A Convenient and Efficient Synthesis of Coumarin-Containing Phthalides and Derivatives

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Abstract: A highly efficient and convenient procedure to access a series of coumarin-containing phthalides and derivatives is developed. The novel bis-heterocyclic products are obtained via reactions between 4-hydroxycoumarins (or 4-hydroxy-2-quinolones) with different 2-formylbenzoic acids in water as an environmentally friendly solvent. 4-Aryl substituted derivatives of 3-(4-hydroxy)coumarinylphthalide are obtained in excellent yields by initial conversion into the corresponding triflate and subsequent palladium-catalyzed Suzuki–Miyaura coupling with arylboronic acids.

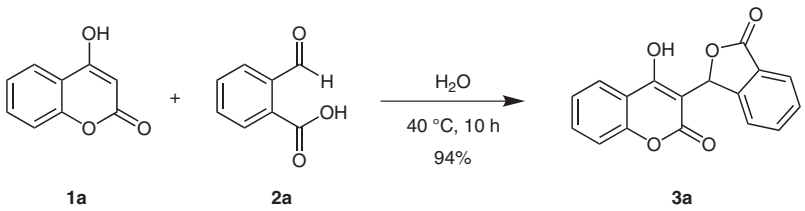
Key words: coumarins, phthalides, bis-heterocyclic, water, Suzuki–Miyaura coupling

Coumarins are an important class of benzopyrones which are present in a wide variety of natural products, as well as in numerous pharmaceutically important compounds.[1] As a privileged scaffold, coumarins show a broad spectrum of biological activity.[2] For example, novobiocin and clorobiocin are coumarin-derived antibiotics, which are used as competitive inhibitors of the bacterial adenosine-5′-triphosphate (ATP) binding gyrase B subunit, blocking negative supercoiling of relaxed DNA.[2a,d] Another example, wedelolactone, is a natural coumarin-containing product used as an antidote of venomous snake-bites.[1h] On the other hand, phthalide frameworks are found as structural subunits in a large number of natural products, many of which demonstrate a wide range of biological activity.[3] Accordingly, the combination of coumarin and phthalide moieties may potentially provide a class of novel drug candidates with unusual biological activities. However, there are few reports that describe the synthesis of such of bis-heterocyclic compounds containing both coumarin and phthalide units.[4]

The development of new, clean and environmentally benign synthetic methods in organic synthesis has gained significant attention. A large number of scientists are involved in the study of water as a reaction medium, due to the fact that it can undoubtedly be considered as the safest solvent available to chemists.[5] Hence, the development of an effective and general method for the synthesis of 3-coumarinylphthalides in water represents an interesting and important challenge.

Our research group has been interested in the synthesis of phthalides and their analogues.[6] In 2008, we reported syntheses of the bis-heterocyclic compounds, 3-indolyl-substituted phthalides, which displayed in vitro activity against Alzheimer's disease, via Friedel–Crafts reactions in water.[6d] Inspired by these results, and in continuation of our interest in medicinal and green chemistry, herein, we report our development of a convenient and highly efficient method for the synthesis of coumarin-containing phthalides and their derivatives.

Initially, the reaction between 4-hydroxycoumarin (**1a**) and 2-formylbenzoic acid (**2a**) (1.5 equiv) was investigated in pure water at 40 °C (Scheme 1). To our delight, the reaction proceeded smoothly to give the desired coupled product **3a** in 94% yield (Table 1, entry 1). While the structure was confirmed from NMR spectroscopic data, the fortuitous crystallization of **3a** provided additional unambiguous support for the structure (Figure 1).[7]



1a 2a 3a

Scheme 1 Synthesis of 3-(4-hydroxy)coumarinylphthalide (**3a**)

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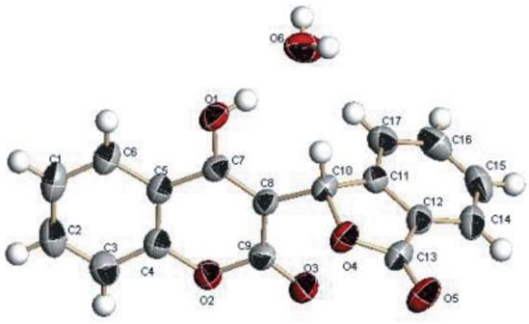
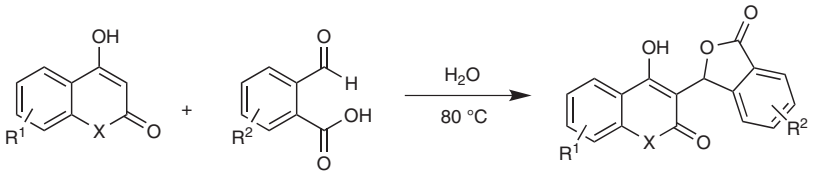


Figure 1 X-ray ORTEP illustration of fused compound **3d** (50% probability ellipsoids)

However, the reaction between 6-methyl-4-hydroxycoumarin (**1b**) and 2-formylbenzoic acid (**2a**) did not occur at 40 °C. When the reaction temperature was raised to 60 °C and the reaction time increased to 24 hours, only a trace amount of product **3b** was obtained. Further optimization of the reaction conditions led to the finding that the reaction proceeded smoothly at 80 °C, over 24 hours, to afford the desired product **3b** in 86% yield (Table 1, entry 2). Under the optimized reaction conditions [coumarin (1 equiv), 2-formylbenzoic acid (1.5 equiv), pure water (1 mL), 24 h, 80 °C], the scope of this protocol was investigated using a range of substituted coumarins and 2-formylbenzoic acid (**2a**) (Table 1, entries 1–7).

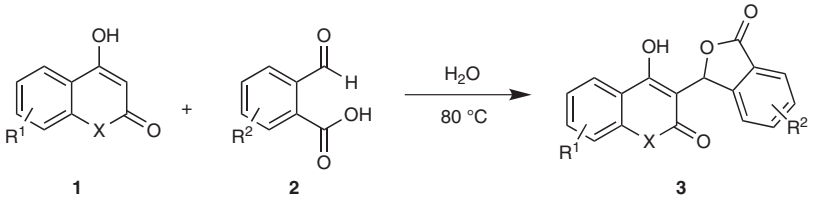
Table 1 Synthesis of Substituted Phthalides in Water[a]



1 2 3

Entry	Heterocycle	Acid	Time (h)	Product	Yield (%)[b]
1[c]	R^1 = H, X = O **1a**	R^2 = H **2a**	10	**3a**	94
2	R^1 = 6-Me, X = O **1b**	R^2 = H **2a**	24	**3b**	86
3	R^1 = 6-Br, X = O **1c**	R^2 = H **2a**	24	**3c**	84[d]
4	R^1 = 6-OMe, X = O **1d**	R^2 = H **2a**	24	**3d**	89
5	R^1 = 7-OMe, X = O **1e**	R^2 = H **2a**	24	**3e**	96
6	R^1 = 6,7-naphthyl, X = O **1f**	R^2 = H **2a**	24	**3f**	91

Table 1 Synthesis of Substituted Phthalides in Water[a] (continued)



1 2 3

Entry	Heterocycle	Acid	Time (h)	Product	Yield (%)[b]
7	R^1 = 5,6-naphthyl, X = O **1g**	R^2 = H **2a**	24	**3g**	75
8	R^1 = H, X = NH **1h**	R^2 = H **2a**	48	**3h**	16
9	R^1 = H, X = NMe **1i**	R^2 = H **2a**	24	**3i**	87
10	R^1 = H, X = O **1a**	R^2 = 5,6-$(OMe)_2$ **2b**	24	**3j**	94
11	R^1 = H, X = O **1a**	R^2 = 5,6-(OCH_2O)- **2c**	24	**3k**	92
12	R^1 = H, X = O **1a**	R^2 = 4-Br **2d**	24	**3l**	81

[a] All reactions were performed with compound **1** (0.3 mmol) and acid **2** (0.45 mmol) in water (1 mL).
[b] Yield of isolated product after chromatographic purification.
[c] The reaction was carried out at 40 °C.
[d] Yield of isolated product after trituration with Et_2O.

Coumarins bearing different substituents reacted smoothly with 2-formylbenzoic acid (**2a**) to afford the desired phthalides **3** in good to excellent yields (Table 1, entries 1–7). In contrast, the reaction between 4-hydroxy-2-quinolone (**1h**) and 2-formylbenzoic acid (**2a**) gave only a 16% yield of the corresponding phthalide due to poor conversion (Table 1, entry 8). However, the reaction of 4-hydroxy-1-methyl-2-quinolone (**1i**) with acid **2a** gave the expected product **3i** in a high 87% yield (Table 1, entry 9).

Subsequently, the reactions between coumarin **1a** and substituted 2-formylbenzoic acids **2b**–**d** were examined. Substrates with electron-donating or electron-withdrawing groups reacted smoothly under the present conditions to afford the corresponding coumarin-containing phthalides in good to excellent yields (81–94%, Table 1, entries 10–12).

With this general and convenient method in hand, and in order to introduce additional diversity to the coumarin

scaffold, we initiated an investigation to prepare 3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-substituted-2*H*-chromen-2-ones **6** starting from 4-hydroxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (**3a**). It is worth noting that 4-substituted coumarins show good activity against the hepatitis C virus (HCV).[8]

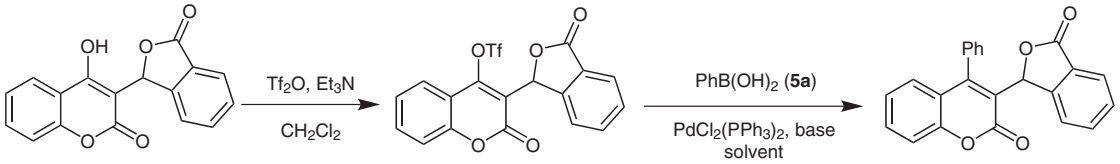
Transition metal catalyzed cross-coupling reactions are powerful and effective methods for carbon–carbon (C–C) bond formation.[9] Among these reactions, the Suzuki–Miyaura coupling is widely used due to its excellent functional group tolerance and the mild nature of the arylboronic acid coupling partners.[10] Therefore, we initially prepared triflate **4** from **3a**, in a straightforward manner, and then examined its reaction with phenylboronic acid (**5a**) via the palladium-catalyzed Suzuki–Miyaura coupling (Table 2).

Treatment of a mixture of triflate **4** (128 mg, 0.3 mmol), phenylboronic acid (**5a**) (41 mg, 0.33mmol), bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$] (10.5 mg, 0.015 mmol), and sodium bicarbonate (76 mg, 0.9 mmol) in methanol (2 mL), at room temperature under an inert nitrogen atmosphere for one hour, produced the desired product **6a** in only 25% yield. The use of sodium carbonate or potassium carbonate as the base also resulted in poor yields (Table 2, entries 1–3). In an attempt to improve the yield, we investigated the effects of commonly used organic and inorganic bases in tetrahydrofuran. Gratifyingly, the reaction was found to proceed efficiently in tetrahydrofuran (r.t., 5 h) when using an aqueous solution of sodium carbonate (2 mol/L, 3.0 equiv) as the base, to give the desired product **6a** in 86% yield (Table 2, entry 4).[10e] The reaction was found to be complete within 15 minutes on increasing the reaction temperature to 50 °C, with the desired product **6a** obtained in 86% yield (Table 2, entry 5). On the basis of these results, the optimized conditions [50 °C, $PdCl_2(PPh_3)_2$ (10.5 mg, 5 mol%) as catalyst, 2 M Na_2CO_3 (aq) (0.9 mmol, 3 equiv) as base, and THF as the solvent] were employed to investigate the reactions of triflate **4** with a series of arylboronic acids **5** (Table 3).

In general, this protocol proved to have wide applicability for a variety of arylboronic acids. It was found that arylboronic acids possessing electron-withdrawing or electron-donating substituents were tolerated under these conditions, affording the desired coupled products **6** in good to excellent yields (86-98%, Table 3, entries 1–7). It was worth noting that even heterocyclic boronic acids, including furan-2-ylboronic acid, thien-2-ylboronic acid and thien-3-ylboronic acid, underwent the coupling reaction under the optimized conditions to afford good yields of the corresponding products (Table 3, entries 8–10).

In summary, we have developed a highly efficient method for the synthesis of 3-(4-hydroxy)coumarinylphthalides **3a**–**g**,**j**–**l** and 3-(4-hydroxy)quinolinylphthalides **3h**,**i**, along with a simple and convenient process for the preparation of 3-(4-aryl substituted)coumarinylphthalides **6a**–**j**. The initial coupling reaction to give phthalides **3** has the advantage of occurring in water as an environmentally friendly solvent, whilst both methods are attractive in terms of their simplicity and the typically high yields of products obtained. The introduction of additional diversity into the present scaffold, and screening of these small molecules for biological activity are currently under investigation in our laboratory.

Table 2 Synthesis of 3-(4-Phenyl)Coumarinylphthalide (**6a**)

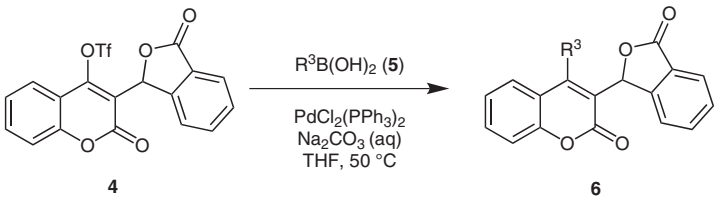


3a 4 6a

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	$NaHCO_3$	MeOH	r.t.	1	25
2	Na_2CO_3	MeOH	r.t.	3	20
3	K_2CO_3	MeOH	r.t.	3	20
4	Na_2CO_3 (aq)[b]	THF	r.t.	5	86
5	Na_2CO_3 (aq)[b]	THF	50	0.25	86

[a] Yield of isolated product.
[b] Na_2CO_3 (aq) = 2 mol/L.

Table 3 Synthesis of 3-(4-Substituted)Coumarinylphthalides



4 6

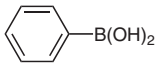
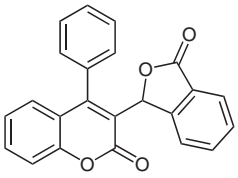
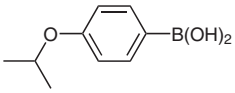
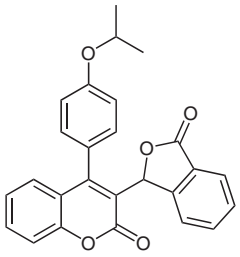
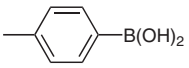
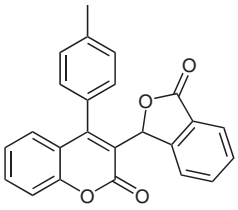
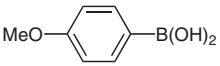
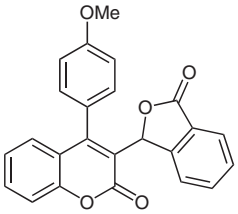
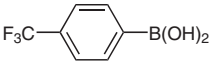
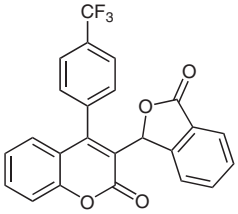
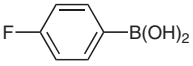
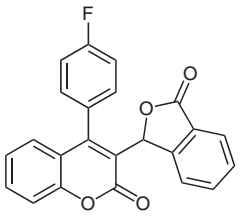
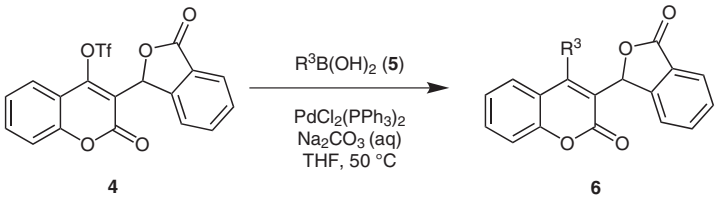
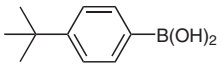
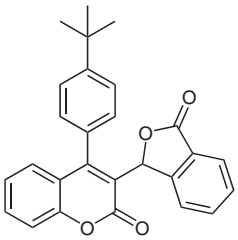
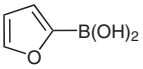
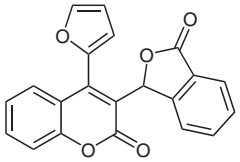
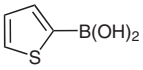
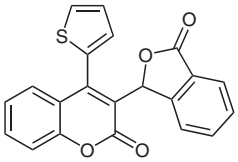
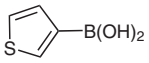
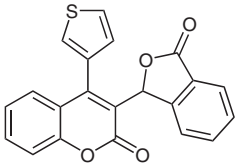
Entry	Boronic acid **5**	Time (min)	Product	Yield (%)[a]
1		15	**6a** 	86
2		15	**6b** 	87
3		15	**6c** 	89
4		15	**6d** 	87
5		15	**6e** 	86
6		20	**6f** 	94

Table 3 Synthesis of 3-(4-Substituted)Coumarinylphthalides (continued)



4 6

Entry	Boronic acid **5**	Time (min)	Product	Yield (%)[a]
7		25	**6g** 	98
8		30	**6h** 	58
9		35	**6i** 	82
10		50	**6j** 	93

[a] Yield of isolated product.

Commercial reagents and solvents were used as received. Unless otherwise stated, all reactions were performed in test tubes. Flash column chromatography was performed using HuangHai silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using HuangHai glass plates precoated with silica gel (0.25 mm, 230–400 mesh), impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were made visual by exposure to UV light. Organic solutions were concentrated on a rotary evaporator at ~20 Torr (house vacuum) at 25–35 °C.Melting points were measured on a Mel-Temp apparatus and are uncorrected. The majority of the 4-hydroxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-ones (**3a**–**l**) were thermally unstable above 120 °C, except for product **3i**. FT-IR spectra were obtained using a Nicolet AV-360 spectrophotometer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on an ECA (400 MHz) or a DMX (500 MHz) spectrometer using TMS as the internal standard; chemical shifts (δ) are quoted in ppm. HRMS was performed using a Waters Micromass GCT Premier spectrometer.

3-(4-Hydroxy)coumarinylphthalides 3; General Procedure

A mixture of 4-hydroxycoumarin **1** (0.3 mmol) and 2-formylbenzoic acid **2** (0.45 mmol, 1.5 equiv) in H_2O (1.0 mL) was stirred at the appropriate temperature and stated period of time (see Table 1). The mixture was diluted with MeOH, dried over anhyd Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to give the corresponding product **3**, apart from compound **3c**, which was obtained as described below.

4-Hydroxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (3a)

Yield: 83 mg (94%); white solid.

IR (KBr): 3496, 3383, 1735, 1677, 1609, 1561, 1350, 1291, 1067, 975, 762, 726 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 10.39 (s, 1 H), 8.11–8.09 (m, 1 H), 7.79 (d, *J* = 7.3 Hz, 1 H), 7.57–7.55 (m, 1 H), 7.47 (s, 2 H), 7.37 (d, *J* = 6.4 Hz, 1 H), 7.27 (d, *J* = 8.2 Hz, 1 H), 7.15 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.2, 173.4, 154.1, 152.0, 133.6, 131.2, 127.7, 127.2, 124.7, 124.1, 122.8, 122.1, 121.4, 115.9, 93.8, 78.8.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{17}H_{10}O_5$: 294.0528; found: 294.0536.

4-Hydroxy-6-methyl-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (3b)

Yield: 79 mg (86%); white solid.

IR (KBr): 3427, 2921, 1776, 1725, 1678, 1631, 1617, 1535, 1456, 1350, 1298, 1221, 1118, 723 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.75–7.71 (m, 2 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.47 (t, J = 7.4 Hz, 1 H), 7.25–7.22 (m, 2 H), 7.03–6.99 (m, 2 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.3, 171.7, 152.5, 133.8, 132.2, 131.6, 128.1, 127.7, 125.3, 124.5, 122.0, 116.1, 93.0, 78.7, 21.0.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{18}H_{12}O_5$: 308.0685; found: 308.0683.

6-Bromo-4-hydroxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (3c)

A mixture of 6-bromo-4-hydroxycoumarin (**1c**) (0.3 mmol) and 2-formylbenzoic acid (**2a**) (0.45 mmol, 1.5 equiv) in H_2O (1.0 mL) was stirred at 80 °C for 24 h. The solvent was removed and the residue triturated with Et_2O, filtered, washed with Et_2O (3 × 5.0 mL), and the resulting solid dried under vacuum to give the desired product **3c**.

Yield: 94 mg (84%); white solid.

IR (KBr): 3433, 1744, 1642, 1596, 1533, 1450, 1350, 1288, 1118, 728 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (s, 1 H), 7.75–7.73 (m, 1 H), 7.59–7.53 (m, 2 H), 7.47–7.43 (m, 1 H), 7.27 (d, J = 7.8 Hz, 1 H), 7.09 (d, J = 7.8 Hz, 1 H), 6.93 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 171.6, 153.6, 152.6, 133.8, 133.5, 128.0, 127.8, 127.7, 125.2, 124.5, 122.0, 118.8, 114.6, 91.5, 78.9, 49.1.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{17}H_9BrO_5$: 371.9633; found: 371.9628.

4-Hydroxy-6-methoxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (3d)

Yield: 86 mg (89%); white solid.

IR (KBr): 3437, 2911, 2849, 1771, 1724, 1672, 1637, 1534, 1466, 1438, 1380, 1278, 1180, 1115, 1047, 733, 625 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.75 (d, J = 7.3 Hz, 1 H), 7.59–7.55 (m, 1 H), 7.45–7.42 (m, 2 H), 7.29 (d, J = 7.3 Hz, 1 H), 7.10–7.06 (m, 2 H), 6.96 (s, 1 H), 3.72 (s, 3 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 174.7, 172.1, 164.3, 155.1, 152.7, 148.7, 133.1, 127.8, 127.4, 124.0, 123.5, 121.7, 118.3, 116.9, 107.4, 92.5, 79.0, 55.1.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{18}H_{12}O_6$: 324.0634; found: 324.0632.

4-Hydroxy-7-methoxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (3e)

Yield: 93 mg (96%); white solid.

IR (KBr): 3440, 2910, 2848, 1773, 1725, 1675, 1638, 1535, 1450, 1118, 1047, 735 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.95 (d, J = 8.3 Hz, 1 H), 7.68 (d, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.3 Hz, 1 H), 7.37 (t, J = 7.4 Hz, 1 H), 7.20 (d, J = 7.3 Hz, 1 H), 7.14 (s, 1 H), 6.60 (d, J = 8.6 Hz, 1 H), 6.51 (s, 1 H), 3.78 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 175.5, 172.5, 164.5, 162.8, 156.8, 153.7, 133.6, 128.8, 127.9, 127.5, 124.6, 122.6, 117.3, 110.4, 100.4, 92.1, 79.7, 55.8.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{18}H_{12}O_6$: 324.0634; found: 324.0636.

4-Hydroxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-benzo[*g*]chromen-2-one (3f)

Yield: 94 mg (91%); white solid.

IR (KBr): 3433, 3234, 2916, 2844, 1769, 1679, 1610, 1478, 1416, 1391, 1273, 1175, 1047, 954, 723 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.37 (d, J = 8.0 Hz, 1 H), 8.20 (d, J = 8.7 Hz, 1 H), 7.95 (d, J = 7.9 Hz, 1 H), 7.76 (d, J = 7.6 Hz, 1 H), 7.71 (d, J = 8.7 Hz, 1 H), 7.66–7.60 (m, 2 H), 7.53–7.51 (m, 1 H), 7.45 (t, J = 7.5 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.17 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8, 171.6, 152.1, 150.8, 135.1, 134.0, 128.3, 127.7, 127.0, 124.6, 123.3, 122.4, 122.3, 122.2, 122.0, 116.7, 93.8, 78.4, 49.1.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{21}H_{12}O_5$: 344.0685; found: 344.0687.

1-Hydroxy-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-3*H*-benzo[*f*]chromen-3-one (3g)

Yield: 77 mg (75%); yellow solid.

IR (KBr): 3431, 3049, 1735, 1626, 1580, 1518, 1454, 1438, 1420, 1344, 1293, 1211, 1108, 1072, 1016, 821, 723 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 10.17 (d, J = 8.6 Hz, 1 H), 7.81 (d, J = 8.9 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 7.4 Hz, 1 H), 7.41 (t, J = 7.5 Hz, 1 H), 7.33–7.20 (m, 4 H), 7.13 (d, J = 8.9 Hz, 1 H), 7.08 (d, J = 7.2 Hz, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 177.7, 172.0, 163.6, 154.4, 152.3, 132.8, 127.7, 127.1, 127.0, 124.4, 121.5, 117.3, 114.2, 92.0, 78.8.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{21}H_{12}O_5$: 344.0685; found: 344.0688.

4-Hydroxy-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)quinolin-2(1*H*)-one (3h)

Yield: 14 mg (16%); white solid.

IR (KBr): 3430, 3162, 2930, 1738, 1649, 1617, 1596, 1499, 1406, 1206, 1077, 728 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.11 (d, J = 8.3 Hz, 1 H), 7.86 (d, J = 8.3 Hz, 1 H), 7.73–7.67 (m, 2 H), 7.59–7.53 (m, 2 H), 7.44 (t, J = 7.3 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 6.95 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 162.6, 150.9, 139.4, 134.4, 132.0, 128.9, 127.4, 124.9, 123.8, 122.2, 121.8, 115.9, 76.0.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{17}H_{11}NO_4$: 293.0688; found: 293.0694.

4-Hydroxy-1-methyl-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)quinolin-2(1*H*)-one (3i)

Yield: 80 mg (87%); white solid; mp 242–243 °C.

IR (KBr): 3427, 2957, 1723, 1642, 1627, 1622, 1601, 1576, 1509, 1468, 1413, 1397, 1324, 1309, 1286, 1242, 1206, 1159, 1080, 965, 929, 757, 748, 693, 688 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.39 (s, 1 H), 8.09 (d, J = 6.8 Hz, 1 H), 7.86 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1 H), 7.72–7.63 (m, 2 H), 7.59–7.48 (m, 2 H), 7.40 (d, J = 7.2 Hz, 1 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.07 (s, 1 H), 3.49 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.8, 161.0, 160.4, 150.1, 139.6, 133.9, 132.1, 128.4, 127.0, 124.4, 123.8, 121.6, 115.6, 114.9, 105.3, 75.6, 28.9.

HRMS (EI, 70 eV): m/z [M]$^+$ calcd for $C_{18}H_{13}NO_4$: 307.0845; found: 307.0842.

3-(4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-hydroxy-2*H*-chromen-2-one (3j)

Yield: 100 mg (94%); white solid.

IR (KBr): 3435, 2936, 2839, 1735, 1655, 1601, 1530, 1498, 1459, 1426, 1355, 1270, 1051, 970, 903, 761, 708 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.80 (d, J = 6.9 Hz, 1 H), 7.38 (t, J = 8.3 Hz, 1 H), 7.23 (d, J = 8.3 Hz, 1 H), 7.10–7.02 (m, 2 H), 6.83–6.79 (m, 2 H), 3.88 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 173.9, 169.2, 154.6, 151.6, 147.3, 146.1, 130.3, 125.4, 121.9, 120.4, 119.1, 116.3, 115.7, 77.2, 61.2, 56.3.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{19}H_{14}O_7$: 354.0740; found: 354.0757.

6-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-[1,3]dioxolo[4,5-*e*]isobenzofuran-8(6*H*)-one (3k)
Yield: 93 mg (92%); white solid.

IR (KBr): 3436, 2938, 2839, 1737, 1657, 1604, 1530, 1460, 1421, 1272, 1054, 767, 730 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.03 (d, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.7 Hz, 1 H), 7.08 (s, 1 H), 7.06–6.92 (m, 2 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.64 (d, *J* = 7.8 Hz, 1 H), 6.11 (s, 2 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 174.8, 169.3, 164.3, 155.3, 148.6, 146.8, 144.5, 131.2, 126.3, 123.6, 122.8, 116.5, 114.5, 113.6, 111.7, 103.6, 94.4, 79.8.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{18}H_{10}O_7$: 338.0427; found: 338.0434.

3-(6-Bromo-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-hydroxy-2*H*-chromen-2-one (3l)
Yield: 91 mg (81%); white solid.

IR (KBr): 3433, 2890, 1776, 1676, 1590, 1543, 1450, 1355, 1287, 1115, 731 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.85–7.54 (m, 3 H), 7.43–7.36 (m, 2 H), 7.11–6.95 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.0, 173.9, 170.7, 170.5, 155.0, 154.5, 154.4, 131.3, 127.9, 127.1, 126.5, 125.6, 125.0, 122.6, 116.3, 116.2, 89.4.

HRMS (EI, 70 eV): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_9BrO_5Na$: 394.9526; found: 394.9533.

2-Oxo-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-4-yl trifluoromethanesulfonate (4)
Tf_2O (0.25 mL, 1.5 equiv) was added to a cooled (ice–H_2O bath) mixture of compound **3a** (294 mg, 1 mmol) and Et_3N (0.22 mL, 1.5 mmol) in anhyd CH_2Cl_2 (10 mL) under an N_2 atm. The resulting mixture was stirred for 3 h and then concentrated under reduced pressure. The obtained residue was purified by flash chromatography on silica gel to give the corresponding triflate **4** (383 mg, 90%) as a white solid.

Yield: 383 mg (90%); white solid; mp 170–171 °C.

IR (KBr): 3451, 3076, 1769, 1735, 1631, 1608, 1576, 1494, 1459, 1429, 1357, 1311, 1282, 1241, 1211, 1125, 1053, 1037, 1013, 992, 906, 850, 757, 741, 721, 598, 538 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.5 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.9 Hz, 1 H), 7.67 (t, *J* = 7.3 Hz, 1 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.54–7.46 (m, 2 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 6.61 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 157.0, 154.6, 153.0, 145.9, 135.0, 134.4, 129.9, 127.3, 125.9, 125.6, 124.1, 122.1, 120.2 (q, *J* = 319 Hz), 117.3, 116.4, 114.2, 73.4.

HRMS (EI, 70 eV): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{10}F_3O_7S$: 4427.0094; found: 427.0087.

4-Substituted Chromen-2-ones 6; General Procedure
$PdCl_2(PPh_3)_2$ (10.5 mg, 5 mol%) was added to a mixture of triflate **4** (128 mg, 0.3 mmol), arylboronic acid **5** (0.33 mmol, 1.1 equiv), 2 M Na_2CO_3 (aq) (0.9 mmol, 3 equiv) in THF (2 mL), in a Schlenk tube under an N_2 atm. The mixture was stirred at 50 °C for the appropriate period of time (see Table 3). Following completion of the reaction (monitored by TLC), the mixture was purified directly by flash column chromatography on silica gel to afford the corresponding product **6**.

3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-4-phenyl-2*H*-chromen-2-one (6a)
Yield: 91 mg (86%); white solid; mp 197–198 °C.

IR (KBr): 3435, 3075, 2926, 1767, 1725, 1605, 1565, 1454, 1362, 1282, 1061, 994, 767, 756, 720, 706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.6 Hz, 1 H), 7.61–7.53 (m, 3 H), 7.50–7.45 (m, 2 H), 7.42–7.40 (m, 2 H), 7.35 (s, 1 H), 7.33 (s, 1 H), 7.20 (t, *J* = 7.9 Hz, 1 H), 7.10 (s, 1 H), 7.04–7.02 (m, 1 H), 6.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 158.7, 156.1, 153.2, 148.1, 132.6, 129.0, 128.9, 128.4, 128.1, 124.4, 121.3, 116.7, 76.9.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{23}H_{14}O_4$: 354.0892; found: 354.0891.

4-(4-Isopropoxyphenyl)-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (6b)
Yield: 108 mg (87%); white solid; mp 163–164 °C.

IR (KBr): 3430, 2973, 1767, 1724, 1605, 1506, 1447, 1350, 1280, 1247, 1122, 1055, 990, 846, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.3 Hz, 1 H), 7.61–7.53 (m, 2 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.35–7.27 (m, 3 H), 7.22–7.13 (m, 2 H), 7.05–7.03 (m, 2 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 6.41 (s, 1 H), 4.63–4.61 (m, 1 H), 1.41–1.38 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 158.7, 156.6, 153.3, 148.3, 132.5, 129.9, 128.9, 128.3, 124.3, 121.2, 116.8, 116.0, 115.9, 70.1, 29.6, 21.9.

HRMS (EI, 70 eV): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{20}O_5Na$: 435.1203; found: 435.1195.

3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-4-(*p*-tolyl)-2*H*-chromen-2-one (6c)
Yield: 98 mg (89%); white solid; mp 158–159 °C.

IR (KBr): 3432, 2916, 2844, 1769, 1733, 1603, 1451, 1356, 1282, 1185, 1055, 994, 758, 726, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.3 Hz, 1 H), 7.61–7.53 (m, 2 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.39–7.24 (m, 5 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.10 (d, *J* = 7.3 Hz, 2 H), 6.33 (s, 1 H), 2.43 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 158.5, 156.5, 153.3, 148.1, 139.4, 132.5, 129.5, 128.9, 128.4, 128.2, 124.3, 121.2, 116.7, 77.1, 21.2.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{24}H_{16}O_4$: 368.1049; found: 368.1050.

4-(4-Methoxyphenyl)-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (6d)
Yield: 100 mg (87%); white solid; mp 167–168 °C.

IR (KBr): 3435, 2947, 2921, 2839, 1767, 1730, 1604, 1509, 1452, 1355, 1283, 1247, 1176, 1058, 1031, 758, 720, 564 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.4 Hz, 1 H), 7.60–7.51 (m, 2 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.33–7.26 (m, 3 H), 7.20 (t, *J* = 7.1 Hz, 1 H), 7.12–7.06 (m, 3 H), 6.95 (d, *J* = 8.2 Hz, 1 H), 6.36 (s, 1 H), 3.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 160.3, 156.4, 153.3, 148.2, 133.7, 132.5, 129.8, 128.9, 128.2, 124.3, 121.2, 120.2, 116.7, 114.4, 77.1, 55.4.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{24}H_{16}O_5$: 384.0998; found: 384.0999.

3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-4-[4-(trifluoromethyl)phenyl]-2*H*-chromen-2-one (6e)
Yield: 109 mg (86%); white solid; mp 155–156 °C.

IR (KBr): 3436, 3300, 2917, 2850, 1773, 1736, 1638, 1604, 1453, 1323, 1283, 1163, 1135, 1107, 1065, 759, 722 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.3 Hz, 1 H), 7.71 (d, *J* = 7.3 Hz, 1 H), 7.61–7.53 (m, 4 H), 7.47 (t, *J* = 7.3 Hz, 1 H), 7.37–7.34 (m, 2 H), 7.21 (t, *J* = 8.3 Hz, 1 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.38 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 158.9, 154.6, 153.3, 148.1, 136.0, 134.1, 133.1, 131.5 (q, *J* = 32.6 Hz), 129.3 (q, *J* = 3.4 Hz), 128.6, 126.7 (q, *J* = 269.3 Hz), 126.6, 126.1, 125.9, 124.8, 122.6, 121.6, 120.6, 119.7, 117.0, 76.6.

^{19}F NMR (400 MHz, $CDCl_3$): δ = –63.4 (s).

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{24}H_{13}F_3O_4$: 422.0766; found: 422.0763.

4-(4-Fluorophenyl)-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (6f)
Yield: 105 mg (94%); white solid; mp 194–195 °C.

IR (KBr): 3424, 3060, 2921, 1770, 1726, 1604, 1560, 1508, 1454, 1360, 1283, 1225, 1060, 991, 759, 718, 557 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.3 Hz, 1 H), 7.63–7.55 (m, 2 H), 7.50 (t, *J* = 8.2 Hz, 1 H), 7.42–7.39 (m, 1 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.28–7.24 (m, 1 H), 7.22 (t, *J* = 7.4 Hz, 1 H), 7.07–7.00 (m, 3 H), 6.40 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 163.0 (d, *J* = 248.8 Hz), 158.8, 155.3, 153.3, 148.2, 134.0, 132.9, 130.6 (d, *J* = 8.0 Hz), 130.1 (d, *J* = 7.8 Hz), 129.2, 128.2, 127.9, 126.7, 125.5, 124.6, 121.4, 120.4, 120.1, 116.9, 116.1 (d, *J* = 21.3 Hz), 116.1, 76.8.

^{19}F NMR (400 MHz, $CDCl_3$): δ = –111.2 (s).

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{23}H_{13}FO_4$: 372.0798; found: 372.0794.

4-[4-(*tert*-Butyl)phenyl]-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (6g)
Yield: 120 mg (98%); white solid; mp 213–214 °C.

IR (KBr): 3442, 2957, 1768, 1733, 1602, 1565, 1452, 1363, 1280, 1053, 995, 756, 723 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.3 Hz, 1 H), 7.61–7.52 (m, 3 H), 7.47–7.41 (m, 2 H), 7.35–7.32 (m, 3 H), 7.21 (t, *J* = 8.2 Hz, 1 H), 7.11 (d, *J* = 7.3 Hz, 2 H), 6.37 (s, 1 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 157.0, 153.6, 152.8, 148.5, 134.1, 132.9, 129.5, 129.2, 128.6, 128.5, 128.2, 127.1, 126.2, 126.1, 125.7, 124.7, 121.6, 120.4, 120.1, 117.0, 77.4, 35.1, 31.5.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{27}H_{22}O_4$: 410.1518; found: 410.1525.

4-(Furan-2-yl)-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-2*H*-chromen-2-one (6h)
Yield: 60 mg (58%); white solid; mp 181–182 °C.

IR (KBr): 3419, 3157, 3044, 2921, 1772, 1723, 1603, 1540, 1454, 1380, 1353, 1280, 1211, 1185, 1055, 1016, 1001, 753, 721, 590 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.3 Hz, 1 H), 7.69 (d, *J* = 1.8 Hz, 1 H), 7.66 (t, *J* = 7.3 Hz, 1 H), 7.60–7.56 (m, 2 H), 7.54–7.49 (m, 2 H), 7.36–7.27 (m, 2 H), 6.84 (d, *J* = 3.6 Hz, 1 H), 6.67–6.66 (m, 1 H), 6.48 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 158.2, 153.4, 147.9, 145.1, 144.4, 143.9, 133.9, 132.7, 129.2, 127.5, 126.9, 125.6, 124.6, 121.7, 121.1, 118.4, 117.0, 115.1, 111.9, 77.3.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{21}H_{12}O_5$: 344.0685; found: 344.0687.

3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-4-(thien-2-yl)-2*H*-chromen-2-one (6i)
Yield: 88 mg (82%); white solid; mp 215–216 °C.

IR (KBr): 3432, 2916, 2849, 1766, 1728, 1604, 1560, 1453, 1280, 1058, 981, 754, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.2 Hz, 1 H), 7.55–7.50 (m, 2 H), 7.47 (d, *J* = 6.4 Hz, 1 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.31–7.08 (m, 6 H), 6.37 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 157.9, 152.9, 149.5, 147.7, 133.8, 132.8, 129.1, 128.6, 127.9, 127.8, 125.5, 124.6, 121.4, 120.2, 116.7, 77.0.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{21}H_{12}O_4S$: 360.0456; found: 360.0454.

3-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-4-(thien-3-yl)-2*H*-chromen-2-one (6j)
Yield: 100 mg (93%); white solid; mp 166–167 °C.

IR (KBr): 3434, 3101, 2921, 1766, 1725, 1601, 1560, 1453, 1344, 1281, 1056, 981, 785, 759, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.3 Hz, 1 H), 7.53–7.45 (m, 3 H), 7.41–7.39 (m, 2 H), 7.25–7.23 (m, 2 H), 7.18–7.05 (m, 3 H), 6.37 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 158.6, 153.0, 152.0, 133.8, 132.7, 131.9, 129.0, 127.8, 127.5, 125.5, 124.5, 121.2, 120.0, 116.7, 76.9.

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_{21}H_{12}O_4S$: 360.0456; found: 360.0459.

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