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Ru(II)-Catalyzed Selective C−H Amination of Xanthones and Chromones with Sulfonyl Azides: Synthesis and Anticancer Evaluation

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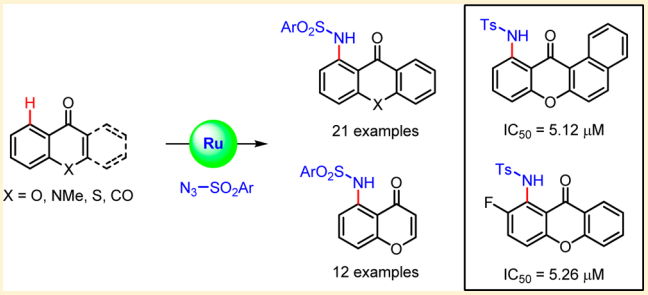
Supporting Information

ABSTRACT: A ketone-assisted ruthenium-catalyzed selective amination of xanthones and chromones C−H bonds with sulfonyl azides is described. The reactions proceed efficiently with a broad range of substrates with excellent functional group compatibility. This protocol provides direct access to 1-aminoxanthones, 5-aminochromones, and 5-aminoflavonoid derivatives known to exhibit potent anticancer activity.



INTRODUCTION

Xanthones (9*H*-xanthen-9-ones) and chromones (4*H*-chromen-4-ones) are among the most interesting discoveries in the field of natural products and have attracted considerable attention by virtue of their interesting biological properties.[1] In fact, this class of compounds is known to have diverse biological profiles, including antioxidant activity,[2] topoisomerase II inhibitory activity,[3] antitumor activity,[4] α-glucosidase inhibitory activity,[5] cholesterol acyltransferase inhibitory activity,[6] and antibacterial/antifungal activity.[7] The biological activities of these compounds are associated with their tri- and bicyclic scaffolds but vary depending on the nature and/or position of the different substituents. As a consequence, a variety of synthetic analogues of xanthones and chromones have been prepared and evaluated for clinical applications.[1a,e,8] In particular, 1-aminoxanthones and 5-aminochromones have shown promising antitumor properties against several cancer cell lines. For example, 1-aminopyranoxanthone **1** and its pyrazole-fused counterpart **2**, respectively, displayed potent antiproliferative activity toward the leukemia L1210 cell line and solid tumor cell lines (Figure 1).[9,10] The xantheno-imidazole **3** showed significant inhibitory effect against the human breast MDA-MB-231 cell line.[11] In addition, aminoflavone (NSC686288, **4**) is a new anticancer drug that has recently entered phase II clinical trials and exhibits potent antitumor activity against MCF-7 human breast cancer cells and neoplastic cells of renal origin.[12]

Organic chemists continue to strive toward the development of atom and step economical processes for the synthesis of complex molecular structures from simple precursors. In this regard, transition-metal-catalyzed selective cross-coupling reaction via C−H bond activation has played a pivotal role for carbon−carbon and carbon−heteroatom bond formation reactions due to the minimization of stoichiometric metallic waste and of the costs associated with substrate preactivation.[13] Catalytic direct C−N bond formation via C−H bond activation is one of the most important research topics because of the prevalence of nitrogen-containing bioactive molecules.[14] Although great advances in catalytic C−H amination or amidation reactions have been made, stoichiometric byproducts generated from external oxidants, bases, and halide salts lead to the development of truly green transformation.[15,16] Chang and co-workers have made a significant breakthrough for direct *N*-arylation via Rh(III)-catalyzed amination reactions of sp^2 C−H bonds using sulfonyl, aryl, and alkyl azides as new amine equivalents without external oxidants and bases.[17] Recently, the Ir(III)-catalyzed C−H amidation using sulfonyl and acyl azides has been reported to give access to the corresponding amides.[18]

Since the pioneering report by Murai,[19] ruthenium catalysts have tremendously contributed to the discovery of cheaper and efficient catalytic systems in C−H bond activation.[20] In this context, there has been a great deal of effort in the area of Mirozoki−Heck-type reactions, redox-neutral biaryl synthesis, hydroalkenylation, acylation, hydroxylation, and oxidative annulations. Despite these achievements, however, the ruthenium-catalyzed selective C−H amination reaction of xanthones and chromones containing a weakly coordinating ketone group still remains unexplored.[21] Our continued efforts

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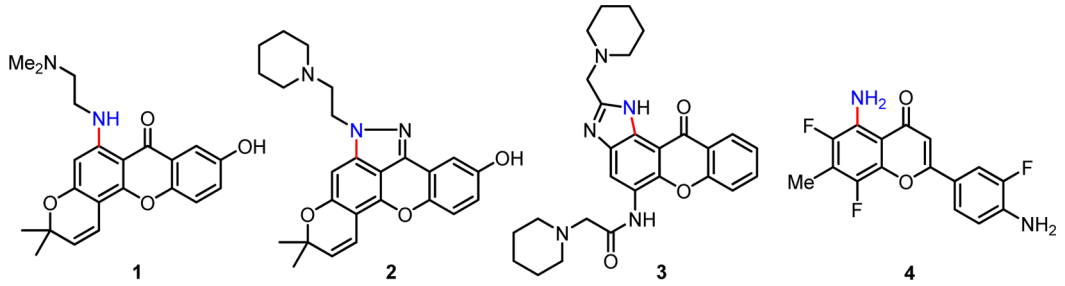
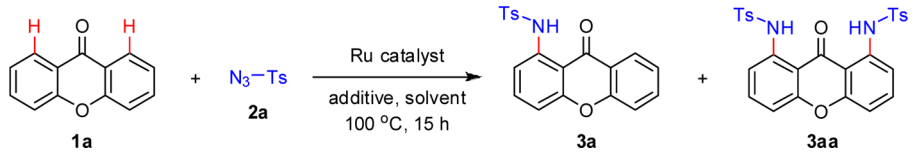


Figure 1. Structure of biologically active 1-aminoxanthones and 5-aminochromones.

Table 1. Selected Optimization of Reaction Conditions[a]



				yield (%)[b]	
entry	catalyst (mol %)	additive (mol %)	solvent	3a	3aa
1	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)		DCE	12	trace
2	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)		DCE	N.R.	
3	$AgSbF_6$ (10)		DCE	N.R.	
4	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	NaOAc (30)	DCE	50	trace
5	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	CsOAc (30)	DCE	64	trace
6	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	$Cu(OAc)_2$ (30)	DCE	68	3
7	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgNTf_2$ (10)	$Cu(OAc)_2$ (30)	DCE	62	6
8	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)	$Cu(OAc)_2$ (30)	DCE	N.R.	
9	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	$Cu(OAc)_2$ (100)	DCE	75	14
10	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	$Cu(OAc)_2$ (30)	THF	4	
11	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	$Cu(OAc)_2$ (30)	MeCN	N.R.	
12	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	$Cu(OAc)_2$ (30)	DMSO	N.R.	
13	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), $AgSbF_6$ (10)	$Cu(OAc)_2$ (30)	CH_2Cl_2	75	2

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), $AgSbF_6$ or $AgNTf_2$ (10 mol %), additive (quantity noted), and solvent (1 mL) in pressure tubes. [b]Isolated yield by flash column chromatography.

in transition-metal-catalyzed C−H bond activation and cross-coupling reactions[22] prompted us to explore the ruthenium-catalyzed coupling reaction of xanthones and chromones with sulfonyl azides and to evaluate the cytotoxic effect of amination products against the human breast adenocarcinoma MCF-7 cell line.

RESULTS AND DISCUSSION

In our initial study, 9*H*-xanthen-9-ones (**1a**) and *p*-toluenesulfonyl azide (**2a**) were chosen as model substrates for optimizing the reaction conditions, and selected results are summarized in Table 1. To our delight, the combination of $[Ru(p\text{-cymene})Cl_2]_2$ and $AgSbF_6$ in DCE solvent promoted the coupling of **1a** and **2a** to provide monoaminated compound **3a** in 12% isolated yield (Table 1, entry 1). In the absence of either $[Ru(p\text{-cymene})Cl_2]_2$ or $AgSbF_6$, no formation of product was detected, indicating that both catalysts are required in the coupling reaction (Table 1, entries 2 and 3). After screening of acetate additives under otherwise identical conditions, $Cu(OAc)_2$ was found to be most effective in this coupling reaction, affording exclusively monoaminated product **3a** in 68% yield with a mono-selectivity of 23:1, whereas other additives such as NaOAc and CsOAc were less effective in the coupling reaction (Table 1, entries 4−6). Further investigations revealed that cationic Ru catalysts generated from $[Ru(p\text{-cymene})Cl_2]_2$ and silver salts are unique in their ability to facilitate high levels of conversion (Table 1, entries 7 and 8). Further study showed that the increased loading of Cu additive displayed the improved catalytic activity to afford monoaminated compound **3a** and bisaminated compound **3aa** in 89% combined yield, albeit resulting in a low level of monoselectivity (5.4:1), as shown in entry 9. After further optimization, we found that a treatment of 2.5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ and 10 mol % of $AgSbF_6$, in the presence of 30 mol % of $Cu(OAc)_2$ in CH_2Cl_2 solvent at 100 °C for 15 h provided the desired 1-aminoxanthone **3a** in high yield (75%) (Table 1, entries 10−13).

Having established the optimized reaction conditions, the substrate scope was examined with respect to xanthones and their structural analogues (Table 2). The amidation reaction of unsymmetrical xanthones **1b−1d** with tosyl azide (**2a**) occurred exclusively at the less sterically hindered position to afford the corresponding products **3b−3d** in moderate to good yields. However, 2-fluoro-substituted xanthone **1e** furnished a separable mixture of **3e** and **3ee**, albeit providing the regioisomers at C8 and C1 with a 3:1 ratio. These data suggest that the steric effect of the substrates strongly interferes with either the formation of the cycloruthenated intermediate or the proximity of tosyl azide into the

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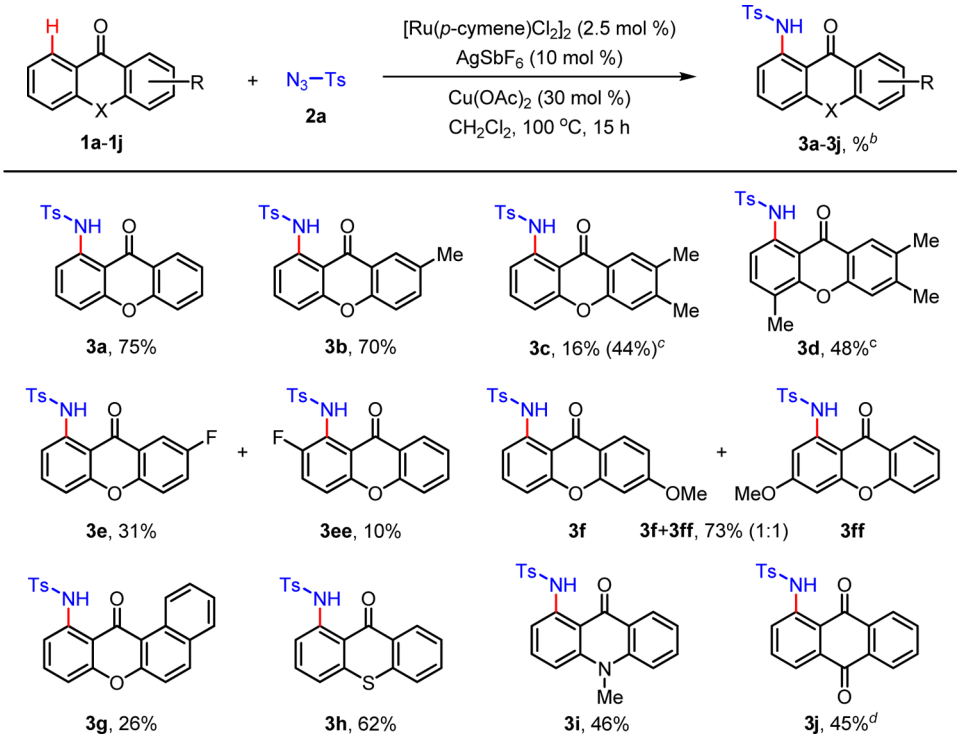
Table 2. Scope of Xanthones[a,b,c,d]



[a]Reaction conditions: **1a–1j** (0.3 mmol), **2a** (0.45 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (30 mol %), CH_2Cl_2 (1 mL) in pressure tubes. [b]Isolated yield by flash column chromatography. [c]DCE was used as a solvent. [d]40 h.

cyclometalated intermediate. As expected, xanthone **1f** with a methoxy group at the C3 position exhibited poor regioselectivity to afford an inseparable mixture of **3f** and **3ff** in 73% combined yield with a 1:1 ratio. The 2-substituted xanthone **1g** was found to be less reactive in this catalyst system. Finally, xanthone analogues such as thioxanthone (**1h**), acridinone (**1i**), and anthraquinone (**1j**) also smoothly underwent amidation reaction to generate the corresponding products **3h–3j**, respectively.

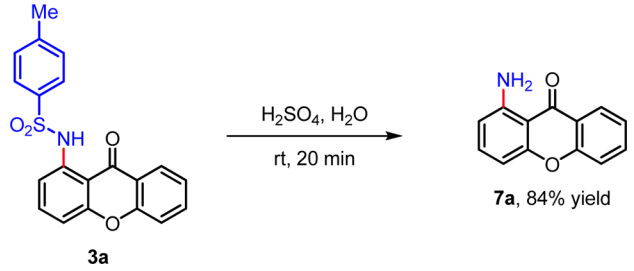
To further examine the substrate scope of this process, a broad range of azides was screened to couple with xanthone (**1a**), as shown in Table 3. The reaction between **1a** and sulfonyl azides **2b–2j** with either electron-rich or electron-deficient groups, regardless of the substituent position on the arene ring, was found to be favored in the amidation reaction to afford the corresponding products **4b–4j** in high yields. Particulary, this transformation was compatible with acetanilide or bromo groups as versatile functionalities for further cross-coupling reaction. It should be noted that the reaction exclusively provided the monoaminated product in all cases, and a trace amount (<5%) of bisaminated product was observed by ^1H NMR or GC-MS analysis. In contrast, benzoyl azide (**2k**) and phenyl azide (**2l**) were unreactive under the present reaction conditions.

After successful exploration of direct amidation of xanthones with sulfonyl azides, we turned our attention to C5-selective amidation of chromones due to structural similarities between xanthones and chromones as well as potent anticancer activity of 5-aminochromones (Table 4).

To our pleasure, chromone (**5a**) was efficiently coupled with tosyl azide (**2a**) to produce our desired C5-aminated product **6a** in 61% yield under ruthenium catalysis. The optimal reaction condition was obtained in a very similar fashion to that for ruthenium-catalyzed amination reaction of xanthones. This reaction condition was also compatible with C3- or C2-substituted chromones, furnishing the corresponding products **6b** and **6c**. This protocol was also successfully applied to highly substituted isoflavones **5d** and **5e** and flavone **5f**. In addition, C5-amidation reaction of 5**a** with a wide range of sulfonyl azides proceeded smoothly to give the corresponding products **6g–6l** in moderate to good yields.

To demonstrate the further transformation of sufonyl amide substituted xanthones and chromones, a *N*-sulfonyl group of **3a** was removed under hydrolysis conditions to give 1-aminoxanthone (**7a**) in 84% yield (Scheme 1).

Scheme 1. Deprotection of an *N*-Sulfonyl Group



To obtain the mechanistic insight, we carried out an intramolecular competition experiment of deuterio-**1a** with tosyl azide (**2a**) under standard reaction conditions for 30 min, which results in a kinetic isotope effect (k_H/k_D) of 2.1 (Scheme 2), thus indicating that C–H bond cleavage might be involved in the rate-determining step.[23]

A possible mechanistic pathway of the Ru-catalyzed amidation reaction is proposed in Scheme 3. Initially, the

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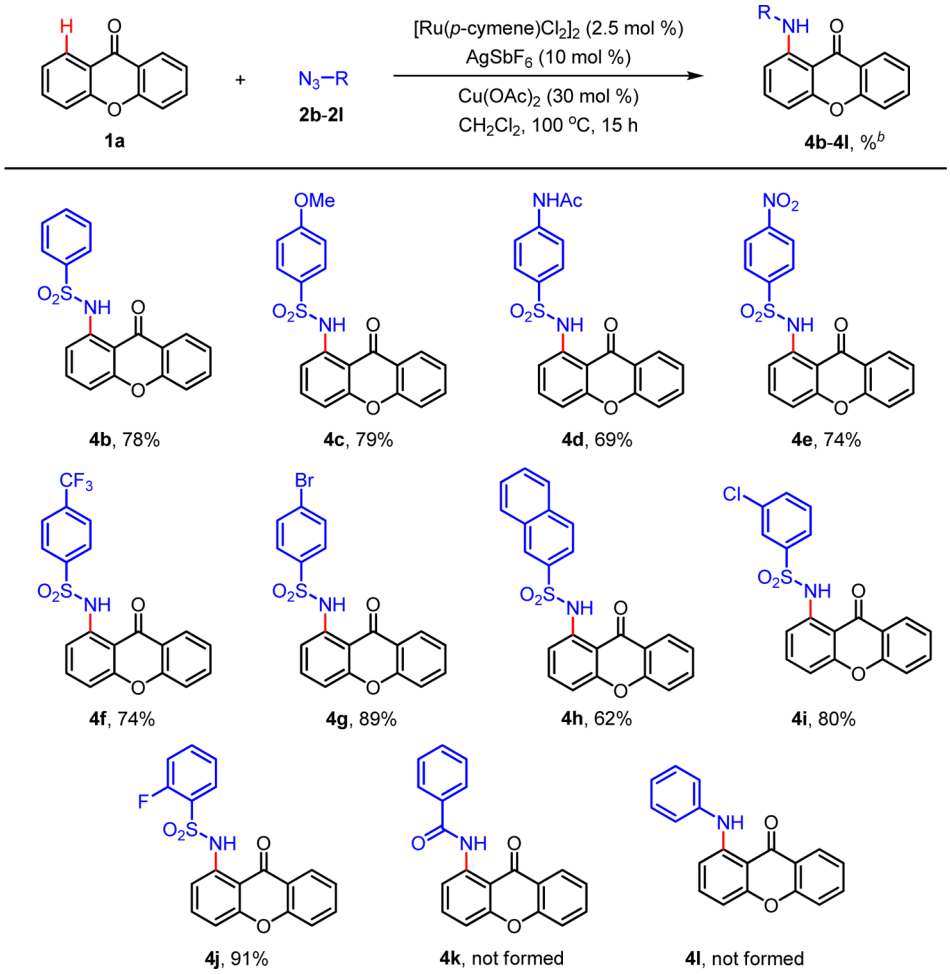
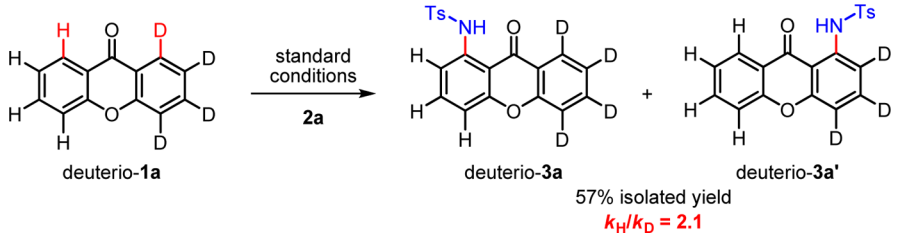
Table 3. Scope of Azides[a,b]



[a]Reaction conditions: **1a** (0.3 mmol), **2b**–**2l** (0.45 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (30 mol %), CH_2Cl_2 (1 mL) in pressure tubes. [b]Isolated yield by flash column chromatography.

Scheme 2. Intramolecular Kinetic Isotope Experiment



removal of a chloride ligand by a Ag salt from the $[RuCl_2(p\text{-cymene})]_2$ complex initiates the catalytic reaction. Though the exact role of $Cu(OAc)_2$ is not clear, we believe that it provides an OAc source to the active ruthenium species in order to accelerate the *ortho*-metalation. The coordination of the carbonyl oxygen in **1b** with the active Ru(II) catalyst delivers the metallacycle intermediate **I**.[20] Subsequently, tosyl azide coordinates with intermediate **I** to form the ruthenacycle **II**, followed by migratory insertion of the sulfonamido moiety with the evolution of N_2 gas leads to the intermediate **III**.[21e,h] Finally, the active ruthenium complex is generated by protonolysis, and the amidation product **3b** is obtained.

All the synthesized 1-aminoxanthones and 5-aminochromones were screened for growth inhibition activity against human breast cancer MCF-7 cells, and the results of inhibitory activity are summarized in Table 5. Cancer cells were exposed to increasing concentrations of compounds **3a**–**3j**, **4b**–**4j**, and **6a**–**6l** for 24 h, and cell survival was determined using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.[24] Several of the synthetic 1-aminoxanthones, e.g., **3e**, **3ee**, **3g**, and **4j**, showed promising growth inhibition of MCF-7 cells. In particular, compounds **3ee** and **3g** displayed the most potent activities (IC_{50} = 5.26 μM for **3ee** and IC_{50} = 5.12 μM for **3g**) among the tested compounds. The antiproliferative activities of **3ee** and **3g** were about 1.5-fold stronger than that of the well-known anticancer agent doxorubicin (IC_{50} = 7.57 μM) as a positive control.[25] On the other hand, synthetic 5-aminochromones **6a**–**6i** were relatively less effective than 1-aminoxanthone derivatives for MCF-7 cell growth inhibition. These results show that 1-

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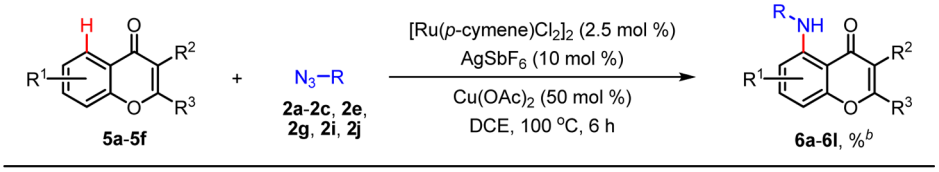
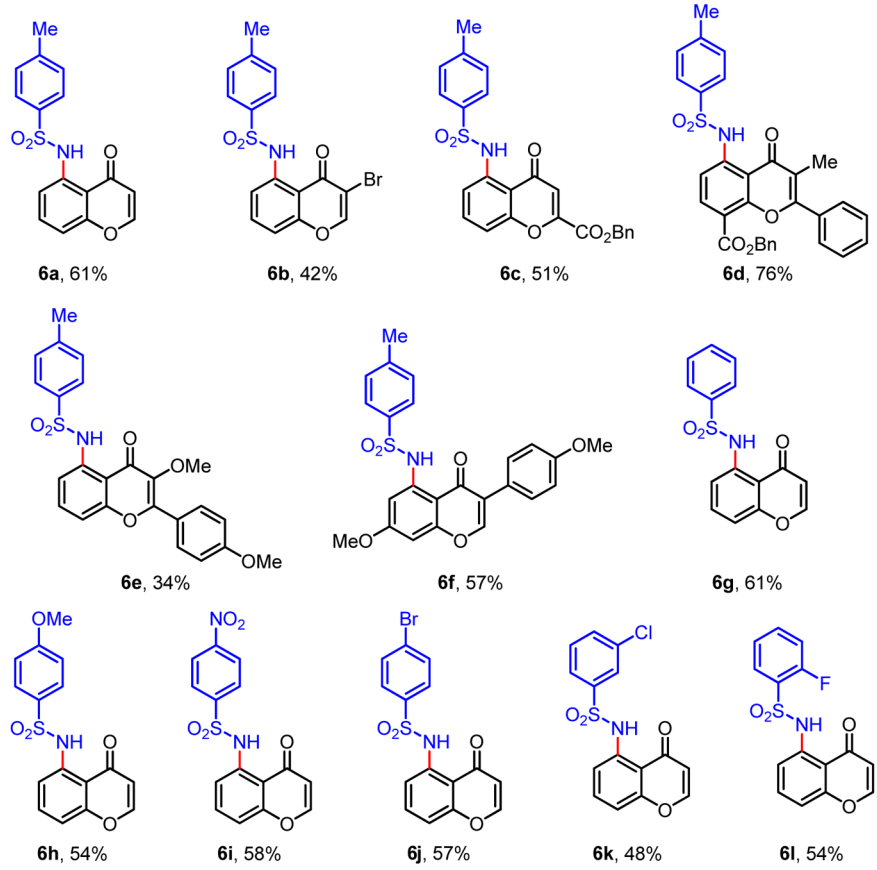
Table 4. Scope of Chromones[a,b]





[a]Reaction conditions: **5a−5f** (0.3 mmol), sulfonyl azide (0.45 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (50 mol %), DCE (1 mL) in pressure tubes. [b]Isolated yield by flash column chromatography.

amidated xanthone derivatives represent a new class of strong inhibitors against human breast cancer cells.

CONCLUSION

In conclusion, we described the ruthenium-catalyzed direct C−H amination of xanthones and chromones with sulfonyl azides. These transformations have been applied to a wide range of substrates and typically proceed with an excellent level of regio- and chemoselectivity as well as with high functional group tolerance. Furthermore, synthetic 1-amino-xanthones and 5-aminochromones were evaluated for in vitro anticancer activity. Compounds **3ee** and **3g** proved to be highly cytotoxic, with an activity competitive with anticancer doxorubicin. Further detailed studies to determine the biological mechanism of these compounds are currently under investigation.

EXPERIMENTAL SECTION

Typical Procedure for the Amidation of Xanthones (1a−1j) with Sulfonyl Azides (2a−2l). To an oven-dried sealed tube with 9*H*-xanthen-9-one (**1a**) (58.9 mg, 0.3 mmol, 100 mol %), $[Ru(p\text{-cymene})Cl_2]_2$ (4.6 mg, 0.075 mmol, 2.5 mol %), $AgSbF_6$ (10.3 mg, 0.03 mmol, 10 mol %), and $Cu(OAc)_2$ (16.3 mg, 0.09 mmol, 30 mol %) in CH_2Cl_2 (1 mL) was added tosyl azide (**2a**) (88.7 mg, 0.45 mmol, 150 mol %). The reaction mixture was allowed to stir at 100 °C for 15 h. After cooling at room temperature, the reaction mixture was evaporated onto silica gel. Purification of the product by flash column chromatography (SiO_2: *n*-hexanes/EtOAc = 10:1) provided **3a** (81.7 mg, 0.224 mmol, 75% yield) and **3aa** (3.3 mg, 0.006 mmol, 2% yield), respectively.

*4-Methyl-N-(9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**3a**).* 81.7 mg (75%); pale yellow solid; mp = 159−165 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.50 (s, 1H), 8.20 (dd, J = 8.1, 1.5 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.70−7.67 (m, 1H), 7.51 (t, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.2, 1.0 Hz, 1H), 7.37 (dd, J = 8.4, 0.5 Hz, 1H), 7.34−7.32 (m, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.01 (dd, J = 8.3, 1.1 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.5, 156.9, 155.3, 143.9, 140.9, 136.5, 135.7, 135.5, 129.7, 127.3, 126.4, 124.3, 121.0, 117.6, 111.4, 111.2, 109.3, 21.5; IR (KBr) υ 3032, 2920, 2169, 2005, 1627, 1604, 1568, 1467, 1382, 1296, 1232, 1152, 1047, 930, 883, 734 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{20}H_{15}NO_4S$ $[M]^+$ 365.0722, found 365.0718.

*N,N′-(9-Oxo-9H-xanthene-1,8-diyl)bis(4-methylbenzene-sulfonamide) (**3aa**).* 3.3 mg (2%); pale yellow solid; mp = 230−249 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 11.98 (s, 2H), 7.84 (dd, J = 6.6, 1.7 Hz, 4H), 7.53 (t, J = 8.3 Hz, 2H), 7.48 (dd, J = 8.3, 1.1 Hz, 2H), 7.25 (dd, J = 8.5, 0.5 Hz, 4H), 6.97 (dd, J = 8.3, 1.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 184.0, 156.5, 144.5, 141.1,

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Scheme 3. Proposed Mechanistic Pathway

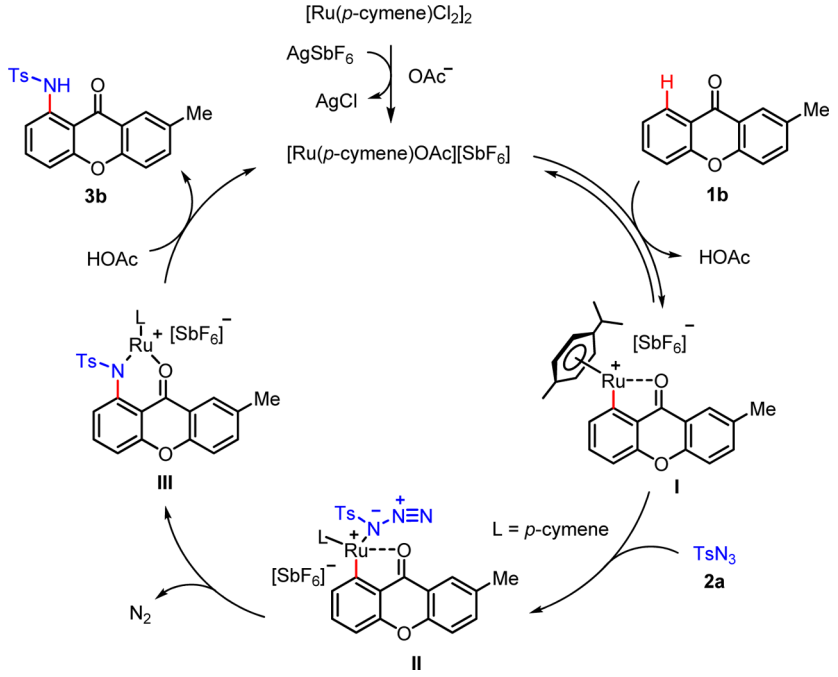

Table 5. Cytotoxicity of 1-Aminoxanthones and 5-Aminochromones with Human Breast Cancer Cells[a]

compounds	IC_{50} (μM)	compounds	IC_{50} (μM)	compounds	IC_{50} (μM)
3a	>50	**4b**	20.53	**6c**	>50
3b	22.57	**4c**	>50	**6d**	>50
3c	21.34	**4d**	>50	**6e**	>50
3d	>50	**4e**	>50	**6f**	42.24
3e	9.26	**4f**	>50	**6g**	25.81
3ee	5.26	**4g**	30.11	**6h**	>50
3f/3ff	>50	**4h**	>50	**6i**	>50
3g	5.12	**4i**	>50	**6j**	>50
3h	40.38	**4j**	5.44	**6k**	>50
3i	45.38	**6a**	26.68	**6l**	20.61
3j	32.51	**6b**	24.77	doxorubicin	7.57

[a]IC_{50} value: substance concentration necessary for 50% inhibition of cell viability.

136.7, 136.6, 130.0, 127.6, 111.8, 111.2, 109.0, 21.8; IR (KBr) υ 3355, 3259, 3054, 2923, 2167, 2025, 1600, 1475, 1385, 1299, 1155, 1092, 1037, 900, 815 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{27}H_{22}N_2O_6S_2$ $[M]^+$ 534.0919, found 534.0919.

*4-Methyl-N-(7-methyl-9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**3b**).* 79.7 mg (70%); light yellow solid; mp = 199−218 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.55 (s, 1H), 8.01 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.52−7.46 (m, 3H), 7.30 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.02 (dd, J = 8.3, 1.1 Hz, 1H), 2.44 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.6, 157.0, 153.6, 143.9, 141.0, 136.9, 136.6, 135.6, 134.2, 129.7, 127.4, 125.7, 120.8, 117.4, 111.4, 111.1, 109.4, 21.5, 20.9; IR (KBr) υ 3032, 2923, 2169, 2018, 1623, 1604, 1468, 1291, 1156, 1088, 1048, 965, 885, 806, 737 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{21}H_{17}NO_4S$ $[M]^+$ 379.0878, found 379.0878.

*N-(6,7-Dimethyl-9-oxo-9H-xanthen-1-yl)-4-methylbenzenesulfonamide (**3c**).* 51.9 mg (44%); light yellow solid; mp = 233−244 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.63 (s, 1H), 7.92 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.49−7.46 (m, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.15 (s, 1H), 6.99 (dd, J = 8.1, 1.1 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.4, 156.9, 153.9, 146.5, 143.8, 140.9, 136.7, 135.3, 133.6, 129.7, 127.4, 125.9, 118.9, 117.7, 111.4, 111.0, 109.3, 21.5, 20.6, 19.3; IR (KBr) υ 3027, 2922, 2166, 2018, 1605, 1566, 1467, 1332, 1249, 1157, 1089, 1053, 917, 810, 777 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{22}H_{19}NO_4S$ $[M]^+$ 393.1035, found 393.1045.

*4-Methyl-N-(4,6,7-trimethyl-9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**3d**).* 58.7 mg (48%); pale yellow solid; mp = 222−231 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.91 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 8.1 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.6, 154.8, 153.8, 146.4, 143.6, 138.6, 136.7, 136.2, 133.5, 129.6, 127.4, 125.8, 120.5, 118.8, 117.8, 110.9, 109.4, 21.5, 20.6, 19.3, 15.5; IR (KBr) υ 3027, 2920, 2156, 1982, 1625, 1595, 1487, 1466, 1367, 1282, 1232, 1157, 1089, 1071, 959, 889, 812 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{23}H_{21}NO_4S$ $[M]^+$ 407.1191, found 407.1194.

*N-(7-Fluoro-9-oxo-9H-xanthen-1-yl)-4-methylbenzenesulfonamide (**3e**).* 35.7 mg (31%); pale yellow solid; mp = 224−238 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 11.85 (s, 1H), 8.22 (dd, J = 7.9, 1.4 Hz, 1H), 7.44−7.37 (m, 3H), 7.26−7.24 (m, 2H), 7.16 (dd, J = 9.1, 3.6 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.3, 155.5, 152.8, 149.4 (d, J_{C-F} = 245.5 Hz), 143.6, 137.7 (d, J_{C-F} = 23.9 Hz), 135.8, 129.2, 127.6 (d, J_{C-F} = 13.7 Hz), 127.3, 126.5, 124.5, 123.8 (d, J_{C-F} = 22.5 Hz), 120.6, 117.6, 113.4 (d, J_{C-F} = 7.4 Hz), 112.4 (d, J_{C-F} = 2.8 Hz), 21.5; IR (KBr) υ 3076, 2920, 2157, 2029, 1638, 1610, 1471, 1391, 1303, 1234, 1155, 1090, 886, 810, 753

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cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{20}H_{14}FNO_4S$ $[M]^+$ 383.0628, found 383.0629.

*N-(2-Fluoro-9-oxo-9H-xanthen-1-yl)-4-methylbenzenesulfonamide (**3ee**).* 11.5 mg (10%); pale yellow solid; mp = 215−221 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.34 (s, 1H), 7.87 (dd, J = 8.2, 2.7 Hz, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.55 (t, J = 8.2 Hz, 1H), 7.49 (dd, J = 8.2, 0.9 Hz, 1H), 7.44−7.42 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 8.2, 0.9 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.8, 158.8 (d, J_{C-F} = 244.4 Hz), 156.9, 151.6, 144.0, 140.9, 136.5, 136.0, 129.7, 127.4, 123.8 (d, J_{C-F} = 25.3 Hz), 122.0 (d, J_{C-F} = 7.4 Hz), 119.7 (d, J_{C-F} = 3.0 Hz), 111.4, 111.3, 111.2, 108.7, 21.5; IR (KBr) υ 3054, 2921, 2157, 2039, 1628, 1605, 1571, 1471, 1388, 1285, 1227, 1158, 1090, 1048, 881, 819 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{20}H_{14}FNO_4S$ $[M]^+$ 383.0628, found 383.0629.

*N-(6-Methoxy-9-oxo-9H-xanthen-1-yl)-4-methylbenzenesulfonamide (**3f**) and N-(3-methoxy-9-oxo-9H-xanthen-1-yl)-4-methylbenzenesulfonamide (**3ff**).* 86.6 mg (73%); light yellow solid; mp = 166−169 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.67 (s, 1H), 12.65 (s, 1H), 8.20 (dd, J = 7.9, 1.4 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.81 (t, J = 8.4 Hz, 4H), 7.65 (dt, J = 7.7, 1.6 Hz, 1H), 6.98 (dd, J = 7.7, 1.6 Hz, 1H), 6.90 (dd, J = 8.9, 2.3 Hz, 1H), 6.76 (d, J = 2.3 Hz, 1H), 6.46 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.5, 179.2, 165.6, 165.3, 158.6, 157.3, 156.9, 155.2, 143.9, 143.8, 142.4, 140.9, 136.6, 136.5, 135.1, 134.9, 129.7, 129.6, 127.9, 127.4, 127.3, 126.3, 124.1, 121.1, 117.3, 114.9, 113.8, 111.3, 111.1, 109.1, 103.9, 99.7, 99.2, 95.2, 55.9, 55.8, 21.6, 21.5; IR (KBr) υ 3058, 2932, 2180, 2028, 1601, 1566, 1466, 1440, 1319, 1232, 1148, 1088, 1049, 963, 883, 804, 769 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{21}H_{17}NO_5S$ $[M]^+$ 395.0827, found 395.0825.

*4-Methyl-N-(12-oxo-12H-benzo[a]xanthen-11-yl)benzenesulfonamide (**3g**).* 32.4 mg (26%); light yellow solid; mp = 225−236 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.89 (s, 1H), 9.92 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.9 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.79−7.77 (m, 1H), 7.61−7.59 (m, 1H), 7.53−7.52 (m, 2H), 7.45 (d, J = 8.9 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.19 (dd, J = 7.0, 2.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 182.3, 157.1, 155.6, 143.9, 140.7, 137.7, 136.7, 134.8, 130.6, 130.3, 130.0, 129.7, 128.7, 127.4, 126.8, 126.5, 117.4, 114.1, 111.9, 111.1, 110.9, 21.5; IR (KBr) υ 3021, 2920, 2157, 1981, 1626, 1590, 1485, 1468, 1336, 1244, 1152, 1090, 1037, 999, 891, 818, 751 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{24}H_{17}NO_4S$ $[M]^+$ 415.0878, found 415.0881.

*4-Methyl-N-(9-oxo-9H-thioxanthen-1-yl)benzenesulfonamide (**3h**).* 70.9 mg (62%); yellow solid; mp = 183−189 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 13.18 (s, 1H), 8.51 (dd, J = 8.1, 1.0 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.61−7.58 (m, 2H), 7.48−7.45 (m, 2H), 7.41 (t, J = 8.1 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.14 (dd, J = 8.0, 1.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 183.9, 143.9, 143.4, 139.8, 136.6, 136.5, 133.2, 132.8, 130.0, 129.7, 129.3, 127.4, 126.6, 125.3, 120.0, 116.0, 114.9, 21.5; IR (KBr) υ 3071, 2922, 2156, 2004, 1582, 1443, 1340, 1285, 1219, 1157, 1086, 973, 916, 828, 744 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{20}H_{15}NO_3S_2$ $[M]^+$ 381.0493, found 381.0490.

*4-Methyl-N-(10-methyl-9-oxo-9,10-dihydroacridin-1-yl)benzenesulfonamide (**3i**).* 52.2 mg (44%); yellow solid; mp = 220−225 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 13.98 (s, 1H), 8.39 (dd, J = 8.1, 1.5 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.68−7.67 (m, 1H), 7.45−7.44 (m, 2H), 7.32 (dd, J = 8.1, 0.6 Hz, 1H), 7.25−7.23 (m, 1H), 7.16 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.8, 143.8, 143.5, 142.1, 141.8, 137.0, 134.6, 134.4, 129.5, 127.4, 127.3, 122.0, 121.8, 114.7, 109.9, 108.5, 108.3, 34.6, 21.5; IR (KBr) υ 3356, 3259, 2921, 2157, 2029, 1596, 1499, 1465, 1304, 1258, 1156, 1089, 1017, 930, 888, 812 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{21}H_{18}N_2O_3S$ $[M]^+$ 378.1038, found 378.1045.

*N-(9,10-Dioxo-9,10-dihydroanthracen-1-yl)-4-methylbenzenesulfonamide (**3j**).* 50.9 mg (45%); yellow solid; mp = 214−228 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.27−8.25 (m, 1H), 8.21−8.20 (m, 1H), 8.00 (dd, J = 8.4, 1.1 Hz, 1H), 7.94 (dd, J = 7.6, 1.1 Hz, 1H), 7.81−7.76 (m, 4H), 7.63 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 186.9, 182.3, 144.4, 141.3, 136.4, 135.5, 134.6, 134.4, 134.3, 132.8, 129.9, 127.5, 127.3, 127.1, 123.4, 122.4, 117.7, 21.5; IR (KBr) υ 3077, 3032, 2922, 2157, 2028, 1666, 1638, 1588, 1466, 1376, 1335, 1275, 1154, 1088, 1022, 912, 805, 707 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{21}H_{15}NO_4S$ $[M]^+$ 377.0722, found 377.0720.

*N-(9-Oxo-9H-xanthen-1-yl)benzenesulfonamide (**4b**).* 82.2 mg (78%); pale yellow solid; mp = 168−170 °C; ^1H NMR (700 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.19 (dd, J = 7.9, 1.6 Hz, 1H), 7.95−7.94 (m, 2H), 7.89 (dt, J = 7.7, 1.6 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.64−7.61 (m, 2H), 7.58−7.56 (m, 2H), 7.51−7.49 (m, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 156.4, 154.9, 139.8, 138.3, 136.6, 136.4, 133.7, 129.6, 127.0, 125.8, 124.7, 120.4, 117.8, 111.8, 110.6, 108.6; IR (KBr) υ 3066, 2925, 2156, 2016, 1625, 1601, 1568, 1470, 1387, 1293, 1238, 1156, 1089, 929, 883, 753 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{19}H_{13}NO_4S$ $[M]^+$ 351.0565, found 351.0562.

*4-Methoxy-N-(9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**4c**).* 90.4 mg (79%); pale yellow solid; mp = 163−168 °C; ^1H NMR (700 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.19 (dd, J = 7.9, 1.5 Hz, 1H), 7.90−7.87 (m, 3H), 7.47 (t, J = 8.3 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 163.0, 156.4, 154.9, 140.1, 136.6, 136.4, 129.8, 129.4, 125.8, 124.7, 120.4, 117.8, 114.7, 111.6, 110.5, 108.5, 55.7; IR (KBr) υ 3065, 2925, 1633, 1605, 1572, 1471, 1385, 1297, 1261, 1239, 1158, 1093, 1048, 930, 882, 783, 759 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{20}H_{15}NO_5S$ $[M]^+$ 381.0671, found 381.0665.

*N-(4-(N-(9-Oxo-9H-xanthen-1-yl)sulfamoyl)phenyl)acetamide (**4d**).* 84.5 mg (69%); light yellow solid; mp = 199−204 °C; ^1H NMR (700 MHz, DMSO-d_6) δ 12.50 (s, 1H), 10.32 (s, 1H), 8.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.91−7.87 (m, 3H), 7.76−7.71 (m, 3H), 7.64 (d, J = 8.1 Hz, 1H), 7.52−7.49 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 169.0, 156.4, 154.9, 143.8, 140.0, 136.6, 136.3, 131.6, 128.5, 125.9, 124.7, 120.4, 118.8, 117.9, 111.6, 110.4, 108.5, 24.0; IR (KBr) υ 3056, 2922, 2144, 2026, 1703, 1630, 1604, 1591, 1529, 1474, 1401, 1295, 1239, 1157, 1092, 1048, 930, 885, 736 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{21}H_{16}N_2O_5S$ $[M]^+$ 408.0780, found 408.0780.

*4-Nitro-N-(9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**4e**).* 88.0 mg (74%); yellow solid; mp = 210−213 °C; ^1H NMR (700 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.36−8.34 (m, 2H), 8.23−8.19 (m, 3H), 7.93 (t, J = 8.5 Hz, 1H), 7.77 (t, J = 8.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 156.5, 154.9, 150.2, 143.7, 139.2, 136.7, 136.5, 128.7, 125.8, 124.9, 124.8, 120.4, 117.8, 112.5, 110.9, 108.9; IR (KBr) υ 3098, 2922, 2186, 2015, 1628, 1606, 1529, 1467, 1348, 1299, 1231, 1161, 1089, 1046, 892, 849, 779, 734 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{19}H_{12}N_2O_6S$ $[M]^+$ 396.0416, found 396.0415.

*N-(9-Oxo-9H-xanthen-1-yl)-4-(trifluoromethyl)benzenesulfonamide (**4f**).* 93.1 mg (74%); light yellow solid; mp = 144−147 °C; ^1H NMR (700 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.18−8.16 (m, 3H), 7.65 (d, J = 8.4 Hz, 2H), 7.89 (td, J = 7.7, 1.6 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 156.4, 154.9, 142.3, 139.3, 136.7, 136.5, 133.2 (q, J_{C-F} = 32.5 Hz), 128.1, 126.9, 125.8, 124.7, 123.2 (q, J_{C-F} = 270.9 Hz), 120.3, 117.8, 112.3, 110.7, 108.7; IR (KBr) υ 3060, 2924, 2185, 2035, 1632, 1606, 1568, 1475, 1321, 1300, 1232, 1164, 1131, 1061, 931, 892, 850, 708 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{20}H_{12}F_3NO_4S$ $[M]^+$ 419.0439, found 419.0439.

*4-Bromo-N-(9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**4g**).* 114.9 mg (89%); yellow solid; mp = 177−180 °C; ^1H NMR (700 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.18 (dd, J = 7.9, 1.4 Hz, 1H), 7.90−7.87 (m, 3H), 7.84−7.74 (m, 3H), 7.62 (d, J = 8.4 Hz, 1H),

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7.49 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 156.4, 154.9, 139.5, 137.6, 136.6, 136.4, 132.7, 129.0, 127.7, 125.8, 124.7, 120.4, 117.8, 112.1, 110.7, 108.7; IR (KBr) υ 3087, 2917, 1633, 1605, 1569, 1471, 1385, 1300, 1239, 1159, 1087, 1048, 1006, 889, 756, 735 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{19}H_{12}BrNO_4S$ [M]$^+$ 428.9670, found 428.9677.

*N-(9-Oxo-9H-xanthen-1-yl)naphthalene-2-sulfonamide (**4h**).* 74.7 mg (62%); pale yellow solid; mp = 154−158 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.67 (s, 1H), 8.53 (s, 1H), 8.24 (dd, J = 7.9, 1.4 Hz, 1H), 7.92−7.89 (m, 2H), 7.84 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.69 (dt, J = 7.6, 1.6 Hz, 1H), 7.56−7.49 (m, 4H), 7.38−7.34 (m, 2H), 7.01 (dd, J = 8.3, 1.1 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.8, 157.1, 155.5, 141.0, 136.5, 136.0, 135.7, 135.1, 132.1, 129.7, 129.5, 129.2, 129.1, 128.0, 127.7, 126.6, 124.5, 122.5, 121.3, 117.8, 111.7, 111.4, 109.5; IR (KBr) υ 3055, 2923, 2145, 2044, 1569, 1628, 1604, 1474, 1456, 1330, 1237, 1158, 1046, 930, 882, 733 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{23}H_{15}NO_4S$ [M]$^+$ 401.0722, found 401.0719.

*3-Chloro-N-(9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**4i**).* 92.6 mg (80%); pale yellow solid; mp = 139−142 °C; ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.62 (s, 1H), 8.16 (dd, J = 7.9, 1.4 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.60 (t, J = 7.9 Hz, 2H), 7.49 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.1, 156.4, 154.8, 140.3, 139.4, 136.6, 136.4, 134.1, 133.8, 131.7, 126.6, 125.8, 125.7, 124.7, 120.3, 117.8, 112.2, 110.8, 108.7; IR (KBr) υ 3071, 2923, 1633, 1605, 1570, 1470, 1386, 1297, 1240, 1165, 1049, 930, 888, 784, 759 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{19}H_{12}ClNO_4S$ [M]$^+$ 385.0176, found 385.0179.

*2-Fluoro-N-(9-oxo-9H-xanthen-1-yl)benzenesulfonamide (**4j**).* 100.8 mg (91%); yellow solid; mp = 176−179 °C; ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.06 (t, J = 6.8 Hz, 1H), 7.90 (t, J = 8.4 Hz, 1H), 7.74−7.71 (m, 2H), 7.67−7.62 (m, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.44−7.40 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 180.2, 158.0 (d, J_{C-F} = 252.5 Hz), 156.5, 156.4, 139.3, 136.9 (d, J_{C-F} = 8.7 Hz), 136.5 (d, J_{C-F} = 24.3 Hz), 134.5 (d, J_{C-F} = 7.7 Hz), 130.9, 128.3, 125.8, 124.8, 120.3, 117.8, 117.5 (d, J_{C-F} = 19.9 Hz), 116.9 (d, J_{C-F} = 20.6 Hz), 112.0, 109.9, 108.4; IR (KBr) υ 2919, 2851, 2187, 2015, 1628, 1607, 1569, 1468, 1334, 1299, 1156, 1074, 891, 824, 759, 714 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{19}H_{12}FNO_4S$ [M]$^+$ 369.0471, found 369.0473.

Typical Procedure for the Amidation of Chromomes (5a−5f) with Sulfonyl Azides (2a−2c, 2e, 2g, 2i, and 2j). To an oven-dried sealed tube with 4*H*-chromen-4-ones (**5a**) (43.8 mg, 0.3 mmol, 100 mol %), $[Ru(p\text{-cymene})Cl_2]_2$ (4.6 mg, 0.075 mmol, 2.5 mol %), $AgSbF_6$ (10.3 mg, 0.03 mmol, 10 mol %), and $Cu(OAc)_2$ (27.2 mg, 0.15 mmol, 50 mol %) in DCE (1 mL) was added tosyl azide (**2a**) (88.7 mg, 0.45 mmol, 150 mol %). The reaction mixture was allowed to stir at 100 °C for 6 h. After cooling at room temperature, the reaction mixture was evaporated onto silica gel. Purification of the product by flash column chromatography (SiO_2: *n*-hexanes/EtOAc = 2:1) provided **6a** (57.7 mg, 0.183 mmol) in 61% yield.

*4-Methyl-N-(4-oxo-4H-chromen-5-yl)benzenesulfonamide (**6a**).* 71.1 mg (72%); white solid; mp = 163−172 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.31 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 5.9 Hz, 1H), 7.49−7.45 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.00 (dd, J = 7.9, 1.4 Hz, 1H), 6.24 (d, J = 5.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.4, 157.4, 155.3, 144.1, 140.3, 136.7, 134.8, 129.8, 127.5, 113.0, 112.7, 112.6, 111.8, 21.7; IR (KBr) υ 3354, 3258, 3054, 2921, 1631, 1480, 1380, 1285, 1153, 1089, 1004, 883 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{16}H_{13}NO_4S$ [M]$^+$ 315.0565, found 315.0573.

*N-(3-Bromo-4-oxo-4H-chromen-5-yl)-4-methylbenzenesulfonamide (**6b**).* 49.7 mg (42%); light yellow solid; mp = 183−187 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 11.99 (s, 1H), 8.12 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 7.9 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 175.7, 156.9, 153.8, 144.1, 140.1, 136.3, 135.1, 129.7, 127.4, 112.9, 111.4, 110.9, 109.8, 21.5; IR (KBr) υ 3088, 2924, 2208, 2035, 1628, 1603, 1569, 1480, 1346, 1279, 1158, 1091, 1025, 879, 804, 738 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{16}H_{12}BrNO_4S$ [M]$^+$ 392.9670, found 392.9669.

*Benzyl 5-(4-Methylphenylsulfonamido)-4-oxo-4H-chromene-2-carboxylate (**6c**).* 68.8 mg (51%); light yellow solid; mp = 115−118 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.01 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.54−7.53 (m, 2H), 7.41−7.36 (m, 5H), 7.20 (d, J = 8.5 Hz, 2H), 7.14−7.12 (m, 1H), 6.99 (s, 1H), 5.37 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.8, 159.6, 156.7, 151.7, 144.1, 140.0, 136.3, 135.6, 134.2, 129.7, 129.0, 128.8, 128.6, 127.3, 114.8, 113.1, 112.2, 112.0, 68.6, 21.5; IR (KBr) υ 3054, 2922, 2851, 2194, 2021, 1745, 1640, 1607, 1486, 1466, 1334, 1253, 1153, 1120, 1089, 986, 808, 732 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{24}H_{19}NO_6S$ [M]$^+$ 449.0933, found 449.0939.

*Benzyl 3-Methyl-5-(4-methylphenylsulfonamido)-4-oxo-2-phenyl-4H-chromene-8-carboxylate (**6d**).* 123.0 mg (76%); light yellow solid; mp = 181−185 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 13.23 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 7.1 Hz, 2H), 7.41 (t, J = 8.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.25−7.23 (m, 5H), 7.17 (d, J = 8.0 Hz, 2H), 5.23 (s, 2H), 2.28 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.9, 163.6, 161.1, 155.9, 143.3, 144.2, 137.6, 136.3, 135.5, 131.9, 130.8, 129.7, 129.3, 128.5, 128.4, 128.3, 128.2, 127.3, 117.4, 112.7, 110.1, 109.7, 67.0, 21.5, 11.3; IR (KBr) υ 3032, 2921, 2851, 2113, 2022, 1715, 1627, 1591, 1489, 1367, 1258, 1151, 1130, 1087, 1021, 981, 869, 804, 752 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{31}H_{25}NO_6S$ [M]$^+$ 539.1403, found 539.1398.

*N-(3-Methoxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-5-yl)-4-methylbenzenesulfonamide (**6e**).* 46.1 mg (34%); light yellow solid; mp = 173−192 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.48 (s, 1H), 8.04 (d, J = 9.1 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.50−7.45 (m, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.07 (dd, J = 8.1, 1.2 Hz, 1H), 6.99 (d, J = 9.1 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 178.0, 161.9, 155.8, 155.6, 143.8, 140.0, 139.9, 136.6, 134.1, 130.2, 129.6, 127.3, 122.3, 114.1, 111.9, 111.7, 111.4, 59.9, 55.4, 21.5; IR (KBr) υ 3000, 2925, 2851, 2035, 1596, 1481, 1438, 1342, 1259, 1182, 1153, 1086, 993, 847, 807, 732 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{24}H_{21}NO_6S$ [M]$^+$ 451.1090, found 451.1086.

*N-(7-Methoxy-3-(4-methoxyphenyl)-4-oxo-4H-chromen-5-yl)-4-methylbenzenesulfonamide (**6f**).* 77.2 mg (57%); light yellow solid; mp = 178−181 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.66 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.77 (s, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.10 (s, 1H), 6.95 (d, J = 8.7 Hz, 2H), 6.44 (s, 1H), 3.82 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.2, 164.2, 159.8, 158.7, 151.7, 143.8, 141.8, 136.5, 130.2, 129.6, 127.4, 124.7, 123.0, 114.0, 106.4, 100.3. 95.0, 55.8, 55.3, 21.5; IR (KBr) υ 3065, 2927, 2840, 2165, 2035, 1635, 1612, 1510, 1446, 1315, 1245, 1141, 1087, 963, 884, 814, 735 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{24}H_{21}NO_6S$ [M]$^+$ 451.1090, found 451.1088.

*N-(4-Oxo-4H-chromen-5-yl)benzenesulfonamide (**6g**).* 55.1 mg (61%); white solid; mp = 150−153 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.36 (s, 1H), 7.90 (dd, J = 8.4, 1.1 Hz, 2H), 7.74 (d, J = 5.9 Hz, 1H), 7.51−7.46 (m, 3H), 7.41 (t, J = 8.1 Hz, 2H), 7.01 (d, J = 7.4 Hz, 1H), 6.23 (d, J = 5.9 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.2, 157.2, 155.2, 140.0, 139.4, 134.6, 133.0, 129.0, 127.2, 112.8, 112.6, 112.4, 111.8; IR (KBr) υ 3087, 2923, 2851, 2160, 2029, 1633, 1609, 1573, 1480, 1335, 1282, 1159, 1090, 1007, 883, 831, 760 cm^{-1}; HRMS (quadrupole, EI) m/z calcd for $C_{15}H_{11}NO_4S$ [M]$^+$ 301.0409, found 301.0407.

*4-Methoxy-N-(4-oxo-4H-chromen-5-yl)benzenesulfonamide (**6h**).* 53.7 mg (54%); light yellow solid; mp = 140−144 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 12.25 (s, 1H), 7.81 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 5.8 Hz, 1H), 7.47−7.46 (m, 2H), 7.00−6.98 (m, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6.22 (d, J = 5.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.1, 163.1, 157.2, 155.1, 140.1, 134.5, 130.9, 129.4, 114.2, 112.8, 112.5, 112.4, 111.5, 55.5; IR (KBr) υ

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3055, 2927, 2928, 2158, 2011, 1641, 1596, 1482, 1337, 1261, 1156, 1092, 1003, 835, 730 cm^{-1}; HRMS (quadrupole, EI) *m/z* calcd for $C_{16}H_{13}NO_5S$ $[M]^+$ 331.0514, found 331.0521.

*4-Nitro-N-(4-oxo-4H-chromen-5-yl)benzenesulfonamide (**6i**).* 60.3 mg (58%); yellow solid; mp = 164−173 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.24 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 5.8 Hz, 1H), 7.54−7.53 (m, 2H), 7.09 (dd, *J* = 7.0, 2.4 Hz, 1H), 6.26 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.2, 157.3, 155.5, 150.2, 145.1, 139.1, 134.8, 128.5, 124.3, 113.0, 112.8, 112.6; IR (KBr) υ 3013, 2923, 2853, 2169, 2015, 1637, 1609, 1572, 1532, 1482, 1347, 1281, 1162, 1085, 1003, 836, 737 cm^{-1}; HRMS (quadrupole, EI) *m/z* calcd for $C_{15}H_{10}N_2O_6S$ $[M]^+$ 346.0260, found 346.0264.

*4-Bromo-N-(4-oxo-4H-chromen-5-yl)benzenesulfonamide (**6j**).* 65.0 mg (57%); white solid; mp = 154−156 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.40 (s, 1H), 7.76 (d, *J* = 5.8 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.50−7.49 (m, 2H), 7.05−7.03 (m, 1H), 6.24 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.2, 157.2, 155.3, 139.6, 138.4, 134.7, 132.3, 128.7, 128.1, 112.8, 112.7, 112.5, 112.2; IR (KBr) υ 3080, 2928, 2851, 2130, 2009, 1633, 1571, 1461, 1342, 1283, 1162, 1004, 829, 768, 731 cm^{-1}; HRMS (quadrupole, EI) *m/z* calcd for $C_{15}H_{10}BrNO_4S$ $[M]^+$ 378.9514, found 378.9512.

*3-Chloro-N-(4-oxo-4H-chromen-5-yl)benzenesulfonamide (**6k**).* 48.3 mg (48%); light yellow solid; mp = 164−173 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.46 (s, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 5.8 Hz, 2H), 7.52−7.44 (m, 3H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.25 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.2, 157.2, 155.3, 141.2, 139.5, 135.2, 134.7, 133.2, 130.4, 127.3, 125.3, 112.8, 112.6, 112.4, 112.2; IR (KBr) υ 3263, 3080, 2921, 2852, 2223, 2009, 1638, 1613, 1574, 1482, 1342, 1284, 1161, 1112, 1078, 1005, 886, 836, 790 cm^{-1}; HRMS (quadrupole, EI) *m/z* calcd for $C_{15}H_{10}ClNO_4S$ $[M]^+$ 335.0019, found 335.0018.

*2-Fluoro-N-(4-oxo-4H-chromen-5-yl)benzenesulfonamide (**6l**).* 51.7 mg (54%); yellow solid; mp = 160−168 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.97 (t, *J* = 7.3 Hz, 1H), 7.77 (d, *J* = 5.8 Hz, 1H), 7.52−7.49 (m, 1H), 7.45−7.41 (m, 2H), 7.24−7.21 (m, 1H), 7.08 (t, *J* = 9.1 Hz, 1H), 7.01 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.27 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 181.0, 158.9 (d, J_{C-F} = 256.1 Hz), 157.2, 155.2, 139.5, 135.5 (d, J_{C-F} = 8.8 Hz), 134.5, 130.8, 127.2 (d, J_{C-F} = 13.3 Hz), 124.2 (d, J_{C-F} = 41.4 Hz), 117.3 (d, J_{C-F} = 20.8 Hz), 112.8, 112.2, 111.8, 111.7; IR (KBr) υ 3324, 3236, 2922, 2851, 2225, 2011, 1636, 1474, 1343, 1263, 1167, 1125, 1005, 835, 735 cm^{-1}; HRMS (quadrupole, EI) *m/z* calcd for $C_{15}H_{10}FNO_4S$ $[M]^+$ 319.0315, found 319.0309.

Experimental Procedure for the Deprotection of an *N*-Sulfonyl Group of 3a. To a stirred solution of *ortho*-amidated xanthone **3a** (39.1 mg, 0.107 mmol) in H_2O (0.2 mL) was added to conc. H_2SO_4 (0.2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 min and quenched with saturated NaOH solution. The resulting mixture was extracted with EtOAc (5 mL × 2). The organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford 1-amino-9*H*-xanthen-9-one (**7a**) (18.9 mg, 0.089 mmol) in 84% yield.

*1-Amino-9H-xanthen-9-one (**7a**).* 18.9 mg (84%); yellow solid; mp = 147−154 °C (lit. 150−151 °C);[26] ^1H NMR (700 MHz, DMSO-d_6) δ 8.10 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.98−7.52 (m, 3H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.41−7.37 (m, 2H), 6.55 (d, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 178.6, 156.9, 154.8, 152.1, 135.6, 134.8, 125.5, 123.7, 121.3, 117.3, 108.9, 105.8, 101.5; IR (KBr) υ 3419, 3319, 2922, 2851, 1636, 1604, 1589, 1552, 1474, 1450, 1364, 1303, 1246, 924, 747 cm^{-1}; HRMS (quadrupole, EI) *m/z* calcd for $C_{13}H_9NO_2$ $[M]^+$ 211.0633, found 211.0632.

Cancer Cell Growth Inhibition Assay (MTT Assay). Human breast cancer MCF-7 cells were grown in DMEM medium supplemented with 1% of penicillin/streptomycin, and 10% fetal bovine serum (all from Life Technologies, Grand Island, NY). Cells were seeded in 96-well plates (5 × 10^3 cells/well) containing 50 μL of growth medium for 24 h. After medium removal, 100 μL of fresh medium containing individual analogue compounds at different concentrations was added to each well and incubated at 37 °C for 72 h. After 24 h of culture, the cells were supplemented with 10 μL of test compounds dissolved in DMSO (less than 0.25% in each preparation). After 24 h of incubation, 15 μL of the MTT reagent was added to each well. After 4 h incubation at 37 °C, the supernatant was aspirated, and the formazan crystals were dissolved in 100 μL of DMSO at 37 °C for 10 min with gentle agitation. The absorbance per well was measured at 540 nm using a VERSA max Microplate Reader (Molecular Devices Corp., USA). The IC_{50} was defined as the compound concentration required inhibiting cell proliferation by 50% in comparison with cells treated with the maximum amount of DMSO (0.25%) and considered as 100% viability.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all products, the selected optimization of reaction conditions for chromone (**5a**), and an intramolecular kinetic isotope experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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