2	117.7	152.2	14.3 $COOCH_2\underline{C}H_3$ 61.2 $COO\underline{C}H_2CH_3$ 162.2 $\underline{C}OOCH_2CH_3$	17.0 CH_3	157.9

6-311+G(d, p) basis set [24] level of theory. The GaussView 3.0 [25] program was used to get visual animation. At the same theoretical level, analytical frequency calculations were performed to ensure true minima ($N_{img} = 0$). All theoretical calculations were performed with the GAUSSIAN 03 program package [26]. The bonding characteristics of the compounds studied were investigated using natural population (NPA) analysis of Reed and Weinhold [27,28]. Values for the atomic natural total charges have been retrieved.

Results and discussion

Chemistry

4-Oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides were synthesized by two different processes (Scheme 1). In the first method, a one-pot condensation reaction, chromone-2-carboxylic acid is activated by reaction with benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and the *in situ* formed intermediate reacts with the aminothiazole or its derivatives giving rise to the intended chromone. In the second method the chromone carboxamides have been obtained by a condensation reaction that requires the previous activation of the chromone-2-carboxylic with phosphorus oxychloride and subsequent addition of the aminothiazole derivative to the formed acyl chloride in a process assisted by microwave. Moderate yields have been obtained by both methods. However, it must be stressed that PyBOP reactions were more time-consuming and that the coupling reagent is quite expensive.

FTIR analysis

From the infrared spectra of the chromone–thiazole hybrids a characteristic band correspondent to the N—H str (stretching) at 3349–3435 cm^{-1} was observed. The carbonyl group is confirmed by a C=O str band at 1674 cm^{-1} for compounds **1** and **2** and 1683 and 1686 cm^{-1} for compounds **3** and **4,** respectively. In addition, an N—H bending vibration of the amide group is also detected (1651–1637 cm^{-1}) in the infrared spectra of all compounds. The C=O bond of ester function present in compound **4** is observed at 1708 cm^{-1}. The FTIR data confirmed the formation of the amide functional group generated in the amidation reaction of chromone carboxylic acid.

NMR analysis

The structural characterisation of compounds **1**–**4** was achieved from NMR, ESI-MS data, and by a single crystal structure determination. The numbering of chromone carboxamide core used along the analysis is depicted in Fig. 2.

The assignment of the protons of compound **1** was done using 1D and 2D ^{1}H NMR. The protons at position H3 (δ = 7.05 as singlet), H5 (δ = 8.06 as double doublet), H3' (δ = 7.38 as doublet) and the amide proton (δ = 13.32 as broad singlet) were easily assigned by their chemical shifts (δ) and multiplicities (Table 1). The other protons of chromone **1** were assigned by a ^{1}H—^{1}H COSY (COrrelation SpectroscopY) experiment as it clearly indicate correlation with coupled that is determined by cross peaks (correlation peaks). In the present case cross peaks between H5 and H6 (δ = 7.55, *ddd*), H6 and H7 (δ = 7.90, *ddd*), H7 and H8 (δ = 7.84, *dd*) and H3′ and H4′ (δ = 7.55, *d*) where observed (Fig. 3). The assignment of the

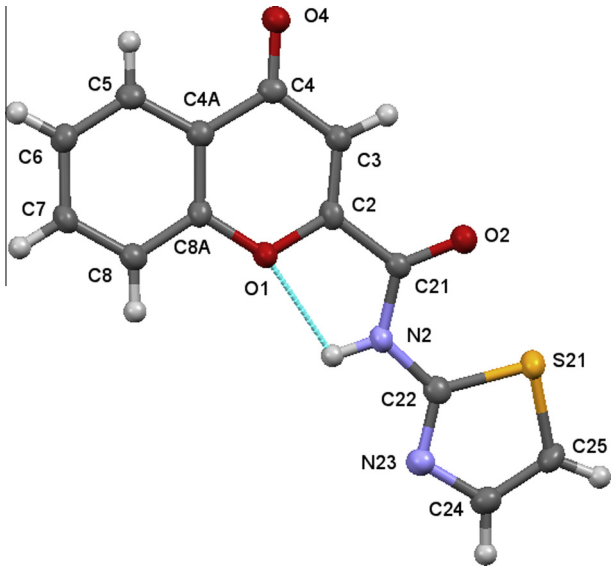


Fig. 6. Thermal ellipsoid (70%) plot of 4-Oxo-*N*-(thiazol-2-yl)-4*H*-chromene-2-carboxamide (**1**).

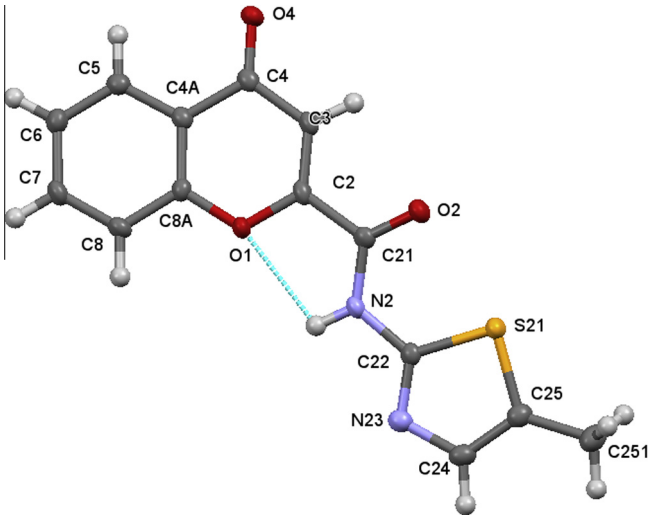


Fig. 7. Thermal ellipsoid (70%) plot of *N*-(5-methylthiazol-2-yl)-4-oxo-4*H*-chromene-2-carboxamide (**2**).

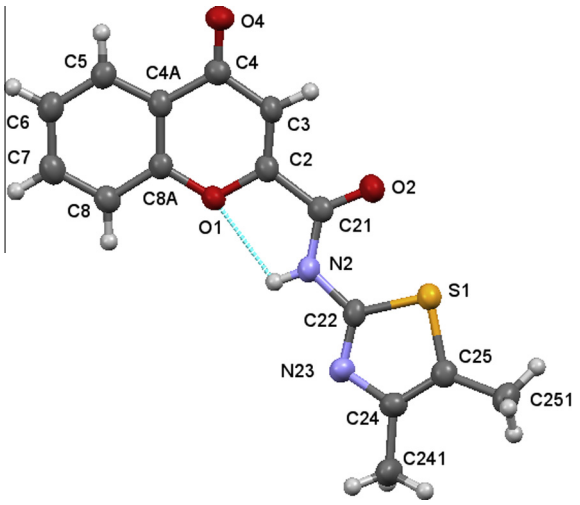


Fig. 8. Thermal ellipsoid (70%) plot of *N*-(4,5-dimethylthiazol-2-yl)-4-oxo-4*H*-chromene-2-carboxamide (**3**).

protons of the other chromones were done by 1D NMR based on a comparison of chemical shifts (δ), multiplicities and the structural similarity with compound **1** (Table 1): The protons of the chromone rings were assigned as H3 (δ = 7.04–7.32), H5 (δ = 7.04–7.32), H6 (δ = 7.46–7.58), H8 (δ = 7.83–7.44) and H7 (δ = 7.90–7.76). The protons of the heterocyclic ring and substituents (R_1 and R_2) were also allocated: the hydrogen at position 4′ of compound **2** was observed to δ = 7.64 ppm and the methyl substituent of compound **2** was observed at δ = 2.39 as a doublet and the methyl substituent of compounds **3** and **4** were observed at δ = 2.26, 2.70 ppm as a singlet. The ethyl group of the compound **4** was detected as a triplet (δ = 1.39) and quadruplet (δ = 4.35). The protons of the amide group were observed as a broad singlet (δ = 13.32–10.22), except the proton of the compound **4** that was not detected in the present experimental conditions. The carbons linked to the protons of compound **1** were assigned by heteronuclear NMR, namely ^{1}H—^{13}C HSQC (*Heteronuclear Single Quantum Coherence)* spectroscopy experiments (Fig. 4). Cross peaks between the following protons and carbons were observed: H3 and C3 (δ = 111.8), H5 and C5 (δ = 124.9), H6 and C6 (δ = 126.2), H7 and C7 (δ = 135.1), H8 and C8 (δ = 119.1), H3′ and C3′ (δ = 114.7) and H4′ and C4′ (δ = 135.1). The quaternary carbons at position C4a (δ = 123.8) and C4 (δ = 177.4) were easily assigned by their chemical shifts. The other quaternary carbons of the chromone were assigned by HMBC (Heteronuclear Multiple Bond Correlation) spectroscopy experiment (Fig. 5) where cross peaks between C1' (δ = 159.5) and H3, H3' and H4' and between C2, C8a, CONH (δ = 155.3) and H3, H5, H6, H7 and H8 were observed. For the other compounds the carbons (*Distortionless Enhancement by Polarisation Transfer*) (Table 2): C2 (δ = 157.3–155.4), C3 (δ = 118.8–111.7), C4 (δ = 177.6–177.4), C4a (δ = 129.4–124.4), C6 (δ = 126.3–126.6), C5 (δ = 126.3–124.9), C7 (δ = 135.2–134.9), C8 (δ = 119.1–118.0), C8a (δ = 155.4–155.1), C1′ (δ = 156.2–155.3), C3′ (δ = 123.8–114.7), C4′ (δ = 152.2–135.1), CONH (δ = 157.9–155.3). The methyl substituents were observed at a high field between δ = 11.0 and δ = 17.0 ppm. The methylenic and carbonyl groups of the ester substituent present in compound **4** were detected at δ = 61.2 and 162.2 ppm, respectively.

Molecular conformation

Thermal ellipsoid diagrams with the adopted atomic labelling are shown in Figs. 6–9. Compound **4** crystallised with two molecules in the asymmetric unit that are identified as molecule #1 and #2.

The conformation around the C—N rotamer for chromone carboxamides can be either *-anti* or *-syn*. The former conformation appears to be more probable in these compounds since it lowers the steric hindrance between the two aromatic rings as compared to the *-syn* rotamer conformation. Structural characterisations made previously in other 4*H*-chromene-2-carboxamides [29] show that, when the amide oxygen atom is *trans* related to the pyran oxygen atom the *-anti* conformation predominates since it permits the establishment of a short intramolecular N—H···O(pyran) contact, as depicted in the A1 representation in Fig. 10. Compounds **1**–**4** follow this pattern as can be seen from Figs. 3–6: they present an hydrogen bond that forms a S(5) ring [29,30]. The values for parameters characterising those intramolecular interactions are given in Table 3. In all compounds the S atom of the thiazole ring is in a *-cis* position with respect to the carbonyl O atom of the amide.

Relevant data for the discussion of molecular geometry and conformation is presented in Table 4; $\theta_{Chr-Thz}$ refers to the dihedral angle between the mean planes of the chromone and thiazole

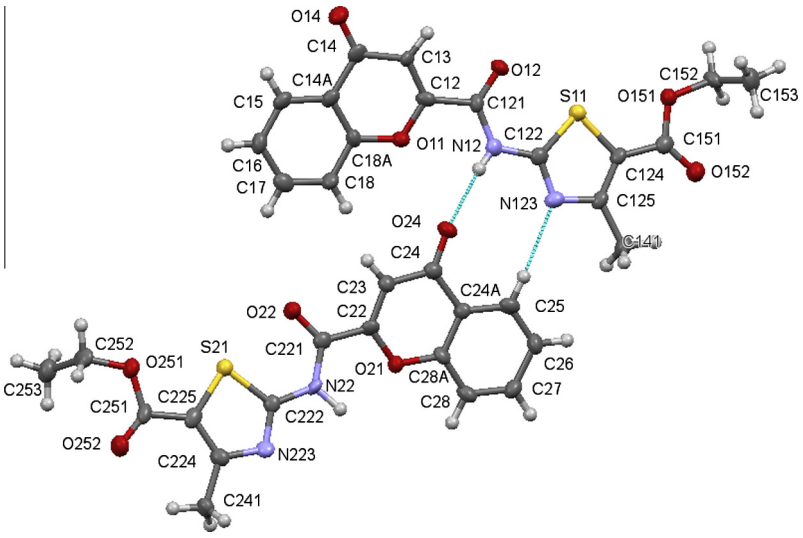


Fig. 9. Thermal ellipsoid (70%) plot of ethyl-4-methyl-2-(4-oxo-4*H*-chromene-2-carboxamido)thiazole-5-carboxylate (**4**).

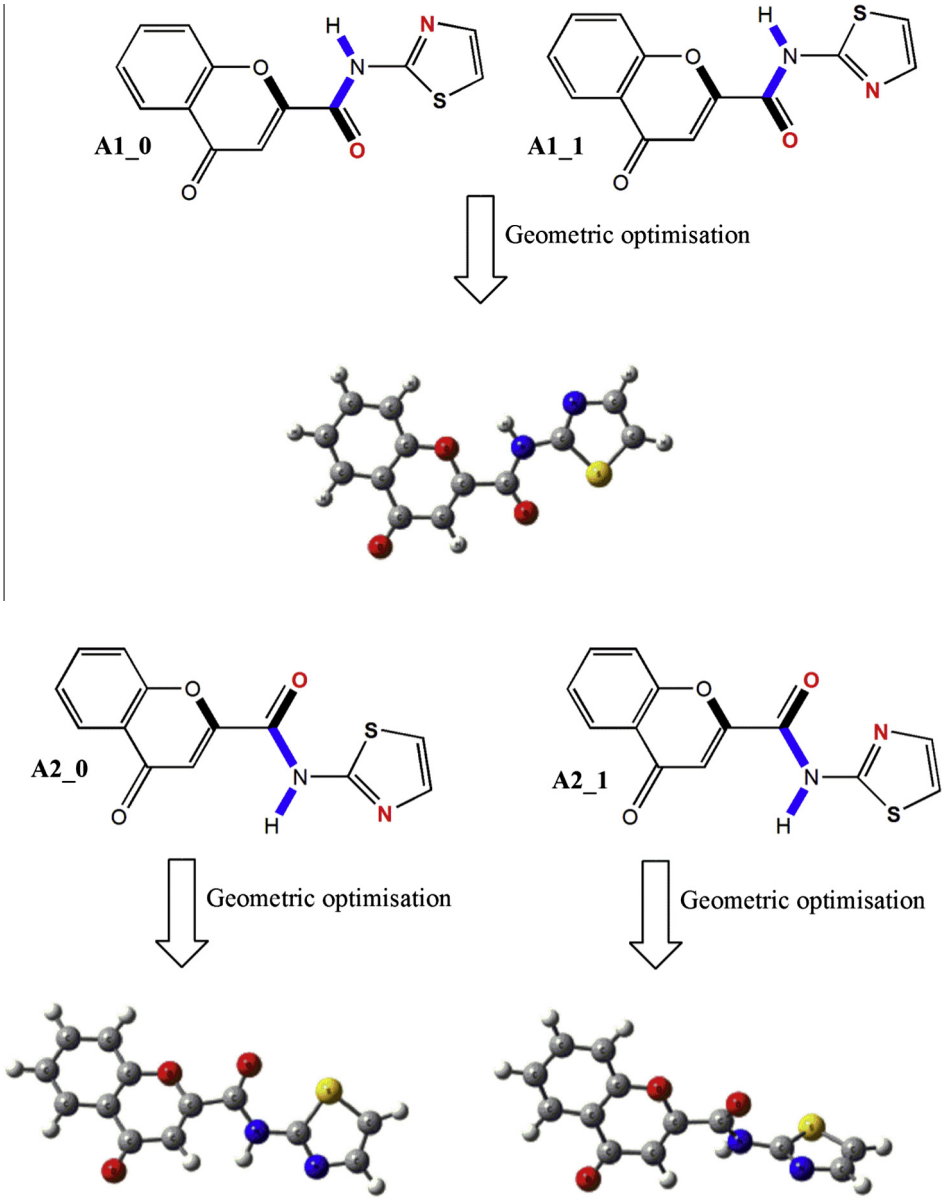


Fig. 10. Possible *-anti* rotamer conformations for the studied compounds. A1 – with the amide oxygen atom *-trans* related with the pyrone oxygen atom; A2 – with the amide oxygen atom *-cis* related with the pyrone oxygen atom; depending on the rotation of the thiazole ring, the oxygen atom of the amide and the nitrogen atom of the thiazole may be *-trans* related (A1_0 and A2_0) or *-cis* related (A1_1 and A2_1). The presented compounds present the A1_0 *-anti* conformation allowing for the establishment of a short intramolecular N—H···O(pyran) contact. Molecular representations are referred to the conformations obtained from quantum chemical gas phase geometry optimisations at the B3LYP/6-311+G(d) level of theory.

rings, $\theta_{Chr-amide}$ to the dihedral angle between the best plane of the chromone and the plane defined by atoms O2—C21—N2 of the amide moiety whereas $\theta_{Thz-amide}$ refers to the dihedral angle between this plane and the best plane of the thiazole ring. Values for d_{C2} and d_{C22} are the deviations of the C2 and C22 atoms from the plane defined by the O2—C21—N2 atoms. The relative conformational position of the heteroaromatic rings with respect to the O2—C21—N2 plane of the amide may be evaluated according to the d_{C2} and d_{C22} values: when the vectors d_{C2} and d_{C22} have the same directions as in **3** and in molecule #1 of compound **4** the molecule has a butterfly conformation as seen in Fig. 11. In **1** and **2** C2 is co-planar with the O2—C21—N2 plane. As said before, dihedral θ angles may also be used as quantitative parameters for evaluation of the overall conformation of those molecules. Since the heteroaromatic rings are practically planar, the dihedral $\theta_{Chr-Thz}$ quantifies the degree of bend and/or twist between them and can be used for evaluation of the distortion of the molecule from planarity when one of the dihedrals, $\theta_{Chr-amide}$ or $\theta_{Thz-amide}$, is relatively small. This is the case for compound **4** where the deviation to planarity for both molecules is mainly due to the torsion of the chromone residue. In **1** and **2** and since both $\theta_{Chr-amide}$ and $\theta_{Thz-anide}$ assume values significantly different from zero, the conformation of the molecule may be better analysed looking at those values. Since C2 is co-planar with the O2—C21—N2 plane in both compounds, they assume a conformation where the chromone rings are predominantly twisted relatively to the amide plane while in **3** the heteroaromatic rings are predominantly bent with respect to that plane giving the butterfly conformation, as can be seen in Fig. 8. Those observations suggest that these molecules may have several energetically accessible conformations that can be present in the biological environment indicating a degree of flexibility for the docking with substrates.

Table 3
Selected hydrogen-bond parameters.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
1				
N2—H2···O1	0.89 (3)	2.30 (3)	2.652 (4)	103 (2)
N2—H2···O4[a]	0.89 (3)	2.01 (3)	2.887 (3)	165 (3)
C5—H5···O2[b]	0.95	2.33	3.244 (4)	161.2
C7—H7···N23[c]	0.95	2.59	3.266 (4)	128.8
C7—H7···S21[d]	0.95	2.81	3.628 (3)	144.6
2				
N2—H2···O1	0.866 (19)	2.362 (19)	2.6751 (18)	101.7 (15)
N2—H2···O4[e]	0.87 (2)	2.03 (2)	2.8835 (17)	169.2 (18)
C5—H5···O2[f]	0.95	2.34	3.276 (2)	166.6
3				
N2—H2···O1	0.82 (9)	2.29 (8)	2.627 (5)	105 (6)
N2—H2···O4[g]	0.82 (9)	2.20 (9)	3.012 (5)	171 (8)
C8—H8···O4[g]	0.95	2.57	3.348 (6)	138.9
4				
N12—H12···O11	0.82 (5)	2.39 (5)	2.687 (6)	103 (4)
N12—H12···O24	0.82 (5)	2.12 (6)	2.934 (7)	174 (5)
N22—H22···O14[h]	0.97 (5)	1.97 (5)	2.923 (6)	169 (4)
N22—H22···O21	0.97 (5)	2.32 (4)	2.686 (6)	102 (3)
C15—H15···N223[i]	0.95	2.48	3.432 (7)	175.6
C25—H25···N123	0.95	2.52	3.405 (8)	154.4

Symmetry code(s):
[a] $x, -y+1/2, z-1/2$.
[b] $-x+1, y-1/2, -z+3/2$.
[c] $-x+1, y-1/2, -z+1/2$.
[d] $x-1, -y+1/2, z-1/2$.
[e] $x, -y+3/2, z+1/2$.
[f] $-x+1, y+1/2, -z+1/2$.
[g] $x, -y+1, z+1/2$.
[h] $x, y+1, z$.
[i] $x, y-1, z$.

Supramolecular structures

Values for intermolecular H bonds and contacts are presented in Table 3. In all compounds the main feature is the formation of an intermolecular N2—H2···O4 hydrogen bond which links the molecules into C(7) chains [30] that run parallel to the *c*-axis an example, compound **1**, is shown in Fig. 12. These bonds are supplemented by weak C—H···O interactions as shown in Fig. 13. The symmetry codes are inserted in Table 4. Detailed discussion of the supramolecular structures for all compounds is given in S2 Supplementary Information.

Gaseous phase quantum chemical calculations

Adiabatic quantum chemical calculations were performed in order to get some inside concerning the configurations and conformations for those compounds as given by X-ray crystallography results. Geometric optimisations of conformers of compound **1** were made with different starting geometries that were identified as A1_0, A1_1, A2_0 and A2_1, Fig. 10. A1 and A2 refer to the *-anti* rotamer configurations; depending on the rotation of the thiazole ring, the oxygen atom of the amide and the nitrogen atom of the thiazole may be *-trans* related (A1_0 and A2_0) or *-cis* related (A1_1 and A2_1).

The total electronic energies, at the B3LYP/6-311+G(d, p) level of theory, are given in Supporting information S3.The zero-point energy correction was scaled using a 0.9887 scaling factor. The cartesian coordinates as obtained from quantum chemical gas phase geometry optimisations, at the B3LYP/6-311+G(d) level of theory, are given in Table Supporting information S3. The geometries obtained after optimisations are depicted in Fig. 10.

Conformers A1 optimised to the same final geometry as can be seen in Fig. 10. This conformer as obtained from geometry optimisation is the most stable in gas phase taking the B3LYP/6-311+G(d, p) level of theory. The geometry obtained is similar to that presented in the solid state given by single crystal diffractometry. The molecule is mostly planar with dihedral angles between the amide moiety and the chromone/thiazole rings being close to 180°. Opposed to this, the geometrical optimisation made for the conformers A2 show two distinct local minima that present torsions of the heterorings around the amide rotamer. In conformer A2_0 the dihedral angle between the chromone ring and the amide moiety, $\theta_{Chr-amide}$, is of 28° and the dihedral angle between the thiazole and the amide spacer, $\theta_{Thz-amide}$, is of 1° showing that loss of planarity is due to the twist of the chromone ring with respect to the amide. In conformer A2_1 those dihedrals are of 30° and 61° respectively indicating for significant torsions of both rings.

Furthermore, in order to obtain the natural atomic charges, a population analysis was performed, using the natural bond orbital (NBO) analysis [27,28]. Natural atomic charges represent nuclear charges minus the summed natural populations of the natural atomic orbitals on the atoms and characterise the ground electronic state of the molecule. The calculated charges potentially give some insight into the electronic distribution around the molecule and, thus, contribute to an understanding of the preferred geometries for compound 1. The charge distributions for all the optimisations are shown in figures in Supporting Information S4 and are presented within a relative charge range of −1.000 to +1.000. Fig. 14 shows some charge values for the most stable configuration, A1; negative charges are located at the two N atoms and at the three oxygen atoms while the positive charges reside at the amide carbon as well as at the sulphur atom of the thiazole ring. The same qualitative pattern is observed in the other conformers A2. The geometry obtained for conformation A1 allows the

Table 4
Selected dihedral angles and distances for compounds.

	$\theta°_{Chr-Thz}$	$\theta°_{Chr-amide}$	$\theta°_{Thz-amide}$	d_{C2} (Å)	d_{C22} (Å)
1	8.64(15)	13.4(5)	7.9(5)	−0.001(2)	−0.073(2)
2	12.30(8)	17.4(2)	6.2(2)	0.0046(16)	−0.0716(16)
3	14.4(2)	7.1(4)	11.5(4)	0.053(5)	0.084(5)
4 #1	17.75(16)	14.4(6)	3.9(8)	0.026(5)	0.062(5)
4 #2	15.6(2)	18.3(6)	2.9(8)	−0.060(5)	0.023(5)

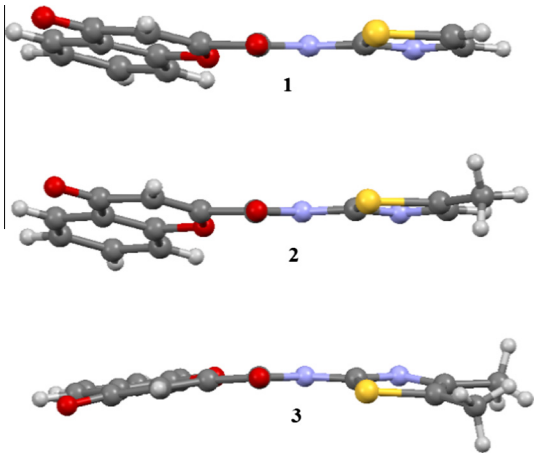


Fig. 11. A perspective view of the molecules **1**–**3** (from top to bottom) through the amide plane depicting the differences in conformation of the molecules that are given by the twist and/or bent of the heteroaromatic rings in relation to the amide plane. In molecules **1** and **2** the rings are predominantly twisted while molecule **3** they are predominantly bent to the same direction conferring a "butterfly" conformation to the molecule.

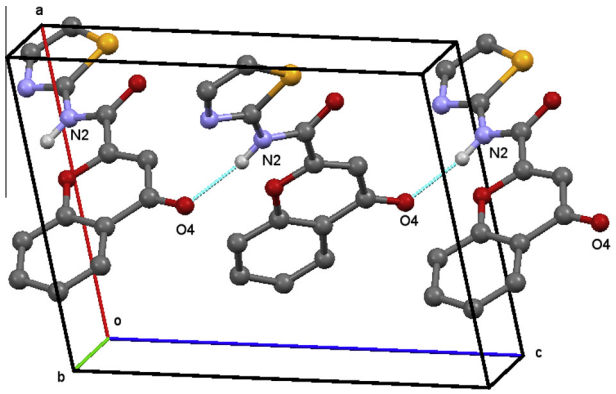


Fig. 12. Representation of the C(7) chain running along the *c*-axis for 1. Compounds **2** and **3** make similar chains. The hydrogen atoms not involved in the connectivity were omitted for clarity.

minimisation of steric hindrance between the oxygen atoms of the amide and the pyrone in the planar geometry while conformers A2 does not. In addition, conformation A1 is probably further stabilized by the *cis* related nitrogen where the sulphur is pointing to the carboxyl oxygen atom of the amide. In A2 the torsion of the chromone ring with respect to the amide permits a minimisation of the steric hindrance between the carboxylic amide oxygen atom and the pyrone oxygen atom and in A2_1 the torsion of the thiazole ring is probably related with the minimisation of the of the hindrance between the two nitrogen atoms since the stabilisation of the geometry in which the thiazole ring is planar with the amide is not present due to the position of the positive charged sulphur atom that is far from the range field of the negative charged atoms.

Conclusion

New 4-oxo-*N*-(substituted-thiazol-2-yl)-4*H*-chromene-2-carboxamides were synthesized from chromone-2-carboxylic acid by two different amidation methods. The development of dissimilar synthetic approaches provided the possibility of working with diverse reaction conditions, namely with conventional heating and/or microwave irradiation. Relevant data related to the molecular geometry and conformation of the chromone–thiazole hybrids has been acquired which can be of the utmost importance to understand ligand–receptor binding.

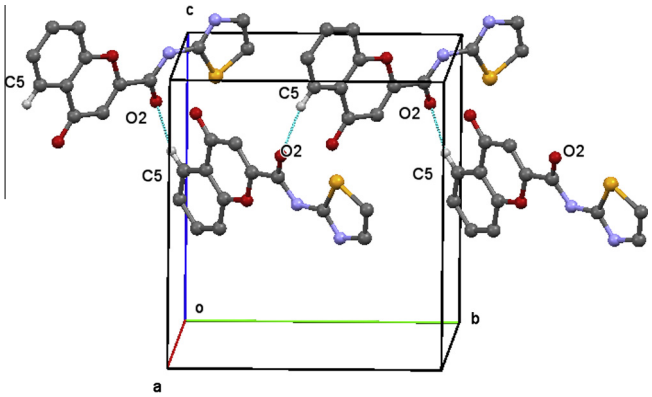


Fig. 13. Representation of the C(8) chain parallel to the *b*-axis made by the weak C5—H5···O2 hydrogen contact for compound **1**. Compounds **2** and **3** exhibit similar patterns. The hydrogen atoms not involved in the connectivity were omitted for clarity.

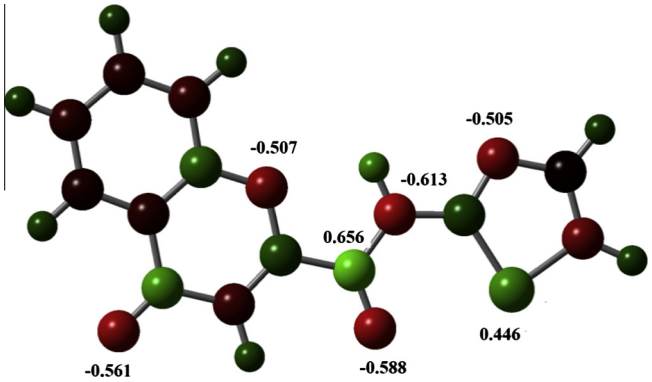


Fig. 14. Natural atomic charges from population analysis (NBO), at the B3LYP/6-311+G(d) level of theory for the most stable configuration, A1. The charge distributions are presented within a relative charge range of −1.000 to +1.000.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2015.02.009.

References

[1] A. Gaspar, M.J. Matos, J. Garrido, E. Uriarte, F. Borges, Chem. Rev. 114 (2014) 4960.
[2] A.M. Helguera, G. Perez-Machado, M.N. Cordeiro, F. Borges, Med. Chem. 12 (2012) 907.
[3] S. Alcaro, A. Gaspar, F. Ortuso, N. Milhazes, F. Orallo, E. Uriarte, M. Yanez, F. Borges, Bioorg. Med. Chem. Lett. 20 (2010) 2709.
[4] A. Gaspar, J. Reis, A. Fonseca, N. Milhazes, D. Vina, E. Uriarte, F. Borges, Bioorg. Med. Chem. Lett. 21 (2011) 707.
[5] A. Gaspar, T. Silva, M. Yanez, D. Vina, F. Orallo, F. Ortuso, E. Uriarte, S. Alcaro, F. Borges, J. Med. Chem. 54 (2011) 5165.
[6] A. Gaspar, F. Teixeira, E. Uriarte, N. Milhazes, A. Melo, M.N. Cordeiro, F. Ortuso, S. Alcaro, F. Borges, ChemMedChem 6 (2011) 628.
[7] A. Gaspar, J. Reis, S. Kachler, S. Paoletta, E. Uriarte, K.N. Klotz, S. Moro, F. Borges, Biochem. Pharmacol. 84 (2012) 21.
[8] A. Gaspar, J. Reis, M.J. Matos, E. Uriarte, F. Borges, Eur. J. Med. Chem. 54 (2012) 914.
[9] K.D. Hargrave, F.K. Hess, J.T. Oliver, J. Med. Chem. 26 (1983) 1158.
[10] W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, D.G. Taylor, J. Med. Chem. 35 (1992) 2562.
[11] N. Ergenc, G. Capan, N.S. Gunay, S. Ozkirimli, M. Gungor, S. Ozbey, E. Kendi, Arch. Pharm. Pharm. Med. Chem. 332 (1999) 343.
[12] J.C. Jean, L.D. Wise, B.W. Caprathe, H. Tecle, S. Bergmeier, J. Med. Chem. 33 (1990) 311.
[13] M.V.N. Souza, J. Sulfur Chem. 26 (2005) 429.
[14] N. Siddiqui, M.F. Arshad, W. Ahsan, M.S. Alam, Int. J. Pharm. Sci. Drug Res. 1 (2009) 136.
[15] R.N. Sharma, F.P. Xavier, K.K. Vasu, S.C. Chaturvedi, S.S. Pancholi, J. Enzyme Inhib. Med. Chem. 24 (2009) 890.
[16] K. Jung, S. Kim, Z. Gao, A.S. Gross, N. Melman, K.A. Jacobson, Y. Kim, Bioorg. Med. Chem. 12 (2004) 613.
[17] G.M. Sheldrick, Acta Cryst. A64 (2008) 112.
[18] P. McArdle, K. Gilligan, D. Cunningham, R. Dark, M. Mahon, CrystEngComm 6 (2004) 303–309.
[19] A.L. Spek, Acta Cryst. D65 (2009) 148–155.
[20] C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J.J. van de Streek, Appl. Cryst. 39 (2006) 453.
[21] C.B. Hübschle, G.M. Sheldrick, B.J. Dittrich, Appl. Cryst. 44 (2011) 1281.
[22] A.D. Becke, J. Chem. Phys. 107 (1997) 8554.
[23] C. Lee, W. Yang, G.R. Parr, Phys. Rev. B 37 (1988) 785.
[24] W.J. Hehre, L. Radom, P.V.R. Schleyer, J.A. Pople, Ab Initio Molecular Orbital Theory, Wiley, New York, 1986.

[25] R. Dennington II, T. Keith, J. Millam, GaussView, Version 4.1.2, Semichem, Inc., Shawnee Mission, KS, 2007. <http://www.gaussian.com>.
[26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, GAUSSIAN 03, Revision D.02, Gaussian, Inc., Wallingford, CT, 2004.
[27] A.E. Reed, F.J. Weinhold, Chem. Phys. 78 (1983) 4066.
[28] A.E. Reed, L.A. Curtiss, F. Weinhold, Chem. Rev. 88 (1988) 899.
[29] L.R. Gomes, J.N. Low, F. Cagide, A. Gaspar, J. Reis, F. Borges, Acta Cryst. B69 (2013) 294.
[30] J. Bernstein, R.E. Davis, I. Shimoni, N.-L. Chang, Angew. Chem. Int. Ed. Engl. 34 (1995) 1555.
[31] S.J. Coles, P.A. Gale, Chem. Sci. 3 (2012) 683.