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Synthesis of difluoromethylated 2-oxindoles and quinoline-2,4-diones *via* visible light-induced tandem radical cyclization of *N*-arylacrylamides†

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Visible light-induced difluoromethylation of *N*-arylacrylamides to afford difluoromethylated 2-oxindoles and quinoline-2,4-diones with difluoromethyl 2-pyridyl sulfones as radical precursors has been disclosed. This method provides convenient access to a variety of 2-oxindoles and quinoline-2,4-diones under mild conditions *via* a proposed tandem radical addition/cyclization process along with good tolerance to various functional groups. In addition, preliminary experimental studies have revealed that water is a key factor in difluoromethylation and the reaction involves an oxidative quenching cycle of the photocatalyst.

Introduction

In the past few decades, selective fluorination and fluoroalkylation have been hot topics for synthetic chemists and medicinal chemists[1] on account of the their beneficial effects on membrane permeability, bioavailability, binding affinity, and lipophilicity.[2] Among them, selective introduction of the difluoromethyl group (CF_2) is of great value to the design of structural libraries and drug discovery since the CF_2 moiety is known to be isosteric to mimic the steric and electronic features of an oxygen atom or a carbonyl group to increase the acidity of neighbouring groups, enhance dipole moments, and induce conformational changes.[3] Although various methodologies for fluoroalkylation have been developed, the visible light induced radical process still contributes greatly to the synthesis of fluoro-containing molecules, benefitting the fields of environment, energy, health, and safety.[4] Compounds HCF_2LG (LG = leaving group)[5] and XCF_2FG (X = Br or I; FG = functional group)[6] have been reported as precursors to release electrophilic difluoromethyl radicals under visible light irradiation. Recently, Hu reported difluoromethyl 2-pyridyl sulfones as CF_2H radical precursors *via* C–S bond cleavage in the presence of a photoredox catalyst and visible light with sulfinate anions being formed.[7] The subsequent radical addition reaction to unsaturated bonds including alkenes, alkynes, isocyanides, and arenes would generate the corresponding difluoromethylated products followed by further transformations. Additionally, a difluoromethylated cyclic skeleton would be achieved if any tandem intramolecular cyclization is involved.

Oxindoles, as well-known heterocycles of high value, are ubiquitously applied in pharmaceuticals and agrochemicals and significantly employed in drug discovery due to their unique biological activities and physical properties.[8] Moreover, quinoline-2,4-diones, with good antiplatelet, antibacterial, and herbicidal activities, are widely found in natural products and pharmaceuticals.[9] Therefore, the development of efficient and straightforward methods for synthesizing oxindoles[10] and quinoline-2,4-dione derivatives[11] is of high significance. Direct cyclization of *N*-arylacrylamides[12] is one of the most efficient routes to prepare 2-oxindoles[13] and quinoline-2,4-diones,[14] which can be initiated by the radical addition to C–C double bonds followed by an intramolecular radical cyclization onto the aryl or cyano substituent (and imine hydrolysis).

In light of the biological and synthetic importance of fluoro-containing compounds, oxindoles, and quinoline-2,4-diones in the field of organic chemistry and medicinal chemistry, the introduction of the difluoromethyl group into oxindoles and quinoline-2,4-diones remains highly desirable.[15] Recently, difluoromethyl radical addition of activated alkenes has been demonstrated as an efficient method to construct difluoromethylated oxindoles and quinoline-2,4-diones.[16] Herein, we present an efficient photoredox-catalyzed radical

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addition/cyclization of *N*-arylacrylamides with difluoromethyl 2-pyridyl sulfones for the construction of difluoromethylated 2-oxindoles and quinoline-2,4-diones.

Results and discussion

Initially, *N*-methyl-*N*-phenyl-methacrylamide (**1a**) was selected as the model substrate to optimize the reaction conditions (Table 1). Compared with $Ru(bpy)_3Cl_2$ ($E_{1/2}^{III/*II}$=−0.81 V *vs.* SCE in CH_3CN), *fac*-Ir(ppy)$_3$ was a better choice as the catalyst to generate the HCF_2 radical due to its relatively more negative reduction potential ($E_{1/2}^{IV/*III}$=−1.73 V *vs.* SCE in CH_3CN).[17] When acrylamide **1a** was treated with difluoromethyl 2-pyridyl sulfone in the presence of 1 mol% of *fac*-Ir(ppy)$_3$ and 2.0 equiv. of K_2CO_3 in DMF under blue light irradiation, the reaction, to our delight, proceeded smoothly and afforded the desired difluoromethylated 2-oxindole along with the sulfonated product.[18] Considering the chemical equation, difluoromethyl 2-pyridyl sulfone asked for 2.0 equiv. of *N*-arylacrylamides. After an extensive solvent screening, DMSO was demonstrated to be the optimal solvent for this reaction with the desired product being produced in a moderate yield. Additionally, sodium carbonate was the best candidate to serve as a base for deprotonation.

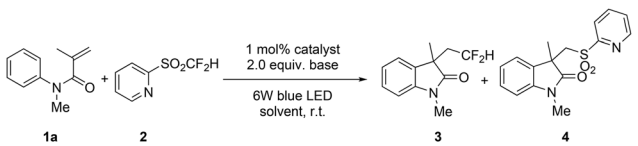
Obviously, there was a competition between the difluoromethylation and sulfonation processes. For acrylamide **1b**, the difluoromethylation and sulfonation took place at a similar rate. For acrylamides **1c** and **1d**, the conversion ratio of difluoromethylation was higher than that of sulfonation, which was in contrast to **1a** and **1e** (Table 2).

Factors influencing the competition between difluoromethylation and sulfonation apart from the inherent characteristics of different substitutions were investigated based on the established data. A mechanism study was conducted firstly to gain insights into the reaction. Control experiments showed that both the blue light source and photoredox catalyst were essential for the formation of difluoromethylated and sulfonated 2-oxindoles (Scheme 1a). Moreover, the added methyl iodide under standard conditions captured the sulfinate ion to obtain 2-(methylsulfonyl)pyridine as the major product (Scheme 1b).

As might be expected, in the presence of the radical scavenger TEMPO, the cyclization reaction was absolutely inhibited (for details, see the ESI†), indicating that free radical intermediates were perhaps involved in the reaction (Scheme 1c). These observations elucidated that the cascade cyclization might proceed *via* a difluoromethyl radical and a sulfonyl radical possibly formed by the oxidation of the sulfinate ion.[18d,f,19]

The sulfonated process may be inhibited *via* trapping the sulfinate ion. To support our hypothesis, a proton donator, such as proton acid and water, was added to the system under standard conditions (Scheme 2). It was found that the presence of a proton donator weakened the sulfonation process. With the addition of water (200 μL), difluoromethylation

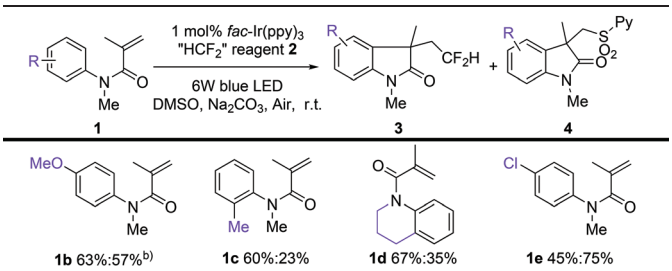
Table 1 Optimization of reaction conditions[a]



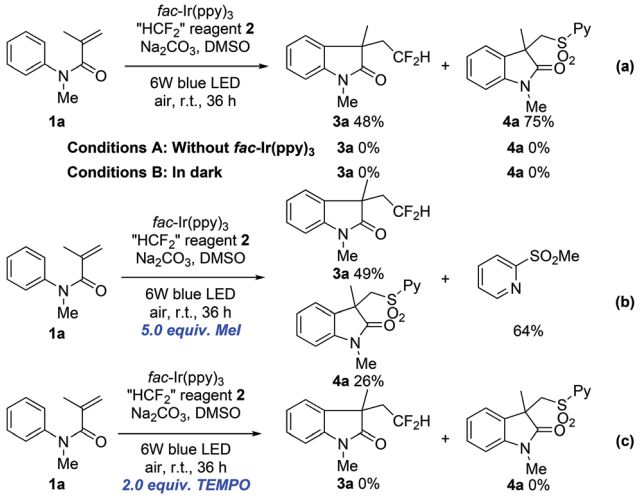
Entry	Catalyst	Base	Solvent	Yield of **3** : **4**/%[b]
1	$Ru(bpy)_3Cl_2$	K_2CO_3	DMF	—
2	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	44 : 37
3	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMF	30 : 30
4	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	—
5	*fac*-Ir(ppy)$_3$	Na_2CO_3	THF	—
6	***fac*-Ir(ppy)$_3$**	***Na_2CO_3***	***DMSO***	***48 : 75***
7	*fac*-Ir(ppy)$_3$	K_2HPO_4	DMSO	42 : 37
8	*fac*-Ir(ppy)$_3$	KH_2PO_4	DMSO	48 : 35

[a] Reaction conditions: **1a** (0.2 mmol, 2.0 equiv.), **2** (0.1 mmol, 1.0 equiv.), catalyst (0.001 mmol, 1 mol%), base (0.2 mmol, 2.0 equiv.) in solvent (1 mL) were irradiated with a 6 W blue LED for 36 h at room temperature under an air atmosphere. [b] Isolated yields were determined.

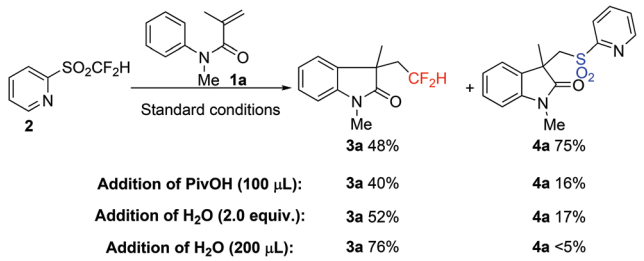
Table 2 Substrate tolerance of the methodology[a]



[a] Reaction conditions: **1** (0.2 mmol, 2.0 equiv.), **2** (0.1 mmol), *fac*-Ir(ppy)$_3$ (0.001 mmol, 1 mol%), Na_2CO_3 (0.2 mmol, 2.0 equiv.) in DMSO (1 mL) were irradiated with a 6 W blue LED for 36 h at room temperature under an air atmosphere. [b] Isolated yields of **3** : **4** were determined.



Scheme 1 Experiments for mechanistic studies.

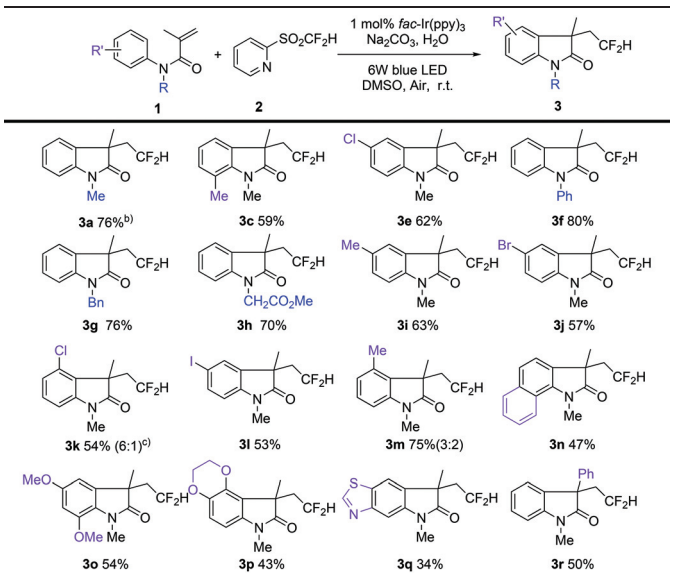


Scheme 2 Process study of difluoromethylation and sulfonation.

became dominant while the sulfonation process stopped completely.

The functional group tolerance and the scope of the difluoromethylation reaction were investigated under the optimized conditions and the results are summarized in Table 3. The effect of the N-protecting group was first examined. Substrates bearing methyl, phenyl, and benzyl protecting groups on the nitrogen atom were beneficial for this transformation while the replacement of the methyl group by the electron-withdrawing groups such as tosyl and ester group stopped the cyclization process, demonstrating that the electron-donating protecting group was necessary to stabilize the cyclized radical intermediates and the subsequent carbon cations. Regarding substrates with various substituents R′ on the aromatic ring, all reacted smoothly to afford products in moderate to good yields with either electron-donating (*i.e.*, methoxy) or electron-withdrawing groups such as Cl, Br, or I. In addition, substrates bearing a *meta* substituent (**1k** and **1m**) showed good reactivity and moderate regioselectivity with the C-2 position being preferred. When *N*-naphthalene amide was used as a substrate, the desired oxindole **3n** could be isolated in a moderate yield. No obvious steric effect on the phenyl ring was observed in this cascade reaction considering that the *ortho*-substituted acrylamides (**1c**) also exhibited a satisfactory reactivity. Polysubstituted amides (**1o** and **1p**) reacted well with difluoromethyl 2-pyridyl sulfone providing the corresponding 2-oxindole in the yield of 54% and 43%, respectively. With regard to the acrylamide part, replacing the methyl group by the phenyl group (**1r**) resulted in a smoothly proceeding reaction with a moderate yield as well. It is worth noting that a heterocyclic substrate, benzothiazole (**1q**), was also compatible with this cascade reaction.

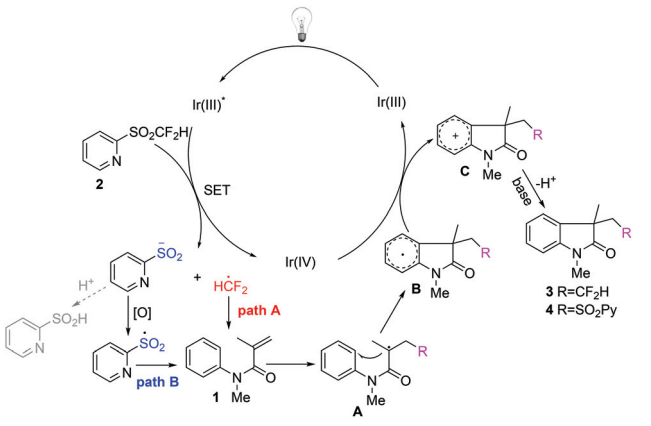
Table 3 Substrate tolerance of the difluoromethylation process[a]



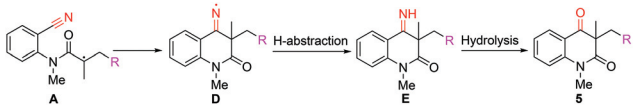
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol, 1.0 equiv.), *fac*-Ir(ppy)$_3$ (0.001 mmol, 1 mol%), Na_2CO_3 (0.2 mmol, 2.0 equiv.), and H_2O (200 μl) in DMSO (1 mL) were irradiated with a 6 W blue LED for 12 h at room temperature under an air atmosphere. [b] Isolated yields were determined. [c] Ratio of regional isomers.

A plausible catalytic cycle of the radical pathway is proposed for this transformation (Scheme 3) based on our current and previous investigations. According to the reduction potential of sulfone **2** and the photocatalyst,[17] we inferred that the difluoromethylation reaction involves an oxidative quenching cycle of the photocatalyst which was verified by the luminescence quenching experiments (for details, see the ESI†). Initially, the photoredox catalyst Ir(III) is stimulated to the excited state Ir(III)* under visible light irradiation, which subsequently donates an electron to sulfone **2** to generate the sulfinate ion and the HCF_2 radical. The generated sulfinate ion could be oxidized to the corresponding sulfonyl radical. The process would stop by the addition of a proton donator. The addition reaction of the sulfonyl or HCF_2 radical to the activated C=C bond of *N*-arylacrylamide **1** affords alkyl radical intermediate **A** followed by an intramolecular cyclization producing the radical intermediate **B** with an aryl ring, which is then oxidized by Ir(IV) releasing Ir(III) and a cation intermediate **C** to end the catalytic cycle. Ultimately, alkaline assisted deprotonation yields the difluoromethylated and sulfonated product.

Inspired by previous work, we revisited the aforementioned plausible mechanism and hypothesized that if *ortho*-cyanoarylacrylamide derivatives were used, the generated alkyl radical **A** might attack the nitrile group to afford imine intermediate **D**,



Scheme 3 Proposed reaction mechanism.



Scheme 4 Proposed synthesis process of quinoline-2,4-diones.

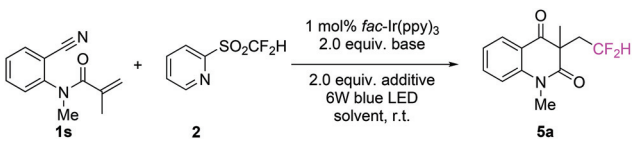
which would undergo H-abstraction and hydrolysis to form quinoline-2,4-dione (Scheme 4).

N-(2-Cyanophenyl)-*N*-methyl-methacrylamide **1s** was chosen as the model substrate to explore our hypothesis (Table 4). Obviously, water was necessary for the final hydrolysis while in the meantime the sulfonation process was thus inhibited. As expected, the difluoro-containing quinoline-2,4-dione **5a** was obtained in the presence of 1 mol% of *fac*-Ir(ppy)$_3$ and 2.0 equiv. of Na_2CO_3 in DMSO/H_2O (5 : 1). Detailed solvent and base screening suggested THF/H_2O (1 : 1) and sodium bicarbonate as the most suitable solvent and base, respectively. TBAF would probably act as a phase transfer catalyst and influence the reaction significantly. Thus, the optimum reaction conditions could be summarized as follows: substrate **1** (1.0 equiv.), sulfone **2** (1.5 equiv.), *fac*-Ir(ppy)$_3$ (1 mol%), $NaHCO_3$ (2.0 equiv.), and TBAF (2.0 equiv.) in THF/H_2O (1 : 1) under blue-LED irradiation for 12 h.

Various *ortho*-cyanoarylacrylamide derivatives were used and the results are tabulated in Table 5. An investigation into different N-protection groups showed that the electron-donating groups including methyl and benzyl worked well for this reaction. Substrates with electron-withdrawing or electron-donating groups demonstrated good tolerance, and the corresponding quinoline-2,4-diones are produced in moderate to good yields. Substrates with substituents at an *ortho* site of the cyano group exhibited lower reactivity with relatively lower yields. Interestingly, the *ortho*-bromide substituted substrate selectively gave the dehalogenation product **5a** in 54% yield *via* a proposed insertion of iridium to the C–Br bond.[20] The poly-substituted substrate also reacted well, and the expected product **5f** was obtained in a moderate yield.

Furthermore, the reaction between **1s** and **2** in the presence of $H_2{}^{18}O$ afforded the ^{18}O-labeled product **5a′** in 60% yield (Scheme 5), demonstrating that the carbonyl oxygen atom of quinoline-2,4-dione originated from water as per our initial assumption.

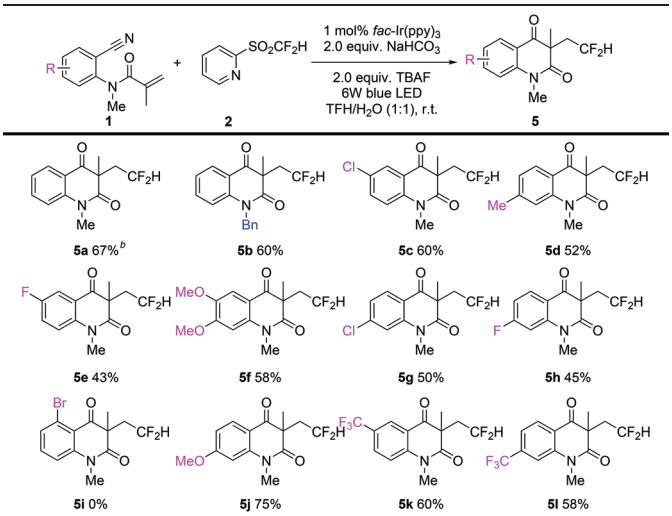
Table 4 Condition optimization of quinoline-2,4-dione synthesis[a]



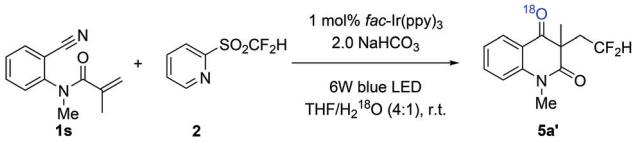
Entry	Base	Additive	Solvent	Yield of **5**[b]/%
1	Na_2CO_3	—	DMSO/H_2O (5 : 1)	17
2	$NaHCO_3$	—	THF/H_2O (5 : 1)	29
3	$NaHCO_3$	—	CH_3CN/H_2O (5 : 1)	Trace
4	$NaHCO_3$	—	THF/H_2O (3 : 2)	35
5	NaOAc	—	THF/H_2O (3 : 2)	31
6	$NaHCO_3$	—	THF/H_2O (3 : 1)	41
7	$NaHCO_3$	—	THF/H_2O (1 : 1)	57
8	$NaHCO_3$	TBAB	THF/H_2O (1 : 1)	56
9	***$NaHCO_3$***	***TBAF***	***THF/H_2O (1 : 1)***	*67*

[a] Reaction conditions: **1s** (0.1 mmol), **2** (0.15 mmol, 1.5 euqiv.), *fac*-Ir(ppy)$_3$ (0.001 mmol, 1 mol%), base (0.2 mmol, 2.0 equiv.) in the solvent (1 mL) were irradiated with a 6 W blue LED for 12 h at room temperature under an air atmosphere. [b] Isolated yields were determined.

Table 5 Substrate scope of quinoline-2,4-dione synthesis[a]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol, 1.5 euqiv.), *fac*-Ir(ppy)$_3$ (0.001 mmol, 1 mol%), $NaHCO_3$ (0.2 mmol, 2.0 equiv.), and TBAF (0.2 mmol, 2.0 equiv.) in THF/H_2O 1 : 1 (1 mL) were irradiated with a 6 W blue LED for 12 h at room temperature under an air atmosphere. [b] Isolated yields were determined.



Scheme 5 $H_2{}^{18}O$-labeling experiment.

Conclusions

To summarize, a novel visible-light photocatalytic synthesis of difluoromethylated 2-oxindoles and quinoline-2,4-diones from *N*-arylacrylamides has been developed through a cascade radical addition/cyclization process. This transformation is featured with good functional group tolerance and a wide substrate scope providing convenient and highly efficient access to diverse fluoro-containing 2-oxindoles and quinoline-2,4-diones. Further studies on the mechanistic investigation and the synthetic applications concerning this transformation are underway in our laboratory.

Experimental

Materials and methods

All reagents were purchased from Adamas and used without further purification unless specified otherwise. Solvents for chromatography were of technical grade and distilled prior to use. Flash chromatography was performed using 200–300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. The developed chromatogram was visualized by UV absorbance (254 nm). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR data were recorded on Bruker 600 M nuclear resonance spectrometers (^{1}H: 600 MHz, ^{13}C: 150 MHz, ^{19}F: 565 MHz) unless otherwise specified, respectively. Chemical shifts (δ) in ppm are reported relative to the residual signals of chloroform (^{1}H 7.26 ppm or ^{13}C 77.16 ppm). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants (J) are reported in hertz (Hz). ^{13}C NMR spectra were recorded with total proton decoupling. HRMS (ESI) analysis was performed by The Analytical Instrumentation Center at School of Pharmaceutical Sciences, South-Central University for Nationalities, and (HRMS) data were reported with ion mass/charge (m/z) ratios as values in atomic mass units.

General procedure for the synthesis of difluoromethylated 2-oxindole

fac-Ir(ppy)$_3$ (0.001 mmol, 1 mol%), *N*-arylacrylamide **1** (0.1 mmol), difluoromethyl 2-pyridyl sulfone **2** (0.1 mmol, 1.0 eq.), and Na_2CO_3 (0.2 mmol, 2.0 eq.) were sequentially weighed into a tube. H_2O (200 μL) and DMSO (1.0 mL) were added by using a syringe. The mixture was irradiated with a 6 W blue LED at room temperature under an air atmosphere for 12 h. Then the volatile solvent and reagents were removed by rotary evaporation and the residue was purified by silica gel flash chromatography using petroleum ether/EtOAc.

3-(2,2-Difluoroethyl)-1,3-dimethylindolin-2-one (3a). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.16 to −114.49 (m). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.31 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 5.58 (tdd, J = 56.1, 6.4, 3.5 Hz, 1H), 3.23 (s, 3H), 2.50 (qd, J = 14.4, 6.4 Hz, 1H), 2.28 (dtd, J = 22.0, 14.5, 3.5 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.11, 142.87, 131.97, 128.47, 122.74, 115.09 (t, J = 239.7 Hz), 108.47, 44.55 (dd, J = 6.1, 4.5 Hz), 41.31 (t, J = 21.8 Hz), 26.37, 24.35. HRMS (ESI): m/z = 226.1038, calcd for $C_{12}H_{14}ONF_2$ ([M + H$^+$]) 226.1043.

3-(2,2-Difluoroethyl)-5-methoxy-1,3-dimethylindolin-2-one (3b). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.12 to −114.43 (m). ^{1}H NMR (600 MHz, chloroform-*d*) δ 6.86–6.80 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 5.60 (tdd, J = 56.1, 6.4, 3.4 Hz, 1H), 3.80 (s, 3H), 3.20 (s, 3H), 2.49 (qd, J = 14.6, 6.4 Hz, 1H), 2.25 (dtd, J = 22.5, 14.3, 3.5 Hz, 1H), 1.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.74, 156.11, 136.31, 133.36, 116.96–113.18 (m), 112.27, 110.51, 108.74, 55.78, 45.16–44.64 (m), 41.28 (t, J = 21.9 Hz). 26.41, 24.36. HRMS (ESI): m/z = 256.1142, calcd for $C_{13}H_{16}O_2NF_2$ ([M + H$^+$]) 256.1149.

(2,2-Difluoroethyl)-1,3,7-trimethylindolin-2-one (3c). ^{19}F NMR (565 MHz, chloroform-*d*) δ −113.88 to −115.01 (m). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.04 (d, J = 7.3 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 5.56 (tdd, J = 56.2, 6.5, 3.4 Hz, 1H), 3.50 (s, 3H), 2.59 (s, 3H), 2.49 (qd, J = 14.6, 6.5 Hz, 1H), 2.24 (dddd, J = 24.3, 14.7, 12.6, 3.3 Hz, 1H), 1.38 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.86, 140.61, 132.55, 132.13, 122.64, 120.60, 120.15, 115.11 (t, J = 239.6 Hz), 43.86 (dd, J = 6.9, 3.7 Hz),41.57 (t, J = 21.8 Hz)., 29.66, 24.75, 19.04. HRMS (ESI): m/z = 240.1194, calcd for $C_{13}H_{16}ONF_2$ ([M + H$^+$]) 240.1200.

1-(2,2-Difluoroethyl)-1-methyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2(1*H*)-one (3d). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.17 (t, J = 14.0 Hz), −114.27 (t, J = 16.3 Hz), −114.37 (dd, J = 23.4, 13.2 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.06 (d, J = 2.3 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 5.62 (tdd, J = 56.1, 6.4, 3.5 Hz, 1H), 3.74–3.71 (m, 2H), 2.79 (t, J = 5.2 Hz, 2H), 2.48 (qd, J = 14.7, 6.4 Hz, 1H), 2.28 (dtd, J = 23.2, 14.5, 14.1, 3.5 Hz, 1H), 2.01 (p, J = 6.0 Hz, 2H), 1.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.01, 138.69, 130.52, 127.24, 122.17, 120.64, 120.60, 115.26 (t, J = 239.8 Hz), 45.84 (dd, J = 6.5, 4.0 Hz), 41.15 (t, J = 21.8 Hz), 38.93, 24.58, 24.02, 21.11. HRMS (ESI): m/z = 252.1195, calcd for $C_{14}H_{16}ONF_2$ ([M + H$^+$]) 252.1200.

5-Chloro-3-(2,2-difluoroethyl)-1,3-dimethylindolin-2-one (3e). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.37 (dt, J = 55.8, 16.0 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.28 (dd, J = 8.3, 2.1 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 5.61 (tdd, J = 55.9, 6.2, 3.5 Hz, 1H), 3.21 (s, 3H), 2.50 (qd, J = 14.3, 6.2 Hz, 1H), 2.27 (tdd, J = 18.1, 14.7, 3.5 Hz, 1H), 1.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.61, 141.45, 133.72, 128.45, 128.16, 123.43, 114.83 (t, J = 240.2 Hz), 109.44, 44.80 (t, J = 5.2 Hz), 41.14 (t, J = 22.0 Hz), 26.50, 24.36. HRMS (ESI): m/z = 260.0648, calcd for $C_{12}H_{13}$ $ONClF_2$ ([M + H$^+$]) 260.0654.

3-(2,2-Difluoroethyl)-3-methyl-1-phenylindolin-2-one (3f). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.73 (dq, J = 55.7, 15.0, 14.3 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.56–7.50 (m, 2H), 7.43 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 1.4 Hz, 1H), 7.39 (s, 1H), 7.31–7.28 (m, 1H), 7.24 (td, J = 7.7, 1.3 Hz, 1H), 7.13 (td, J = 7.5, 1.0 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 5.63 (tdd, J = 56.1, 6.9, 3.1 Hz, 1H), 2.65 (qd, J = 13.5, 6.9 Hz, 1H), 2.45–2.28 (m, 1H), 1.54 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.58, 142.95, 134.25, 131.53, 129.62, 128.40, 128.17, 126.57, 123.15, 123.00, 115.18 (t, J = 239.9 Hz), 109.76, 44.62 (dd, J = 5.9, 4.4 Hz), 41.69 (t, J = 21.8 Hz), 24.74. HRMS (ESI): m/z = 288.1193 calcd for $C_{17}H_{16}ONF_2$ ([M + H$^+$]) 288.1200.

1-Benzyl-3-(2,2-difluoroethyl)-3-methylindolin-2-one (3g). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.05 to −114.27 (m).^{1}H NMR (600 MHz, chloroform-*d*) δ 7.32 (t, J = 7.3 Hz, 2H), 7.30–7.25 (m, 5H), 7.23 (d, J = 7.4 Hz, 1H), 7.18 (td, J = 7.7, 1.3 Hz, 1H), 7.06 (td, J = 7.5, 1.0 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 5.61 (tdd, J = 56.0, 6.6, 3.4 Hz, 1H), 4.98 (d, J = 15.7 Hz, 1H), 4.87 (d, J = 15.7 Hz, 1H), 2.60 (qd, J = 14.0, 6.5 Hz, 1H), 2.35 (dddd, J = 19.8, 16.4, 14.5, 3.4 Hz, 1H), 1.47 (s, 3H). ^{13}C

NMR (150 MHz, $CDCl_3$) δ 179.20, 141.97, 135.68, 131.84, 128.77, 128.37, 127.63, 127.22, 122.79, 122.74, 115.09 (t, J = 239.9 Hz), 109.57, 44.55 (t, J = 5.3 Hz), 43.83, 41.17 (t, J = 21.9 Hz). 24.95. HRMS (ESI): m/z = 302.1351, calcd for $C_{18}H_{18}ONF_2$ ([M + H^+]) 302.1356.

Ethyl 2-(3-(2,2-difluoroethyl)-3-methyl-2-oxoindolin-1-yl) acetate (3h). ^{19}F NMR (565 MHz, chloroform-d) δ −113.46 to −113.71 (m). ^{1}H NMR (600 MHz, chloroform-d) δ 7.28 (td, J = 7.8, 1.2 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 7.11 (td, J = 7.5, 1.0 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 5.64 (tdd, J = 55.9, 5.6, 4.1 Hz, 1H), 4.57–4.35 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.53 (dtd, J = 16.2, 14.5, 14.1, 5.6 Hz, 1H), 2.42–2.23 (m, 1H), 1.45 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.16, 167.44, 141.48, 131.72, 128.48, 123.18, 123.12, 115.03 (t, J = 239.7 Hz), 108.46, 61.87, 44.65 (t, J = 5.5 Hz), 41.57, 41.48–41.19 (m). 24.61, 14.06. HRMS (ESI): m/z = 298.1249, calcd for $C_{15}H_{18}O_3NF_2$ ([M + H^+]) 298.1255.

3-(2,2-Difluoroethyl)-1,3,5-trimethylindolin-2-one (3i). ^{19}F NMR (565 MHz, chloroform-d) δ −113.99 to −114.60 (m). ^{1}H NMR (600 MHz, chloroform-d) δ 7.10 (d, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.76 (d, J = 7.9 Hz, 1H), 5.58 (tdd, J = 56.2, 6.5, 3.4 Hz, 1H), 3.20 (s, 3H), 2.48 (qd, J = 14.6, 6.5 Hz, 1H), 2.35 (s, 3H), 2.32–2.19 (m, 1H), 1.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.10, 140.51, 132.36, 132.04, 128.73, 123.61, 115.18 (t, J = 239.7 Hz), 108.23, 44.63 (dd, J = 6.7, 3.9 Hz), 41.36 (t, J = 21.8 Hz), 26.40, 24.40, 21.16. HRMS (ESI): m/z = 240.1193, calcd for $C_{13}H_{16}ONF_2$ ([M + H^+]) 240.1200.

5-Bromo-3-(2,2-difluoroethyl)-1,3-dimethylindolin-2-one (3j). ^{19}F NMR (565 MHz, chloroform-d) δ −114.40 (dt, J = 55.3, 16.2 Hz). ^{1}H NMR (600 MHz, chloroform-d) δ 7.43 (dd, J = 8.3, 1.9 Hz, 1H), 7.34 (d, J = 1.9 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.61 (tdd, J = 55.9, 6.2, 3.5 Hz, 1H), 3.21 (s, 3H), 2.50 (qd, J = 14.3, 6.3 Hz, 1H), 2.27 (tdd, J = 18.2, 14.8, 3.5 Hz, 1H), 1.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.52, 141.97, 134.12, 131.38, 126.18, 115.43 (t, J = 240.1 Hz), 113.24, 109.97, 44.78 (t, J = 5.2 Hz), 41.18 (t, J = 22.0 Hz), 26.50, 24.40. HRMS (ESI): m/z = 304.0143, calcd for $C_{12}H_{13}ONBrF_2$ ([M + H^+]) 304.0149.

4-Chloro-3-(2,2-difluoroethyl)-1,3-dimethylindolin-2-one (3k). ^{19}F NMR (565 MHz, chloroform-d) δ −114.90 (ddt, J = 289.3, 55.1, 12.9 Hz), −116.75 (dddd, J = 288.1, 55.4, 28.7, 13.3 Hz). ^{1}H NMR (600 MHz, chloroform-d) δ 7.26 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 5.47 (tdd, J = 55.9, 6.9, 3.2 Hz, 1H), 3.22 (s, 3H), 2.77 (dddd, J = 28.2, 14.4, 9.3, 3.1 Hz, 1H), 2.62 (qd, J = 14.6, 6.9 Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.59, 144.80, 130.65, 129.78, 127.84, 123.58, 115.09 (t, J = 240.0 Hz), 107.00, 45.84 (dd, J = 8.3, 2.5 Hz), 39.05–38.64 (m), 26.65, 22.02. HRMS (ESI): m/z = 260.0648, calcd for $C_{12}H_{13}ONClF_2$ ([M + H^+]) 260.0654.

3-(2,2-Difluoroethyl)-5-iodo-1,3-dimethylindolin-2-one (3l). ^{19}F NMR (565 MHz, chloroform-d) δ −114.34 to −114.49 (m). ^{1}H NMR (600 MHz, chloroform-d) δ 7.62 (dd, J = 8.2, 1.6 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 5.60 (tdd, J = 55.9, 6.3, 3.5 Hz, 1H), 3.20 (s, 2H), 2.50 (qd, J = 14.3, 6.3 Hz, 1H), 2.31–2.19 (m, 1H), 1.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.32, 142.61, 137.30, 134.42, 131.64, 114.78 (t, J = 240.1 Hz), 110.51, 85.17, 44.58, 44.55 (t, J = 5.2 Hz), 44.51, 41.13 (t, J = 22.0 Hz), 26.40, 24.34. HRMS (ESI): m/z = 352.0004, calcd for $C_{12}H_{13}ONF_2I$ ([M + H^+]) 325.0010.

3-(2,2-Difluoroethyl)-1,3,7-trimethylindolin-2-one (3m). ^{1}H NMR (600 MHz, chloroform-d) δ 7.21 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.75–6.67 (m, 1H), 5.43 (tdd, J = 56.1, 6.4, 3.3 Hz, 1H), 3.21 (s, 3H), 2.64 (qd, J = 14.4, 6.4 Hz, 1H), 2.54–2.43 (m, 1H), 2.39 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.10, 142.15, 137.63, 133.15, 127.29, 124.17, 114.09 (t, J = 239.9 Hz), 105.21, 44.24 (dd, J = 7.1, 3.4 Hz), 38.83 (t, J = 21.8 Hz), 25.42, 21.58, 17.25.

3-(2,2-Difluoroethyl)-1,3,6-trimethylindolin-2-one (3m′). ^{1}H NMR (600 MHz, chloroform-d) δ 7.10 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.76–6.66 (m, 3H), 5.57 (tdd, J = 56.2, 6.5, 3.5 Hz, 1H), 2.55–2.42 (m, 2H), 2.39 (s, 3H), 2.26 (dtd, J = 23.0, 14.0, 3.4 Hz, 1H), 1.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.41, 141.92, 127.94, 127.57, 122.18, 121.49, 114.16 (t, J = 239.7 Hz), 108.39, 43.32 (dd, J = 6.5, 4.1 Hz), 40.33 (t, J = 21.8 Hz), 25.29, 23.40, 20.77, 40.33 (t, J = 21.8 Hz).

Inseparable mixture of **3o**/**3o′**, 75% yield, 3 : 2, as a colorless oil; ^{19}F NMR (565 MHz, chloroform-d) δ −114.02 to −114.66 (m). HRMS (ESI): m/z = 240.1194, calcd for $C_{13}H_{16}ONF_2$ ([M + H^+]) 240.1200.

2-(2,2-Difluoroethyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*g*] indol-2-one (3n). ^{19}F NMR (565 MHz, chloroform-d) −113.77 to −114.78 (m), −115.96 (dddd, J = 289.3, 55.7, 26.9, 12.0 Hz). ^{1}H NMR (600 MHz, chloroform-d) δ 7.76 (d, J = 8.1 Hz, 1H), 7.55 (dd, J = 15.7, 7.6 Hz, 2H), 7.46 (t, J = 8.3 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 5.50 (tdd, J = 56.2, 6.4, 3.5 Hz, 1H), 3.55 (s, 3H), 3.03 (tdd, J = 15.6, 11.8, 6.5 Hz, 1H), 2.45 (dddd, J = 26.8, 14.5, 8.9, 3.4 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.92, 136.35, 135.98, 133.42, 126.91, 126.67, 126.64, 122.91, 122.68, 118.98, 115.86 (t, J = 239.7 Hz), 108.80, 46.41 (t, J = 21.3 Hz), 43.81 (dd, J = 7.5, 3.3 Hz), 32.01, 29.81. HRMS (ESI): m/z = 276.1194, calcd for $C_{16}H_{16}ONF_2$ ([M + H^+]) 276.1200.

3-(2,2-Difluoroethyl)-5,7-dimethoxy-1,3-dimethylindolin-2-one (3o). ^{19}F NMR (565 MHz, chloroform-d) δ −114.22 (ddt, J = 56.4, 42.6, 11.5 Hz). ^{1}H NMR (600 MHz, chloroform-d) δ 6.44 (d, J = 2.3 Hz, 1H), 6.40 (d, J = 2.3 Hz, 1H), 5.60 (tdd, J = 56.1, 6.4, 3.5 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.45 (s, 3H), 2.48 (qd, J = 14.5, 6.4 Hz, 1H), 2.21 (dtd, J = 22.7, 14.1, 3.4 Hz, 1H), 1.38 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.98, 156.79, 146.19, 134.19, 124.13, 115.12 (t, J = 239.8 Hz), 100.35, 99.27, 55.85, 55.82, 45.16 (dd, J = 6.5, 4.0 Hz), 41.50 (t, J = 21.9 Hz), 29.54, 24.63. HRMS (ESI): m/z = 286.1248, calcd for $C_{14}H_{18}O_3NF_2$ ([M + H^+]) 286.1255.

8-(2,2-Difluoroethyl)-6,8-dimethyl-2,3,6,8-tetrahydro-7*H*-[1,4] dioxino[2,3-*f*]indol-7-one (3p). ^{19}F NMR (565 MHz, chloroform-d) δ −114.51 to −115.35 (m). ^{1}H NMR (600 MHz, chloroform-d) δ 6.76 (s, 1H), 6.41 (s, 1H), 5.60 (tdd, J = 56.2, 6.5, 3.4 Hz, 1H), 4.30–4.25 (m, 2H), 4.26–4.22 (m, 2H), 3.15 (s, 3H), 2.45 (qd, J = 14.5, 6.5 Hz, 1H), 2.28–2.14 (m, 1H), 1.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.92, 140.84, 139.94, 136.97, 117.75, 116.31, 115.49 (t, J = 239.5 Hz), 101.19, 64.65, 64.09, 45.06 (dd, J = 6.9, 4.3 Hz), 39.43 (t, J = 21.7 Hz), 26.47, 22.43. HRMS (ESI): m/z = 284.1092, calcd for $C_{14}H_{16}O_3NF_2$ ([M + H^+]) 284.1098.

7-(2,2-Difluoroethyl)-5,7-dimethyl-5,7-dihydro-6*H*-thiazolo[5,4-*f*]indol-6-one (3q). ^{19}F NMR (565 MHz, chloroform-*d*) δ −114.09 to −114.34 (m). ^{1}H NMR (600 MHz, chloroform-*d*) δ 9.01 (s, 1H), 7.79 (s, 1H), 7.58 (s, 1H), 5.64 (tdd, *J* = 55.9, 6.2, 3.7 Hz, 1H), 3.33 (s, 3 H), 2.58 (qd, *J* = 14.6, 6.2 Hz, 1H), 2.42–2.30 (m, 1H), 1.49 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.53, 154.61, 153.38, 142.28, 131.77, 128.02, 116.28, 114.90 (t, *J* = 240.1 Hz), 102.93, 44.65–44.28 (m), 41.50 (t, *J* = 21.9 Hz), 26.68, 24.83. HRMS (ESI): *m*/*z* = 283.0710, calcd for $C_{13}H1_3ON_2F_2S$ ([M + H$^+$]) 283.0717.

3-(2,2-Difluoroethyl)-1-methyl-3-phenylindolin-2-one (3r). ^{19}F NMR (565 MHz, chloroform-*d*) δ −113.71 (ddt, *J* = 289.4, 56.9, 12.5 Hz), −114.88 (dddd, *J* = 289.8, 56.2, 26.2, 12.0 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.39 (t, *J* = 7.7 Hz, 1H), 7.34–7.29 (m, 5H), 7.28–7.24 (m, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 5.52 (tdd, *J* = 55.9, 6.5, 3.3 Hz, 1H), 3.22 (s, 3H), 3.07 (tdd, *J* = 14.3, 11.9, 6.5 Hz, 1H), 2.76 (dddd, *J* = 27.0, 14.6, 9.6, 3.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.13, 143.77, 138.94, 129.72, 129.02, 128.76, 126.50, 122.81, 115.26 (t, *J* = 240.2 Hz), 108.80, 52.36 (dd, *J* = 7.9, 2.8 Hz), 41.25 (t, *J* = 22.4 Hz), 26.62. HRMS (ESI): *m*/*z* = 288.1193, calcd for $C_{17}H_{16}ONF_2$ ([M + H$^+$]) 288.1200.

1,3-Dimethyl-3-((pyridin-2-ylsulfonyl)methyl)indolin-2-one (4a). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.69 (d, *J* = 4.3 Hz, 1H), 7.60 (td, *J* = 7.8, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.6, 1.2 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 6.52 (t, *J* = 7.5 Hz, 1H), 4.35 (d, *J* = 15.0 Hz, 1H), 3.94 (d, *J* = 15.0 Hz, 1H), 3.26 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.68, 157.33, 149.83, 143.47, 137.79, 129.32, 128.27, 126.83, 123.27, 121.90, 121.49, 108.20, 57.27, 45.18, 26.62, 24.72. HRMS (ESI): *m*/*z* = 317.0954, calcd for $C_{16}H_{17}O_3N_2S$ ([M + H$^+$]) 317.0960.

5-Methoxy-1,3-dimethyl-3-((pyridin-2-ylsulfonyl)methyl)indolin-2-one (4b). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.70 (d, *J* = 4.6 Hz, 1H), 7.59 (td, *J* = 7.7, 1.7 Hz, 1H), 7.40 (dd, *J* = 6.9, 4.7 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 4.30 (d, *J* = 15.0 Hz, 1H), 3.91 (d, *J* = 15.0 Hz, 1H), 3.56 (s, 3H), 3.24 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.32, 157.26, 155.20, 149.83, 137.41, 137.02, 130.58, 126.80, 121.72, 112.74, 110.61, 108.47, 57.38, 55.28, 45.57, 26.70, 24.64. HRMS (ESI): *m*/*z* = 347.1059, calcd for $C_{17}H_{19}O_4N_2S$ ([M + H$^+$]) 347.1066.

1,3,7-Trimethyl-3-((pyridin-2-ylsulfonyl)methyl)indolin-2-one (4c). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.68 (d, *J* = 4.0 Hz, 1H), 7.62 (td, *J* = 7.7, 1.6 Hz, 1H), 7.44–7.38 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 6.9 Hz, 1H), 6.40 (t, *J* = 7.4 Hz, 1H), 4.30 (d, *J* = 15.0 Hz, 1H), 3.94 (d, *J* = 15.0 Hz, 1H), 3.54 (s, 3H), 2.56 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.52, 157.38, 149.84, 141.30, 137.75, 131.89, 129.90, 126.79, 121.82, 121.53, 121.18, 119.89, 57.58, 44.60, 30.03, 25.17, 19.07. HRMS (ESI): *m*/*z* = 331.1110, calcd for $C_{17}H_{19}O_3N_2S$ ([M + H$^+$]) 331.1116.

1-Methyl-1-((pyridin-2-ylsulfonyl)methyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2(1*H*)-one (4d). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.69 (d, *J* = 4.6 Hz, 1H), 7.62 (td, *J* = 7.7, 1.7 Hz, 1H), 7.41 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.44 (q, *J* = 7.6 Hz, 2H), 4.32 (d, *J* = 14.9 Hz, 1H), 3.92 (d, *J* = 14.9 Hz, 1H), 3.77 (dddd, *J* = 49.0, 12.6, 7.1, 4.4 Hz, 2H), 2.76 (dddt, *J* = 22.9, 16.2, 12.4, 5.4 Hz, 2H), 2.09–1.98 (m, 2H), 1.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.55, 157.43, 149.87, 139.26, 137.81, 127.98, 126.97, 126.86, 121.47, 121.44, 121.14, 120.37, 57.28, 46.39, 39.16, 24.59, 24.36, 21.04. HRMS (ESI): *m*/*z* = 343.1111, calcd for $C_{18}H_{19}O_3N_2O_3S$ ([M + H$^+$]) 343.1116.

5-Chloro-1,3-dimethyl-3-((pyridin-2-ylsulfonyl)methyl)indolin-2-one (4e). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.74 (d, *J* = 4.6 Hz, 1H), 7.62 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.7, 4.6, 1.1 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.06 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 1H), 4.39 (d, *J* = 15.1 Hz, 1H), 3.91 (d, *J* = 15.1 Hz, 1H), 3.26 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.31, 156.90, 150.01, 142.34, 137.61, 130.93, 128.51, 127.45, 127.14, 124.03, 121.50, 109.17, 56.96, 45.40, 26.82, 24.59. HRMS (ESI): *m*/*z* = 351.0564, calcd for $C_{16}H_{16}O_3N_2ClS$ ([M + H$^+$]) 351.0570.

General procedure for synthesis of difluoromethylated quinoline-2,4-dione

N-(2-Cyanophenyl)-*N*-methyl-methacrylamide **1** (0.1 mmol), difluoromethyl 2-pyridyl sulfone **2** (0.15 mmol, 1.5 euqiv.), *fac*-Ir(ppy)$_3$ (0.001 mmol, 1 mol%), $NaHCO_3$ (0.2 mmol, 2.0 equiv.), and TBAF (0.2 mmol, 2.0 equiv.) were sequentially weighed into a tube. THF (0.5 mL) and H_2O (0.5 mL) were added by using a syringe. The mixture was irradiated with a 6 W blue LED at room temperature under an air atmosphere for 12 h. Then the volatile solvent and reagents were removed by rotary evaporation and the residue was purified by silica gel flash chromatography using petroleum ether/EtOAc.

3-(2,2-Difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5a). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.24 (ddt, *J* = 57.4, 30.0, 16.3 Hz). ^{1}H NMR (600 MHz, chloroform-d) δ 8.06 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.69–7.65 (m, 1H), 7.23–7.18 (m, 2H), 5.91 (tt, *J* = 56.9, 5.1 Hz, 1H), 3.50 (s, 3H), 2.84–2.63 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.52, 172.44, 143.01, 136.46, 128.53, 123.37, 119.28, 115.30 (t, *J* = 239.9 Hz) 114.95, 53.12, 39.45 (t, *J* = 22.3 Hz), 29.93, 26.89. HRMS (ESI): *m*/*z* = 254.0987, calcd for $C_{13}H_{13}F_2NO_2$ ([M + H$^+$]) 254.0993.

1-Benzyl-3-(2,2-difluoroethyl)-3-methylquinoline-2,4(1*H*,3*H*)-dione (5b). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.28 (ddt, *J* = 57.1, 29.1, 15.7 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.06 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.53–7.47 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.22 (s, 1H), 7.21 (s, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.99 (tt, *J* = 57.1, 5.1 Hz, 1H), 5.32 (s, 2H), 2.83 (td, *J* = 16.0, 5.1 Hz, 2H), 1.59 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.37, 172.84, 142.23, 136.36, 135.67, 129.00, 128.62, 127.50, 126.14, 123.44, 119.45, 115.92, 115.38 (t, *J* = 240.0 Hz), 53.32, 46.18, 39.14 (t, *J* = 22.3 Hz), 27.27. HRMS (ESI): *m*/*z* = 330.1300, calcd for $C_{19}H_{18}O_2NF_2$ ([M + H$^+$]) 330.1306.

6-Chloro-3-(2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5c). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.26 (dt, *J* = 56.4, 15.2 Hz). ^{1}H NMR (600 MHz, chloro-

form-*d*) δ 8.00 (d, J = 2.6 Hz, 1H), 7.60 (dd, J = 8.8, 2.5 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 5.89 (tt, J = 56.9, 5.0 Hz, 1H), 3.48 (s, 3H), 2.73 (tdd, J = 16.2, 7.2, 5.1 Hz, 2H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.44, 172.08, 141.49, 136.04, 129.21, 127.95, 120.26, 116.59, 115.13 (t, J = 240.1 Hz), 53.15, 53.12, 53.08, 39.46 (t, J = 22.3 Hz), 30.09, 26.83. HRMS (ESI): m/z = 288.0596, calcd for $C_{13}H_{12}ClF_2NO_2$ ([M + H$^+$]) 288.0603.

3-(2,2-Difluoroethyl)-1,3,7-trimethylquinoline-2,4(1*H*,3*H*)-dione (5d). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.12 to −115.52 (m). ^{1}H NMR (600 MHz, chloroform-d) δ 7.94 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.98 (s, 1H), 5.89 (tt, J = 56.9, 5.1 Hz, 1H), 3.48 (s, 3H), 2.79–2.62 (m, 2H), 2.46 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.09, 172.71, 147.99, 143.06, 128.54, 124.39, 116.91, 115.32 (t, J = 239.9 Hz) 113.74, 52.86 (t, J = 5.2 Hz), 39.55 (t, J = 22.3 Hz), 29.84, 26.98, 22.44. HRMS (ESI): m/z = 268.1143, calcd for $C_{14}H_{15}F_2NO_2$ ([M + H$^+$]) 268.1149.

3-(2,2-Difluoroethyl)-6-fluoro-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5e). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.28 (dt, J = 56.6, 15.4 Hz), −119.05. ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.73 (dd, J = 8.0, 3.1 Hz, 1H), 7.38 (ddd, J = 9.1, 7.4, 3.1 Hz, 1H), 7.18 (dd, J = 9.1, 4.0 Hz, 1H), 5.90 (tt, J = 56.9, 5.0 Hz, 1H), 3.49 (s, 3H), 2.81–2.65 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (150 MHz, chloroform-*d*) δ 194.69, 171.98, 158.55 (d, J = 245.8 Hz), 139.40 (d, J = 2.3 Hz), 123.45 (d, J = 23.4 Hz), 120.45 (d, J = 6.3 Hz), 116.82 (d, J = 7.2 Hz), 115.17 (t, J = 240.0 Hz), 114.21 (d, J = 23.3 Hz), 52.94 (t, J = 5.1 Hz), 39.51 (t, J = 22.3 Hz), 30.19, 26.87. HRMS (ESI): m/z = 272.0892, calcd for $C_{13}H_{12}F_3NO_2$ ([M + H$^+$]) 272.0898.

3-(2,2-Difluoroethyl)-6,7-dimethoxy-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5f). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.45 (tt, J = 58.4, 15.7 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.49 (s, 1H), 6.62 (s, 1H), 5.86 (tt, J = 56.9, 5.1 Hz, 1H), 4.02 (s, 3H), 3.93 (s, 3H), 3.50 (s, 3H), 2.72 (dtd, J = 26.7, 14.0, 13.2, 7.0 Hz, 2H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.11, 172.93, 155.95, 145.39, 139.32, 115.35 (t, J = 239.9 Hz), 111.83, 108.92, 98.09, 56.35, 56.20, 52.33 (t, J = 5.2 Hz), 39.91 (t, J = 22.2 Hz), 27.41. HRMS (ESI): m/z = 314.1196, calcd for $C_{15}H_{17}F_2NO_4$ ([M + H$^+$]) 314.1204.

7-Chloro-3-(2,2-difluoroethyl)-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5g). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.27 (dt, J = 56.6, 15.6 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.99 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 1.5 Hz, 1H), 7.18 (dd, J = 8.3, 1.6 Hz, 1H), 5.88 (tt, J = 56.9, 5.0 Hz, 1H), 3.47 (s, 3H), 2.80–2.65 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.37, 172.45, 143.93, 142.85, 129.92, 123.64, 117.59, 115.29, 115.13 (t, J = 240.1 Hz), 53.08, 39.52 (t, J = 22.3 Hz), 30.04, 26.91. HRMS (ESI): m/z = 288.0597, calcd for $C_{13}H_{12}ClF_2NO_2$ ([M + H$^+$]) 288.0603.

3-(2,2-Difluoroethyl)-7-fluoro-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5h). ^{19}F NMR (565 MHz, chloroform-*d*) δ −94.30 to −103.23 (m), −115.32 (dq, J = 53.8, 17.3 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.09 (dd, J = 8.4, 6.7 Hz, 1H), 6.96–6.76 (m, 2H), 5.88 (tt, J = 56.9, 5.0 Hz, 1H), 3.46 (s, 3H), 2.73 (dddd, J = 18.3, 14.1, 8.8, 5.0 Hz, 2H), 1.49 (s, 3H). ^{13}C NMR (150 MHz, chloroform-*d*) δ 193.97, 172.59, 167.73 (d, J = 256.8 Hz), 145.32 (d, J = 11.7 Hz), 131.55 (d, J = 11.2 Hz), 115.83 (d, J = 2.4 Hz), 115.16 (t, J = 240.0 Hz), 110.82 (d, J = 22.3 Hz), 102.60 (d, J = 27.6 Hz), 52.93, 39.56 (t, J = 22.3 Hz), 30.08, 26.99. HRMS (ESI): m/z = 272.0893, calcd for $C_{13}H_{12}F_3NO_2$ ([M + H$^+$]) 272.0898.

3-(2,2-Difluoroethyl)-7-methoxy-1,3-dimethylquinoline-2,4(1*H*,3*H*)-dione (5j). ^{19}F NMR (565 MHz, chloroform-*d*) δ −115.12 to −115.64 (m). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.03 (d, J = 8.7 Hz, 1H), 6.72 (dd, J = 8.7, 2.2 Hz, 1H), 6.62 (d, J = 2.2 Hz, 1H), 5.87 (tt, J = 56.9, 5.1 Hz, 1H), 3.92 (s, 3H), 3.46 (s, 3H), 2.71 (tddd, J = 22.2, 14.2, 11.9, 5.1 Hz, 2H), 1.47 (s, 3H). ^{13}C NMR (150 MHz, chloroform-*d*) δ 193.93, 172.99, 166.22, 145.00, 131.03, 115.34 (t, J = 239.8 Hz), 113.09, 108.52, 100.95, 55.81, 52.50, 39.73 (t, J = 22.2 Hz), 29.86, 27.14. HRMS (ESI): m/z = 284.1092, calcd for $C_{14}H_{15}F_2NO_3$ ([M + H$^+$]) 284.1098.

3-(2,2-Difluoroethyl)-1,3-dimethyl-6-(trifluoromethyl)quinoline-2,4(1*H*,3*H*)-dione (5k). ^{19}F NMR (565 MHz, chloroform-*d*) δ −62.48, −115.25 (dt, J = 57.0, 15.8 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.32 (d, J = 1.8 Hz, 1H), 7.89 (dd, J = 8.7, 2.1 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 5.91 (tt, J = 56.8, 5.0 Hz, 1H), 3.53 (s, 3H), 2.94–2.65 (m, 2H), 1.51 (s, 3H). ^{13}C NMR (150 MHz, chloroform-*d*) δ 194.35, 172.39, 145.34, 132.82 (q, J = 3.4 Hz), 126.07 (q, J = 3.7 Hz), 125.71 (d, J = 34.1 Hz), 123.40 (d, J = 271.9 Hz), 119.06, 115.57, 115.04 (t, J = 240.1 Hz), 53.34, 39.45 (t, J = 22.3 Hz), 30.22, 26.85. HRMS (ESI): m/z = 322.0860, calcd for $C_{14}H_{12}F_5NO_2$ ([M + H$^+$]) 322.0866.

3-(2,2-Difluoroethyl)-1,3-dimethyl-7-(trifluoromethyl)quinoline-2,4(1*H*,3*H*)-dione (5l). ^{19}F NMR (565 MHz, chloroform-*d*) δ −63.54, −115.19 (dq, J = 56.5, 15.3 Hz). ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.17 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.42 (s, 1H), 5.91 (tt, J = 56.9, 5.0 Hz, 1H), 3.54 (s, 3H), 2.76 (tdd, J = 18.0, 7.9, 5.0 Hz, 2H), 1.50 (s, 3H). ^{13}C NMR (151 MHz, chloroform-*d*) δ 194.68, 172.13, 143.30, 137.46 (q, J = 32.9 Hz), 129.47, 121.32, 119.81 (q, J = 3.5 Hz), 115.06 (t, J = 240.1 Hz), 112.13 (q, J = 3.9 Hz), 53.42, 39.42 (t, J = 22.3 Hz), 30.13, 26.72. HRMS (ESI): m/z = 322.0862, calcd for $C_{14}H_{12}F_5NO_2$ ([M + H$^+$]) 322.0866.

Conflicts of interest

There are no conflicts to declare.

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