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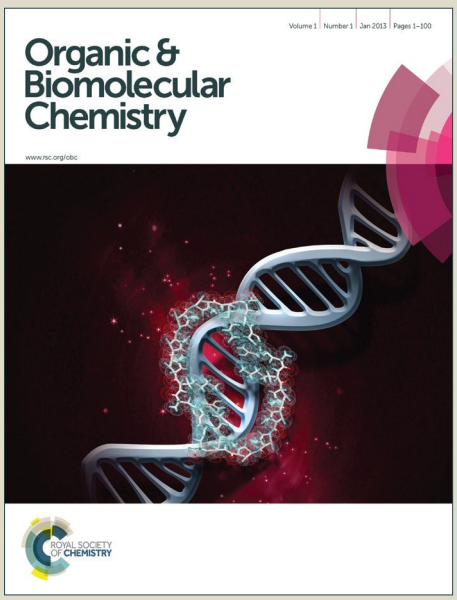

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ARTICLE

Synthesis of furo[3,2-*c*]coumarin derivatives using visible-light-promoted radical alkyne insertion with bromocoumarins

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Synthesis of privileged structures, which are potent drug condidates, is one of impetus for drug discovery. The construction of heterocyclic framework furo[3,2-c]coumarins using a visible-light promoted photoredox neutral coupling of 3-bromo-4-hydroxycoumarins with commercially available alkynes has been reported. These reactions can be carried out at room temperature under visible light irradiation with good chemical yields. This work presents 17 furocoumarins and 12 of which are new. Three of the newly synthesized compounds show potent cytotoxicity, and one shows moderate acetylcholinesterase inhibitory activity with IC_{50} values of 2.16 ± 0.13 μM.

Introduction

The naturally occurring coumarins represent a large family of heterocyclic molecules with a benzo-α-pyrone moiety, which might be considered as a source of potential materials[1] and candidates for drug discovery.[2] Coumarin derivatives have driven both chemists and pharmacologists to orchestrate the strategies for their chemical synthesis since their broad spectrum of bioactivities, including anti-inflammatories, anticancer, anti-microbials and antivirals.[3]

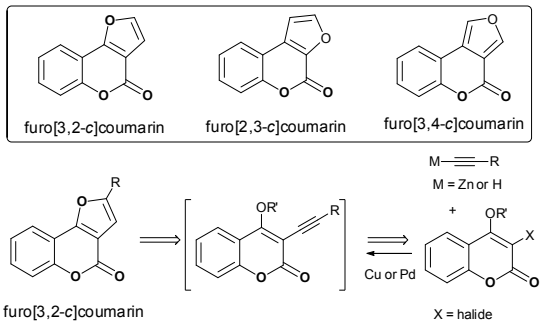
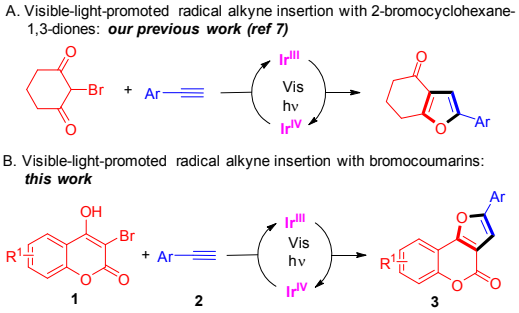


Fig. 1 Typical furan fused coumarins and established methods for the synthesis of furo[3,2-*c*]coumarin.

Furocoumarins, a class of furan-fused coumarin derivatives, have attracted great attention of researchers due to their biological properties and chemosynthesis challenge.[4] Thus, more efforts have been performed to establish new synthetic methods toward this type of compounds.[5] Furo[3,2-*c*]coumarins are one of the most common representatives of this class of compounds. The established methods for the synthesis of furo[3,2-*c*]coumarin are highly relied on the transition metal-catalyzed coupling of halocoumarins derivatives with alkynes or alkyl metal reagents and sequential cyclization in stepwise or one-pot manner (Fig. 1).[6] Despite these advances, methods for the rapid preparation of furo[3,2-*c*]coumarin derivatives with high reaction efficiency under mild conditions are still desired. Herein, we would like to report our efforts on the synthesis of furo[3,2-*c*]coumarin using visible-light-promoted radical alkyne insertion with bromocoumarins.

Results and discussion

Recently, we have reported synthesis of polysubstituted furans using visible-light-promoted radical alkyne insertion with 2-bromo-1,3-dicarbonyl compounds (Fig. 2A).[7] In this work, the bromides must be derived from cyclohexane-1,3-diones.Thus, only cyclohexanone-fused furans could be synthesized using this strategy. In order to expand the synthetic potential of this visible-light-promoted radical alkyne insertion chemistry, we turned our attention to synthesis of coumarin-fused furans by coupling of coumarin-derived bromides with alkynes (Fig. 2B).



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†Electronic Supplementary Information (ESI) available: Full experimental procedures and characterization data for all the compounds.

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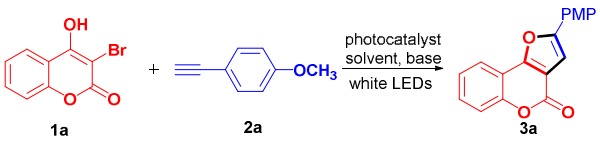
Fig. 2 Visible-light-promoted radical alkyne insertion with 2-bromo-1,3-dicarbonyl compounds.

This idea was first examined using 3-bromo-4-hydroxycoumarin (**1a**) and 4-ethynylanisole (**2a**) as model substrates (Table 1). When a solution of **1a** and **2a** in DMF was irradiated by 13 W white LEDs in the presence of photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) and Na_2HPO_4 for 12 h, it was pleased to find that the desired furocoumarin **3a** was isolated in 78% yield (entry 1). Different solvent was then tested. It was found that EtOH, CH_3CN and CH_2Cl_2 could not give improved results (entries 2-4) while 84% isolated yield was achieved when DMSO was used as the solvent (entry 5). A variety of bases were examined (entries 6-9) and $NaHCO_3$ proved to be the most suitable base (entry 6). Other photocatalysts, such as $Ir(ppy)_3$ (**II**) and $Ru(bpy)_3(PF_6)_2$ (**III**) were not superior to $Ir(ppy)_2(dtbbpy)PF_6$(**I**) (entries 10-11). Control experiments verified the necessity of the base, irradiation, and photocatalyst (entries 12–14).

Table 1 Condition screening [a]



Entry	Catalyst	Base	Solvent	Yield/%[b]
1	I	Na_2HPO_4	DMF	78
2	I	Na_2HPO_4	C_2H_5OH	59
3	I	Na_2HPO_4	CH_3CN	73
4	I	Na_2HPO_4	CH_2Cl_2	45
5	I	Na_2HPO_4	DMSO	84
6	I	$NaHCO_3$	DMSO	86
7	I	K_3PO_4	DMSO	45
8	I	K_2HPO_4	DMSO	08
9	I	Na_2CO_3	DMSO	46
10	II	$NaHCO_3$	DMSO	37
11	III	$NaHCO_3$	DMSO	33
12	I	none	DMSO	trace
13	none	Na_2HPO_4	DMSO	trace
14[c]	I	Na_2HPO_4	DMSO	NR

[a] Reaction conditions: A solution of **1a** (0.2 mmol), **2a** (0.1 mmol), base (0.12 mmol) and photocatalyst (0.001 mmol, 1.0 mol %) in the indicated solvent (1.5 mL) was irradiated by 13 W white LED at rt for 12 h. [b] Isolated yield. [c] was performed with no irradiation. NR = no reaction.

With the optimized conditions in hand, we then turn to explore the scope of this transformation. First, a set of alkynes were tested, as shown in Fig. 3. It was found that electron-rich or neutral phenylacetylenes gave the desired furocoumarins **3a**-**3g** with decent yields (52-93%). p-F phenylacetylene could gave the desired furocoumarin **3h** in acceptable yield (60%) while p-Cl phenylacetylene was not suitable in this transformation (22%). 6-Methoxy-2-naphthylacetylene could also undergo this transformation smoothly to provide the desired product **3i** in 70 % yield (**2j**). Internal alkynes and alkyl terminal alkynes were not suitable coupling partners in this transformation. Coumarin-derived bromides could be also varied. 7-MeO- substituted coumarin-derived bromide reacted smoothly with a series of alkynes to give the corresponding furocoumarins **3j**-**3o** with satisfactory yields (44-85%). 6-halogen-substituted furocoumarins **3p**-**3q** could be also prepared using this method.

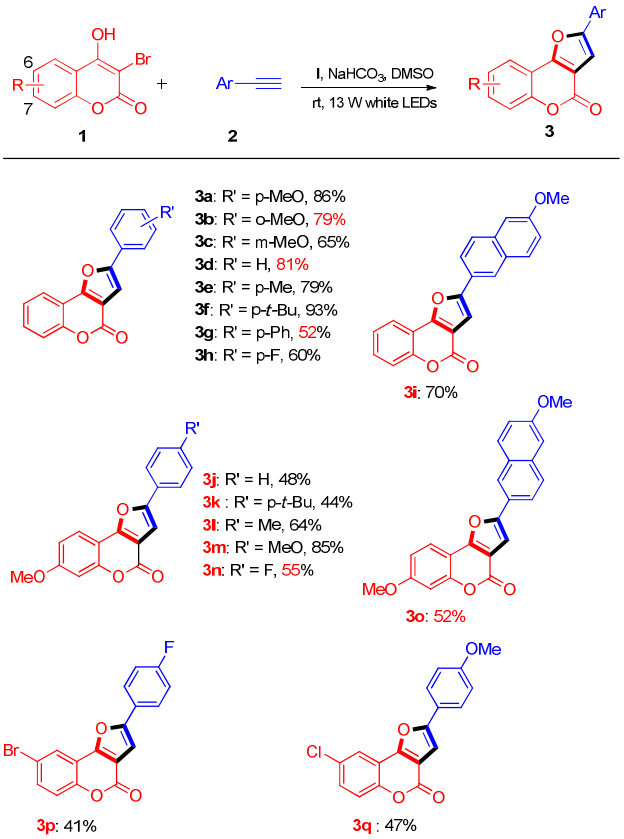


Fig. 3 Scope of alkynes. Reaction conditions: A solution of **1** (0.2 mmol), **2** (0.1 mmol), NaHCO3 (0.12 mmol) and Ir(ppy)2(dtbbpy) PF6 (I) (0.001 mmol, 1.0 mol %) in dry DMSO (1.5 mL) was irradiated by 13 W white LEDs for 12 h. Isolated yield.

Based on our previous work and other literature precedents,[8] a possible catalytic cycle is proposed for this transformation (Fig. 4). First, photocatalyst Ir complex is irradiated to the excited state Ir^{III}* and oxidatively quenched by coumarin-derived bromide **1a** with generation of Ir^{IV} complex and radical species **4** respectively. Radical **4** adds onto alkyne **2a** to generate vinyl radical intermediate **5**. Then the vinyl radical **5** attacks the carbonyl group intramolecularly to give radical intermediate **6**, which is oxidized by Ir^{IV} to form carbon cation **7** and regenerate Ir^{III}. Ultimately, furocoumarin **3a** is formed by deprotonation assisted by base.

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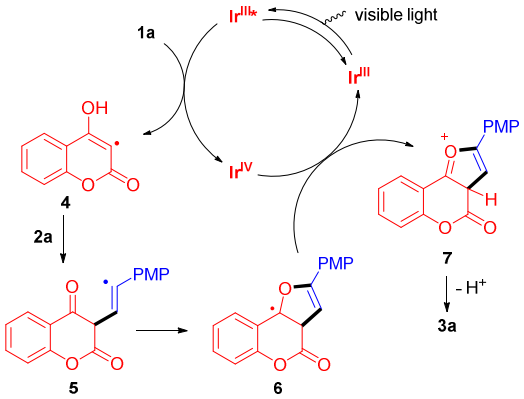

Fig. 4 Proposed mechanism.

All the synthesized compounds were evaluated biologically. We test their inhibitory potential against three human tumor cell lines (human lung carcinoma A549, human promyelocytic leukemia HL-60 and human colon carcinoma SW480) by MTT assay. Some of compounds show a significant activity (Table 2). More significantly, the compound **3k** was found to be a potent inhibitor of HL-60 with the inhibitory value of IC_{50} =2.88 ± 0.12 μM compared to the inhibitory value of other two cell lines. It is suggested that compounds containing both 2-(4-(tert-butyl)phenyl) and 7-methoxy showed a higher activity towards many human tumor cell lines and has a better selectivity. At the same time, all compounds were also evaluated for the inhibitory effect on acetylcholinesterase, and compound **3g** was found to be a good inhibitor of acetylcholinesterase with the inhibitory value of IC_{50} = 2.16 ± 0.13 μM, which is comparable to that (IC_{50} = 0.161 ± 0.007) of Huperzine A, a prescribed acetylcholinesterase inhibitor coassessed as a positive control.

Table 2 Inhibition of multiple human tumor cell Lines by the synthesized compounds and positive control

Compounds	IC_{50},[a] μM		
	SW480	HL-60	A549
3a	9.57 ± 0.12	9.09 ± 0.26	> 10
3i	8.95 ± 0.21	>10	9.33 ± 0.19
3k	7.61 ± 0.16	2.88 ± 0.12	7.10 ± 0.08
Doxorubicin[b]	1.17 ± 0.11	0.87 ± 0.04	1.76 ± 0.13

[a] IC_{50} represents the concentration of compounds required to inhibit 50% of the activity of cell proliferative. [b] Doxorubicin is the reference standard used in the present study. Data are presented as the mean ± SD.

Conclusions

In summary, we have developed a mild and efficient synthetic approach to prepare furo[3,2-c]coumarins using photoredox neutral coupling of alkynes with 3-bromo-4-hydroxycoumarins. These reactions proceeded at room temperature in good to excellent chemical yields under environmentally friendly conditions. Easily available starting materials 3-bromo-4-hydroxycoumarins and alkynes, no external stoichiometric oxidants also feature the advantages of this methodology. Preliminary biological evaluation shows some of the resultant furo[3,2-c]coumarins possess inhibitory potential against three human tumor cell lines and acetylcholinesterase.

Experimental

General information

All reagents were used as received without further purification. The 3-bromo-4-oxycoumarins were known compounds and prepared according to the literature procedures.[9] Alkynes were commercial available. Thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F254, Art 5715) and visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid or potassium permanganate, respectively. Column chromatography was performed on Silica Gel 60 (300–400 Mesh) using a forced flow of 0.5–1.0 bar. 1H NMR (400 MHz), 13C NMR (100 MHz) and 19F (376 MHz) were measured on a Bruker AVANCE III–400 spectrometer. Chemical shifts are expressed in parts per million (ppm) with respect to the residual solvent peak. Coupling constants are reported as Hertz (Hz), signal shapes and splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

General procedures

A 10 mL round bottom flask equipped with a rubber septum and magnetic stir bar was charged with **1** (0.2 mmol, 2.0 equiv), **2**(0.1 mmol, 1.0 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (0.001 mmol, 0.01 equiv) and $NaHCO_3$ (0.12 mmol, 1.2 equiv). The flask was evacuated and backfilled with N_2 for 3 times. DMSO (1.5 mL, 0.1 M) was added with syringe under N_2. The mixture was then irradiated by a 13W white LED strips. After the reaction was complete (as judged by TLC analysis), the mixture was poured into a separatory funnel containing 20 mL of H_2O and 20 mL of EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc for 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The crude product was purified by flash chromatography on silica gel to afford the desired product **3**.

2-(4-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (3a).[10] According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2a** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3a** (25.1 mg, 86%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.47 (td, *J* = 7.2, 1.5, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.33 (td, *J* = 8.0, 1.1 Hz, 1H), 7.00 (s, 1H), 6.97(d, *J* = 8.0 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 158.3, 156.7, 156.3, 152.4, 130.3, 126.1, 124.5, 121.7, 120.6, 117.3, 114.4, 112.8, 112.6, 100.9, 55.4;

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HRMS (ESI) calcd for $C_{18}H_{13}O_4$ $[M+H]^+$: 293.0814, found: 293.0814.

2-(2-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (3b). According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2b** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3b** (23.0 mg, 79%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.50 (td, *J* = 8.8, 1.6 Hz, 1H), 7.49 (s, 1H), 7.44 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.08 (td, *J* = 8.0, 1.0 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.2, 155.9, 153.0, 152.6, 130.4, 129.9, 126.2, 124.5, 120.8, 120.8, 118.0, 117.4, 112.8, 112.8, 111.2, 107.5, 55.5; HRMS (ESI) calcd for $C_{18}H_{13}O_4$ $[M+H]^+$: 293.0814, found : 293.0823.

2-(3-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (3c). According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2c** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3c** (19.0 mg, 65%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.54 (td, *J* = 7.2, 1.5 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.42-7.34 (m, 4H), 7.18 (s, 1H), 6.95 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 158.2, 158.9, 156.4, 152.7, 130.7, 130.2, 124.6, 120.8, 117.4, 117.1, 114.7, 112.8, 112.5, 110.2, 103.0, 55.4; HRMS (ESI) calcd for $C_{18}H_{13}O_4$ $[M+H]^+$: 293.0814, found: 293.0819.

2-phenyl-4H-furo[3,2-c]chromen-4-one (3d).[10] According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2d** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3d** (21.2 mg, 81%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.81 (dd, *J* = 7.2, 1.4 Hz, 2H), 7.52-7.44 (m, 4H), 7.40-7.35 (m, 2H), 7.17 (s, 1H); ^{13}C NMR (100 MHz, CDC_{l3}) δ 158.3, 156.9, 156.7, 152.7, 130.6, 129.2, 129.1, 129.0, 124.6, 120.8, 117.4, 112.8, 112.6, 102.7; HRMS (ESI) calcd for $C_{17}H_{10}O_3Na$ $[M+Na]^+$: 285.0528, found : 285.0536.

2-(p-tolyl)-4H-furo[3,2-c]chromen-4-one (3e).[10] According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2e** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3e** (21.8 mg, 79%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.51 (td, *J* = 8.4, 1.5 Hz, 1H), 7.44 (d, *J* = 7.56 Hz, 1H), 7.37 (td, *J* = 7.4, 1.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 2.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 157.1, 156.8, 152.7, 139.5, 130.6, 129.9, 126.4, 124.7, 120.9, 117.5, 113.0, 112.7, 102.1, 21.6; HRMS (ESI) calcd for $C_{18}H_{12}O_3Na$ $[M+Na]^+$: 299.0684, found: 299.0692.

2-(4-(tert-butyl)phenyl)-4H-furo[3,2-c]chromen-4-one (3f).[11] According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2f** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3f** (29.6 mg, 93%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 4.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.52-7.45 (m, 4H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 1.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 157.0, 156.8, 152.7, 152.7, 130.6, 126.3, 126.1, 124.7, 124.5, 120.9, 117.5, 112.9, 112.6, 102.1, 35.0, 31.3; HRMS (ESI) calcd for $C_{21}H_{18}O_3Na$ $[M+Na]^+$: 341.1154, found : 341.1149.

2-([1,1'-biphenyl]-4-yl)-4H-furo[3,2-c]chromen-4-one (3g). According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2g** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (I) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3g** (17.6 mg, 52%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.0, 2H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.56-7.46 (m, 4H), 7.39 (t, *J* = 7.2Hz, 2H), 7.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.0, 156.4, 152.6, 141.9, 140.1, 130.7, 129.0, 127.8, 127.7, 127.0, 125.0, 124.6, 120.9, 117.4, 112.8, 112.6, 102.8; HRMS (ESI) calcd for $C_{23}H_{14}O_3$ $[M+Na]^+$: 361.0841, found : 361.0839.

2-(4-fluorophenyl)-4H-furo[3,2-c]chromen-4-one (3h).[10] According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2h** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3h** (16.8 mg, 60%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.82-7.79 (m, 2H), 7.54 (td, *J* = 8.5, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.39 (td, *J* = 7.8, 1.0 Hz, 1H), 7.18 (td, *J* = 8.6, 2.0 Hz, 1H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.2 (d, *J* = 249 Hz), 158.2, 156.9, 155.7, 152.6, 130.7, 126.6 (d, *J* = 9.1 Hz), 125.4 (d, *J* = 3.0 Hz), 124.6, 120.8, 117.5, 116.3 (d, *J* = 22.0 Hz), 112.7, 112.6, 102.5; HRMS (ESI) calcd for $C_{17}H_9FO_3Na$ $[M+Na]^+$: 303.0433, found: 303.0435.

2-(6-methoxynaphthalen-2-yl)-4H-furo[3,2-c]chromen-4-one (3i). According to general procedure, **1a** (0.2 mmol, 2.0 equiv), **2j** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3i** (23.9 mg, 70%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.03 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.83 (m, 3H), 7.54 (td, *J* = 8.8, 1.5 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.40 (td, *J* = 8.0, 1.0 Hz, 1H), 7.23 (s, 1H), 7.22 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.16 (d, *J* = 2.3 Hz), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.4, 157.1, 156.8, 152.7, 134.9, 130.6, 130.0, 128.8, 127.7, 124.7, 124.2, 123.6, 122.8, 120.9, 119.9, 117.5, 112.9, 112.7, 106.1, 102.4, 55.5; HRMS (ESI) calcd for $C_{22}H_{15}O_4$ $[M+H]^+$: 343.0970, found: 343.0966.

7-methoxy-2-phenyl-4H-furo[3,2-c]chromen-4-one (3j). According to general procedure, **1b** (0.2 mmol, 2.0 equiv), **2d** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3j** (14.0 mg, 48%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.16 (s, 1H), 7.00-6.98 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.8, 157.8, 155.9, 154.6, 129.3, 129.2, 129.1, 124.6, 122.0, 113.1, 110.0, 106.4, 102.7, 101.7, 56.0; HRMS (ESI) calcd for $C_{18}H_{15}O_4$ $[M+H]^+$: 293.0814, found: 293.0823.

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2-(4-(tert-butyl)phenyl)-7-methoxy-4H-furo[3,2-c]chromen-4-one (3k). According to general procedure, **1b** (0.2 mmol, 2.0 equiv), **2f** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3k** (15.3 mg, 44%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.01 (s, 1H), 6.88 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.87 (s, 1H), 3.82 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.7, 156.5, 155.0, 153.4, 151.3, 125.4, 125.0, 123.3, 120.8, 111.9, 109.1, 105.3, 100.9, 100.5, 54.8, 33.9, 30.3; HRMS (ESI) calcd for $C_{22}H_{20}O_4Na$ $[M+Na]^+$: 371.1259, found: 371.1265.

7-methoxy-2-(p-tolyl)-4H-furo[3,2-c]chromen-4-one (3l). According to general procedure, **1b** (0.2 mmol, 2.0 equiv), **2e** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (I) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3l** (19.6 mg, 64%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.18 (*J* = 8.0 Hz, 2H), 6.97 (s, 1H), 6.86 (*J* = 8.0 Hz, 1H), 6.85 (s, 1H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 157.4, 156.0, 154.4, 139.1, 129.7, 126.5, 124.4, 121.8, 112.9, 110.1, 106.3, 101.7, 101.5, 55.8, 21.4; HRMS (ESI) calcd for $C_{19}H_{15}O_4$ $[M+H]^+$: 307.0970, found: 307.0975.

7-methoxy-2-(4-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (3m). According to general procedure, **1b** (0.2 mmol, 2.0 equiv), **2a** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3m** (27.3 mg, 85%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.00–6.94 (m, 5H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 160.4, 158.9, 157.3, 156.1, 154.4, 126.2, 122.2, 121.8, 114.6, 113.0, 110.3, 106.5, 101.7, 101.0, 56.0, 55.6; HRMS (ESI) calcd for $C_{19}H_{14}O_5Na$ $[M+Na]^+$: 345.0739, found: 345.0743.

2-(4-fluorophenyl)-7-methoxy-4H-furo[3,2-c]chromen-4-one (3n). According to general procedure, **1b** (0.2 mmol, 2.0 equiv), **2h** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3n** (17.1 mg, 55%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.3 Hz, 1H), 7.79-7.76 (m, 2H), 7.19-7.15 (m, 2H), 7.08 (s, 1H), 6.98-6.95 (m, 2H), 3.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ163.1 (d, *J* = 216 Hz), 158.5, 157.6, 154.8, 154.4, 126.4 (d, *J* = 8.3 Hz), 125.5, 121.7, 116.2 (d, *J* = 22.0 Hz), 112.9, 110.1, 106.1, 102.2 (d, *J* = 1.5 Hz), 101.5, 100.0, 55.8; HRMS (ESI) calcd for $C_{18}H_{11}FO_4Na$ $[M+Na]^+$: 333.0539, found: 333.0542.

7-methoxy-2-(6-methoxynaphthalen-2-yl)-4H-furo[3,2-c]chromen-4-one (3o). According to general procedure, **1b** (0.2 mmol, 2.0 equiv), **2j** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3o** (19.4 mg, 52%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 2H), 7.21 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.19 (s, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.97 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 158.3, 157.4, 156.0, 154.3, 134.5, 129.7, 128.6, 127.5, 124.2, 123.2, 122.6 121.7, 119.6, 112.8, 110.1, 106.2, 105.8, 102.0, 101.4, 55.7, 55.3; HRMS (ESI) calcd for $C_{23}H_{16}O_5Na$ $[M+Na]^+$: 395.0895, found: 395.0894.

8-bromo-2-(4-fluorophenyl)-4H-furo[3,2-c]chromen-4-one (3p). According to general procedure, **1c** (0.2 mmol, 2.0 equiv), **2h** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3p** (14.7 mg, 41%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.2 Hz, 1H), 7.82-7.79 (m, 2H), 7.61 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.35 (d, *J* = 8.8, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, *J* = 250 Hz), 157.6, 156.5, 155.5, 151.4, 133.5, 126.8 (d, *J* = 8.0 Hz), 125.1, 123.4, 119.3, 117.6, 116.5 (d, *J* = 22 Hz), 114.2, 113.3, 102.6; HRMS (ESI) calcd for $C_{17}H_8BrFO_3Na$ $[M+Na]^+$: 380.9505, found : 380.9503.

8-chloro-2-(4-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one (3q). According to general procedure, **1d** (0.2 mmol, 2.0 equiv), **2a** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (0.12 mmol, 1.2 equiv) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.001 mmol, 0.01 equiv, 1.0 mol%) in dry DMSO (1.5 mL) afforded **3q** (15.3 mg, 47%) as a white solid after purification on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.3 Hz, 1H), 7.76 (d, *J* = 1.9 Hz, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.9 Hz, 2.4 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 3.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.7, 157.4, 154.9, 150.6, 130.1, 130.0, 126.2, 121.4, 120.1, 118.7, 114.5, 113.8, 113.3, 100.9, 55.4; HRMS (ESI) calcd for $C_{18}H_{11}ClO_4Na$ $[M+Na]^+$: 349.0244, found: 349.0249.

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