Synthesis of 4-Sulfanylcoumarins Using Thiourea and Alkyl Halides as the Sulfanylation Agent in Polyethylene Glycol–Water

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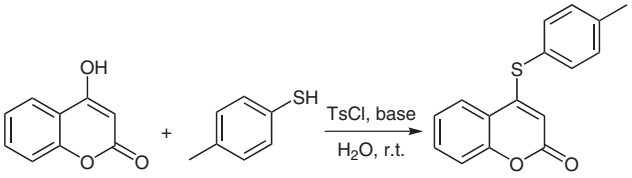
Abstract: A novel and efficient route for the synthesis of 4-sulfanylcoumarins is disclosed. The direct sulfanylation of 4-tosyloxycoumarins with thiourea and various alkyl halides in polyethylene glycol 200–water (PEG 200–H_2O), at room temperature under an air atmosphere, affords the corresponding 4-sulfanylcoumarins in moderate to excellent yields. This transformation shows good substrate scope and takes place in a green solvent.

Key words: 4-sulfanylcoumarins, 4-tosyloxycoumarins, thiourea, alkyl halides, polyethylene glycol 200

Coumarins are distributed widely in plant species and many of them show interesting biological properties.[1] The prominence of coumarins in natural products and biologically active molecules has prompted considerable efforts toward their synthesis.[2] 4-Sulfanylcoumarins have shown promising activity against the hepatitis C virus (HCV), and their synthesis has attracted significant attention.[3] They have been synthesized either for biological evaluation, or as key intermediates for the generation of complex molecules. However, their syntheses usually suffer from the requirement for multiple synthetic steps, harsh reaction conditions, and poor substituent tolerance.[4] Thus, it is highly desirable to develop general and efficient methods for the synthesis of 4-sulfanylcoumarins, in particular, via green processes.

Our group has previously developed a novel, metal-free synthesis of 4-sulfanylcoumarins from 4-hydroxycoumarins and thiols[5] (Scheme 1). However, the use of unpleasant mercaptans not only results in serious environmental problems, but also limits the potential for expansion of the reaction scope. The reported odorless protocols for the formation of thioethers,[6–10] and the use of thiourea and alkyl halides[11–13] as reagents for the formation of thioethers, encouraged us to apply these methods for the synthesis of 4-sulfanylcoumarins.



Scheme 1 Metal-free synthesis of 4-sulfanylcoumarins

Initially, optimization studies were carried out using 4-tosyloxycoumarin (**1a**) (prepared from the reaction of 4-hydroxycoumarin and TsCl in the presence of trimethylamine), thiourea (**2**) and benzyl bromide (**3a**), as model substrates (Table 1). When the reaction was performed in polyethylene glycol 200–water (PEG 200–H_2O) in the presence of trimethylamine, we observed formation of the desired product **4a** in 57% yield (Table 1, entry 1). Further screening of bases (including inorganic and organic bases) revealed that potassium carbonate (3 mmol with respect to 4-tosyloxycoumarin) was the best choice. Under these conditions, the desired 4-sulfanylcoumarin **4a** was isolated in 92% yield (Table 1, entry 3). It is also noteworthy that this reaction could be carried out under an air atmosphere without any reduction in the yield. Next, screening of the solvent revealed that the presence of a small amount of water was important, and that the optimum ratio of polyethylene glycol/water was 10:1.

The scope of this reaction was investigated by applying the optimized conditions [K_2CO_3, PEG 200–H_2O (10:1), r.t., air] and the results are summarized in Table 2. In all but one case, the 4-tosyloxycoumarin **1** reacted with thiourea (**2**) and the aliphatic halide **3** leading to the corresponding products **4** in moderate to excellent yields. For example, primary alkyl halides, including benzyl chloride, alkyl bromides and methyl iodide, underwent the sulfanylation reaction with thiourea and 4-tosyloxycoumarin to give the desired products **4a**–**c** in high yields (Table 2, entries 1–4). The reaction with the long-chain alkyl halide, 1-bromotetradecane, was less efficient affording a low 49% yield (Table 2, entry 5). Secondary halides such as bromocyclopentane (**3f**) and 2-iodobutane (**3g**) gave the corresponding products **4e** and **4f** in good yields (Table 2, entries 6 and 7). However, reaction of the tertiary alkyl halide **3h** resulted in only a trace amount of the

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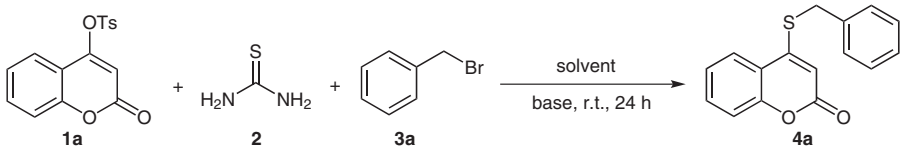
Table 1 Optimization of the Reaction Conditions for the Synthesis of 4-Sulfanylcoumarin **4a**



1a **2** **3a** **4a**

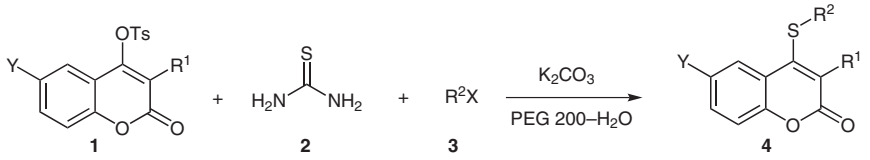
Entry	Solvent	Base	Yield (%)[a]
1	PEG 200–H_2O	Et_3N	57
2	PEG 200–H_2O	NaOH	60
3	PEG 200–H_2O	K_2CO_3	92
4	PEG 200–H_2O	DBU	40
5	PEG 200–H_2O	$NaHCO_3$	55
6	1,4-dioxane	K_2CO_3	37
7	1,4-dioxane–H_2O	K_2CO_3	50
8	SDS–H_2O[b]	K_2CO_3	58

[a] Yield of isolated product based on 4-tosyloxycoumarin.
[b] SDS = sodium dodecyl sulfate.

expected product being detected (Table 2, entry 8). Other 4-tosyloxycoumarin derivatives were also examined, and it transpired that the different substituents on the coumarin ring did not affect the reaction markedly. For example, 6-methyl-, 6-chloro-, and 6-fluoro-4-tosyloxycoumarins reacted with benzyl bromide to give the corresponding products in 92–97% yields (Table 2, entries 9, 13 and 17).

The reactions of other primary and secondary alkyl halides with these 4-tosyloxycoumarins also gave the desired products in good to excellent yields (Table 2, entries 10–12, 14–16 and 18–20). A very good yield of 93% was obtained when 3-phenyl-4-tosyloxycoumarin was reacted with thiourea and benzyl bromide (Table 2, entry 21).

Table 2 The Scope of the Reaction of 4-Tosyloxycoumarins with Thiourea and Alkyl Halides under the Optimized Conditions



1 **2** **3** **4**

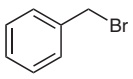
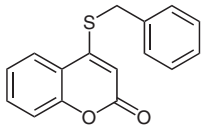
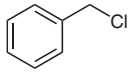
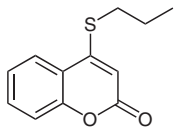
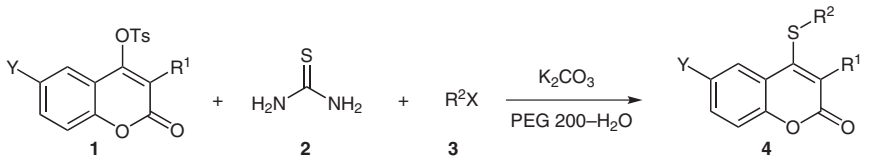
Entry	Coumarin[a]	R^2X	Product	Yield (%)[b]
1	**1a**	 **3a**	 **4a**	92
2	**1a**	 **3b**	**4a**	86
3	**1a**	PrBr **3c**	 **4b**	82

Table 2 The Scope of the Reaction of 4-Tosyloxycoumarins with Thiourea and Alkyl Halides under the Optimized Conditions (continued)



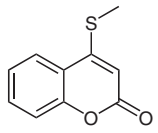
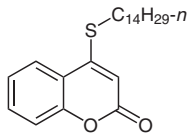
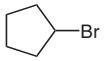
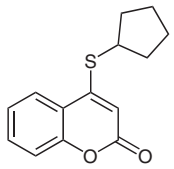
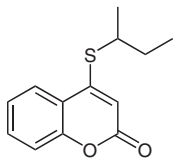
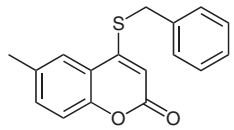
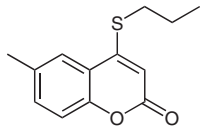
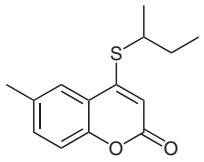
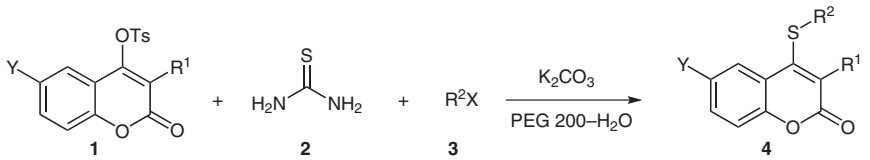
Entry	Coumarin[a]	R^2X	Product	Yield (%)[b]
4	**1a**	MeI **3d**	 **4c**	86
5	**1a**	*n*-$C_{14}H_{29}Br$ **3e**	 **4d**	49
6	**1a**	 **3f**	 **4e**	84
7	**1a**	*s*-BuI **3g**	 **4f**	67
8	**1a**	*t*-BuBr **3h**	–	trace
9	**1b**	**3a**	 **4g**	97
10	**1b**	**3c**	 **4h**	94
11	**1b**	**3g**	 **4i**	86

Table 2 The Scope of the Reaction of 4-Tosyloxycoumarins with Thiourea and Alkyl Halides under the Optimized Conditions (continued)



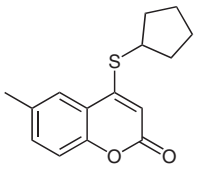
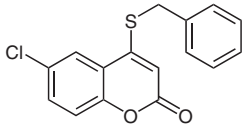
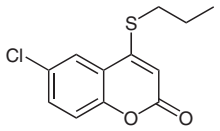
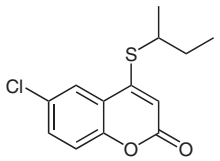
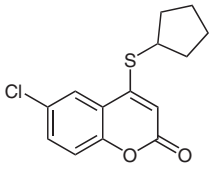
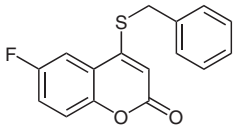
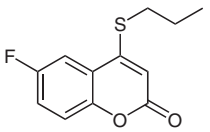
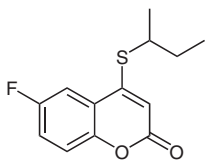
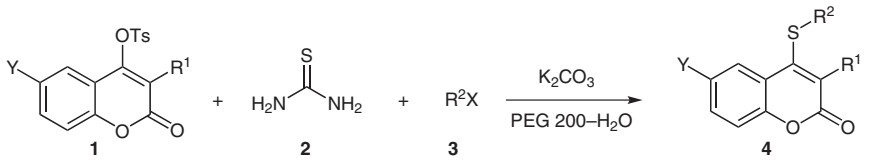
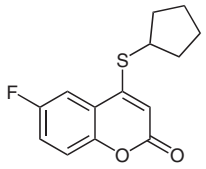
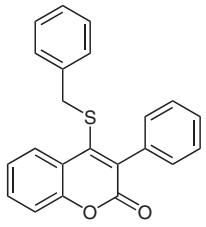
Entry	Coumarin[a]	R^2X	Product	Yield (%)[b]
12	**1b**	**3f**	 **4j**	77
13	**1c**	**3a**	 **4k**	97
14	**1c**	**3c**	 **4l**	86
15	**1c**	**3g**	 **4m**	84
16	**1c**	**3f**	 **4n**	83
17	**1d**	**3a**	 **4o**	92
18	**1d**	**3c**	 **4p**	74
19	**1d**	**3g**	 **4q**	83

Table 2 The Scope of the Reaction of 4-Tosyloxycoumarins with Thiourea and Alkyl Halides under the Optimized Conditions (continued)

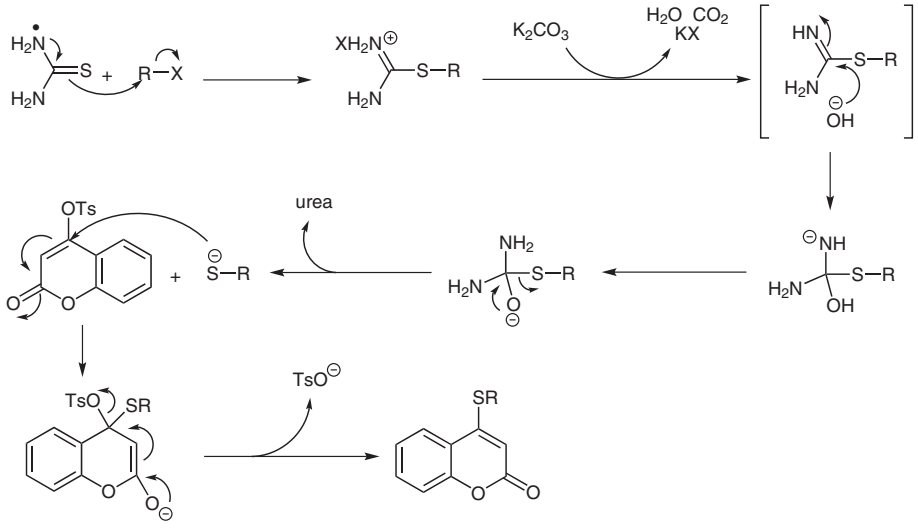


Entry	Coumarin[a]	R^2X	Product	Yield (%)[b]
20	**1d**	**3f**	 **4r**	64
21	**1e**	**3a**	 **4s**	93

[a] **1a**: Y = H, R^1 = H; **1b**: Y = Me, R^1 = H; **1c**: Y = Cl, R^1 = H; **1d**: Y = F, R^1 = H; **1e**: Y = H, R^1 = Me.
[b] Yield of isolated product based on the 4-tosyloxycoumarin.

We have proposed a general pathway for the reaction as presented in Scheme 2. We reasoned that the sulfur anion, formed in situ from the reaction between thiourea and the alkyl halide, is a key intermediate, which attacks the 4-tosyloxycoumarin to afford the 4-sulfanylcoumarin product.

In conclusion, we have described an efficient and novel route for the synthesis of 4-sulfanylcoumarins via direct sulfanylation of 4-tosyloxycoumarins with thiourea and alkyl halides. This transformation was performed in polyethylene glycol 200–water at room temperature without the exclusion of air. The efficiency of this method, combined with the operational simplicity should make it attractive for the preparation of compound libraries.



Scheme 2 A proposed reaction mechanism

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using Qingdao Haiyang silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using Qingdao Haiyang glass plates, pre-coated with silica gel (0.25 mm, 230–400 mesh) impregnated with a fluorescent indicator (254 nm); the plates were visualized by exposure to UV light. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. Organic solutions were concentrated by rotary evaporation at ~20 Torr and at 25–35 °C. Melting points were recorded using a Taike X-6 apparatus. IR spectra were obtained using a Perkin-Elmer FTIR 683 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are recorded in parts per million with tetramethylsilane as the internal standard. Coupling constants (*J*) are quoted in Hz. High-resolution mass spectrometry (HRMS) was performed using a Bruker micrOTOF II instrument.

4-Sulfanylcoumarins; General Procedure

A mixture of haloalkane **3** (0.4 mmol), thiourea (**2**) (0.5 mmol) and K_2CO_3 (0.6 mmol) in PEG 200 (3 mL) and H_2O (0.3 mL) was stirred magnetically at r.t. for several hours. Following completion of this step as indicated by TLC, the 4-tosyloxycoumarin **1** (0.2 mmol) was added and the mixture was stirred at r.t. for 24–48 h. After completion of the reaction as indicated by TLC, the mixture was extracted with EtOAc (3 × 2 mL), and the combined organic layer washed with H_2O (3 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel chromatography (PE–EtOAc, 10:1–8:1) afforded the desired product **4**. The structures of the products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

4-Benzylsulfanylcoumarin (4a)[3a]

Yield: 49.3 mg (92%); white solid; mp 176–178 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (s, 2 H), 6.23 (s, 1 H), 7.25–7.45 (m, 7 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.73 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.8, 106.9, 116.7, 117.5, 123.3, 123.6, 127.7, 128.4, 128.9, 129.1, 131.6, 133.2, 151.7, 156.6, 158.7.

4-Propylsulfanylcoumarin (4b)[5]

Yield: 36.1 mg (82%); white solid; mp 83–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.4 Hz, 3 H), 1.82–1.87 (m, 2 H), 3.00 (t, *J* = 7.2 Hz, 2 H), 6.14 (s, 1 H), 7.25–7.32 (m, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 21.2, 32.7, 106.7, 117.1, 118.3, 123.8, 123.9, 132.0, 152.1, 156.6, 159.3.

4-Methylsulfanylcoumarin (4c)

Yield: 33 mg (86%); white solid; mp 119–121 °C.

IR (KBr): 3443, 1717, 1346, 1254, 708, 619 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 6.10 (s, 1 H), 7.26–7.32 (m, 2 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 7.71 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 106.5, 117.1, 118.1, 123.7, 124.0, 132.1, 152.0, 157.2, 159.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_8O_2SNa$: 215.0143; found: 215.0164.

4-Tetradecylsulfanylcoumarin (4d)

Yield: 36.7 mg (49%); white solid; mp 79–80 °C.

IR (KBr): 3443, 2921, 1716, 1341, 1272, 704, 619 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.26–1.82 (m, 24 H), 3.01 (t, *J* = 7.2 Hz, 2 H), 6.15 (s, 1 H), 7.25–7.33 (m, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.7, 28.9, 29.1, 29.3, 29.4, 29.5, 29.6, 30.9, 31.9, 106.8, 117.2, 118.3, 123.8, 123.9, 132.0, 152.2, 156.7, 159.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{34}O_2SNa$: 397.2177; found: 397.2139.

4-Cyclopentylsulfanylcoumarin (4e)

Yield: 41.3 mg (84%); yellow solid; mp 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67–1.82 (m, 6 H), 2.26–2.29 (m, 2 H), 3.72–3.73 (m, 1 H), 6.22 (s, 1 H), 7.24–7.27 (m, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 33.2, 43.2, 107.7, 117.2, 118.3, 123.9, 124.0, 132.0, 152.2, 157.2, 159.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}O_2SNa$: 269.0612; found: 269.0586.

4-*sec*-Butylsulfanylcoumarin (4f)

Yield: 31.4 mg (67%); yellow solid; mp 85–86 °C.

IR (KBr): 3442, 2919, 1714, 1594, 1341, 1233, 740, 703, 642 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.2 Hz, 3 H), 1.49 (d, *J* = 6.4 Hz, 3 H), 1.73–1.89 (m, 2 H), 3.41–3.44 (m, 1 H), 6.19 (s, 1 H), 7.26–7.34 (m, 2 H), 7.55 (t, *J* = 7.8 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 19.9, 29.0, 41.9, 107.3, 117.2, 118.4, 123.9, 124.0, 132.0, 152.3, 156.2, 159.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}O_2S$: 257.0612; found: 257.0592.

4-Benzylsulfanyl-6-methylcoumarin (4g)[5]

Yield: 54.7 mg (97%); white solid; mp 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (s, 3 H), 4.23 (s, 2 H), 6.19 (s, 1 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 7.30–7.47 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 35.8, 107.3, 116.9, 117.6, 123.6, 128.2, 129.0, 129.1, 133.2, 133.8, 133.9, 150.3, 155.9, 159.4.

6-Methyl-4-propylsulfanylcoumarin (4h)

Yield: 44 mg (94%); white solid; mp 104–105 °C.

IR (KBr): 3444, 3063, 1709, 1301, 1234, 1139, 1122, 699, 618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.82–1.87 (m, 2 H), 2.41 (s, 3 H), 2.99 (t, *J* = 7.2 Hz, 2 H), 6.12 (s, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.52 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 20.9, 21.2, 32.7, 106.6, 116.9, 117.9, 123.6, 133.1, 133.8, 150.2, 156.5, 159.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}O_2SNa$: 257.0612; found: 257.0606.

4-*sec*-Butylsulfanyl-6-methylcoumarin (4i)

Yield: 42.7 mg (86%); yellow solid; mp 122–123 °C.

IR (KBr): 3414, 2954, 1702, 1348, 1222, 679, 613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.2 Hz, 3 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.72–1.88 (m, 2 H), 2.41 (s, 3 H), 3.38–3.43 (m, 1 H), 6.16 (s, 1 H), 7.19–7.35 (m, 2 H), 7.54 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 19.9, 20.9, 29.0, 41.8, 107.1, 116.9, 118.1, 123.8, 133.1, 133.7, 150.3, 156.0, 159.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}O_2S$: 271.0769; found: 271.0760.

4-Cyclopentylsulfanyl-6-methylcoumarin (4j)

Yield: 40 mg (77%); white solid; mp 150–152 °C.

IR (KBr): 3415, 2959, 2918, 1697, 1350, 1267, 777, 617 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71–1.82 (m, 6 H), 2.26–2.29 (m, 2 H), 2.40 (s, 3 H), 3.71 (d, *J* = 4.4 Hz, 1 H), 6.20 (s, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.50 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 25.0, 33.2, 43.1, 107.6, 116.9, 117.9, 123.7, 133.0, 133.7, 150.3, 157.0, 159.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{16}O_2SNa$: 283.0769; found: 283.0775.

4-Benzylsulfanyl-6-chlorocoumarin (4k)
Yield: 58.6 mg (97%); white solid; mp 135–136 °C.

IR (KBr): 3412, 2920, 1713, 1339, 1244, 740, 680, 614 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (s, 2 H), 6.23 (s, 1 H), 7.22–7.65 (m, 7 H), 7.66 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.9, 108.2, 118.6, 119.0, 123.4, 128.4, 129.0, 129.1, 129.6, 132.1, 133.4, 150.6, 154.9, 158.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{11}ClO_2SNa$: 325.0094; found: 325.0066.

6-Chloro-4-propylsulfanylcoumarin (4l)
Yield: 43.7 mg (86%); white solid; mp 102–103 °C.

IR (KBr): 3443, 2926, 1741, 1463, 1383, 1337, 1243, 701, 745, 614 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.82–1.88 (m, 2 H), 3.01 (t, *J* = 7.2 Hz, 2 H), 6.16 (s, 1 H), 7.26 (d, *J* = 8.8 Hz, 1 H), 7.48 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 21.1, 32.9, 107.5, 118.6, 119.3, 123.5, 129.6, 132.0, 150.6, 155.5, 158.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}ClO_2SNa$: 277.0066; found: 277.0085.

4-(*sec*-Butylsulfanyl)-6-chlorocoumarin (4m)
Yield: 45 mg (84%); white solid; mp 109–111 °C.

IR (KBr): 3443, 3073, 1724, 1338, 1229, 741, 705, 612 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.2 Hz, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 1.71–1.88 (m, 2 H), 3.40–3.45 (m, 1 H), 6.19 (s, 1 H), 7.26 (d, *J* = 9.2 Hz, 1 H), 7.46 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.73 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 19.8, 28.9, 42.2, 107.9, 118.6, 119.5, 123.7, 129.5, 131.9, 150.7, 155.1, 158.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}ClO_2SNa$: 291.0222; found: 291.0247.

6-Chloro-4-cyclopentylsulfanylcoumarin (4n)
Yield: 46.5 mg (83%); white solid; mp 139–140 °C.

IR (KBr): 3442, 2960, 2918, 1736, 1337, 1266, 704, 681, 613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.82 (m, 6 H), 2.26–2.29 (m, 2 H), 3.71–3.73 (m, 1 H), 6.23 (s, 1 H), 7.27 (t, *J* = 7.2 Hz, 1 H), 7.46 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.67 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 33.1, 43.4, 108.4, 118.6, 119.4, 123.6, 129.5, 131.9, 150.6, 156.0, 158.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}ClO_2SNa$: 303.0222; found: 303.0257.

4-Benzylsulfanyl-6-fluorocoumarin (4o)
Yield: 52.6 mg (92%); yellow solid; mp 118–119 °C.

IR (KBr): 3442, 2958, 1708, 1348, 1225, 696, 613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (s, 2 H), 6.26 (s, 1 H), 7.26–7.44 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.9, 108.3, 109.7 (d, $^2J_{C–F}$ = 26 Hz), 118.7, 118.8, 118.9, 119.6 (d, $^2J_{C–F}$ = 24 Hz), 128.4, 128.9, 129.1, 133.5, 148.4, 155.0, 158.6 (d, $^1J_{C–F}$ = 243 Hz), 158.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{11}FO_2SNa$: 309.0361; found: 309.0346.

6-Fluoro-4-propylsulfanylcoumarin (4p)
Yield: 35.2 mg (74%); white solid; mp 110–111 °C.

IR (KBr): 3413, 3113, 2872, 1720, 1344, 1225, 712, 613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.6 Hz, 3 H), 1.83–1.90 (m, 2 H), 3.01 (t, *J* = 7.2 Hz, 2 H), 6.17 (s, 1 H), 7.25–7.31 (m, 2 H), 7.39–7.41 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 21.1, 32.9, 107.5, 109.7 (d, $^2J_{C–F}$ = 25 Hz), 118.7 (d, $^3J_{C–F}$ = 8 Hz), 119.0 (d, $^3J_{C–F}$ = 9 Hz), 119.5 (d, $^2J_{C–F}$ = 24 Hz), 148.3, 155.6, 158.5 (d, $^1J_{C–F}$ = 242 Hz), 158.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{11}FO_2SNa$: 261.0361; found: 261.0367.

4-(*sec*-Butylsulfanyl)-6-fluorocoumarin (4q)
Yield: 41.8 mg (83%); white solid; mp 120–121 °C.

IR (KBr): 3417, 2969, 1711, 1345, 1221, 1134, 701, 612 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.2 Hz, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 1.72–1.86 (m, 2 H), 3.42–3.44 (m, 1 H), 6.21 (s, 1 H), 7.25–7.32 (m, 2 H), 7.43 (dd, *J* = 2.8, 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 19.8, 28.9, 42.2, 108.0, 109.9 (d, $^2J_{C–F}$ = 25 Hz), 118.7 (d, $^3J_{C–F}$ = 9 Hz), 119.2, 119.5 (d, $^2J_{C–F}$ = 25 Hz), 148.4, 155.3, 158.5 (d, $^1J_{C–F}$ = 242 Hz), 159.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}FO_2SNa$: 275.0518; found: 275.0522.

4-Cyclopentylsulfanyl-6-fluorocoumarin (4r)
Yield: 33.8 mg (64%); yellow solid; mp 115–117 °C.

IR (KBr): 3445, 2960, 1707, 1343, 1225, 1135, 716, 625, 612 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.86 (m, 6 H), 2.27–2.30 (m, 2 H), 3.70–3.73 (m, 1 H), 6.25 (s, 1 H), 7.22–7.32 (m, 2 H), 7.38 (dd, *J* = 2.8, 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 33.1, 43.4, 108.4, 109.8 (d, $^2J_{C–F}$ = 26 Hz), 118.7 (d, $^3J_{C–F}$ = 9 Hz), 119.1 (d, $^3J_{C–F}$ = 9 Hz), 119.4 (d, $^2J_{C–F}$ = 25 Hz), 148.3, 156.2, 158.5 (d, $^1J_{C–F}$ = 243 Hz), 159.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{13}FO_2SNa$: 287.0518; found: 287.0506.

4-Benzylsulfanyl-3-phenylcoumarin (4s)
Yield: 64 mg (93%); white solid; mp 159–160 °C.

IR (KBr): 3446, 3062, 1709, 1603, 1586, 1507, 1477, 1328, 1234, 704, 604 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (s, 2 H), 6.90–7.42 (m, 13 H), 8.15 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.2, 116.9, 120.6, 124.4, 127.2, 127.7, 128.2, 128.6, 128.9, 130.4, 131.7, 131.8, 134.6, 136.1, 148.7, 152.1, 159.7.

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