JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00813 • Publication Date (Web): 19 May 2020

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Cross-coupling of amide and amide derivatives to umbelliferone nonaflates: synthesis of coumarin derivatives and fluorescent materials

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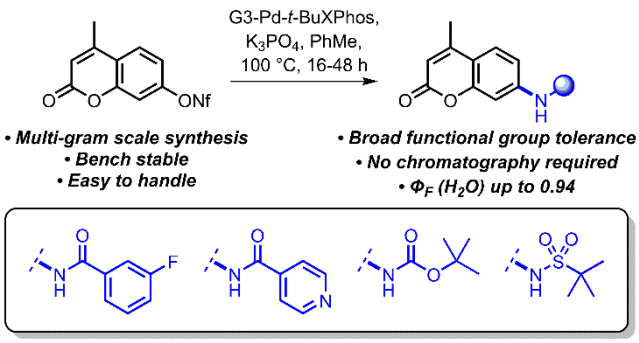
Keywords

Cross-coupling, palladium, Buchwald-Hartwig, umbelliferone, coumarin, fluorescence, hydrogel.



Abstract

The Buchwald-Hartwig cross-coupling reaction between 4-methylumbelliferone derived nonaflates with amides, carbamates, and sulfonamides is described. A wide variety of *N*-substituted 7-amino coumarin analogues were prepared in good to excellent yields. The photophysical properties of aqueous soluble derivatives were determined and displayed auxochrome based variations. Gram scale synthesis provided an acrylamide analogue which

was used to fabricate a fluorescent poly(2-hydroxylethyl methacrylate) (pHEMA) hydrogel that was resistant to leaching in ultrapure H_2O. We envisage our reported protocol to access 4-methylumbelliferone derivatives will find use towards the development of new fluorescent coumarin-based probes by researchers in the field.

Introduction

Fluorogenic materials are essential tools in chemical biology,[1] biochemical and cellular assays,[2,3] and analyte sensing.[4,5] Coumarins, such as 7-amino-4-methylcoumarin (AMC), are frequently employed as reporters for these applications; by masking the amine as an amide the donor-acceptor system properties are altered and the fluorescent signal from AMC is perturbed. Fluorogenic probes are commonly designed using this masking strategy, often through the conjugation of a small peptide to the amine, which upon cleavage under assay conditions (e.g. enzymatic cleavage) restores the fluorescence intensity.[6] In addition to frequently appearing as a scaffold in medicinal chemistry studies,[7-10] functionalised coumarins have been investigated in a number of contexts. For example, benzamide **1** (Figure 1) has been investigated as a probe to monitor cationic photopolymerization reactions.[11] Although long-established,[12,13] sulfonamidyl coumarins were recently highlighted by Sharma *et al.* as a neglected fluorophore; as such, compound **2** was prepared and characterised to demonstrate photophysical properties equivalent to that of AMC in phosphate buffered saline at pH 7.4.[14] Additionally, the 4-nitrobenzylcarbamate **3** was prepared to investigate nitroreductase activity in bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA).[15] Classically, AMC is synthesised using a three-step procedure and then functionalised using acyl[10] or sulfonyl halides.[14] Amide coupling reagents are also used to generate analogues, but standard reagents are not always effective.[13,16]

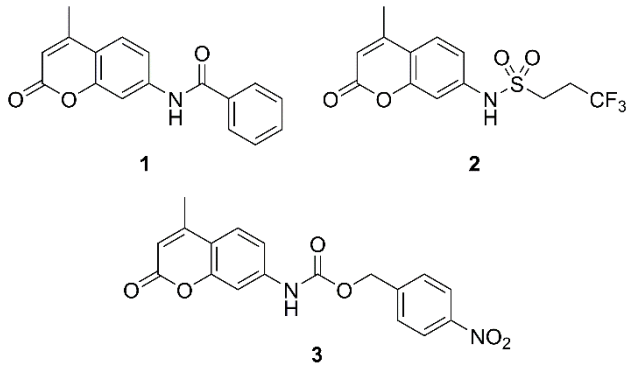


Figure 1. Representative examples of amide, sulfonamide and carbamate substituted coumarins.

The Buchwald-Hartwig cross-coupling reaction has recently emerged as a powerful and indispensable tool for the synthesis of fluorescent probes and has unlocked molecules that are synthetically challenging using traditional methods. This approach has been demonstrated in rhodamine (e.g. the azetidine auxochrome)[17-19] and 1,8-naphthalimide fluorophore development.[17,20-24] The power of the Buchwald-Hartwig cross-coupling methodology stems from the ability to incorporate amines, amides, carbamates and sulfonamides in a single (often terminal) synthetic transformation from common intermediates.[25-28]

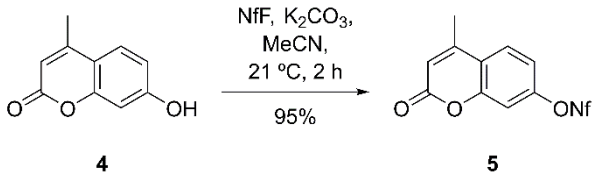
The substitution of amine auxochromes into coumarin systems has been achieved using Buchwald-Hartwig methodology to install amines and anilines.[29,30] Due to a lack of suitable syntheses of halogenated coumarins,[30] the 7-hydroxy coumarins derived from Pechmann condensations are typically converted to the triflate for use as the electrophilic coupling partner. However, triflates are susceptible to hydrolysis and sometimes require high catalyst loadings in order to generate favourable conversion to product.[18,31,32] The related coumarin nonaflate, a more hydrolytically stable sulfonate,[33] has been exploited by the Bodke group for a number of cross-coupling reactions including Buchwald-Hartwig aminations,[34] Suzuki,[35] and Sonogashira.[36] Aside from an isolated example of cross-coupling with acetamide[31] and another report using sulfonamides,[32] there are no investigations detailing Buchwald-Hartwig cross-coupling conditions that facilitate the incorporation of amides and related functional groups

directly onto the coumarin with demonstrated substrate scope. This work establishes a synthetic procedure to access a broad range of amide, carbamate and sulfonamide substituted coumarins from the corresponding nonaflates using Buchwald-Hartwig cross-coupling conditions.

Results and Discussion

Synthesis

The synthesis of **5** proceeded in a straightforward manner; treatment of 4-methylumbelliferone (**4**, Scheme 1) with nonafluorobutanesulfonyl fluoride (NfF, 1.1 equiv.) and K_2CO_3 (1.5 equiv.) in MeCN at ambient temperature for 2 hours lead to full conversion and precipitation of **5** from solution. Dilution of the reaction mixture with H_2O and isolation using vacuum filtration afforded **5** in excellent yield (95%) as an easy to handle powder which was bench-stable for extended periods (>18 months, as evidenced by NMR and HPLC analysis).

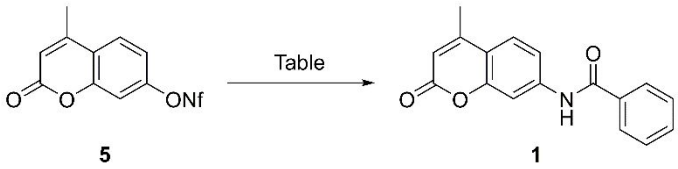


Scheme 1. Synthesis of nonaflate starting material.

Nonaflate **5** and benzamide as model substrates were used to investigate the reaction conditions (Table 1) which were based upon those reported by Joy *et al.* who successfully coupled anilines and pyridinones to **5**.[34] Treatment of nonaflate **5** with benzamide (1.2 equiv., Entry 1) in the presence of G3-Pd-xantphos (1 mol%) and Cs_2CO_3 (1.4 equiv.) in 1,4-dioxane (1 mL per 0.1 mmol of **5**) at 100 °C led to full consumption of the starting material after 22 hours and compound **1** was isolated in 22% yield using column chromatography. The low yield of **1** was partially attributed to limited compound solubility in the solvent mixtures required for column chromatography and potential decomposition on silica gel which was indicated by two-dimensional TLC. For the remaining entries in Table 1 compound **1** was isolated by trituration

using Et_2O. Unlike reports from Bodke,[34-36] we found that the addition of fluoride (as TBAF) resulted in sulfonate hydrolysis as the dominant reaction while no cross-coupling product was observed (Entry 2). A modest increase in yield of amide **1** (38%, Entry 3) was achieved when using 2.0 equivalents of Cs_2CO_3.

Table 1. Optimisation of reaction conditions.



5 **1**

Entry	$BzNH_2$ (equiv.)	G3-Pd-L (mol%)	Base (equiv.)	Solvent (M)	T (°C)	t (h)	Yield (%)
1	1.2	xantphos (1)	Cs_2CO_3 (1.4)	1,4-Dioxane (0.1)	100	22	22[a]
2[b]	1.2	xantphos (1)	Cs_2CO_3 (1.4)	1,4-Dioxane (0.1)	100	16	0[c]
3	1.2	xantphos (1)	Cs_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	24	38
4	1.2	DPPF (1)	Cs_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	24	0[c]
5	1.2	JackiePhos (1)	Cs_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	24	35
6	1.2	*t*-BuBrettPhos (1)	Cs_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	16	59
7	1.2	*t*-BuXPhos (1)	Cs_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	16	59
8	2.0[d]	*t*-BuXPhos (1)	Cs_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	24	24
9	1.2	*t*-BuXPhos (1)	K_2CO_3 (2.0)	1,4-Dioxane (0.1)	100	24	42
10	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	1,4-Dioxane (0.1)	100	24	61
11	1.2	*t*-BuXPhos (1)	K_3PO_4 (3.0)[d]	1,4-Dioxane (0.1)	100	16	24
12	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	PhMe (0.1)	100	16	67
13	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	*i*-PrOH (0.1)	83	16	64
14	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	*t*-BuOH (0.1)	82	16	59
15	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	PhMe (0.2)	100	16	70
16	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	PhMe (0.4)	100	16	85
17[e]	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	PhMe (0.6)	100	16	79
18	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	*t*-BuOH (0.4)	82	16	74
19	1.2	*t*-BuXPhos (1)	K_3PO_4 (2.0)	*i*-PrOH (0.4)	83	16	59

a) Purified using column chromatography; b) 2.0 equivalents of TBAF were used; c) Compound **4** was the major product; d) Drying of the reagent did not improve the yield; e) Conducted on a 1.5 mmol scale. All other reaction performed at 0.5 mmol.

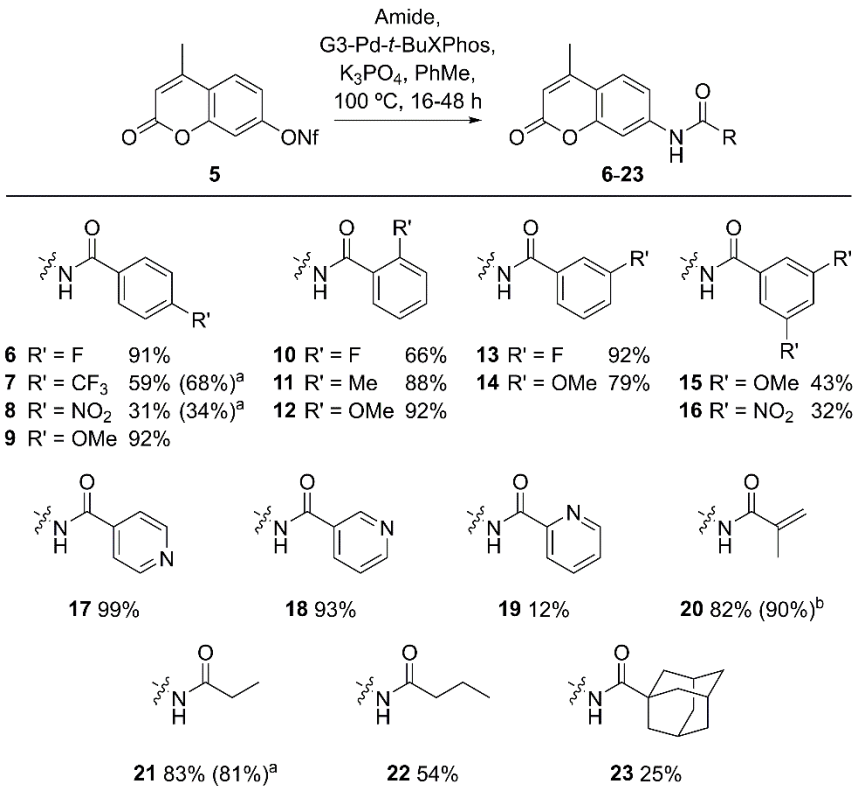
When G3-Pd-dppf was used in place of G3-Pd-xantphos (Table 1, Entry 4) the formation of **1** was not observed, instead, the isolated material was predominantly 4-methylumbelliferone (**4**).

Biaryl phosphine ligands were then trialled: G3-Pd-JackiePhos (Entry 5) effected the formation of **1** in 35% yield whereas *t*-BrettPhos and *t*-BuXPhos ligands (used as G3-precatalysts) both afforded the product in 59% yield (Entries 6 and 7). Given the relative cost, but comparable performance of the *t*-BrettPhos and *t*-BuXPhos ligands, the use of G3-Pd-*t*-BuXPhos was favoured for this investigation.

When the reaction was performed using 2.0 equivalents of $BzNH_2$ (Entry 8) the yield of **1** was reduced to 24%. A lower yield of **1** (42%, Entry 9) was obtained using K_2CO_3 (2.0 equiv.), while K_3PO_4 (2.0 equiv.) gave a comparable yield of **1** (61%, Entry 10) to that obtained when Cs_2CO_3 was employed. On the basis of relative cost between K_3PO_4 and Cs_2CO_3, the use of the former was favoured. When 3.0 equivalents of K_3PO_4 were used, a decreased yield was obtained (24%, Entry 11). PhMe at 100 °C was found to be a suitable solvent for this transformation giving the benzamide product in 67% yield after 16 hours (Entry 12). Similar results were obtained using *i*-PrOH and *t*-BuOH (64 and 59%, Entries 13 and 14, respectively) despite the reactions being conducted at a lower temperature. No product was obtained when trial reactions were performed in DMF, DMSO or MeCN.

Finally, performing the reaction at higher concentration led to improved yields; at 0.2 M and 0.4 M of **5** in PhMe, the product was isolated in 70 and 85% yield, respectively (Entries 15 and 16). A yield of 79% was obtained when the reaction was performed at 0.6 M in PhMe, however at this concentration the reaction becomes impractical due to difficulties with stirring. Prompted by this observation, we reinvestigated the reaction at 0.4 M in *t*-BuOH, which gave a modest improvement in yield to 74% (Entry 18) compared with the reaction performed at 0.1 M. A slight decrease in yield of **1** (59%) was obtained when carrying out the reaction in *i*-PrOH at a concentration of 0.4 M (Entry 19) compared to the more dilute conditions (Entry 13).

With reliable conditions in hand (Entry 16), the reaction scope was investigated using a representative set of amides. The cross-coupling reaction with 4-fluorobenzamide proceeded efficiently to give **6** in 91% yield (Scheme 2). However, more electron deficient 4-trifluoromethyl or 4-nitrobenzamides gave lower yields of amides **7** and **8** (59 and 31%, respectively). Conversely, using the electron rich 4-methoxybenzamide gave **9** in a 92% yield. Substitution in the 2-position of the benzamide was tolerated with 2-fluorobenzamide giving **10** in a modest yield of 66%, while 2-methyl **11** and 2-methoxy derivatives **12** were isolated in high yields (88 and 92%, respectively). Both 3-fluoro and 3-methoxybenzamides were incorporated in good yields giving **13** and **14** in 92 and 79% yield, respectively. The 3,5-dimethoxy **15** and 3,5-dintiro **16** analogues were isolated in 43 and 37% yield, respectively. It is noteworthy that the commercially available 3,5-dimethoxybenzamide required recrystallisation prior to use or no product formation was observed.



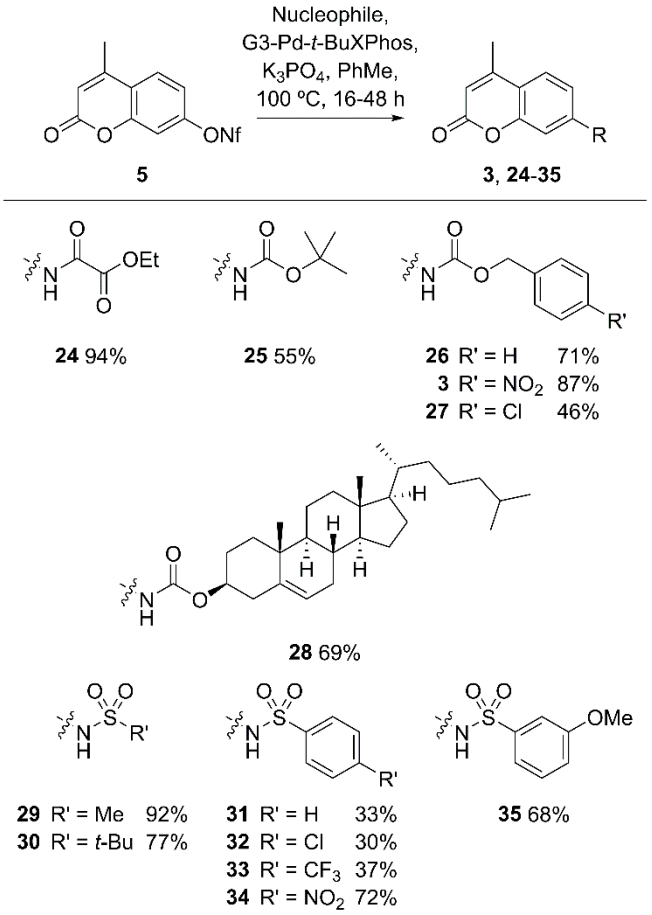
Scheme 2. *Reagents and conditions*: **5** (0.50 mmol), amide (1.2 equiv.), G3-Pd-*t*-BuXPhos (1–2 mol%), K_3PO_4 (2.0 equiv.), PhMe (2.6 mL per mmol), 100 °C, 16–48 h.; a) G3-Pd-*t*-BuBrettPhos (1 mol%) was used in place of G3-Pd-*t*-BuXPhos; b) The reaction was performed using 1 gram (2.2 mmol) of **5**.

In general, benzamides gave high yields of the desired product, although lower yields were obtained in the presence of strong electron withdrawing substituents. The reduced nucleophilicity of these benzamides likely hinders transmetalation on the Pd(II) oxidative addition species.[37] Based on results obtained during our optimisation (Table 1 Entry 6 *cf* Entry 7) and reported superiority the *t*-BuBrettPhos ligand was investigated for the synthesis of **7** and **8**.[27,38,39] In both instances a modest increase in yield was found using G3-Pd-*t*-BuBrettPhos (1 mol%): compound **7** was isolated in 68%, while **8** was still prepared in low yield (34%).

Pyridyl 4- and 3-carboxamides reacted smoothly giving amides **17** and **18** in 99 and 93% yield, respectively. The cross-coupling of **5** with pyridine-2-carboxamide afforded **19** in 12% yield; a result which is in keeping with previous reports.[22] Acrylamide **20** was produced in 82% yield when performed on a 0.5 mmol scale; conducting the reaction on a gram scale (2.2 mmol of **5**) gave **20** in 90% yield. Reactions performed using propanamide with either the *t*-BuXPhos or *t*-BuBrettPhos ligand gave **21** in high yield (83 and 81%, respectively) while **22** was obtained in 54% yield. For the aliphatic amides significant hydrolysis was observed during the standard work-up procedure; acidification with saturated KH_2PO_4 (pH 5) prior to dilution with H_2O prevented this loss. The isolation of **23** from the crude mixture by trituration with MeOH resulted in some product loss and low yield (25%).

Ethyl oxamate was introduced to give the phosphate reactive coumarin **24** in 94% yield (Scheme 3),[40] while *tert*-butyl carbamate was installed in 55% yield providing the masked 7-amino coumarin **25**, which itself, can be converted to benzamide analogues using $[RhCl(cod)]_2$ and arylboroxines.[41] Similarly, benzyl carbamate was successfully coupled to give Cbz-protected analogue **26** in 71% yield. Substituted benzyl carbamates such as 4-nitrobenzyl

carbamate and 4-chlorobenzyl carbamate were added to the coumarin scaffold to give the corresponding fluorogenic compounds **3** and **27** in 87 and 46% yield, respectively. The latter example provides a synthetic handle for further elaboration and could be applied to the synthesis of fluorogenic probes with self-immolative linkers.[42] A cholesterol derived carbamate was also a suitable cross-coupling partner giving **28** in 69% yield.

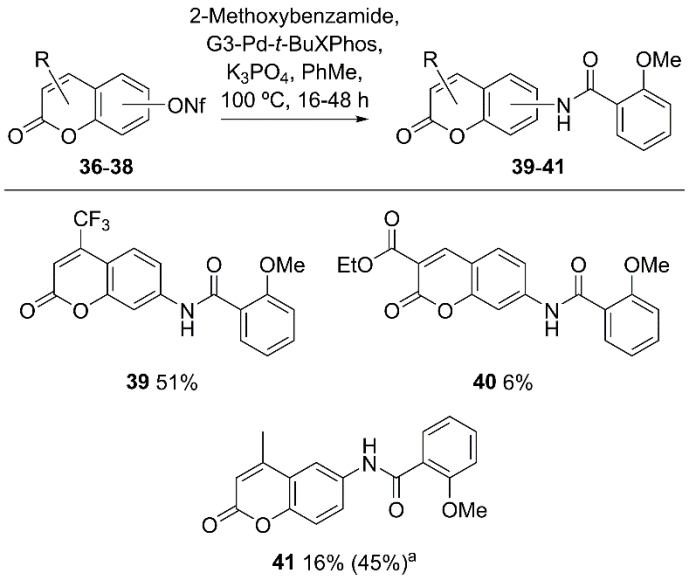


Scheme 3. *Reagents and conditions*: **5** (0.5 mmol), nucleophile: oxamate, carbamate or sulfonamide (1.2 equiv.), G3-Pd-*t*-BuXPhos (1–2 mol%), K_3PO_4 (2.0 equiv.), PhMe (2.6 mL per mmol), 100 °C, 16–48 h.

Alkyl sulfonamides were found to be good substrates for the cross-coupling reaction with **5**; methanesulfonamide and *tert*-butylsulfonamide gave **29** and **30** in 92 and 77% yield, respectively (Scheme 3). Reactions employing benzenesulfonamides were not as productive as the related benzamides shown in Scheme 1, and they also displayed sensitivity to arene substitution. The unsubstituted derivative **31** was isolated in 30% following the standard

conditions and similar results were obtained using 4-chloro and 4-(trifluoromethyl)benzene sulfonamide giving **32** and **33** in 30 and 37% yield, respectively. Conversely, the reaction using 4-nitrobenzene sulfonamide gave the desired coumarin **34** in 72% yield. Similarly, the presence of a weakly electron withdrawing 3-methoxy substituent gave the corresponding product **35** in good yield (68%).

To investigate the modularity of this approach, reactions between substituted coumarin nonaflates and 2-methoxybenzamide were performed. When a trifluoromethyl group was present in the 4-position of the coumarin the reaction gave the desired amide **39** in a modest 51% yield (Scheme 4). The presence of an ethyl ester at the 3-position of the coumarin scaffold adversely impacted the yield obtained for the cross-coupling product **40** (6%) compared to 92% for the 4-methyl analogue (**12**, Scheme 2). Similarly, a low yield (16%) of **41** was obtained when the nonaflate was in the 6-position of the coumarin framework; this was improved to 45% using G3-Pd-*t*-BuBrettPhos. These results highlight the need to develop this chemistry and identify the scope and limitations governed by the inherent reactivity of the coupling partners.



Scheme 4. *Reagents and conditions*: **39–41** (0.5 mmol), 2-methoxybenzamide (1.2 equiv.), G3-Pd-*t*-BuXPhos (1 mol%), K_3PO_4 (2.0 equiv.), PhMe (2.6 mL per mmol), 100 °C, 16–48 h.; a) G3-Pd-*t*-BuBrettPhos (1 mol%) was used in place of G3-Pd-*t*-BuXPhos.

Photophysical Characterisation

For all compounds which were soluble in 1% DMSO in H_2O (*ca.* pH = 8), key photophysical properties were determined (Table 2) to provide an insight into their potential application as probes in aqueous environments. The absorption maxima measured for most of the 7-substituted derivatives is independent of structure and are in the range of 321–331 nm. The presence of the 4-trifluoromethyl moiety of **39** exhibited an anticipated change in absorbance to 340 nm (Entry 15) when compared with the 4-methyl scaffold.[43] Additionally, the 6-amide substituted coumarin **41** had an absorbance maximum at 265 nm (Entry 16), which results from a lack of conjugation of the 6-substituent, and is more characteristic of an unsubstituted coumarin,[44] despite the near planarity of the compound in the solid state (Figure 2). In addition to the expected reduced conjugation from a nitrogen lone pair in the 6-position, further explanation for the absence of a strong charge transfer band in the absorbance spectra of **41** can be derived from the single crystal X-ray structure (Figure 2). The C-N bond length between the amide and the coumarin (1.473(2) Å) is notably longer than the distance measured for the one other 6-amide substituted coumarin[45] reported in the Cambridge Structural Database (CSD, accessed 16/01/2020, C-N distance 1.434(2) Å) and considerably longer than the equivalent distance in the eleven 7-amide substituted coumarin derivatives (C-N bond distance range 1.385(3)–1.418(9) Å; mean 1.40 Å) also reported in the CSD.[46-48] Additionally, the N-C distance (1.309(2) Å) measured between the nitrogen and carbonyl carbon, indicates strong delocalisation of the nitrogen lone pair within the amide bond rather than into the π-system of the coumarin as observed for other 6- and 7-amide substituted coumarins (mean amide bond length 1.37 Å).

Table 2. Photophysical data of coumarin derivatives in 1% DMSO in H_2O.

Entry	Compound	Absorption Properties		Emission Properties				
		λ_{abs} (nm)	ε_{max} (M^{-1} cm^{-1})	λ_{em} (nm)	Stokes shift (nm)	Stokes shift (cm^{-1})	Φ_F	Brightness (M^{-1} cm^{-1})
1	**1**	322	8,300	430	108	7,800	0.06	500
2	**11**	328	11,000	420	92	6,678	0.06	600
3	**12**	326	3,300	443	117	8,101	0.09	300
4	**17**	327	7,900	445	118	8,109	0.03	300
5	**18**	327	5,500	432	105	7,433	<0.01	30
6	**19**	331	3,900	396	65	4,959	<0.01	30
7	**20**	328	8,500	402	74	5,612	<0.01	50
8	**21**	325	15,000	398	73	5,644	0.71	10,700
9	**22**	325	4,800	399	74	5,707	0.68	3,200
10	**25**	327	15,600	403	76	5,767	0.94	14,600
11	**29**	321	7,100	458	137	9,319	0.49	3,500
12	**30**	323	13,400	458	135	9,126	0.48	6,400
13	**31**	321	13,000	458	137	9,319	0.55	7,100
14	**33**	322	11,000	458	136	9,222	0.02	200
15	**39**	340	3,600	434	94	6,370	0.07	200
16	**41**	265	7,100	441	176	15,060	0.05	300

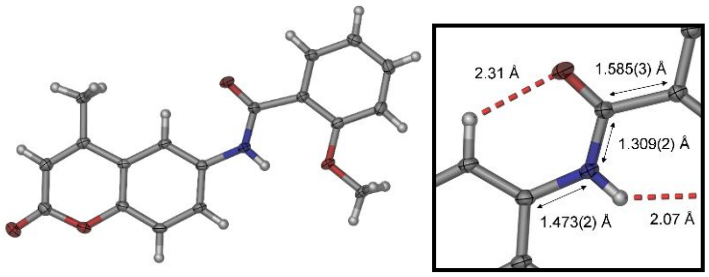


Figure 2. Crystal structure of **41**. Thermal ellipsoids are shown at the 50% confidence interval. Inset: enlarged view of the amide with key distances highlighted.

The emission maxima for amide analogues were observed between 399–445 nm. Subtle variations of the emission wavelength were demonstrated between the unsubstituted benzamide **1** (λ_{em} 430 nm), 2-methylbenzamide **11** (λ_{em} 420 nm) and the 2-methoxybenzamide derivative **12** (λ_{em} 443 nm); however, all displayed low quantum yield (Φ_F <0.10). The emission maxima also varied for the pyridine regioisomers with the 4-pyridine **17** and 3-pyridinecarboxamide **18** analogues emitting blue light (λ_{em} 445 and 432 nm, respectively), while the 2-pyridyl analogue gave a purple emission (λ_{em} 392 nm). In contrast to the benzamide analogues, the propyl and butyl amides **21** and **22** displayed similar absorption and emission properties to the 2-pyridyl system but with enhanced quantum yields (Φ_F 0.71 and 0.68, respectively). The *tert*-butyl

carbamate protected analogue **25** (Entry 10) was the brightest compound in this series; excitation at the absorbance maxima (λ_{abs} 327 nm, ε_{max} 15,600 M^{-1} cm^{-1}) results in emission at 403 nm with a quantum yield of 0.94 resulting in a brightness of 14,600 M^{-1} cm^{-1}. The quantum yield of **25** decreases in DMSO (49%), $CHCl_3$ (32%) and $PhCH_3$ (4%) (Table S2) which could be suggestive of an aggregate induced emission.

The sulfonamide derivatives **29–31** and **33** (Entries 12–15) all demonstrated maximal emission of 458 nm (λ_{ex} ~320 nm) with a shoulder at ~390 nm, as opposed to all other derivatives whose absorption bands were structureless (see ESI for spectra). To investigate this further, a pH titration was conducted on compound **30** at 50 μM between pH 3–9. As the pH of the solution increased, the absorption band at 322 nm decreased while the band at 355 nm increased (Figure 3). An isosbestic point was observed at approximately 331 nm and a pK_a of 8.2 was calculated for compound **30**. When excited at 322 nm, the emission spectra of **30** showed a decline in the 395 nm band and an increase in the 470 nm band as the pH was increased. Furthermore, the pH responsiveness was reversible with the reverse titration from pH 9 to 3 strongly matching the data shown in Figure 4 (see ESI for spectra). This data suggests that the observed shoulder in Figures S178 and S179 (sulfonamides **29** and **30**, respectively) are due to the presence of both protonated and deprotonated species which exist at pH 8 in the 1% DMSO in H_2O; consistent with previous reports.[13] Similar to the observations by Sharma *et al.*,[14] the sulfonamide analogues typically displayed good quantum yields (Φ_F ~0.50, λ_{ex} ~320 nm, λ_{em} 458 nm) for alkyl (**29** and **30**) and benzene (**31**) derivatives. The presence of the 4-trifluoromethyl group in the benzene sulfonamide derivative **33** resulted in reduced efficiency (Φ_F 0.02) despite similar absorption and emission properties (λ_{abs} 322 nm, ε_{max} 11,000 M^{-1} cm^{-1}, λ_{em} 458 nm) to **31**.

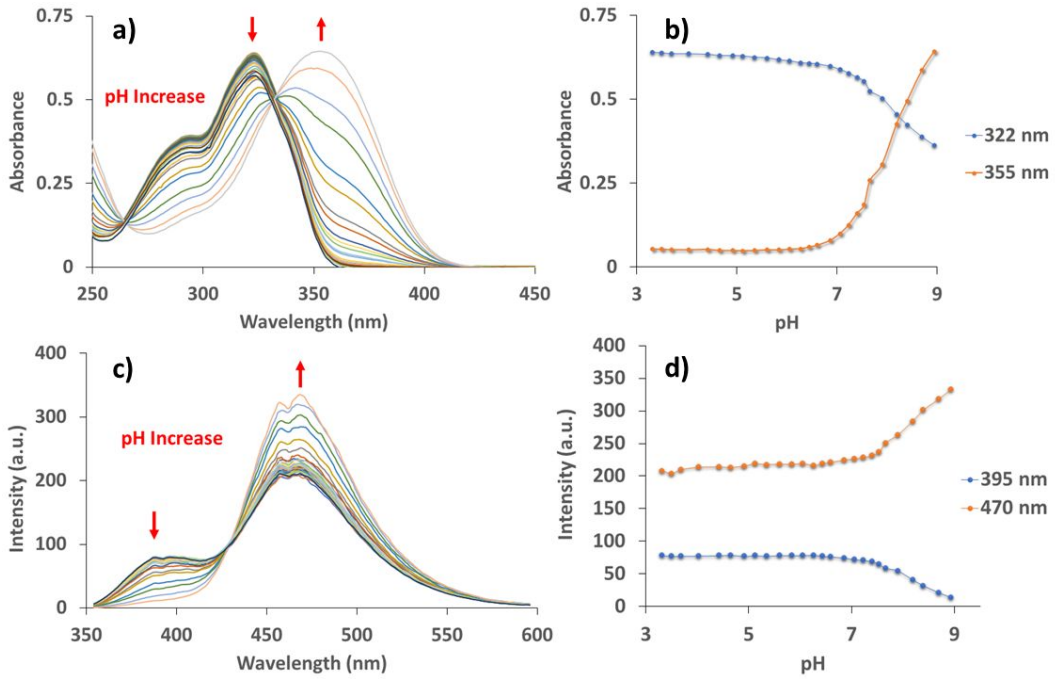


Figure 3. pH titration of compound **30** (50 μM) over a pH range of 3–9 in a 10 mM NaCl solution. a) absorption spectra; b) absorption versus pH at 322 and 355 nm; c) emission spectra (λ_{ex} = 322 nm); and d) emission intensity versus pH at 395 and 470 nm.

These results demonstrate the impact of subtle auxochrome structural variations on the photophysical properties of coumarin compounds. Notably, the high quantum yields for several of the analogues in aqueous conditions, where typical organic fluorophores undergo significant non-radiative decay, suggest that these types of compounds could find use in aqueous sensing applications. Furthermore, the operationally simple Buchwald-Hartwig protocol described should make this family of compounds readily accessible to those interested.

Hydrogel Formation

Given the relatively high quantum efficiency and brightness of the aliphatic amide coumarins (Table 2, Entries 8 and 9) we envisaged that the practically non-fluorescent acrylamide analogue (**20**) would be a suitable reagent for the fabrication of leach-resistant fluorescent cross-linked polymer materials. With this in mind, copolymerisation of **20** with 2-hydroxylethyl methacrylate and ethylene glycol dimethacrylate (crosslinker) was performed to

prepare a coumarin poly(2-hydroxylethyl methacrylate) (pHEMA) derived hydrogel **20**-pHEMA (see ESI for synthesis details). Two hydrogels were also prepared as controls; one in the absence of a fluorophore (pHEMA) and one in the presence of propanamide **22**,[49] which is not competent in radical polymerisation reactions, to give **22**-pHEMA. Each method gave hydrogels that were transparent in visible light (Figure 4A). Both **20**-pHEMA and **22**-pHEMA gave detectable fluorescence upon irradiation at 365 nm (Figure 4B) while the non-fluorescent control performed as expected with no observable emission. The intense visible fluorescence of the acrylamide (**20**) derived gel was an indication of successful cross-linking as the acrylamide itself is essentially non-fluorescent with a brightness of 50 M^{-1} cm^{-1} (Table 2, Entry 7). Effective cross-linking of the acrylamide **20** polymer was demonstrated by its relative resistance to leaching in ultrapure H_2O (Figure 4C). After soaking for 20 hours, the cross-linking gel displayed no change in fluorescence intensity. In contrast, the **22**-pHEMA exhibited a decrease in fluorescent intensity of 12% over the same period, indicating that the non-covalently linked coumarin leached out of the gel matrix.

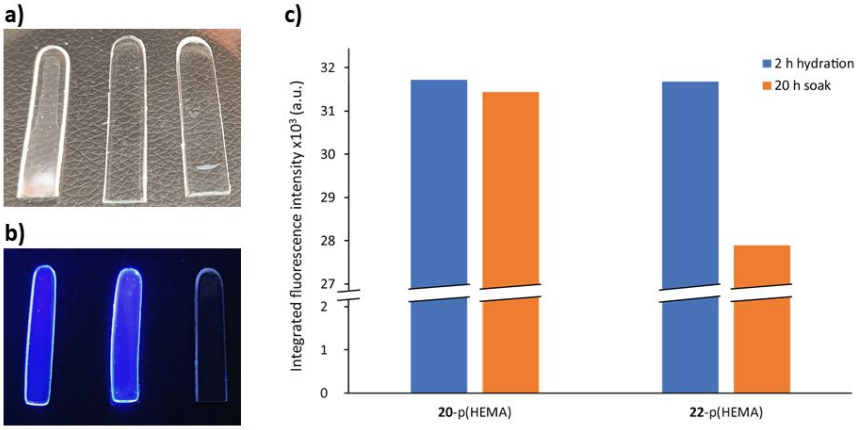


Figure 4. a) and b) show photographs of the fabricated hydrogels illuminated by white and UV (365 nm) light respectively. From left to right the hydrogels are; **20**-pHEMA, **22**-pHEMA, and pHEMA; c) shows the decrease in fluorescence intensity from the **20**-pHEMA and **22**-pHEMA following a 20 h soak in 1 L ultrapure H_2O. A decrease of 0.86 and 11.95% was measured for **20**-pHEMA and **22**-pHEMA, respectively.

Conclusion

The Buchwald-Hartwig cross-coupling reported herein contributes to the growing toolbox for fluorophore synthesis. The bench-stable and easily synthesised hydroxy coumarin derived nonaflates were suitable substrates for the incorporation of a variety of amide, carbamate, and sulfonamide nucleophiles in good to excellent yields. Some aliphatic amides and electron deficient coumarin scaffolds were found to be less competent substrates for the reaction, but in most cases still gave isolatable product. The photophysical properties of all aqueous soluble analogues prepared were established. The aliphatic amides investigated displayed good quantum yields (Φ_F >0.60) while a boc-protected 7-amino-4-methylcoumarin **25** was surprisingly bright (14,600 M^{-1} cm^{-1}) with a purple emission (λ_{em} 403 nm, λ_{ex} 327 nm, Φ_F 0.94) in 1% DMSO in H_2O. Conversely, the benzamide analogues were typically non-fluorescent. Sulfonamide substituted 4-methyl coumarins were typically efficient fluorophores (Φ_F ~ 0.50, λ_{ex} ~320 nm, λ_{em} 458 nm). Furthermore, the sulfonamide proton was found to be more acidic compared to their amide counterparts; *tert*-butylsulfonamide **30** has a pK_a of approximately 8.2. Finally, a non-fluorescent acrylamide derived coumarin **20** was prepared in a gram-scale reaction and found to be a suitable monomer for the preparation of a fluorescent and leach-resistant cross-linked polymer hydrogel **20**-pHEMA. We envisage that our reported conditions to generate 4-methylumbelliferone derivatives will be of great use to researchers wanting to access coumarin-based probes for an array of fluorogenic applications.

Experimental

Unless otherwise indicated all reagents were used as purchased from commercial sources. Purification of 3,5-dimethoxybenzamide was achieved by recrystallisation from hot $CHCl_3$/*n*-hexane. Anhydrous PhMe and MeCN was obtained by drying over freshly activated 3 Å molecular sieves. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates

purchased from Merck (Australia). All reactions performed at elevated temperatures were conducted using a heating mantle. All melting points were obtained using a digital ISG® melting point apparatus and are uncorrected. All ^{1}H, ^{13}C and ^{19}F NMR spectra were collected on a BRUKER AVANCE III 500 MHz FT-NMR spectrometer. All NMR experiments were performed at 25 °C. 2D NMR experiments were performed on most compounds to ensure correct characterisation and can be provided upon request. Samples were dissolved in either $CDCl_3$ or DMSO-d_6, with the residual solvent peak used as the internal reference—$CDCl_3$; 7.26 (^{1}H) and 77.0 (^{13}C), DMSO-d_6; 2.50 (^{1}H) and 39.52 (^{13}C).[50] Fluorine spectra are externally referenced using 0.05% α,α,α-trifluorotoluene in $CDCl_3$; −63.72 (^{19}F). High resolution mass spectral data was collected using an AB SCIEX TripleTOF 5600 mass spectrometer in a 95% MeOH in H_2O solvent system containing 0.1% formic acid. Analyte solutions were prepared in HPLC grade methanol (conc. ~1 mg mL^{-1}). RP-HPLC experiments were conducted on a Shimadzu Prominence UltraFast Liquid Chromatography (UFLC) system equipped with a CBM-20A communications bus module, a DGU-20ASR degassing unit, an LC-20AD liquid chromatograph pump, an SIL-20AHT autosa-sampler, and SPD-M20A photo diode array detector, a CTO-20A column oven and a Phenomenex Kinetex 5 mM C18 100 Å 250 mm × 4.60 mm column. The solvent system used was a gradient beginning at 5% MeOH in H_2O containing 0.1% formic acid over 8 min, followed by 50% MeOH in H_2O containing 0.1% formic acid over 2 min, followed by 95% MeOH in H_2O containing 0.1% formic acid over 5 min. A flow rate of 1 mL min^{-1} was maintained throughout. UV-Vis spectra were recorded over the range of 200–800 nm on a Varian Cary 50 UV-Vis spectrophotometer (Agilent) in a 10 mm pathlength quartz cuvette. A 1% DMSO solution was used for background correction for all synthesised compounds except for pH titrations where a 0.01 M NaCl solution was used. For quinine sulfate, 0.1 M H_2SO_4 was used for background correction. Fluorescence spectra were recorded on a Varian Cary Eclipse spectrophotometer (Agilent) over

315–600 nm. Excitation and emission slit widths were set at 2.5 nm each and a 10 mm pathlength quartz cuvette was used for all experiments. A 1% DMSO solution was used for background correction for all synthesised compounds except for pH titrations where a 0.01 M NaCl solution was used. For quinine sulfate, 0.1 M H_2SO_4 was used for background correction. Fluorescence quantum yields were determined by the comparative method using quinine sulfate as the reference standard (Φ_F = 0.54 in 0.1 M H_2SO_4). A concentration series for each compound was prepared in 1% DMSO, from a 0.01 M stock solution of each compound in DMSO. The concentration series were prepared such that the maximum and minimum absorbencies fell between 0.10 and 0.01. pH measurements of compound **30** were determined using a pre-calibrated Orion Ross pH meter. Absorbance and fluorescence measurements were performed as described previously. Boiled ultra-pure H_2O was used to prepare all aqueous solutions. A stock solution of **30** was prepared in DMSO (10 mM) which was diluted to 50 μM using aqueous 10 mM NaCl. The pH was adjusted to the stirring solution of **30** using dilute HCl and NaOH solutions. Care was taken to minimise the amount of acid/base added per addition and measurements were taken every 0.2–0.3 pH units.

General Procedure for Buchwald-Hartwig Cross-Coupling Reactions

A mixture of **Aryl ONf** (0.500 mmol), amide/carbamate/sulfonamide reagent (1.2 equiv.), K_3PO_4 (213 mg, 1.00 mmol, 2.0 equiv.), G3-Pd-*t*-BuXPhos (4 mg, 0.005 mmol, 0.01 equiv.) and anhydrous PhMe (1.3 mL) was degassed and then stirred at 100 °C for 16 h (unless otherwise specified). The reaction mixture was concentrated under a stream of N_2 to give a solid which was collected using vacuum filtration and washed with H_2O (*ca.* 250 mL).* The crude material was suspended in Et_2O (5 mL), stirred and allowed to settle for 2 min before being drained. This step was repeated once more to give the title compound.

* *For sulfonamide derivatives, the pH of the crude material was adjusted to pH = 1 prior to washing with H_2O.*

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)benzamide (1).** Compound **1** was prepared from **5** and $BzNH_2$, according to the general procedure, to give the title compound (119 mg, 85%) as a white solid. R_f = 0.40 (50% EtOAc in pet. spirits). m.p. 250–252 °C (lit. 246–248 °C).[44] ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.65 (s, 1H), 7.98 (d, J = 10.0 Hz, 2H), 7.95 (br s, H8, 1H), 7.77 (br s, 2H), 7.63 (d, J = 5.0 Hz, 1H), 7.56 (app. t, J = 10.0, 5.0 Hz, 2H), 6.30 (s, 1H), 2.43 (d, J = 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 166.1, 160.1, 153.5, 153.2, 142.6, 134.4, 132.0, 128.5, 127.8, 125.8, 116.2, 115.3, 112.5, 106.6, 18.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{13}NO_3$ 280.0968; found 280.0974. Anal. RP-HPLC: t_R 12.37 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 322 nm (8,300 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 322 nm, λ_{max} = 430 nm (Φ_F = 0.06), Stokes shift = 7,800 cm^{-1}. Data is in accordance with literature.[51]

4-Nitrobenzyl (4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (3). Compound **3** was prepared from **5** and 4-nitrobenzylcarbamate,[22] according to the general procedure, to give a brown solid. The crude material was suspended in *i*-PrOH (20 mL), stirred and allowed to settle for 2 min before being drained. This step was repeated once more to give the title compound (150 mg, 87%) as a teal green solid. m.p. 248–250 °C (lit. >250 °C).[15] ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.42 (s, 1H), 8.28 (d, J = 8.6 Hz, 2H), 7.72–7.70 (m, 3H), 7.55 (d, J = 1.3 Hz, 1H), 7.42 (dd, J = 8.7, 1.3 Hz, 1H), 6.24 (s, 1H), 5.35 (s, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 160.0, 153.8, 153.2, 152.9, 147.2, 144.1, 142.5, 128.6, 126.1, 123.7, 114.5, 114.3, 112.0, 104.6, 65.0, 18.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{18}H_{14}N_2O_6$ 355.0925; found 355.0934. Anal. RP-HPLC: t_R 12.65 min, purity >99%. Data is in accordance with literature.[15]

4-Methyl-2-oxo-2*H*-chromen-7-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (5). A stirring mixture of 4-methylumbelliferone (3.018 g, 17.13 mmol), K_2CO_3 (3.560 g, 25.76 mmol) in MeCN (90 mL) was treated with perfluorobutanesulfonyl fluoride (3.4 mL,

18.93 mmol) for 2 h. After this time H_2O (*ca.* 100 mL) was added to the reaction mixture to give a precipitate which was collected using vacuum filtration. The filter cake was washed with H_2O to give the title compound (7.510 g, 96%) as a fluffy white powder. m.p. 96–97 °C. (lit. 96 °C).[52] ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.96 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 8.9, 2.5 Hz, 1H), 6.52 (d, J = 1.2 Hz, 1H), 2.46 (d, J = 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 159.1, 153.5, 152.4, 150.5, 127.7, 120.2, 117.4, 115.3, 110.3, 18.2. ^{19}F NMR (DMSO-d_6, 470 MHz) δ −80.09 (t, J = 10.1 Hz, 3F), −108.83 (t, J = 14.1 Hz, 2F), −120.74–−120.79 (m, 2F), −125.42–−125.49 (m, 2F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_7F_9O_5S$ 458.9943; found 458.9948. Anal. RP-HPLC: t_R 14.64 min, purity >99%.

4-Fluoro-*N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)benzamide (6). Compound **6** was prepared from **5** and 4-fluorobenzamide, according to the general procedure, to give the title compound (136 mg, 91%) as a white solid. m.p. 286–288 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.65 (s, 1H), 8.05–8.01 (m, 2H), 7.93 (s, 1H), 7.78–7.74 (m, 2H), 7.42–7.39 (m, 2H), 6.30 (s, 1H), 2.42 (d, J = 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 165.0, 164.3 (d, $^1J_{C–F}$ = 248.2 Hz), 160.1, 153.5, 153.1, 142.5, 130.9 (d, $^4J_{C–F}$ = 2.9 Hz), 130.6 (d, $^3J_{C–F}$ = 9.1 Hz), 125.8, 116.2, 115.5 (d, $^2J_{C–F}$ = 21.8 Hz), 115.4, 112.5, 106.6, 18.0. ^{19}F NMR (470 MHz, DMSO-d_6) δ −108.04 (s, 1F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}FNO_3$ 298.0874; found 298.0877. Anal. RP-HPLC: t_R 12.48 min, purity >99%.

4-Trifluoromethyl-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (7). Compound **7** was prepared from **5** and 4-(trifluoromethyl)benzamide, according to the general procedure, to give the title compound (104 mg, 59%) as a white static solid. Compound **7** was also prepared using G3-Pd-*t*-BuBrettPhos (5 mg, 0.005 mmol, 0.01 equiv.) to give the title compound (117 mg, 68%) as a white static solid. m.p. >300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.85 (s, 1H), 8.18 (d, J = 7.7 Hz, 2H), 7.95–7.94 (m, 3H), 7.80–7.75 (m, 2H), 6.31 (s, 1H), 2.43 (d, J = 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 165.0, 160.0, 153.5, 153.1, 142.2, 138.3, 131.7

(q, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 128.8, 125.9, 125.5 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 123.9 (q, $^{1}J_{C\text{-}F}$ = 270.9 Hz), 116.2, 115.6, 112.7, 106.8, 18.0. ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.36 (s, 3F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{12}F_3NO_3$ 348.0842; found 348.0834. Anal. RP-HPLC: t_R 13.08 min, purity >99%.

4-Nitro-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (8). Compound **8** was prepared from **5** and 4-nitrobenzamide, according to the general procedure, to give a brown solid. The crude material was dissolved in DMSO (5 mL), the addition of H_2O (30 mL) gave a precipitate that was collected using vacuum filtration to give the title compound (50 mg, 31%) as a yellow solid. Compound **8** was also prepared using G3-Pd-*t*-BuBrettPhos (5 mg, 0.005 mmol, 0.01 equiv.) and following the same work-up to give the title compound (54 mg, 34%) as a yellow solid. m.p. >300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.95 (s, 1H), 8.40 (d, *J* = 7.8 Hz, 2H), 8.21 (d, *J* = 7.9 Hz, 2H), 7.94 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 6.32 (s, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 164.5, 160.0, 153.5, 153.1, 149.4, 142.1, 140.0, 129.4, 126.0, 123.7, 116.3, 115.8, 112.8, 106.9, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}N_2O_5$ 325.0819; found 325.0815. Anal. RP-HPLC: t_R 12.37 min, purity >98%. Data is in accordance with literature.[53]

4-Methoxy-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (9). Compound **9** was prepared from **5** and 4-methoxybenzamide, according to the general procedure (reaction time was 48 h) to give the title compound (143 mg, 92%) as a white solid. m.p. 233–235 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.94 (s, 1H), 7.75 (s, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.27 (s, 1H), 3.85 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 165.4, 162.3, 160.1, 153.6, 153.2, 142.8, 129.8, 126.4, 125.7, 116.1, 115.1, 113.7, 112.3, 106.5, 55.5, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}NO_4$ 310.1074; found 310.1074. Anal. RP-HPLC: t_R 12.39 min, purity >97%. Data is in accordance with literature.[16]

2-Fluoro-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (10). Compound **10** was prepared from **5** and 2-fluorobenzamide, according to the general procedure (reaction time was 48 h) to give the title compound (100 mg, 66%) as a brown solid. m.p. 195–198 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.86 (d, J = 1.3 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.71 (app. t, J = 7.3 Hz, 1H), 7.65 (dd, J = 8.7, 1.3 Hz, 1H), 7.63–7.60 (m, 1H), 7.40–7.35 (m, 2H), 6.30 (s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 163.3, 160.0, 158.9 (d, $^{1}J_{C–F}$ = 249.1 Hz), 153.6, 153.1, 142.1, 133.0 (d, $^{3}J_{C–F}$ = 8.4 Hz), 130.0 (d, $^{4}J_{C–F}$ = 2.3 Hz) 126.0, 124.7 (d, $^{3}J_{C–F}$ = 3.6 Hz), 124.5 (d, $^{2}J_{C–F}$ = 14.5 Hz), 116.3 (d, $^{2}J_{C–F}$ = 21.6 Hz), 115.7, 115.5, 112.6, 106.2, 18.0. ^{19}F NMR (470 MHz, DMSO-d_6) δ −114.46 (s, 1F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}FNO_3$ 298.0874; found 298.0878. Anal. RP-HPLC: t_R 12.21 min, purity >99%.

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)-2-methylbenzamide (11).** Compound **11** was prepared from **5** and 2-methylbenzamide, according to the general procedure, to give the title compound (128 mg, 88%) as an off-white solid. m.p. 227–229 °C. (lit. 226–228 °C).[51] ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.73 (s, 1H), 7.88 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 7.3 Hz, 1H), 7.42 (app. t, J = 7.3 Hz, 1H), 7.34–7.30 (m, 2H), 6.29 (s, 1H), 2.42 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 168.4, 160.0, 153.6, 153.1, 142.6, 136.6, 135.4, 130.7, 130.1, 127.3, 125.9, 125.7, 115.6, 115.3, 112.4, 106.1, 19.3, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}NO_3$ 294.1125; found 294.1122. Anal. RP-HPLC: t_R 12.33 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 328 nm (11,000 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 328 nm, λ_{max} = 420 nm (Φ_F = 0.06), Stokes shift = 6,678 cm^{-1}. Data is in accordance with literature.[51]

2-Methoxy-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (12). Compound **12** was prepared from **5** and 2-methoxybenzamide, according to the general procedure, to give the title compound (141 mg, 92%) as a light brown solid. m.p. 217–219 °C. ^{1}H NMR (DMSO-d_6, 500

MHz) δ 10.52 (s, 1H), 7.90 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.63 (dd, J = 7.5, 1.3 Hz, 1H), 7.53 (app. t, J = 8.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.09 (app. t, J = 7.5 Hz, 1H), 6.28 (s, 1H), 3.90 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 165.3, 160.1, 156.5, 153.7, 153.1, 142.4, 132.4, 129.6, 125.9, 124.7, 120.5, 115.7, 115.2, 112.4, 112.0, 106.1, 55.9, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}NO_4$ 310.1074; found 310.1078. Anal. RP-HPLC: t_R 12.89 min, purity >98%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 326 nm (3,300 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 326 nm, λ_{max} = 443 nm (Φ_F = 0.09), Stokes shift = 8,101 cm^{-1}.

3-Fluoro-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (13). Compound **13** was prepared from **5** and 3-fluorobenzamide, according to the general procedure, to give the title compound (138 mg, 92%) as an off-white static solid. m.p. 282–284 °C. ^1H NMR (DMSO-d_6, 500 MHz) δ 10.69 (s, 1H), 7.93 (s, 1H), 7.84–7.74 (m, 3H), 7.64–7.60 (m, 1H), 7.51–7.47 (m, 1H), 6.30 (s, 1H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 164.7 (d, $^4J_{C–F}$ = 2.7 Hz), 161.9 (d, $^1J_{C–F}$ = 243.0 Hz), 160.0, 153.5, 153.1, 142.3, 136.7 (d, $^3J_{C–F}$ = 7.0 Hz), 130.7 (d, $^3J_{C–F}$ = 8.0 Hz), 125.9, 124.1 (d, $^4J_{C–F}$ = 2.8 Hz), 118.9 (d, $^2J_{C–F}$ = 20.9 Hz), 116.2, 115.5, 114.7 (d, $^2J_{C–F}$ = 22.8 Hz), 112.6, 106.8, 18.0. ^{19}F NMR (470 MHz, DMSO-d_6) δ −112.5 (s, 2F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}FNO_3$ 298.0874; found 298.0872. Anal. RP-HPLC: t_R 17.53 min, purity >99%.

3-Methoxy-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (14). Compound **14** was prepared from **5** and 3-methoxybenzamide, according to the general procedure, to give a beige solid. The crude material was purified using column chromatography (EtOAc) to give the title compound (119 mg, 79%) as a fine white solid. R_f = 0.30 (EtOAc). m.p. 195–197 °C. ^1H NMR (DMSO-d_6, 500 MHz) δ 10.60 (s, 1H), 7.94 (s, 1H), 7.78–7.74 (m, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.50–7.46 (m, 2H), 7.20 (dd, J = 8.2, 1.7 Hz, 1H), 6.29 (s, 1H), 3.85 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 165.8, 160.0, 159.2, 153.5, 153.1, 142.5, 135.8, 129.7,

125.8, 120.0, 117.7, 116.2, 115.4, 113.1, 112.5, 106.7, 55.4, 18.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{18}H_{15}NO_4$ 310.1074; found 310.1071. Anal. RP-HPLC: t_R 12.32 min, purity >99%.

3,5-Dimethoxy-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzamide (15). Compound **15** was prepared from **5** and 3,5-dimethoxybenzamide, according to the general procedure to give a brown solid. The crude material was dissolved in DMSO (3 mL) and H_2O (3 mL) was added to cause immediate precipitation. The mixture was cooled on ice and the title compound was collected using vacuum filtration as a beige solid (72 mg, 43%). m.p. 247–249 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.55 (1H, s), 7.93 (1H, s), 7.78–7.74 (2H, m), 7.12 (2H, s), 6.75 (1H, s), 6.30 (1H, s), 3.83 (6H, s), 2.42 (3H, s). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 165.6, 160.4, 160.1, 153.5, 153.2, 142.4, 136.4, 125.8, 116.3, 115.4, 112.5, 106.7, 105.8, 103.7, 55.6, 18.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{17}NO_5$ 340.1179; found 340.1180. Anal. RP-HPLC: t_R 12.87 min, purity >99%.

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)-3,5-dinitrobenzamide (16).** Compound **16** was prepared from **5** and 3,5-dinitrobenzamide, according to the general procedure (0.02 equiv. of catalyst was required) to give a brown solid. The crude material was washed with EtOH (120 mL) to give the title compound (60 mg, 32%) as an amorphous grey solid. m.p. >300 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.15 (s, 1H), 9.17 (s, 2H), 9.01 (s, 1H), 7.91 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 6.32 (s, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 161.8, 159.9, 153.4, 153.0, 148.1, 141.6, 136.9, 128.2, 125.9, 121.4, 116.4, 116.0, 113.0, 107.2, 18.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{11}N_3O_7$ 370.0670; found 370.0674. *RP-HPLC was not performed on this compound as its solubility was restricted to DMSO and halogenated solvents.*

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)isonicotinylamide (17).** Compound **17** was prepared from **5** and isonicotinamide, according to the general procedure, to give the title compound (140 mg, 99%) as an off-white solid. m.p. >300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.88 (s, 1H), 8.81 (d, J = 5.5 Hz, 2H), 7.93 (s, 1H), 7.89 (d, J = 5.5 Hz, 2H), 7.80 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H), 6.31 (s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 164.7, 160.0, 153.5, 153.1, 150.3, 142.4, 141.7, 125.9, 121.7, 116.4, 115.7, 112.6, 106.9, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_3$ 281.0921; found 281.0924. Anal. RP-HPLC: t_R 11.26 min, purity >97%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 327 nm (7,900 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 327 nm, λ_{max} = 445 nm (Φ_F = 0.03), Stokes shift = 8,109 cm^{-1}. Data is in accordance with literature.[16]

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)nicotinylamide (18).** Compound **18** was prepared from **5** and nicotinamide, according to the general procedure, to give a brown solid. The crude material dissolved in hot DMSO (4 mL) and the title compound was isolated by adding H_2O (30 mL) and collecting the resulting white solid using vacuum filtration (128 mg, 93%). m.p. 270–272 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.82 (s, 1H), 9.13 (s, 1H), 8.79 (d, J = 3.9 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.61–7.57 (m, 1H), 6.30 (s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 164.7, 160.0, 153.5, 153.1, 152.5, 148.8, 142.2, 135.7, 130.2, 125.9, 123.6, 116.2, 115.6, 112.7, 106.7, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_3$ 281.0921; found 281.0917. Anal. RP-HPLC: t_R 11.34 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 327 nm (5,500 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 327 nm, λ_{max} = 432 nm (Φ_F <0.01), Stokes shift = 7,433 cm^{-1}. Data is in accordance with literature.[53]

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)picolinylamide (19).** Compound **19** was prepared from **5** and picolinamide, according to the general procedure, to give the title compound (17 mg, 12%) as a staticky white solid. m.p. 223–225 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.09

(s, 1H), 8.78–8.77 (m, 1H), 8.20–8.19 (m, 1H), 8.19–8.09 (m, 2H), 7.97 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.73–7.71 (m, 1H), 6.31 (s, 1H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 163.2, 160.1, 153.5, 153.2, 149.4, 148.5, 141.8, 138.3, 127.3, 125.8, 122.7, 116.4, 115.6, 112.6, 106.8, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_3$ 281.0921; found 281.0921. Anal. RP-HPLC: t_R 12.33 min, purity >96%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 328 nm (3,900 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 328 nm, λ_{max} = 396 nm (Φ_F = <0.01), Stokes shift = 4,959 cm^{-1}. Data is in accordance with literature.[16]

***N*-(7-amino-4-methyl-2-oxo-2*H*-chromen-7-yl)methylacrylamide (20).** Compound **20** was prepared from **5** (1.015 g, 2.21 mmol) and methacrylamide, according to the general procedure, to give the title compound (483 mg, 90%) as a grey solid. m.p. 217–219 °C. ^1H NMR (DMSO-d_6, 500 MHz) δ 10.19 (s, 1H), 7.84 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 6.27 (s, 1H), 5.87 (s, 1H), 5.61 (s, 1H), 2.40 (d, J = 1.2 Hz, 3H), 1.96 (s, 1H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 167.3, 160.1, 153.5, 153.1, 142.5, 140.0, 125.7, 120.9, 115.9, 115.1, 112.4, 106.4, 18.6, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{13}NO_3$ 244.0968; found 244.0962. Anal. RP-HPLC: t_R 11.56 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 328 nm (8,500 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 328 nm, λ_{max} = 402 nm (Φ_F <0.01), Stokes shift = 5,612 cm^{-1}. Data is in accordance with literature.[54]

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)propanamide (21).** Compound **21** was prepared from **5** and propanamide, according to the general procedure. The reaction mixture was concentrated and then acidified using sat. KH_2PO_4 (20 mL), before the solid was collected using vacuum filtration and washed according to the general procedure, to give the title compound (95 mg, 83%) as a fluffy white solid. Compound **21** was also prepared using G3-Pd-*t*-BuBrettPhos (5 mg, 0.005 mmol, 0.01 equiv.) to give the title compound (92 mg, 81%) as a fluffy white solid. m.p. 235–237 °C. ^1H NMR (DMSO-d_6, 500 MHz) δ 10.37 (s, 1H), 7.77 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 6.25 (s, 1H), 2.39–2.36 (m, 5H) 1.09 (t, J = 7.2 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 125 MHz) δ 172.7, 160.1, 153.7, 153.2, 142.7, 125.9, 115.0, 114.7, 112.1, 105.3, 29.6, 18.0, 9.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}NO_3$ 232.0968; found 232.0973. Anal. RP-HPLC: t_R 11.28 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 325 nm (15,000 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 325 nm, λ_{max} = 398 nm (Φ_F = 0.71), Stokes shift = 5,644 cm^{-1}. Data is in accordance with literature.[53]

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)butanamide (22).** Compound **22** was prepared from **5** and butanamide, according to the general procedure. The reaction mixture was concentrated and then acidified using sat. KH_2PO_4 (20 mL), before the solid was collected using vacuum filtration and washed according to the general procedure, to give the title compound (65 mg, 54%) as a fine white solid. m.p. 209–211 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.31 (s, 1H), 7.77 (d, *J* = 1.8 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.48 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.25 (s, 1H), 2.39 (s, 3H), 2.34 (t, *J* = 8.3 Hz, 2H), 1.66–1.60 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 125 MHz) δ 172.0, 160.1, 153.7, 153.2, 142.6, 125.9, 115.0, 114.8, 112.1, 105.4, 38.4, 18.4, 18.0, 13.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}NO_3$ 246.1125; found 246.1132. Anal. RP-HPLC: t_R 11.81 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 325 nm (4,800 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 325 nm, λ_{max} = 399 nm (Φ_F = 0.68), Stokes shift = 5,707 cm^{-1}.

***N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)adamantane-1-carboxamide (23).** Compound **23** was prepared from **5** and adamantane-1-carboxamide, according to the general procedure. The reaction mixture was concentrated and then acidified using sat. KH_2PO_4 (20 mL), before the solid was collected using vacuum filtration and washed with H_2O (100 mL) and MeOH (2 × 5 mL), to give the title compound (41 mg, 25%) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.85 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 6.25 (s, 1H), 2.40 (s, 3H), 2.03 (app. s, 3H), 1.92 (app. s, 6H), 1.71 (app. s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ 176.7, 160.1, 153.5, 153.2, 142.9, 125.6, 115.9, 114.9, 112.2, 106.3, 41.3, 38.1,

35.9, 27.6, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{23}NO_3$ 338.1751; found 338.1751. *RP-HPLC was not performed on this compound as its solubility was restricted to DMSO and halogenated solvents.*

Ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)amino)-2-oxoacetate (24). Compound **24** was prepared from **5** and ethyl oxamate, according to the general procedure (0.02 equiv. of catalyst was required and reaction time was 48 h) to give the title compound (132 mg, 94%) as a beige solid. m.p. 213–215 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.18 (s, 1H), 7.85 (s, 1H), 7.78–7.75 (m, 2H), 6.32 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 160.2, 159.9, 155.8, 153.3, 153.0, 140.9, 126.0, 116.4, 116.2, 113.0, 107.2, 62.6, 18.0, 13.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{13}NO_5$ 276.0866; found 276.0870. Anal. RP-HPLC: t_R 11.36 min, purity >99%.

7-(*tert*-Butoxycarbonylamino)-4-methyl coumarin (25). Compound **25** was prepared from **5** and *t*-butyl carbamate, according to the general procedure (0.02 equiv. of catalyst was required) to give a brown solid. The crude material was purified using column chromatography (50% CH_2Cl_2 in pet. spirits–10% EtOAc in CH_2Cl_2) to give the title compound (76 mg, 55%) as a yellow powder. R_f = 0.62 (10% EtOAc in CH_2Cl_2). m.p. 144–146 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.87 (s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.7, 2.0 Hz, 1H), 6.22 (s, 1H), 2.38 (s, 3H), 1.49 (s, 9H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 160.1, 153.8, 153.2, 152.5, 143.2, 125.9, 114.2, 114.1, 111.7, 104.2, 80.0, 28.0, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}NO_4$ 276.1230; found 276.1223. Anal. RP-HPLC: t_R 12.85 min, purity >94%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 327 nm (15,600 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 327 nm, λ_{max} = 403 nm (Φ_F = 0.94), Stokes shift = 5,767 cm^{-1}. UV-Vis (DMSO): λ_{max} (ε) = 330 nm (18,000 M^{-1} cm^{-1}). Fluorescence (DMSO): λ_{ex} = 330 nm, λ_{max} = 389 nm (Φ_F = 0.49), Stokes shift = 4,596 cm^{-1}. UV-Vis ($CHCl_3$): λ_{max} (ε) = 329 nm (15,600 M^{-1} cm^{-1}). Fluorescence ($CHCl_3$): λ_{ex} = 329 nm, λ_{max} = 389 nm (Φ_F = 0.32),

Stokes shift = 4,688 cm^{-1}. UV-Vis (PhMe): λ_{max} (ε) = 327 nm (15,400 M^{-1} cm^{-1}). Fluorescence (PhMe): λ_{ex} = 327 nm, λ_{max} = 382 nm (Φ_F = 0.04), Stokes shift = 4,403 cm^{-1}. Data is in accordance with literature.[55]

Benzyl (4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (26). Compound **26** was prepared from **5** and benzyl carbamate, according to the general procedure, to give the title compound (115 mg, 71%) as a grey solid. m.p. 208–210 °C (lit. 228–230 °C).[56] ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.55 (s, 1H), 7.45 (app. d, J = 7.1 Hz, 2H), 7.41 (app. t, J = 7.4 Hz, 3H), 7.36 (app. t, J = 6.7 Hz, 1H), 7.23 (s, 1H), 5.19 (s, 2H), 1.31 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 160.0, 153.8, 153.2, 153.2, 142.7, 136.2, 128.5, 128.3, 128.2, 126.1, 114.4, 114.2, 111.9, 104.4, 66.3, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}NO_4$ 310.1074; found 310.1080. Anal. RP-HPLC: t_R 12.87 min, purity >97%. Data is in accordance with literature except for the recorded melting point which was measured after recrystallisation from EtOH as per literature precedent.[56]

4-Chlorobenzyl (4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (27). Compound **27** was prepared from **5** and 4-chlorobenzylcarbamate (**42**), according to the general procedure (0.02 equiv. of catalyst was required and reaction time was 48 h) to give a beige solid. The crude material was dry loaded onto SiO_2 in MeOH and purified using column chromatography (50% EtOAc in pet. spirits) to give the title compound (77 mg, 46%) as a yellow powder. R_f = 0.48 (EtOAc in pet. spirits). m.p. 239–241 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.31 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.55 (s, 1H), 7.47 (br s, 4H), 7.41 (d, J = 8.7 Hz, 1H), 6.24 (s, 1H), 5.19 (s, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 160.0, 153.8, 153.2, 153.1, 142.6, 135.3, 132.8, 130.1, 128.5, 126.1, 114.5, 114.3, 112.0, 104.5, 65.4, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}{}^{35}ClNO_4$ 344.0684; found 344.0681. Anal. RP-HPLC: t_R 13.22 min, purity >91%.

5-Cholesten-3β-yl-(4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (28). Compound **28** was prepared from **5** and cholesterol carbamate **43**, according to the general procedure (reaction time was 48 h) to give the title compound (203 mg, 69%) as an off-white solid. m.p. 264–266 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 1H), 6.18 (s, 1H), 5.41 (d, *J* = 4.9 Hz, 1H), 4.67–4.61 (m, 1H), 2.45–2.34 (m, 5H), 2.03–1.80 (m, 5H), 1.68–0.85 (m, 33H), 0.68 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 161.3, 154.6, 152.6, 152.4, 141.8, 139.5, 125.5, 123.2, 115.5, 114.4, 113.2, 105.9, 75.7, 56.8, 56.3, 50.1, 42.5, 39.9, 39.7, 38.5, 37.1, 36.7, 36.3, 35.9, 32.1, 32.0, 28.4, 28.18, 28.16, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 18.7, 12.0. *HRMS and RP-HPLC were not performed on this compound as its solubility was restricted to halogenated solvents.*

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)methanesulfonamide (29).** Compound **29** was prepared from **5** and methane sulfonamide, according to the general procedure (0.02 equiv. of catalyst was required and reaction time was 48 h) to give the title compound (115 mg, 92%) as a light brown solid. m.p. 198–217 °C (slow decomposition). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.50 (d, *J* = 9.2 Hz, 1H), 6.90–6.89 (m, 2H), 6.02 (s, 1H), 2.85 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 160.6, 154.7, 153.4, 150.0, 125.6, 116.4, 111.4, 109.2, 104.2, 40.0, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{11}NO_4S$ 254.0482; found 254.0486. Anal. RP-HPLC: t_R 10.16 min, purity >97%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 321 nm (7,100 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 321 nm, λ_{max} = 458 nm (Φ_F = 0.49), Stokes shift = 9,319 cm^{-1}.

2-Methyl-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)propane-2-sulfonamide (30). Compound **30** was prepared from **5** and *tert*-butylsulfonamide, according to the general procedure, to give the title compound (109 mg, 77%) as a grey solid. m.p. 226–228 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.22 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.24–7.20 (m, 2H), 6.22 (s, 1H), 2.37 (s, 3H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 159.9, 153.9, 153.1, 144.7, 126.2, 114.8,

114.3, 111.7, 104.8, 61.1, 24.2, 18.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{17}NO_4S$ 296.0951; found 296.0958. Anal. RP-HPLC: t_R 11.55 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 323 nm (13,400 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 323 nm, λ_{max} = 458 nm (Φ_F = 0.48), Stokes shift = 9,126 cm^{-1}.

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)benzenesulfonamide (31).** Compound **31** was prepared from **5** and benzenesulfonamide, according to the general procedure, to give a beige solid. The crude material dissolved in hot DMSO (7 mL) and the title compound was isolated by adding H_2O (40 mL) and collecting the resulting white static solid using vacuum filtration (51 mg, 33%). m.p. 226–228 °C lit. (245–246 °C).[57] ^1H NMR (DMSO-d_6, 500 MHz) δ 10.99 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.64–7.57 (m, 4H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.04 (s, 1H), 6.23 (s, 1H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 159.7, 153.7, 153.0, 141.3, 139.1, 133.4, 129.5, 126.7, 126.6, 115.3, 114.7, 112.5, 105.2, 17.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{13}NO_4S$ 316.0638; found 316.0646. Anal. RP-HPLC: t_R 11.54 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 321 nm (13,000 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 321 nm, λ_{max} = 458 nm (Φ_F = 0.55), Stokes shift = 9,319 cm^{-1}. Data is in accordance with literature.[57]

4-Chloro-*N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)sulfonamide (32). Compound **32** was prepared from **5** and 4-chlorobenzenesulfonamide, according to the general procedure (0.02 equiv. of catalyst was required) to give a grey solid. The crude material was purified using column chromatography (50% CH_2Cl_2 in pet. spirits–10% EtOAc in CH_2Cl_2) to give the title compound (53 mg, 30%) as a green waxy solid. R_f = 0.28 (10% EtOAc in CH_2Cl_2). ^1H NMR (DMSO-d_6, 500 MHz) δ 11.05 (s, 1H), 7.86–7.82 (m, 2H), 7.66–7.60 (m, 3H), 7.09–7.05 (m, 2H), 6.22 (s, 1H), 2.30 (d, *J* = 1.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 159.7, 153.7, 152.9, 140.9, 138.3, 137.9, 129.7, 128.7, 126.6, 115.6, 114.8, 112.7, 105.5, 17.9. HRMS

(ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClNO_4S$ 350.0248; found 350.0242. Anal. RP-HPLC: t_R 12.52 min, purity >90%.

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)-4-(trifluoromethyl)benzenesulfonamide (33).** Compound **33** was prepared from **5** and 4-(trifluoromethyl)benzenesulfoanmide, according to the general procedure, to give the title compound (70 mg, 37%) as a beige solid. m.p. 202–204 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.21 (s, 1H), 8.06 (d, J = 7.3 Hz, 2H), 7.99 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.11–7.07 (m, 2H), 6.25 (s, 1H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 159.7, 153.7, 153.0, 143.4, 141.3, 133.7 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 127.7, 126.8 (q, $^3J_{C\text{-}F}$ = 13.0 Hz), 126.7, 123.3 (q, $^1J_{C\text{-}F}$ = 271.2 Hz), 115.5, 115.1, 112.6, 105.6, 17.9. ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.73 (s, 3F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}F_3NO_4S$ 384.0512; found 384.0521. Anal. RP-HPLC: t_R 12.58 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 322 nm (11,000 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 322 nm, λ_{max} = 458 nm (Φ_F = 0.02), Stokes shift = 9,222 cm^{-1}.

***N*-(4-Methyl-2-oxo-2*H*-chromen-7-yl)-4-nitrobenzenesulfonamide (34).** Compound **34** was prepared from **5** and 4-nitrobenzenesulfonamide, according to the general procedure (0.02 equiv. of catalyst was required and reaction time was 48 h) to give the title compound (131 mg, 72%) as a light brown solid. m.p. 254–256 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.27 (s, 1H), 8.38 (d, J = 8.2 Hz, 2H), 8.09 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.5 Hz, 1H), 7.11–7.07 (m, 2H), 6.26 (s, 1H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 159.7, 153.7, 152.9, 150.0, 144.9, 141.4, 128.3, 126.6, 124.8, 115.5, 115.4, 112.6, 105.8, 17.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}N_2O_6S$ 361.0489; found 361.0496. Anal. RP-HPLC: t_R 11.88 min, purity >94%.

3-Methoxy-*N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)benzenesulfonamide (35). Compound **35** was prepared from **5** and 3-methoxybenzenesulfonamide, according to the general procedure,

to give a yellow solid. The crude material was dissolved in hot EtOH (10 mL) and the insoluble impurities were removed using filtration. The filtrate was collected and concentrated under reduced pressure to give the title compound (118 mg, 68%) as a fluffy grey solid. m.p. 200–230 °C (slow decomposition). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.49 (app. t, J = 8.0 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.34 (s, 1H), 7.20 (dd, J = 8.2, 2.2 Hz, 1H), 7.11 (dd, J = 8.6, 1.2 Hz, 1H), 7.05 (s, 1H), 6.24 (s, 1H), 3.78 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 159.7, 159.5, 153.6, 153.0, 141.2, 140.3, 130.8, 126.6, 119.0, 118.8, 115.4, 114.7, 112.6, 111.7, 105.3, 55.6, 17.9. HRMS (ESI-TOF) *m/z*: [M + H]$^{+}$ calcd for $C_{17}H_{15}NO_5S$ 346.0744; found 346.0749. Anal. RP-HPLC: t_R 11.91 min, purity >95%.

4-Trifluoromethyl-2-oxo-2*H*-chromen-7-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (36). To a stirred solution of 7-hydroxy-4-(trifluoromethyl)-2*H*-chromen-2-one[58] (463 mg, 2.01 mmol), K_2CO_3 (419 mg, 3.03 mmol) and MeCN (10 mL) was added perfluoro-1-butanesulfonyl fluoride (670 µL, 3.73 mmol). Stirring was maintained at ambient temperature for 2 h before the reaction was diluted with H_2O (15 mL) and stirred for 15 min. The mixture was then extracted with EtOAc and the organic phase was washed with H_2O (2 × 20 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the title compound (876 mg, 85%) as a white waxy solid. R_f = 0.56 (20% EtOAc in pet. spirits). m.p. 49–49 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.92 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 8.9, 1.3 Hz, 1H), 7.58 (dd, J = 8.9, 2.5 Hz, 1H), 7.19 (s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 157.7, 154.6, 150.9, 138.0 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz), 126.9, 121.5 (q, $^{1}J_{C\text{-}F}$ = 273.5 Hz), 118.9 (q, $^{3}J_{C\text{-}F}$ = 5.4 Hz), 118.3, 113.9, 111.5. ^{19}F NMR (DMSO-d_6, 470 MHz) δ −63.93 (s, 3F), −80.28 (t, J = 9.4 Hz, 3F), −108.84 (t, J = 13.3 Hz, 2F), −120.86– −120.89 (m, 2F), −125.58–−125.64 (m, 2F). HRMS (ESI-TOF) *m/z*: [M + H]$^{+}$ calcd for $C_{14}H_4F_{12}O_5S$ 512.9661; found 512.9666. Anal. RP-HPLC: t_R 15.08 min, purity >97%.

Ethyl 2-oxo-7-(((perfluorobutyl)sulfonyl)oxy)-2*H*-chromene-3-carboxylate (37). To a stirred solution of ethyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate[59] (472 mg, 2.02 mmol), K_2CO_3 (417 mg, 3.02 mmol) and MeCN (10 mL) was added perfluoro-1-butanesulfonyl fluoride (400 μL, 2.23 mmol). The reaction was stirred at ambient temperature for 11 h before H_2O (20 mL) was added. After stirring for a further 10 min the precipitate was collected, washed with H_2O (25 mL), Et_2O (25 mL) and dried using vacuum filtration to give a green solid. This crude material was diluted in $CHCl_3$, filtered and concentrated under a stream of N_2 to give the title compound (513 mg, 49%) as a white solid. m.p. 146–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 7.28 (dd, J = 8.6, 2.3 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.6, 155.8, 155.5, 152.8, 147.1, 131.2, 119.6, 118.4, 117.9, 110.5, 62.5, 14.3. ^{19}F NMR ($CDCl_3$, 470 MHz) δ −63.93 (s, 3F), −80.28 (t, J = 9.4 Hz, 3F), −108.84 (t, J = 13.3 Hz, 2F), −120.86–−120.89 (m, 2F), −125.58–−125.64 (m, 2F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_9F_9O_7S$ 516.9998; found 516.9999. Anal. RP-HPLC: t_R 14.02 min, purity >96%.

4-Methyl-2-oxo-2*H*-chromen-6-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (38). To a stirred solution of 6-hydroxy-4-methyl coumarin (1.044 g, 5.93 mmol), K_2CO_3 (1.234 g, 8.93 mmol) and MeCN (30 mL) was added perfluoro-1-butanesulfonyl fluoride (1.2 mL, 6.68 mmol). Stirring was maintained at ambient temperature for 2 h before H_2O (50 mL) was added. The mixture was cooled on ice for 1 h before the resulting precipitate was collected and dried using vacuum filtration to give the title compound (2.567 g, 85%) as an off-white solid. R_f = 0.41 (50% EtOAc in pet. spirits). m.p. 78–80 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.94 (d, J = 2.9 Hz, 1H), 7.76 (dd, J = 9.1, 2.9 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 6.55 (d, J = 1.2 Hz, 1H), 2.44 (d, J = 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 159.0, 152.20, 152.17, 145.1, 124.8, 121.1, 118.9, 118.6, 116.0, 18.0. ^{19}F NMR (DMSO-d_6, 470 MHz) δ −80.55 (t, J = 10.9

Hz, 3F), −108.24 (t, J = 16.1 Hz, 2F), −120.71–−120.78 (m, 2F), −125.70–−125.77 (m, 2F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_7F_9O_5S$ $[M + H]^+$ calc. 458.9943; found 458.9956. Anal. RP-HPLC: t_R 14.09 min, purity >99%.

2-Methoxy-*N*-(2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl)benzamide (39). Compound **39** was prepared from **36** and 2-methoxybenzamide, according to the general procedure, to give the title compound (94 mg, 51%) as a brown solid. m.p. 191–193 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.68 (s, 1H), 8.03 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 6.6 Hz, 1H), 7.54 (app. t, J = 7.3 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.09 (app. t, J = 7.4 Hz, 1H), 6.92 (s, 1H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 165.6, 118.7, 156.5, 154.7, 143.3, 139.2 (q, $^2J_{C\text{-}F}$ = 32.0 Hz), 132.5, 129.6, 125.4, 124.5, 121.7 (q, $^1J_{C\text{-}F}$ = 273.9 Hz), 120.5, 116.5, 114.5 (q, $^3J_{C\text{-}F}$ = 5.6 Hz), 112.1, 108.5, 106.6, 55.9. ^{19}F NMR (470 MHz, DMSO-d_6) δ −63.57 (s, 3F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{12}F_3NO_4$ 364.0791; found 364.0795. Anal. RP-HPLC: t_R 13.61 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 340 nm (3,600 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 340 nm, λ_{max} = 434 nm (Φ_F = 0.07), Stokes shift = 6,370 cm^{-1}.

Ethyl 7-(2-methoxybenzamido)-2-oxo-2*H*-chromene-3-carboxylate (40). Compound **40** was prepared from **37** and 2-methoxybenzamide, according to the general procedure (reaction time was 48 h) to give beige solid. The crude material was washed with minimal EtOH to give the title compound (11 mg, 6%) as a yellow solid. m.p. 190–192 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.70 (s, 1H), 7.95 (s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.66 (dd, J = 8.5, 1.7 Hz, 1H), 7.62 (app. dd, J = 7.6, 1.6 Hz, 1H), 7.56–7.52 (m, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.09 (app. t, J = 7.3 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 165.6, 162.8, 156.5, 156.3, 155.8, 148.7, 144.7, 132.5, 131.0, 129.6, 124.6, 120.6, 116.2, 114.7, 113.4, 112.1, 105.3, 61.0, 55.9, 14.1. HRMS (ESI-

TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}NO_6$ 368.1129; found 368.1127. Anal. RP-HPLC: t_R 12.77 min, purity >95%.

2-Methoxy-*N*-(4-methyl-2-oxo-2*H*-chromen-6-yl)benzamide (41). Compound **41** was prepared from **38** and 2-methoxybenzamide, according to the general procedure, to give the title compound (26 mg, 16%) as a brown solid. Compound **41** was also prepared using G3-Pd-*t*-BuBrettPhos (5 mg, 0.005 mmol, 0.01 equiv.) to give the title compound (69 mg, 45%) as a brown solid. m.p. 207–209 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.34 (s, 1H), 8.26 (d, J = 2.3 Hz, 1H), 7.89 (dd, J = 8.9, 2.3 Hz, 1H), 7.64 (dd, J = 7.5, 1.4 Hz, 1H), 7.54–7.50 (m, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.08 (app. t, J = 7.5 Hz, 1H), 6.44 (s, 1H), 3.90 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 164.8, 159.8, 156.5, 152.9, 148.9, 135.5, 132.2, 129.6, 124.8, 123.9, 120.5, 119.6, 116.7, 115.1, 114.8, 112.0, 55.9, 18.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}NO_4$ 310.1074; found 310.1068. Anal. RP-HPLC: t_R 12.47 min, purity >99%. UV-Vis (1% DMSO in H_2O): λ_{max} (ε) = 265 nm (7,100 M^{-1} cm^{-1}). Fluorescence (1% DMSO in H_2O): λ_{ex} = 265 nm, λ_{max} = 441 nm (Φ_F = 0.05), Stokes shift = 15,060 cm^{-1}.

4-Chlorobenzyl carbamate (42). A solution of 4-chlorobenzyl alcohol (1.024 g, 7.18 mmol), CDI (1.520 g, 9.37 mmol) and anhydrous THF (24 mL) was stirred at ambient temperature, under an inert atmosphere for 16 h. After the consumption of starting material was observed by TLC analysis, NH_4OH (28%, 6.0 mL, 43.14 mmol) was added and the reaction was stirred at ambient temperature for a further 16 h. The reaction mixture was concentrated under reduced pressure to give a white solid. The material was collected using vacuum filtration and washed with 1 M HCl (50 mL) and H_2O (200 mL) to give the title compound (1.225 g, 92%) as a fine white solid. m.p. 139–141 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.72–6.53 (m, 2H), 4.96 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ

156.5, 136.5, 132.3, 129.5, 128.3, 64.1. Anal. RP-HPLC: t_R 11.45 min, purity >99%. Data is in accordance with literature.[60]

3β-Cholest-5-ene carbamate (43). A solution of cholesterol (1.023 g, 2.65 mmol), CDI (566 mg, 3.49 mmol) and anhydrous THF (9 mL) was stirred at ambient temperature, under an inert atmosphere for 16 h. After the consumption of starting material was observed by TLC analysis, the reaction mixture was concentrated under reduced pressure to give a white solid which was reconstituted in THF (9 mL) and NH_4OH (28%, 2.2 mL, 15.82 mmol). The reaction was stirred at ambient temperature for a further 16 h and then concentrated under reduced pressure to give a white solid. The material was washed with 1 M HCl (30 mL) and H_2O (200 mL) and collected using vacuum filtration to give the title compound (938 mg, 82%) as a fluffy white solid. m.p. 182–205 °C (slow decomposition). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (d, J = 5.2 Hz, 1H), 4.54–4.46 (m, 3H), 2.39–2.26 (m, 2H), 2.02–1.79 (m, 5H), 1.60–0.85 (m, 33H), 0.67 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.5, 139.8, 122.8, 74.9, 56.8, 56.3, 50.2, 42.5, 39.9, 39.7, 38.5, 37.1, 36.7, 36.3, 35.9, 32.04, 32.01, 28.3, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.8, 12.0. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{47}NO_2$ 452.3499; found 452.3492.

Declaration of competing interest

The authors declare no conflict of interest.

Supporting Information

The Supporting Information is available free of charge at https://

The Supporting Information contains the ^{1}H and ^{13}C NMR, HRMS and HPLC spectra for all compounds, crystallography data for **41**, detailed procedure for gel fabrication, normalised absorption and emission spectra for compounds listed in Table 2.

Acknowledgements

S.M.H and D.A.B thank Envision Sciences for financial support. M.J.S was supported through a SIEF STEM+ Fellowship (CSIRO, Puratap Pty. Ltd., UniSA). C.J.S acknowledges the Australian Research Council for equipment provided under grant LE0989336.

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