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PAPER

Conjugate addition of isocyanides to chromone 3-carboxylic acid: an efficient one-pot synthesis of chroman-4-one 2-carboxamides†

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We report a novel Lewis acid catalysed tandem reaction of isocyanides, chromone 3-carboxylic acid and nucleophiles. An experimentally very simple procedure, involving the use of microwave irradiation in the presence of a Lewis acid catalyst, affords a representative collection of chromone-2-carboxamides and chromone-2-carboxamido-3-esters in high yields, in just a few minutes. Such an unprecedented strategy is formally equivalent to a conjugate addition of isocyanides to Michael acceptors.

Introduction

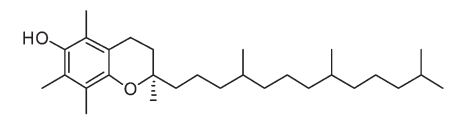
The benzopyran scaffold has been identified as a *privileged structure* able to bind with high affinity to a large number of protein receptors and enzymes, and as a preferential skeleton for the design of drugs.[1] In particular, important classes of bioactive natural products include 2-substituted chromanes and chromanones as structural cores.[2] For example, D-α-tocopherol (vitamin E)[3] (Fig. 1; **1**) is a natural radical scavenger that inhibits lipid peroxidation, and has been reported to retard oxidative damage and disease progression.

Some synthetic derivatives of vitamin E exhibit improved pharmacological profiles. Thus, chroman-2-carboxylic acid Trolox (Fig. 1; **2**)[4] has better pharmacokinetic properties than vitamin E, while keeping its protecting activity against oxidative damage. Likewise, 4-chromanone-2-carboxamides (**3**) have been shown to be more potent antioxidants than vitamin E and Trolox.[5] Moreover, chroman-2-carboxamides have been shown to exert a beneficial action through the specific inhibition of transcription factor NF-κB.[6]

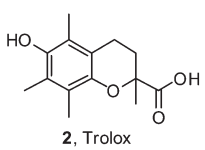
4-Chromanone-2-carboxamides have been frequently synthesised by coupling of the corresponding 4-chromanone-2-carboxylic acids with aromatic or aliphatic amines. A conceivable alternative method to obtain 4-chromanone-2-carboxamides would be the direct conjugate addition of a synthetic equivalent of a carbamoyl anion to chromones. However, despite the interest in 2-substituted-chromanones, methods involving conjugate additions to chromones are scarce in the literature,[7] probably because they readily undergo ring-opening to the chalcone in the presence of nucleophiles.

Isocyanides are a remarkable class of compounds, characterised by possessing a divalent carbon that is able to behave both as a mild nucleophile and electrophile.[8] We are interested in the use of multi-component reactions of isocyanides for the synthesis of heterocycles,[9] including benzopyran derivatives.[10]

Also, we have previously succeeded in using isocyanides as mild nucleophilic synthetic equivalents of carbamoyl anions.[11] We therefore anticipate that isocyanides could be used to introduce the amide functionality in position 2 of chromone derivatives. Isocyanides tend to give α-addition reactions, acting at the same time as nucleophiles and electrophiles.[8b] Consequently, the desired nucleophilic addition of isocyanides to chromones could be favoured by the presence of a nucleophilic group in the appropriate position of the chromone. In fact, isocyanides are known to undergo [4 + 1] cycloaddition reactions with α,β-unsaturated carbonyls,[12] what can be considered as synchronic α-additions of positions 1 and 4 of the unsaturated carbonyl to the isocyanide. With this in mind, we reasoned that a [4 + 1] cycloaddition reaction of 4-oxo-4*H*-chromene-3-carboxylic acids (**4**) with



1, Vitamin E



2, Trolox

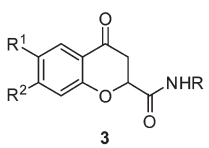


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Fig. 1 Examples of chromanes with antioxidant activity.

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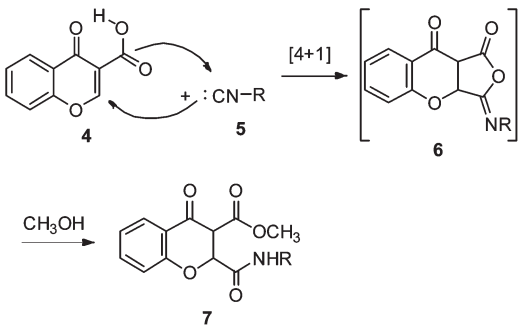
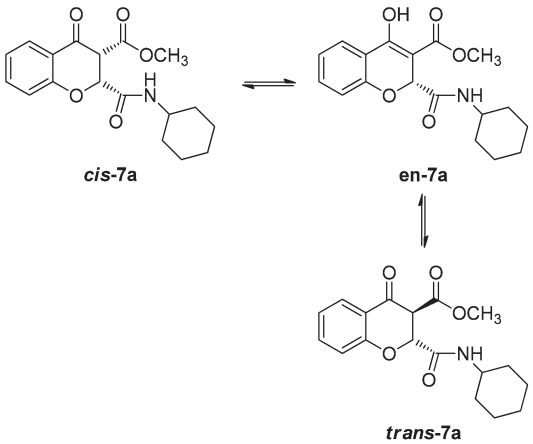
†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all new compounds; electronic energies, frequencies, geometries and thermodynamic magnitudes of the critical structures involved in the reaction mechanisms found at the B3LYP/6-31G(d) theory level. See DOI: 10.1039/c2ob07011a



Scheme 1 One-pot synthesis of 2,3-substituted chromanones.



Scheme 2 Equilibrium of isomers in chromanone **7a**.

isocyanides (**5**) would provide a feasible way to introduce a carbamoyl substituent on position 2 of the chromone, resulting in an easy access to chromane 2-carboxamides (**3**).

Results and discussion

To test out this hypothesis we performed the reaction between chromone-3-carboxylic acid (**4**) and cyclohexyl isocyanide (**5a**) in methanol at room temperature under inert atmosphere. After two weeks, the starting materials had been completely consumed and a product precipitated from the reaction mixture. This product was isolated in a 45% yield by simple filtration, and was identified as amidoester **7a** (R = *c*-C_6H_{11}; Scheme 1). The production of **7** can be rationalised by the formation of an imino–anhydride intermediate (**6**), which is trapped *in situ* with nucleophilic methanol (Scheme 1).

In this reaction, two new stereogenic centres are formed and the product (**7**) was expected to be obtained as a mixture of two diastereoisomers, ***cis*-7a** and ***trans*-7a**. Due to the acidic character of the hydrogen in position 3 of the chromone core, the two possible configurations of C-3 should readily interconvert in solution through tautomeric enol **en-7a** (Scheme 2).

Surprisingly, the NMR spectrum of a recently prepared solution of **7a** corresponds to a mixture of tautomers **en-7a** and ***cis*-7a**, with no traces of ***trans*-7a** present. However, after a few hours in solution, peaks corresponding to isomer ***trans*-7a** become evident in the ^{1}H and ^{13}C NMR spectra. If the solution is left to stand long enough, a thermodynamic equilibrium is reached, in which **en-7a**, ***cis*-7a** and ***trans*-7a** are present in a 0.36 : 0.28 : 0.36 ratio (Fig. 2).

To explain the initial formation of only isomers **en-7** and ***cis*-7** and further equilibria, an entire computational study of all the reactants, products and transition states has been performed at the B3LYP level with the basis 6-31G (d), and single-point energies recalculated for all the B3LYP/6-31G (d) optimised geometries using 6-31G (d,p), 6-31++G (d,p) and 6-31++G (d,p) basis sets. In order to simplify the calculations, the cyclohexyl substituent has been replaced with a methyl group.

Although there are some important differences in the energies calculated at different basis sets, due to a better interpretation of hydrogen-bond with water at the more flexible higher basis sets, there are no significant differences in the relative energies calculated with the four basis sets. Hence the values of the energies given below correspond to the calculations performed at a 6-31G (d) level (for further details see ESI†).

According to the proposed mechanism, chromone-3-carboxylic acid (**4**) and isocyanide (**5**) react to produce intermediate **I** (0.0 kcal mol^{-1}; Scheme 3). The reactive conformation of **4** is the s-*cis* rotamer, which is also more stable than the s-*trans* rotamer by *ca.* 9 kcal mol^{-1}. Intermediate **I** must quickly equilibrate with the most stable keto-tautomer form **IIb** (−5.8 kcal mol^{-1}), where the enol moiety is carried by the chromone's C-4, as the activation barrier is very small. Then, **I** or/and **IIb** could tautomerise to either **IIa** (2.6 kcal mol^{-1}), or **IIc** (−4.6 kcal mol^{-1}) keto isomers.

The calculations explain this process, which is assisted by a molecule of water, and provide evidence that isomerisation of **I** to **IIb** through transition state **TSI-IIb** (−0.2 kcal mol^{-1}) and to **IIc** through transition state **TSIIb-IIc** (20.1 kcal mol^{-1}) takes place through much smaller calculated activation barriers than isomerisation to **IIa** through transition state **TSIIa-IIb** (30.8 kcal mol^{-1}). This is in agreement with the initial formation of only isomers ***en*-7** and ***cis*-7**, since the most rapidly formed intermediates **IIb** and **IIc** should be promptly attacked by a molecule of methanol to give the final products **IIIb** and **IIIc**. Diastereoisomer **IIIa** would only be formed by an epimerisation process from **IIIc**. This would explain the experimental result, in which ***trans*-7** is only formed after a sufficiently long equilibration period. This would also explain why in some cases (see below), when an alcohol different from methanol is used, the only isomer observed immediately after the reaction is the enol tautomer **en-7**, as this should be formed through the less energetic transition state **TSI-IIb**.

As the reaction is performed with anhydrous solvents under inert atmosphere, a molecule of alcohol may play the role assigned to water in the theoretical calculations, making the tautomerisation and epimerisation processes easier. When bulky alcohols are used instead of methanol, these isomerisations should be considerably more difficult than when using water or methanol, what hinders the formation of keto tautomers *cis*-7 and *trans*-7.

The occurrence of **IIIa** after equilibration should come up through the epimerisation of **IIIc**. This epimerisation is likely to take place in very mild conditions as the electron attracting effect of the two α carbonyl groups confers a pronounced acidic character to hydrogen in position 3. DFT calculations confirm that

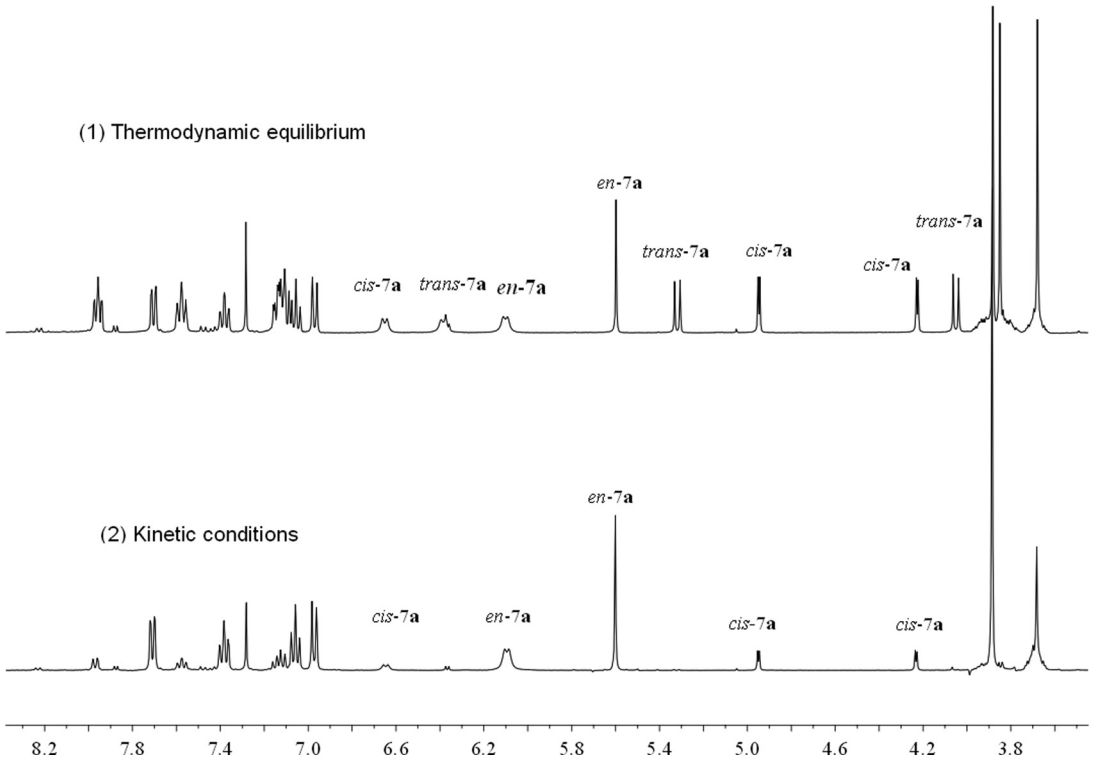
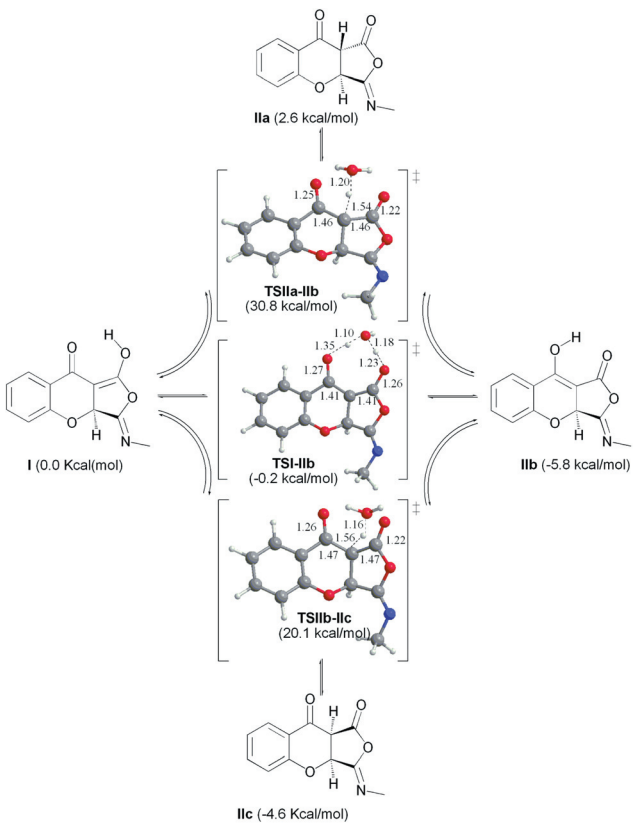


Fig. 2 ^{1}H-NMR of chromanone **7a**: (1) recently prepared solution; (2) after an equilibration period of 15 days.



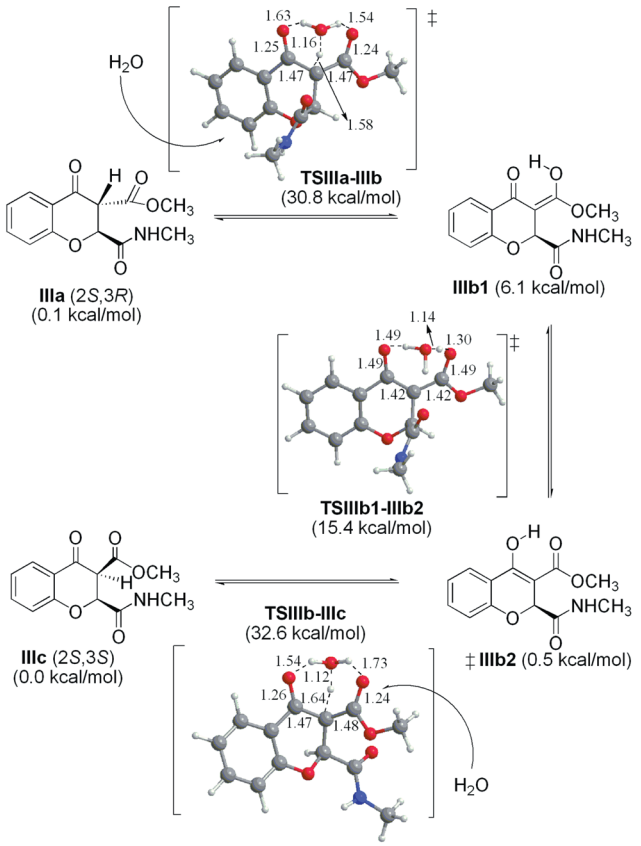
Scheme 3 Possible routes for the formation of different isomers of imino–anhydride intermediate (**6**), as calculated at B3LYP/6-31G(d) level of theory. Main bond distances (in Å) and relative Gibbs energies in gas phase (in kcal mol^{-1}) are also given.

epimerisation to **IIIa** can easily take place through the enolic forms **IIIb1** and **IIIb2**. Here, activation barriers of the keto–enol tautomerisations are again much lower if a water molecule is considered to participate in the transition state (see ESI†). Conversely, the activation barrier of the transformation of enol **IIIb1** into enol **IIIb2** is smaller (3.9 kcal mol^{-1} *vs.* 14.9 kcal mol^{-1}) if no water is involved in the transition state.

Hence the keto α-hydrogen could be removed or restored from the *cis* (**IIIc**) or the *trans* (**IIIa**) chromanones with the help of the water (or alcohol) oxygen atom, at the time that an hydrogen from the water (or alcohol) is given to or taken from an enolic forming group (Scheme 4). The energies of these transition states are very similar (*ca.* 31 and 33 kcal mol^{-1} compared to the most stable chromanone 2-carboxamide **IIIc**) and are in agreement with a slow epimerisation form **IIIc** to **IIIa** through the enolic tautomers **IIIb1** and **IIIb2**.

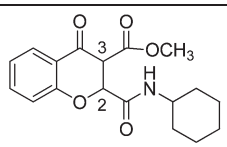
In addition, quantum calculations also demonstrate that the energies in the gas phase of both diastereoisomers **IIIa** and **IIIc** and tautomer **IIIb** are virtually identical, with a difference of *ca.* 1 kcal mol^{-1}, which is within the experimental error. This is in full agreement with the experimental product distribution reached after an equilibration period, supporting the reliability of the quantum chemical calculations. Moreover, conformational search computations show how the pyranone ring of the chromone core in **IIIa** and **IIIc** can adopt different half-chair conformations, resulting in several energetically similar rotamers with energies differing up to 5 kcal mol^{-1}.

Once we had elucidated the mechanism of the reaction, we examined the experimental conditions in order to improve the yield and rate of the reaction. Thus, we investigated both the effect of temperature and Lewis acid catalysts. Heating reduced



Scheme 4 Epimerisation equilibria of chromone amidoesters **7** deduced from B3LYP/6-31G(d) quantum calculations. The geometries of transition states **TSIIIb-IIIc** and **TSIIIa-IIIb** make evident how the C–O bond distances in the keto groups are becoming longer as a result of the hydrogen transfer from the water molecule, while the C–C distances get shorter due to their double bond partial character.

Table 1 Synthesis of methyl 2-(cyclohexylcarbamoyl)-4-oxochroman-3-carboxylate (**7a**)

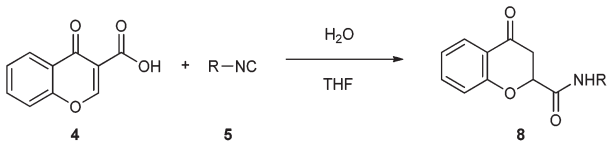


7a

Entry	Solvent	$Sc(OTf)_3$	Conditions	Time	Yield (%)
1	MeOH	—	rt	2 weeks	45
2	MeOH	—	60 °C	12 h	50
3	MeOH	8%	rt	24 h	60
4	$PhCH_3$[a]	8%	60 °C	14 h	86

[a] In this case, 5 equivalents of MeOH were added to the reaction mixture.

the reaction time to just 12 h, though without significant effect on the yield (Table 1, entry 2). To our delight, when an 8% molar of scandium(III) triflate was added to the reaction mixture, the reaction proceeded smoothly at room temperature in less than 24 h to give 2,3-substituted chromanone (**7**) in a good yield



Scheme 5 Synthesis of 2-amido-substituted chromanones (**8**).

Table 2 Optimisation of conditions for the synthesis of *N*-cyclohexyl-4-oxochroman-2-carboxamide (**8a**)

Entry	Conditions	$Sc(OTf)_3$	$c\text{-}C_6H_{11}NC$	Time	Yield (%)
1	rt[a]	—	1 equiv.	5 days	<50
2	rt	8%	1 equiv.	24 h	70
3	mw[b]	—	1 equiv.	8 min	<50
4	mw	8%	1 equiv.	3 min	25
5	mw	4%	2.5 equiv.	3 min	88
6	mw	1%	2.5 equiv.	3 min	95
7	mw	1%	2 equiv.	3 min	93
8	mw	1%	1.5 equiv.	3 min	68
9	mw	1%	1.2 equiv.	3 min	58
10	rt	1%	1 equiv.	24 h	74

[a] Conditions: A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), cyclohexyl isocyanide (**5a**, 0.5 mmol), H_2O (75 μL) and $Sc(OTf)_3$ in 1.5 mL of THF was stirred under N_2 atmosphere. [b] A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), cyclohexyl isocyanide (**5a**), H_2O (75 μL) and $Sc(OTf)_3$ in 1 mL of THF was irradiated at 150 W and 100 °C in a closed vial.

(Table 1, entry 3). Moreover, the reaction takes place equally well with just a small excess of methanol, in an inert solvent as toluene, at 60 °C, in the presence of $Sc(OTf)_3$ (Table 1, entry 4).

With the aim of exploring the scope of the reaction we decided to perform it in the presence of nucleophiles other than methanol. Interestingly, when water is used as a nucleophile, the resulting carboxylic acid undergoes spontaneous decarboxylation in the same flask to yield 2-substituted chromanones (**8**; Scheme 5).

This reaction takes place with cyclohexyl isocyanide (**5a**) in toluene or THF at rt to give chromanone 2-carboxamide **8a** (R = $c\text{-}C_6H_{11}$) in 5 days (Table 2, entry 1). As in the case of methanol, addition of 8% $Sc(OTf)_3$ improves both the yield and reaction time (Table 2, entry 2). To further optimise the reaction conditions we tried activation by means of microwave irradiation and also cutting down the amount of catalyst (Table 2, entries 3–10). Under microwave conditions, in the presence of $Sc(OTf)_3$, cyclohexyl isocyanide (**5a**) is consumed in just three minutes; however a significant proportion of acid **4** remains unreacted (Table 2; entry 4). Apparently, the isocyanide is partially hydrolysed in these conditions, so an excess should be used to complete the reaction.

Finally, we established the optimal conditions for the reaction as using 2.5 equivalents of cyclohexyl isocyanide (**5a**) and 1% molar of $Sc(OTf)_3$ under microwave irradiation for just three minutes (Table 2, entry 6).

We then investigated if the reaction could be generalised to the use of other combinations of reagents. Accordingly, when different isocyanides are used under the optimised reaction conditions, the corresponding chromone 2-carboxamides can be obtained in good to excellent yields (Table 3).

In addition, when the optimised conditions under microwave irradiation are applied to the initial reaction with methanol, chromanone **7a** is obtained in very good yield (Table 4, entry 1). Furthermore, other combinations of different alcohols and isocyanides allow the synthesis of a wide array of differently substituted chromanone amidoesters. Representative examples are listed in Table 4 (entries 2–9), for which yields under thermal and microwave conditions are shown.

Unfortunately, when the reaction was performed in the presence of other types of nucleophiles, such amines (Table 4, entries 10–14), thiols (Table 4, entries 15–16) or azide (Table 4, entry 17), the required diamides or amido thioesters were not obtained. In the case of using primary amines, these nucleophilically add to chromone position 2, precluding any further reaction with the isocyanide (Scheme 6).[13] However, thiols, such as *N*-Boc-cysteine did not react at all. Consequently, the scope of the reaction seems to be limited to the use of alcohols or water as nucleophiles.

We also failed to isolate intermediate **6**. When we performed the reaction in the absence of any nucleophiles, even at low temperature, we could only detect starting material or the product of addition of water.

Table 3 Synthesis of diverse 4-oxochroman-2-carboxamides (**8**)[a]

Entry	Isocyanide	Compound	Yield (%)
1	*t*-Bu (**5b**)	**8b**	100
2	CH_2Ph (**5c**)	**8c**	80
3	2,6-Me_2Ph (**5d**)	**8d**	77
4	$CH_3O(CH_2)_2O(CH_2)_2$ (**5e**)	**8e**	70
5	$tBuO_2CCH_2$ (**5f**)	**8f**	60

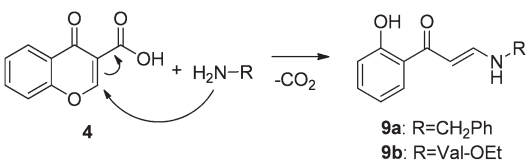
[a] Conditions: A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), isocyanide (5, 1.25 mmol), H_2O (75 μL) and $Sc(OTf)_3$ (1% mol) in 1 mL of THF was irradiated with microwaves 3 min at 150 W and 100 °C in a closed vial.

Further transformation of chromanones **7** and **8** could give access to valuable products. For instance, dehydrogenation of chromanone carboxamides would allow a straightforward synthesis of 2-amidochromenes, which are an important class of compounds with remarkable biological activities. For example, they have been proposed as modulators of metabotropic glutamate receptors (mglur4),[14] melanin-concentrating hormone receptor 1 (mchr1) antagonists,[15] 5-hydroxytryptamine (5-ht1b) antagonists,[16] *Plasmodium falciparum* lactate dehydrogenase inhibitors,[17] calpain inhibitors,[18] *p*-glycoprotein inhibitors,[19] monoamine oxidase inhibitors,[20] and breast cancer resistance protein (abcg2) inhibitors.[21]

Interestingly, chromanone carboxamides **7** and **8** can be readily transformed into the corresponding unsaturated 2-amido chromones by a bromination–dehydrobromination sequence. For example, the treatment of carboxamide **8a** with pyridinium tribromide followed by addition of acetic acid or Et_3N readily gives the chromenone **11** in one-pot (Scheme 7). Analogously, 2,3-disubstituted chromanone **7a** was transformed into the corresponding chromenone **10**[20] by bromination followed by treatment with base.

Conclusions

In conclusion, we have developed a simple and efficient method that allows the preparation of 4-chromanone-2-carboxamides that have potential interest as pharmacological agents to prevent

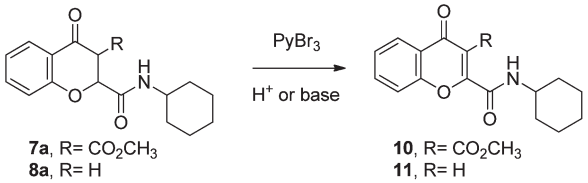


Scheme 6 Reaction of chromone-3-carboxylic acid with amines.

Table 4 Preparation of 2,3-disubstituted chromanones (**7**)

Entry	Isocyanide	Nucleophile (n° equiv.)	Conditions	Time	Product (% yield)	Thermodynamic ratio **en-7** : ***cis*-7** : ***trans*-7**
1	*c*-C_6H_{11} (**5a**)	MeOH (5)	mw[a]	8 min	**7a** (76)	36 : 28 : 36
2	2,6-Me_2Ph (**5d**)	MeOH (5)	mw	20 min	**7b** (50)	42 : 16 : 42
3	*c*-C_6H_{11} (**5a**)	EtOH (5)	thermal[b]	14 h	**7c** (70)	46 : 18 : 36
4	*t*Bu (**5b**)	EtOH (5)	mw	8 min	**7d** (55)	34 : 14 : 52
5	$CH_3O(CH_2)_2O(CH_2)_2$ (**5e**)	EtOH (5)	mw	8 min	**7e** (68)	39 : 19 : 42
6	*c*-C_6H_{11} (**5a**)	*t*BuOH (1)	mw	8 min	**7f** (60) + **8a** (40)	31 : 25 : 44
7	*c*-C_6H_{11} (**5a**)	Geraniol (1)	mw	8 min	**7g** (55)	37 : 26 : 37
8	*t*Bu (**5b**)	Heptanol (1)	mw		**7h** (66)	44 : 39 : 17
9	$CH_3O(CH_2)_2O(CH_2)_2$ (**5e**)	$CH_3O(CH_2)_2O(CH_2)_2OH$ (1)	thermal	15 h	**7i** (60)	40 : 16 : 44
10	*c*-C_6H_{11} (**5a**)	$PhCH_2NH_2$ (5)	thermal	17 h	**9a** (63)	
11	*c*-C_6H_{11} (**5a**)	Val-OEt (5)	rt[c]	24 h	**9b** (36)	
12	*c*-C_6H_{11} (**5a**)	*i*Pr_2NH (5)	rt	5 h	dec.	
13	*c*-C_6H_{11} (**5a**)	5-Bromobenzo[*d*]thiazol-2-amine (1.5)	rt	24 h	**8a** (98)	
14	*c*-C_6H_{11} (**5a**)	Urea (5)	mw	25 min	**8a** (36)	
15	*c*-C_6H_{11} (**5a**)	4-(Mercaptomethyl) quinolin-2(1*H*)-one (1.5)	mw	20 min	**8a** (98)	
16	*c*-C_6H_{11} (**5a**)	*N*-Acetyl-L-cysteine (1.5)	rt	24 h	**8a** (30)	
17	*c*-C_6H_{11} (**5a**)	NaN_3 (1)	rt	24 h	**8a** (35) + **4** (65)	

[a] Conditions: A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), isocyanide (**5**, 0.75 mmol), nucleophile (1–5 equiv.) and $Sc(OTf)_3$ in 1 mL of THF was irradiated at 150 W and 100 °C in a closed vial. [b] A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), isocyanide (**5**, 0.5 mmol), nucleophile (1–5 equiv.) and $Sc(OTf)_3$ (1% mol) in dry toluene was heated at 60–70 °C under N_2 atmosphere. [c] A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), isocyanide (**5**, 0.5 mmol), nucleophile (1–5 equiv.) and $Sc(OTf)_3$ (1% mol) in dry THF was stirred at rt under N_2 atmosphere.



Scheme 7 Formal oxidation of 2-amido-chromanones to the corresponding chromenones.

oxidative cellular damage. This new multicomponent reaction takes place through a novel tandem process involving a [4 + 1] cycloaddition of isocyanides followed by nucleophilic opening of an iminoanhydride intermediate. The proposed reaction mechanism is supported by quantum calculations, which also explain the obtained product profile.

The use of a Lewis acid catalyst and microwave activation effects the reaction in just a few minutes and affords good to excellent yields of the required products. This process tolerates the use of different isocyanides and alcohols, providing a ready access to differently substituted 2,3-disubstituted chroman-4-ones in a combinatorial way. Furthermore, the use of water as a nucleophile yields monosubstituted chroman-4-one 2-carboxamides through decarboxylation of the intermediate chromanone 3-carboxylates.

Finally, one-pot bromination–dehydrobromination of chromanone 2-carboxamide products provides a straightforward method for the preparation of biologically relevant chromone 2-carboxamides and chromone 2-amido-3-esters.

Experimental section

General techniques

Melting points are uncorrected. IR spectra were recorded as KBr pellets. Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR or ^{13}C NMR) spectra were obtained on a 400 MHz or 500 MHz spectrometer. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded using electronic impact (EI, 70 eV), chemical ionization (CI) with CH_4 or FAB with Xe^0 and 2-methoxyethyl disulfide as matrix. Tetrahydrofuran, methanol and toluene are PA ACS grade. Isocyanides and chromone-3-carboxylic acid were purchased from commercial sources, except in the case of isocyanide **5e**, which was synthesised according to the procedure described below. Experiments at room temperature were carried out in stoppered flasks using nitrogen atmosphere. Experiments under microwave irradiation were performed in closed vials, using a focused single-mode microwave reactor CEM Discover BenchMate. Liquid reagents were measured using positive-displacement micropipettes with disposable tips and pistons. Thin layer chromatography was performed on aluminium plates, using 254 nm UV light or a mixture of *p*-anisaldehyde (2.5%), acetic acid (1%) and H_2SO_4 (3.4%) in 95% ethanol as developer.

Computational details

Quantum chemical computations were carried out with the Gaussian 03 series of programs.[22] Full geometry optimizations of stable species and TS were performed in the gas phase by employing the hybrid density functional B3LYP[23] with the 6-31G(d) basis set. To check the reliability of the B3LYP/6-31G(d) results, single-point energy calculations were performed on all the B3LYP/6-31G(d) optimised geometries keeping the DFT B3LYP functional and using respectively 6-31G(d,p), 6-31++G (d,p) and 6-31++G(d,p) basis sets[24] (see ESI†). The B3LYP functional combines the Becke's three-parameter nonlocal hybrid exchange potential with the nonlocal correlation functional of Lee, Yang, and Parr. The nature of the stationary points was verified by analytical computations of harmonic vibrational frequencies. Intrinsic reaction coordinate (IRC) calculations with the Gonzalez and Schlegel method were carried out to check the two minimum energy structures connecting each TS.[25] ΔH, ΔS, and ΔG were also calculated within the ideal gas, rigid rotor, and harmonic oscillator approximations at a pressure of 1 atm and a temperature of 298.15 K.[26]

Synthesis of chromanones 7 and 8

Procedure at room temperature. Chromone-3-carboxylic acid (**4**) (0.5 mmol) was suspended in THF (1.5 mL). $Sc(OTf)_3$ (catalytic), nucleophile (1–5 equiv.) and isocyanide (**5**; 0.5 mmol) were successively added and the mixture was stirred under N_2 atmosphere. The solvent was concentrated and the residue was purified by flash column chromatography (SiO_2; hexane–EtOAc gradient), giving the corresponding product.

Thermal procedure. A solution of chromone-3-carboxylic acid (**4**, 0.5 mmol), isocyanide (**5**, 0.5 mmol), nucleophile (1–5 equiv.) and $Sc(OTf)_3$ (catalytic) in dry toluene was heated at 60–70 °C under N_2 atmosphere. The solvent was concentrated and the residue was purified by flash column chromatography (SiO_2; hexane–EtOAc gradient), giving the corresponding product.

Procedure under microwave irradiation. Chromone-3-carboxylic acid (**4**) (0.5 mmol) was suspended in THF (1 mL). Catalyst, nucleophile (1–5 equiv.) and isocyanide (**5**; 2.5 mmol if Nu is H_2O and 1.5 equiv. for other nucleophiles) were successively added and the mixture was irradiated in a microwave reactor at 150 W and 100 °C in a closed vial for 3–6 min. The solvent was concentrated and the residue was purified by flash column chromatography (SiO_2; hexane–EtOAc gradient), giving the corresponding product.

Methyl 2-(cyclohexylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and methyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7a). (mw: 76%; thermal in MeOH, 8% $Sc(OTf)_3$: 86%), obtained as a white solid; mp 119–121 °C; IR (cm^{-1}) 3286, 2927, 2853, 1739, 1701, 1655, 1629, 1561, 1440, 1099, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ ***en*-7a**: 12.13 (bs, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.09 (d, J = 7.3 Hz, 1H), 5.60 (s, 1H), 3.88 (s, 3H), 3.73–3.61 (m, 1H), 2.10–0.91 (m, 10H); ***cis*-7a**: 7.97 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.13 (dd, J = 14.3, 8.0 Hz, 2H), 6.65 (d, J = 8.5 Hz, 1H), 4.95 (d, J = 3.2 Hz, 1H), 4.23 (d, J = 3.2 Hz, 1H), 3.68 (s, 3H), 3.73–3.61 (m, 1H), 2.10–0.91 (m, 10H); ***trans*-7a**: 7.97 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.13 (dd, J =

14.3, 8.0 Hz, 2H), 6.38 (d, J = 8.0 Hz, 1H), 5.32 (d, J = 10.0 Hz, 1H), 4.05 (d, J = 10.0 Hz, 1H), 3.85 (s, 3H), 3.73–3.61 (m, 1H), 2.10–0.91 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.62 (C), 170.52 (C), 168.64 (C), 165.78 (C), 165.69 (C), 161.87 (C), 159.25 (C), 155.29 (C), 136. 81 (CH), 136.68 (CH), 133.35 (CH), 128.10 (CH), 127.85 (C), 125.27 (CH), 122.91 (CH), 122.87 (CH), 122.35 (CH), 120.11 (C), 117.83 (CH), 117.76 (C), 117.66 (CH), 116.06 (CH), 92.52 (C), 77.65 (CH), 77.12 (CH), 72.46 (CH), 54.87 (CH), 53.68 (CH_3), 52.90 (CH), 52.82 (CH_3), 52.01 (CH_3), 48.40 (CH), 47.98 (CH), 32.97 (CH_2), 32.91 (CH_2), 32.83 (CH_2), 32.75 (CH_2), 25.48 (CH_2), 25.39 (CH_2), 24.96 (CH_2), 24.85 (CH_2), 24.71 (CH_2), 24.65 (CH_2), 24.47 (CH_2), 24.31 (CH_2); MS (EI) m/z (%) 331 (M^+, 3), 272 (7), 218 (41), 206 (99), 146 (100); HRMS (EI) Calcd for $C_{18}H_{21}NO_5$: 331.1420. Found: 331.1407.

Methyl 2-(2,6-dimethylphenylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and methyl 2-(2,6-dimethylphenylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7b). (mw: 50%), obtained as a white solid; mp 186–188 °C; IR (cm^{-1}) 3429, 1732, 1703, 1661, 1538, 1462, 1441, 1344, 772. ^{1}H NMR (400 MHz, $CDCl_3$) δ **en-7b**: 12.16 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.47 (bs, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.20–6.95 (m, 5H), 5.83 (s, 1H), 3.87 (s, 3H), 1.93 (s, 6H); ***cis*-7b**: 8. 14 (bs, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.20–6.95 (m, 6H), 5.17 (d, J = 3.2 Hz, 1H), 4.32 (d, J = 3.2 Hz, 1H), 3.69 (s, 3H), 2.32 (s, 6H); ***trans*-7b**: 7.98 (d, J = 6.3 Hz, 1H), 7.76 (bs, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.20–6.95 (m, 5H), 5.60 (d, J = 7.7 Hz, 1H), 4.24 (d, J = 7.7 Hz, 1H), 3.81 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.31 (C), 185.14 (C), 168.09 (C), 165.57 (C), 158.75 (C), 136.95 (CH), 136.86 (CH), 135.35 (C), 133.57 (CH), 128.34 (CH), 128.14 (CH), 127.99 (CH), 127.88 (CH), 127.51 (CH), 125.30 (CH), 123.12 (CH), 123.00 (CH), 122.62 (CH), 117.80 (CH), 116.45 (CH), 99.99 (C), 78.17 (CH), 77.22 (CH), 72.89 (CH), 54.25 (CH), 53.06 (CH_3), 52.12 (CH_3), 18.10 (CH_3), 18.04 (CH_3); MS (EI) m/z (%) 353 (M^+, 8), 321 (14), 293 (10), 275 (21), 205 (100), 174 (98); HRMS (EI) Calcd for $C_{20}H_{19}NO_5$: 353.1263. Found: 353.1263.

Ethyl 2-(cyclohexylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and ethyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7c). (thermal: 70%), obtained as a white solid; mp 145–146 °C; IR (cm^{-1}) 3291, 2932, 2955, 1652, 1625, 1557, 1276, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ **en-7c**: 12.22 (bs, 1H), 7.70 (dd, J = 7.7, 1.6 Hz, 1H), 7.38 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 7.05 (td, J = 7.6, 1.0 Hz, 1H), 6.98 (dd, J = 8.2, 0.8 Hz, 1H), 6.06 (d, J = 7.7 Hz, 1H), 5.60 (s, 1H), 4.37 (dq, J = 7.1, 1.7 Hz, 2H), 3.18–3.61 (m, 1H), 2.06–0.91 (m, 10H), 1.38 (t, J = 7.1 Hz, 3H); ***cis*-7c**: 7.97 (dd, J = 7.9, 1.6 Hz, 1H), 7.57 (dt, J = 7.7, 1.7 Hz, 1H), 7.18–7.09 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 4.95 (d, J = 3.2 Hz, 1H), 4.21 (d, J = 3.2 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.98–3.93 (m, 1H), 2.06–0.91 (m, 13H); ***trans*-7c**: 7.97 (dd, J = 7.9, 1.6 Hz, 1H), 7.57 (dt, J = 7.7, 1.7 Hz, 1H), 7.18–7.09 (m, 2H), 6.35 (d, J = 7.8 Hz, 1H), 5.32 (d, J = 9.8 Hz, 1H), 4.31 (q, J = 7.3 Hz, 2H), 4.03 (d, J = 9.8 Hz, 1H), 3.86–3.76 (m, 1H), 2.06–0.91 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.02, 186.05, 185.79, 168.64, 167.12, 165.95, 165.71, 165.32, 161.94, 159.24, 158.85, 155.46, 136.74, 136.60, 133.32, 128.03, 127.80, 125.18, 122.84, 122.79, 122.25, 120.34, 120.12, 117.78, 117.77, 117.64, 116.07, 92.63, 77.72, 77.16, 72.49, 62.02, 61.11, 54.91, 53.81, 48.44, 48.34, 47.97, 32.91, 32.83, 32.78, 30.94, 25.49, 25.38, 24.94, 24.86, 24.70, 24.63, 24.51, 24.34, 14.35, 14.05, 13.98; MS (EI) m/z (%) 331 (M^+, 6), 219 (95), 191 816), 172 (96), 120 (100); HRMS (EI) Calcd for $C_{19}H_{23}NO_5$: 345.1576. Found: 345.1564.

Ethyl 2-(*tert*-butylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and ethyl 2-(*tert*-butylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7d). (mw: 55%), obtained as a white oil; IR (cm^{-1}) 3369, 2973, 1739, 1691, 1550, 1537, 1463, 1301, 1261, 1222, 765; ^{1}H NMR (500 MHz, $CDCl_3$) δ **en-7d**: 7.70 (dd, J = 7.7, 1.5 Hz, 1H), 7.38 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 7.15–7.05 (m, 1H), 6.96 (dd, J = 8.2, 0.8 Hz, 1H), 6.00 bs (1H), 5.52 (s, 1H), 4.14 (qd, J = 7.1, 4.8 Hz, 3H), 1.40–1.20 (m, 12H); ***cis*-7d**: 8.00–7.92 (m, 1H), 7.60–7.55 (m, 1H), 7.15–7.05 (m, 2H), 6.60 (bs, 1H), 4.87 (d, J = 3.2 Hz, 1H), 4.42–4.34 (m, 2H), 4.19 (d, J = 3.2, Hz, 1H), 1.40–1.20 (m, 12H); ***trans*-7d**: 8.00–7.92 (m, 1H), 7.60–7.55 (m, 1H), 7.15–7.05 (m, 2H), 6.25 (bs, 1H), 5.24 (d, J = 9.5 Hz, 1H), 4.34–4.28 (m, 2H), 4.03 (d, J = 9.5 Hz, 1H), 1.40–1.20 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.11 (C), 185.92 (C), 168.77 (C), 167.19 (C), 165.92 (C), 165.75 (C), 165.40 (C), 162.06 (C), 159.21 (C), 158.85 (C), 155.55 (C), 147.00 (CH), 136.70 (CH), 136.60 (CH), 133.36 (CH), 131.39 (CH), 128.03 (CH), 127.76 (CH), 125.20 (CH), 122.79 (CH), 122.16 (CH), 122.06 (CH), 120.35 (C), 120.08 (C), 119.23 (CH), 117.78 (CH), 117.72 (CH), 117.63 (CH), 116.03 (CH), 92.59 (C), 78.09 (CH), 72.68 (CH), 62.01 (CH_2), 61.97 (CH_2), 61.15 (CH_2), 60.41 (CH_2), 54.78 (CH), 53.72 (CH), 51.71 (CH), 51.33 (C), 29.70 (CH_3), 28.71 (CH_3), 28.65 (CH_3), 28.59 (CH_3), 14.35 (CH_3), 14.20 (CH_3), 14.04 (CH_3), 14.00 (CH_3); MS (EI) m/z (%) 319 (M^+, <5), 256 (20), 245 (14), 219 (62), 172 (100), 146 (99); HRMS (EI) Calcd for $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1428.

Ethyl 2-(2-(2-methoxyethoxy)ethylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and ethyl 2-(2-(2-methoxyethoxy)ethylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7e). (mw: 68%), obtained as a white oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***en*-7e**: 12.23 (bs, 1H), 7.70 (dd, J = 7.7, 1.6 Hz, 1H), 7.38 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 7.20–6.96 (m, 2H), 6.74 (s, 1H), 5.65 (s, 1H), 4.39–4.28 (m, 2H), 3.72–3.33 (m, 11H), 1.37 (t, J = 7.1 Hz, 3H); ***cis*-7e**: 7.99–7.93 (m, 1H), 7.58 (ddd, J = 8.9, 7.2, 1.7 Hz, 1H), 7.17–6.99 (m, 2H), 4.98 (d, J = 3.2 Hz, 1H), 4.21 (d, J = 3.2 Hz, 1H), 4.19–4.09 (m, 2H), 3.72–3.33 (m, 11H), 1.19 (t, J = 7.1 Hz, 3H); ***trans*-7e**: 7.99–7.93 (m, 1H), 7.58 (ddd, J = 8.9, 7.2, 1.7 Hz, 1H), 7.17–6.99 (m, 2H), 5.36 (d, J = 9.8 Hz, 2H), 4.19–4.09 (m, 2H), 4.05 (d, J = 9.8 Hz, 2H), 3.72–3.33 (m, 11H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.02 (C), 185.73 (C), 170.10 (C), 169.72 (C), 167.09 (C), 167.06 (C), 166.91 (C), 165.26 (C), 162.05 (C), 159.27 (C), 158.90 (C), 155.50 (C), 146.82 (CH), 136.74 (CH), 136.62 (CH), 133.31 (CH), 128.00 (CH), 127.72 (CH), 125.07 (CH), 122.78 (CH), 122.19 (CH), 122.08 (CH), 120.29 (C), 120.17 (C), 117.78 (CH), 117.69 (C), 116.41 (CH), 92.37 (C), 77.68 (CH), 77.24 (CH) 77.21 (CH), 72.49 (CH), 71.85 (CH_2), 71.78 (CH_2), 70.25 (CH_2), 70.23 (CH_2), 70.20, 69.68 (CH_2), 69.64 (CH_2), 69.54 (CH_2), 62.01 (CH_2), 61.14 (CH_2), 59.06 (CH_3), 59.05 (CH_3), 54.78 (CH), 53.80 (CH),

39.22 (CH_2), 39.17 (CH_2), 39.06 (CH_2), 14.28 (CH_3), 14.03 (CH_3), 13.93 (CH_3); MS (EI) *m/z* (%) 365 (M^+, <5), 219 (100), 173 (76); HRMS (EI) Calcd for $C_{18}H_{23}NO_7$: 365.1475. Found: 365.1472.

***tert*-Butyl 2-(cyclohexylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and *tert*-butyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7f).** (mw: 60%), obtained as a yellow oil; IR (cm^{-1}) 3378, 2932, 2855, 1736, 1688, 1656, 1463, 1306, 1145; ^1H NMR (500 MHz, $CDCl_3$) δ ***en*-7f**: 12.37 (bs, 1H), 7.67 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.16–6.94 (m, 2H), 6.01 (d, *J* = 7.5 Hz, 1H.), 5.52 (s, 1H), 3.79–3.65 (m, 1H), 2.06–0.91 (m, 19H); ***cis*-7f**: 7.98–7.91 (m, 1H), 7.56 (ddd, *J* = 8.8, 7.3, 1.7 Hz, 1H), 7.16–6.94 (m, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 4.91 (d, *J* = 3.1 Hz, 1H), 4.11 (d, *J* = 3.2 Hz, 1H), 3.93–3.88 (m, 1H), 2.06–0.91 (m, 19H); ***trans*-7f**: 7.98–7.91 (m, 1H), 7.56 (ddd, *J* = 8.8, 7.3, 1.7 Hz, 1H), 7.16–6.94 (m, 2H), 6.30 (d, *J* = 8.1 Hz, 1H), 5.27 (d, *J* = 9.2 Hz, 1H), 3.95 (d, *J* = 9.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.06–0.91 (m, 19H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.36 (C), 186.32 (C), 168.75 (C), 166.13 (C), 166.04 (C), 165.69 (C), 164.43 (C), 159.13 (C), 158.79 (C), 155.66 (C), 136.52 (CH), 136.33 (CH), 133.11 (CH), 127.87 (CH), 127.67 (CH), 124.97 (CH), 122.68 (CH), 122.65 (CH), 122.05 (CH), 120.50 (C), 120.32 (C), 117.83 (CH), 117.60 (CH), 117.55 (CH), 116.02 (CH), 83.12 (C), 82.86 (C), 78.01 (CH), 77.41 (CH), 72.79 (CH), 55.55 (CH), 54.74 (CH), 48.47 (CH), 48.16 (CH), 47.95 (CH), 32.96 (CH_2), 32.91 (CH_2), 32.87 (CH_2), 28.31 (CH_3), 27.91 (CH_3), 27.76 (CH_3), 25.52 (CH_2), 25.39 (CH_2), 25.38 (CH_2), 24.91 (CH_2), 24.88 (CH_2), 24.66 (CH_2), 24.58 (CH_2), 24.42 (CH_2); MS (EI) *m/z* (%) 373 (M^+, 4), 273 (10), 247 (16), 191 (100), 147 (94); HRMS (EI) Calcd for $C_{21}H_{27}NO_5$: 373.1889. Found: 373.1871.

(*E*)-3,7-Dimethylocta-2,6-dienyl 2-(cyclohexylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and (*E*)-3,7-dimethylocta-2,6-dienyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7g). (mw: 45%), obtained as a white solid; mp 118–120 °C; IR (cm^{-1}) 3281, 2935, 2854, 1669, 1651, 1627, 1557, 1276, 1099; ^1H NMR (500 MHz, $CDCl_3$) δ ***en*-7g**: 12.19 (bs, 1H), 7.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41–7.34 (m, 1H), 7.05 (dd, *J* = 11.3, 3.8 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.60 (s, 1H), 5.43 (t, *J* = 6.5 Hz, 1H), 5.10 (t, *J* = 6.9 Hz, 1H), 4.83 (ddd, *J* = 39.8, 12.4, 7.2 Hz, 2H), 3.73–3.64 (m, 1H), 2.19–0.93 (m, 23H); ***cis*-7g**: 7.96 (dd, *J* = 9.9, 3.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.16–6.95 (m, 2H), 6.63 (d, *J* = 8.2 Hz, 1H), 5.23 (t, *J* = 7.0 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 4.95 (d, *J* = 3.1 Hz, 1H), 4.63–4.54 (m, 2H), 4.21 (d, *J* = 3.1 Hz, 1H), 3.97–3.88 (m, 1H), 2.19–0.93 (m, 23H); ***trans*-7g**: 7.96 (dd, *J* = 9.9, 3.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.16–6.95 (m, 2H), 6.30 (d, *J* = 8.1 Hz, 1H), 5.46–5.36 (m, 1H), 5.34 (d, *J* = 9.1 Hz, 1H), 5.14–5.09 (m, 1H), 4.91–4.72 (m, 2H), 4.08 (d, *J* = 9.1 Hz, 1H), 3.85–3.75 (m, 1H), 2.19–0.93 (m, 23H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.71 (C), 185.68 (C), 169.92 (C), 168.64 (C), 167.14 (C), 165.95 (C), 165.68 (C), 165.31 (C), 162.13 (C), 159.25 (C), 158.81 (C), 155.83 (C), 142.99 (C), 142.86 (C), 142.77 (C), 136.59 (CH), 136.45 (CH), 133.34 (CH), 131.90 (C), 131.81 (C), 131.73 (C), 128.04 (CH), 127.82 (CH), 125.12 (CH), 123.81 (CH), 123.66 (CH), 123.65 (CH), 122.76 (CH), 122.72 (CH), 122.08 (CH), 120.48 (C), 120.24 (C), 117.93 (CH), 117.77 (CH), 117.7 (CH), 117.56 (CH), 117.50 (CH), 116.10 (CH), 92.55 (C), 77.89 (CH), 72.59 (CH), 62.88 (CH_2), 62.84 (CH_2), 61.96 (CH_2), 54.75 (CH), 53.89 (CH), 48.42 (CH), 48.32 (CH), 47.96 (CH), 39.55 (CH_2), 39.50 (CH_2), 39.45 (CH_2), 32.91 (CH_2), 32.83 (CH_2), 32.80 (CH_2), 26.32 (CH_2), 26.30 (CH_2), 26.27 (CH_2), 25.63 (CH_3), 25.52 (CH_2), 25.43 (CH_2), 25.39 (CH_2), 24.92 (CH_2), 24.85 (CH_2), 24.64 (CH_2), 24.55 (CH_2), 24.50 (CH_2), 24.36 (CH_2), 17.67 (CH_3), 17.66 (CH_3), 16.57 (CH_3), 16.49 (CH_3), 16.41 (CH_3); MS (FAB) *m/z* (%) 454 (M^+ + 1, 4), 318 (100), 274 (76), 191 (58); HRMS (FAB) Calcd for $C_{27}H_{36}NO_5$: 454.2593. Found: 454.2571.

Heptyl 2-(*tert*-butylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and heptyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7h). (mw: 60%), obtained as a white solid; mp 66.5–68.5 °C; IR (cm^{-1}) 3288, 2959, 2926, 1683, 1661, 1632, 1559, 1403, 1259, 756; ^1H NMR (500 MHz, $CDCl_3$) δ ***en*-7h**: 12.19 (bs, 1H), 7.71 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.06 (td, *J* = 7.6, 1.0 Hz, 1H), 6.97 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.99 (s, 1H), 5.51 (s, 1H), 4.36–4.24 (m, 2H), 1.80–1.69 (m, 2H), 1.46–1.17 (m, 17H), 0.91 (t, *J* = 6.9 Hz, 3H); ***cis*-7h**: 7.99–7.95 (m, 1H), 7.60–7.54 (m, 1H), 7.16–7.02 (m, 2H), 6.58 (s, 1H), 4.86 (d, *J* = 2.2 Hz, 1H), 4.20 (d, *J* = 2.1 Hz, 1H), 4.13–4.02 (m, 2H), 1.80–1.69 (m, 2H), 1.46–1.17 (m, 17H), 0.91 (t, *J* = 6.9 Hz, 3H); ***trans*-7h**: 7.99–7.95 (m, 1H), 7.60–7.54 (m, 1H), 7.16–7.02 (m, 2H), 6.20 (s, 1H), 5.25 (d, *J* = 9.0 Hz, 1H), 4.13–4.02 (m, 2H), 4.06 (d, *J* = 9.0 Hz, 1H), 1.80–1.69 (m, 2H), 1.46–1.17 (m, 17H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.85 (C), 170.08 (C), 168.62 (C), 167.23 (C), 165.91 (C), 165.66 (C), 165.32 (C), 161.91 (C), 159.19 (C), 158.79 (C), 155.5 (C), 136.56 (CH), 136.46 (CH), 133.27 (CH), 127.98 (CH), 127.76 (CH), 125.17 (CH), 122.73 (CH), 122.71 (CH), 122.13 (CH), 120.50 (C), 120.17 (C), 117.79 (CH), 117.70 (C), 117.54 (CH), 116.03 (CH), 92.67 (C), 78.24 (CH), 77.26 (CH), 72.79 (CH), 66.05 (CH_2), 65.96 (CH_2), 65.20 (CH_2), 54.69 (CH), 53.81 (CH), 51.67 (C), 51.66 (C), 51.28 (CH_2), 31.68 (CH_2), 31.66 (CH_2), 31.58 (CH_2), 28.88 (CH_2), 28.80 (CH_2), 28.70 (CH_3), 28.68 (CH_3), 28.67 (CH_3), 28.58 (CH_3), 28.40 (CH_2), 28.35 (CH_2), 25.80 (CH_2), 25.64 (CH_2), 25.48 (CH_2), 22.53 (CH_2), 22.47 (CH_2), 14.01 (CH_3), 13.99 (CH_3); MS (EI) *m/z* (%) 389 (M^+, 10), 287 (98), 256 (15), 216 (20), 172 (100); HRMS (EI) Calcd for $C_{22}H_{31}NO_5$: 389.2202. Found: 389.2206.

2-(2-Methoxyethoxy)ethyl 2-(2-(2-methoxyethoxy)ethylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and 2-(2-methoxyethoxy)ethyl 2-(2-(2-methoxyethoxy)ethylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate (7i). (thermal: 60%), obtained as a yellow oil; IR (cm^{-1}) 3360, 2931, 1735, 1687, 1609, 1464, 1108; ^1H NMR (500 MHz, $CDCl_3$) δ ***en*-7i**: 12.02 (bs, 1H), 7.68 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.40–7.32 (m, 1H), 7.19–6.95 (m, 2H), 5.67 (s, 1H), 4.55–4.32 (m, 2H), 3.85–3.30 (m, 20H); ***cis*-7i**: 7.98–7.90 (m, 1H), 7.60–7.52 (m, 1H), 7.16–6.96 (m, 2H), 4.98 (d, *J* = 3.2 Hz, 1H), 4.28–4.17 (m, 3H), 3.85–3.30 (m, 20H); ***trans*-7i**: 7.98–7.90 (m, 1H), 7.60–7.52 (m, 1H), 7.16–6.96 (m, 2H), 4.98 (d, *J* = 3.2 Hz, 1H), 5.36 (d, *J* = 9.7 Hz, 1H), 4.09 (d, *J* = 9.7 Hz, 1H), 4.55–4.32 (m, 2H), 3.85–3.30

(m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.76 (C), 185.46 (C), 169.81 (C), 169.64 (C), 166.98 (C), 166.96 (C), 166.88 (C), 165.16 (C), 162.44 (C), 159.31 (C), 158.93 (C), 155.89 (C), 146.64 (C), 136.75 (CH), 136.61 (CH), 133.49 (CH), 127.96 (CH), 127.69 (CH), 125.04 (CH), 122.77 (CH), 122.05 (CH), 120.25 (C), 117.81 (CH), 117.46 (CH), 116.41 (CH), 92.11 (C), 77.64 (CH), 77.21 (CH), 72.43 (CH), 71.87 (CH_2), 71.83 (CH_2), 71.77 (CH_2), 70.47 (CH_2), 70.43 (CH_2), 70.41 (CH_2), 70.21 (CH_2), 70.16 (CH_2), 69.60 (CH_2), 69.51 (CH_2), 68.88 (CH_2), 68.77 (CH_2), 68.48 (CH_2), 65.03 (CH_2), 64.87 (CH_2), 63.80 (CH_2), 59.05 (CH_3), 59.01 (CH_3), 58.98 (CH_3), 54.76 (CH), 53.77 (CH), 39.23 (CH_2), 39.18 (CH_2), 39.11 (CH_2); MS (EI) *m*/*z* (%) 239 (M^+, <5), 293 (91), 242 (56), 216 829), 173 (100); HRMS (EI) Calcd for $C_{21}H_{29}NO_9$: 439.1842. Found: 439.1823.

***N*-Cyclohexyl-3,4-dihydro-4-oxo-2*H*-chromene-2-carboxamide (8a).** (rt: 70%, mw: 95%), obtained as a white solid; mp 144–146 °C; IR (cm^{-1}) 3272, 3072, 2928, 2851, 1696, 1655, 1606, 1563, 1463, 1304, 1228, 1118, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (dd, *J* = 12.2, 5.0 Hz, 1H), 7.11 (dd, *J* = 15.1, 7.8 Hz, 2H), 6.50 (s, 1H), 4.91 (dd, *J* = 12.9, 3.4 Hz, 1H), 3.96–3.82 (m, 1H), 3.21 (dd, *J* = 17.2, 3.4 Hz, 1H), 2.90 (dd, *J* = 17.2, 13.0 Hz, 1H), 2.10–1.05 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.30 (C), 167.22 (C), 159.46 (C), 136.25 (CH), 127.36 (CH), 122.55 (CH), 121.25 (C), 117.70 (CH), 76.64 (CH), 48.16 (CH), 40.16 (CH_2), 32.97 (CH_2), 25.43 (CH_2), 24.78 (CH_2); MS (EI) *m*/*z* (%) 273 (M^+, 18), 192 (22), 147 (100); HRMS (EI) Calcd for $C_{16}H_{19}NO_3$: 273.1365. Found: 273.1362.

***N*-*tert*-Butyl-3,4-dihydro-4-oxo-2*H*-chromene-2-carboxamide (8b).** (rt: 20%, mw: 100%), obtained as a yellow oil; IR (cm^{-1}) 3354, 2968, 2922, 1689, 1606, 1532, 1463, 1304, 1225, 1117, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56–7.50 (m, 1H), 7.08 (td, *J* = 8.5, 0.8 Hz, 2H), 6.47 (s, 1H), 4.80 (dd, *J* = 13.0, 3.4 Hz, 1H), 3.16 (dd, *J* = 17.2, 3.4 Hz, 1H), 3.00–2.75 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.41 (C), 167.28 (C), 159.43 (C), 136.20 (CH), 127.32 (CH), 122.50 (CH), 121.24 (C), 117.69 (CH), 76.81 (CH), 51.48 (C), 40.08 (CH_2), 28.70 (CH_3); MS (CI) *m*/*z* (%) 248 (M^+ + 1, 27), 192 (25), 149 (100); HRMS (CI) Calcd for $C_{14}H_{18}NO_3$: 248.1287. Found: 248.1288.

***N*-Benzyl-3,4-dihydro-4-oxo-2*H*-chromene-2-carboxamide (8c).** (mw: 86%), obtained as a white solid; mp 102–104 °C; IR (cm^{-1}) 3450, 1688, 1660, 1606, 1465, 1307, 1229; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.59–7.49 (m, 1H), 7.43–7.29 (m, 5H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.00 (bs, 1H), 5.00 (dd, *J* = 12.9, 3.4 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 2H), 3.25 (dd, *J* = 17.2, 3.5 Hz, 1H), 2.96 (dd, *J* = 13.8, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.07 (C), 168.20 (C), 159.37 (C), 137.51 (C), 136.31 (CH), 128.87 (CH), 127.81 (CH), 127.42 (CH), 122.65 (CH), 121.26 (C), 117.70 (CH), 76.67 (CH), 43.29 (CH_2), 40.09 (CH_2); MS (CI) *m*/*z* (%) 282 (M^+ + 1, 100), 175 (35), 147 (54); HRMS (CI) Calcd for $C_{17}H_{16}NO_3$: 282.1130. Found: 282.1132.

3,4-Dihydro-*N*-(2,6-dimethylphenyl)-4-oxo-2*H*-chromene-2-carboxamide (8d). (rt: 20%, mw: 77%), obtained as a white solid; mp 177–178 °C; IR (cm^{-1}) 3426, 1692, 1667, 1606, 1466, 1304, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.7 Hz, 1H), 7.92 (bs, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.20–7.07 (m, 5H), 5.17 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.29 (dd, *J* = 17.1, 3.8 Hz, 1H), 3.10 (dd, *J* = 17.1, 11.6 Hz, 1H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.74 (C), 166.76 (C), 159.34 (C), 136.41 (CH), 135.35 (C), 132.43 (C), 128.37 (CH), 127.81 (CH), 127.50 (CH), 122.80 (CH), 121.39 (C), 117.79 (CH), 76.94 (CH), 39.97 (CH_2), 18.27 (CH_3); MS (CI) *m*/*z* (%) 296 (M^+ + 1, 9), 177 (9), 150 (56), 71 (100); HRMS (CI) Calcd for $C_{18}H_{18}NO_3$: 296.1287. Found: 296.1287.

***N*-(2-(2-Methoxyethoxy)ethyl)-3,4-dihydro-4-oxo-2*H*-chromene-2-carboxamide (8e).** (mw: 70%), obtained as a yellow oil; IR (cm^{-1}) 3423, 2880, 1693, 1607, 1539, 1464, 1304, 1226, 1119, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.17 (bs, 1H), 7.13–7.07 (m, 2H), 4.94 (dd, *J* = 12.9, 3.5 Hz, 1H), 3.69–3.55 (m, 8H), 3.42 (s, 3H), 3.19 (dd, *J* = 17.2, 3.5 Hz, 1H), 2.93 (dd, *J* = 17.2, 12.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.20 (C), 168.30 (C), 159.52 (C), 136.24 (CH), 127.33 (CH), 122.49 (CH), 121.24 (C), 117.76 (CH), 76.65 (CH), 71.84 (CH_2), 70.25 (CH_2), 69.60 (CH_2), 59.05 (CH_3), 40.02 (CH_2), 39.02 (CH_2); MS (EI) *m*/*z* (%) 293 (M^+, 23), 217 (66), 171 (100); HRMS (EI) Calcd for $C_{15}H_{19}NO_5$: 293.1263. Found: 293.1264.

***N*-(*tert*-Butylacetate)-3,4-dihydro-4-oxo-2*H*-chromene-2-carboxamide (8f).** (mw: 60%), obtained as a white solid; mp 88–90 °C; IR (cm^{-1}) 3343, 1735, 1697, 1670, 1609, 1466, 1308, 1225, 768; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.56 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.21 (bs, 1H), 7.15–7.10 (m, 2H), 4.98 (dd, *J* = 13.2, 3.4 Hz, 1H), 4.06 (t, *J* = 4.8 Hz, 2H), 3.20 (dd, *J* = 17.2, 3.4 Hz, 1H), 2.99–2.91 (dd, *J* = 17.2, 13.5 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.01 (C), 168.50 (C), 168.30 (C), 159.43 (C), 136.32 (CH), 127.34 (CH), 122.60 (CH), 121.21 (C), 117.81 (CH), 82.78 (C), 76.55 (CH), 41.71 (CH_2), 39.97 (CH_2), 28.06 (CH_3); MS (EI) *m*/*z* (%) 305 (M^+, 11), 232 (12), 205 (69), 146 (100); HRMS (EI) Calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1278.

(*E*)-3-(Benzylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (9a).[13b] (thermal: 63%), obtained as a white solid; m.p. 111–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.40 (s, 1H), 10.26 (bs, 1H), 7.66 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.46–7.29 (m, 5H), 7.07 (dd, *J* = 13.0, 7.7 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.84 (t, *J* = 7.1 Hz, 1H), 5.80 (d, *J* = 7.7 Hz, 1H), 4.52 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.32 (C), 162.37 (C), 154.65 (CH), 137.35 (C), 133.97 (CH), 128.99 (CH), 128.01 (CH), 127.98 (CH), 127.24 (CH), 120.16 (C), 118.31 (CH), 118.26 (CH), 89.49 (CH), 53.05 (CH_2); MS (CI) *m*/*z* (%) 254 (M^+ + 1, 25), 147 (26), 55 (100).

(*S*)-Ethyl 2-((*E*)-3-(2-hydroxyphenyl)-3-oxoprop-1-enylamino)-3-methylbutanoate (9b). (rt: 36%), obtained as a white sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.40 (s, 1H), 10.21 (d, *J* = 10.8 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.39–7.34 (m, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 12.9, 7.7 Hz, 1H), 6.85–6.80 (m, 1H), 5.79 (d, *J* = 7.7 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.69 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.32–2.22 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.53 (C), 170.60 (C), 162.43 (C),

153.38 (CH), 134.04 (CH), 128.01 (CH), 120.11 (C), 118.26 (CH), 89.82 (CH), 68.00 (CH), 61.63 (CH_2), 32.07 (CH), 19.18 (CH_3), 17.47 (CH_3), 14.21 (CH_3); MS (CI) *m/z* (%) 320 (M^+ + C_2H_5, 48), 292 (M^+ + 1, 100), 218 (25), 198 (55).

Synthesis of chromenones (10, 11)

0.2 mmol of pyridinium perbromide were added to a solution of 0.2 mmol of chromanone (**7a** or **8a**) in 2 mL of dry CH_2Cl_2. After 24 h stirring at room temperature under nitrogen atmosphere, 1 mL of a saturated solution of $NaHSO_3$ was added. The mixture was washed with H_2O, extracted with CH_2Cl_2 and dried with Na_2SO_4, and the solvent was removed in the rotary evaporator. The crude of the reaction was dissolved in 2 mL of dry CH_2Cl_2, and Et_3N (1 equiv. for **8a** and 2 equiv. for **7a**) was added. After stirring 24 h at room temperature under nitrogen atmosphere, 1 mL of 10% HCl was added. The mixture was washed with H_2O, extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was eliminated. The residue was purified by flash column chromatography (SiO_2; hexane–EtOAc gradient), giving the corresponding product.

Methyl 2-(cyclohexylcarbamoyl)-4-oxo-4*H*-chromene-3-carboxylate (10). (80%), obtained as a white solid; mp 67–69 °C; IR (cm^{-1}) 3358, 2930, 2855, 1741, 1653, 1529, 1465, 1390, 1118, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, J = 8.0, 1.6 Hz, 1H), 7.78 (ddd, J = 8.7, 7.2, 1.7 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.52–7.46 (m, 1H), 6.80 (d, J = 8.1 Hz, 1H), 4.06–3.90 (m, 1H), 4.01 (s, 3H), 2.10–1.18 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.09 (C), 164.26 (C), 157.46 (C), 154.49 (C), 151.10 (C), 135.05 (CH), 126.38 (CH), 126.30 (CH), 123.43 (C), 120.88 (C), 118.05 (CH), 53.11 (CH_3), 49.19 (CH), 32.83 (CH_2), 25.34 (CH_2), 24.84 (CH_2); MS (EI) *m/z* (%) 329 (M^+, 32), 296 (100), 253 (42), 228 (30), 215 (99), 198 (54), 104 (94); HRMS (EI) Calcd for $C_{18}H_{19}NO_5$: 329.1263. Found: 329.1268.

***N*-Cyclohexyl-4-oxo-2*H*-chromene-2-carboxamide (11).**[20] (77%), obtained as a white solid; mp 165–169 °C dec; IR (cm^{-1}) 3319, 2929, 2852, 1649, 1612, 1552, 1464, 1392, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 8.0, 1.6 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.18 (s, 1H), 6.77 (bs, 1H), 4.04–3.93 (m, 1H), 2.12–1.18 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.24 (C), 158.24 (C), 155.24 (C), 154.94 (C), 134.48 (CH), 126.12 (CH), 125.95 (CH), 124.32 (C), 118.07 (CH), 112.09 (CH), 49.08 (CH), 32.92 (CH_2), 25.41 (CH_2), 24.85 (CH_2); MS (EI) *m/z* (%) 271 (M^+, 24), 228 (12), 189 (100), 149 (43); HRMS (EI) Calcd for $C_{16}H_{17}NO_3$: 271.1208. Found: 271.1208.

Synthesis of 1-(2-methoxyethoxy)-2-isocyanoethane (5e)

2-(2-Methoxyethoxy)ethanamine was prepared from 2-(2-methoxyethoxy)ethanol following the procedure described by Whitesides,[27] except that the mesylate of diethylene glycol monomethyl ether was synthesised in place of the analogous tosylate.

The preparation of **5e** was carried out using a modification of a known synthesis of isocyanides,[9c,28] as follows.

In a 1 L round-bottomed flask fitted with an efficient magnetic stirrer, a reflux condenser and a pressure-equalising dropping funnel, 1.35 mol of NaOH was dissolved in 54 mL of H_2O. A solution of 2-(2-methoxyethoxy)ethanamine (41.33 g, 34.7 mmol), chloroform (2 mL, 36.4 mmol), dichloromethane (54 mL) and triethylbenzylammonium chloride (TEBA) (5%) was added dropwise under vigorous stirring at 45 °C. The reaction mixture was stirred for 2 h at 45 °C and then at rt overnight. Then, dichloromethane (100 mL) was added to the reaction mixture and the phases separated. The organic layer was washed with three 200 mL portions of water and then stirred with a saturated buffer solution (KH_2PO_4–K_2HPO_4 = 16 : 1, 140 mL) for 30 min. If this treatment is omitted the isolation of the isocyanide in a pure form is difficult because of the co-distillation of the unreacted amine. The resulting suspension was filtered through a Celite pad (*ca*. 8 cm diameter) and the precipitate washed with dichloromethane (70 mL). The filtrate was transferred to a separatory funnel and the organic phase separated, dried (Na_2SO_4), and evaporated to dryness. The residue was distilled under atmospheric pressure, collecting the fraction that distilled at *ca.* 155 °C, to give 1-(2-methoxyethoxy)-2-isocyanoethane (21.2 g, 47%).

2-(2-Methoxyethoxy)ethyl methanesulfonate. (93%), obtained as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39–4.35 (m, 2H), 3.76–3.72 (m, 2H), 3.68–3.62 (m, 2H), 3.55– 3.51 (m, 2H), 3.36 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.77 (CH_2), 70.55 (CH_2), 69.26 (CH_2), 69.00 (CH_2), 58.97 (CH_3), 37.59 (CH_3).

2-(2-Methoxyethoxy)ethanamine. (87%), obtained as a colorless liquid; ^{1}H NMR (400 MHz, DMSO) δ 3.52–3.47 (m, 2H), 3.46–3.41 (m, 2H), 3.35 (t, J = 5.8 Hz, 2H), 3.25 (s, 3H), 2.63 (t, J = 5.8 Hz, 2H).

1-(2-Methoxyethoxy)-2-isocyanoethane (5e). (47%), obtained as a colorless liquid; IR (cm^{-1}) 2938, 2896, 1455, 1352, 1175, 1119, 1017, 975, 922; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74–3.66 (m, 4H), 3.61–3.54 (m, 4H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.21 (C), 71.83 (CH_2), 70.78 (CH_2), 68.67 (CH_2), 59.10 (CH_3); MS (EI) *m/z* (%) 98 (M^+ − OCH_3, 10), 84 (86), 72 (25); MS (CI) *m/z* (%) 120 (M^+ − NC + CH_5, 24), 103 (27), 72 (61).

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Notes and references

1 (*a*) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (*b*) G. W. Bemis and M. A. Murcko, *J. Med. Chem.*, 1996, **39**, 2887.
2 (*a*) S. T. Saengchantara and T. W. Wallace, *Nat. Prod. Rep.*, 1986, **3**, 465; (*b*) J. B. Harborne and C. A. Williams, *Nat. Prod. Rep.*, 2001, **18**, 310.
3 (*a*) R. Brigelius-Flohe and F. Galli, *Mol. Nutr. Food Res.*, 2010, **54**, 583; (*b*) R. Brigelius-Flohe, *Free Radical Biol. Med.*, 2009, **46**, 543; (*c*) J. Atkinson, R. F. Epand and R. M. Epand, *Free Radical Biol. Med.*, 2008, **44**, 739.
4 (*a*) T. W. Wu, N. Hashimoto, J. Wu, D. Carey, R. K. Li, D. A. G. Mickle and R. D. Weisel, *Biochem. Cell Biol.*, 1990, **68**, 1189; (*b*) K. Satoh,

T. Kadofuku and H. Sakagami, *Anticancer Res.*, 1997, **17**, 2459; (*c*) P. Raspor, S. Plesnicar, Z. Gazdag, M. Pesti, M. Miklavcic, B. Lah, R. Logar-Marinsek and B. Poljsak, *Cell Biol. Int.*, 2005, **29**, 57; (*d*) H. A. Eum and S. M. Lee, *Br. J. Pharmacol.*, 2004, **142**, 35.

5 H. Lee, K. Lee, J. K. Jung, J. Cho and E. A. Theodorakis, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2745.

6 (*a*) J. H. Kwak, S. W. Won, T. J. Kim, W. Yi, E. H. Choi, S. C. Kim, H. Park, E. Roh, J. K. Jung, B. Y. Hwang, J. T. Hong, Y. Kim, J. Cho and H. Lee, *Arch. Pharmacal Res.*, 2009, **32**, 167; (*b*) B. H. Kim, K. H. Lee, E. Y. Chung, Y. S. Chang, H. Lee, C. K. Lee, K. R. Min and Y. Kim, *Eur. J. Pharmacol.*, 2006, **543**, 158.

7 (*a*) S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 3029; (*b*) K. J. Hodgetts, K. I. Maragkou, T. W. Wallace and R. C. R. Wootton, *Tetrahedron*, 2001, **57**, 6793.

8 (*a*) C. F. Marcos, A. G. Neo and S. Barriga, *Electronic Encyclopedia of Organic Reagents*, John Wiley & sons, Ltd., Chichester, UK, 2006; (*b*) A. Domling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3169.

9 (*a*) A. G. Neo, R. M. Carrillo and C. F. Marcos, *Org. Biomol. Chem.*, 2011, **9**, 4850; (*b*) C. F. Marcos, S. Marcaccini, G. Menchi, R. Pepino and T. Torroba, *Tetrahedron Lett.*, 2008, **49**, 149; (*c*) A. G. Neo, C. F. Marcos, S. Marcaccini and R. Pepino, *Tetrahedron Lett.*, 2005, **46**, 7977; (*d*) C. F. Marcos, S. Marcaccini, R. Pepino, C. Polo and T. Torroba, *Synthesis*, 2003, 691; (*e*) S. Marcaccini, R. Pepino, C. F. Marcos, C. Polo and T. Torroba, *J. Heterocycl. Chem.*, 2000, **37**, 1501; (*f*) R. Bossio, S. Marcaccini, R. Pepino and C. F. Marcos, *J. Chem. Educ.*, 2000, **77**, 382; (*g*) R. Bossio, C. F. Marcos, S. Marcaccini and R. Pepino, *Synthesis*, 1997, 1389; (*h*) R. Bossio, C. F. Marcos, S. Marcaccini and R. Pepino, *Heterocycles*, 1997, **45**, 1589; (*i*) R. Bossio, C. F. Marcos, S. Marcaccini and R. Pepino, *Tetrahedron Lett.*, 1997, **38**, 2519.

10 (*a*) S. Marcaccini, A. G. Neo and C. F. Marcos, *J. Org. Chem.*, 2009, **74**, 6888; (*b*) A. G. Neo, R. M. Carrillo, S. Barriga, E. Moman, S. Marcaccini and C. F. Marcos, *Synlett*, 2007, 327.

11 (*a*) A. Neo, R. Carrillo, J. Delgado, S. Marcaccini and C. Marcos, *Mol. Diversity*, 2011, **15**, 529; (*b*) R. M. Carrillo, A. G. Neo, L. Lopez-Garcia, S. Marcaccini and C. F. Marcos, *Green Chem.*, 2006, **8**, 787; (*c*) A. G. Neo, J. Delgado, C. Polo, S. Marcaccini and C. F. Marcos, *Tetrahedron Lett.*, 2005, **46**, 23.

12 (*a*) I. Yavari, A. Shaabani and M. T. Maghsoodlou, *Monatsh. Chem.*, 1997, **128**, 697; (*b*) I. Yavari, H. Djahaniani and L. Moradi, *Mendeleev Commun.*, 2004, **14**, 38; (*c*) Y. Ito, H. Kato and T. Saegusa, *J. Org. Chem.*, 1982, **47**, 741; (*d*) A. Shaabani, E. Soleimani, A. H. Rezayan, A. Sarvary and H. R. Khavasi, *Org. Lett.*, 2008, **10**, 2581.

13 (*a*) C. K. Ghosh and S. Khan, *Synthesis*, 1981, 719; (*b*) V. A. Zagorevskii, I. D. Tsvetkova, E. K. Orlova, V. G. Vinokurov and V. S. Troitskaya, *Chem. Heterocycl. Compd.*, 1970, **6**, 952.

14 R. Williams, Y. Zhou, C. M. Niswender, Q. Luo, P. J. Conn, C. W. Lindsley and C. R. Hopkins, *ACS Chem. Neurosci.*, 2010, **1**, 411.

15 (*a*) A. J. Souers, R. R. Iyengar, A. S. Judd, D. W. A. Beno, J. Gao, G. Zhao, M. E. Brune, J. J. Napier, M. M. Mulhern, J. K. Lynch, J. C. Freeman, D. Wodka, C. J. Chen, H. D. Falls, S. Brodjian, B. D. Dayton, G. J. Diaz, E. N. Bush, R. Shapiro, B. A. Droz, V. Knourek-Segel, L. E. Hernandez, K. C. Marsh, R. M. Reilly, H. L. Sham, C. A. Collins and P. R. Kym, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 884; (*b*) R. R. Iyengar, J. K. Lynch, M. M. Mulhern, A. S. Judd, J. C. Freeman, J. Gao, A. J. Souers, G. Zhao, D. Wodka, H. Doug Falls, S. Brodjian, B. D. Dayton, R. M. Reilly, S. Swanson, Z. Su, R. L. Martin, S. T. Leitza, K. A. Houseman, G. Diaz, C. A. Collins, H. L. Sham and P. R. Kym, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 874; (*c*) J. K. Lynch, J. C. Freeman, A. S. Judd, R. Iyengar, M. Mulhern, G. Zhao, J. J. Napier, D. Wodka, S. Brodjian, B. D. Dayton, D. Falls, C. Ogiela, R. M. Reilly, T. J. Campbell, J. S. Polakowski, L. Hernandez, K. C. Marsh, R. Shapiro, V. Knourek-Segel, B. Droz, E. Bush, M. Brune, L. C. Preusser, R. M. Fryer, G. A. Reinhart, K. Houseman, G. Diaz, A. Mikhail, J. T. Limberis, H. L. Sham, C. A. Collins and P. R. Kym, *J. Med. Chem.*, 2006, **49**, 6569.

16 (*a*) D. A. Nugiel, J. R. Krumrine, D. C. Hill, J. R. Damewood, P. R. Bernstein, C. D. Sobotka-Briner, J. Liu, A. Zacco and M. E. Pierson, *J. Med. Chem.*, 2010, **53**, 1876; (*b*) D. L. Maier, C. Sobotka-Briner, M. Ding, M. E. Powell, Q. Jiang, G. Hill, J. R. Heys, C. S. Elmore, M. E. Pierson and L. Mrzljak, *J. Pharmacol. Exp. Ther.*, 2009, **330**, 342.

17 S.-r. Choi, A. Pradhan, N. L. Hammond, A. G. Chittiboyina, B. L. Tekwani and M. A. Avery, *J. Med. Chem.*, 2007, **50**, 3841.

18 K. S. Lee, S. H. Seo, Y. H. Lee, H. D. Kim, M. H. Son, B. Y. Chung, J. Y. Lee, C. Jin and Y. S. Lee, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2857.

19 I. B. Paek, H. Y. Ji, M. S. Kim, G. S. Lee and H. S. Lee, *J. Sep. Sci.*, 2006, **29**, 628.

20 A. Gaspar, T. Silva, M. Yanez, D. Vina, F. Orallo, F. Ortuso, E. Uriarte, S. Alcaro and F. Borges, *J. Med. Chem.*, 2011, **54**, 5165.

21 A. Boumendjel, E. Nicolle, T. Moraux, B. Gerby, M. Blanc, X. Ronot and J. Boutonnat, *J. Med. Chem.*, 2005, **48**, 7275.

22 G. W. T. M. J. Frisch, H. B. Schlegel, G. E. Scuseria, M. A. Rob, 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 and J. A. Pople, *GAUSSIAN 03*, Gaussian, Inc., Wallingford, CT, 2003.

23 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*b*) C. T. Lee, W. T. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785; (*c*) A. D. Becke, *Phys. Rev. A: At., Mol., Opt. Phys.*, 1988, **38**, 3098.

24 W. J. R. Hehre, L. Pople and J. A. P. v. R. Schleyer, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.

25 (*a*) C. Gonzalez and H. B. Schlegel, *J. Phys. Chem.*, 1990, **94**, 5523; (*b*) C. Gonzalez and H. B. Schlegel, *J. Chem. Phys.*, 1989, **90**, 2154.

26 D. A. McQuarrie, *Statistical Mechanics*, Harper and Row, New York, 1976.

27 A. Jain, S. G. Huang and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 5057.

28 G. W. Gokel, R. P. Widera and W. P. Weber, *Org. Synth.*, 1976, **55**, 96.

