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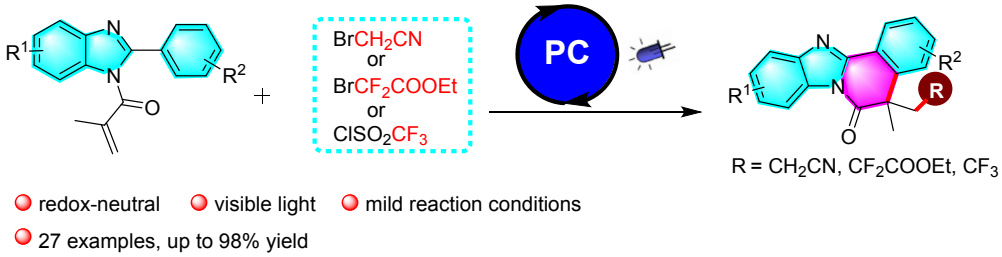
Supporting Information Placeholder



ABSTRACT: A novel method for the synthesis of benzo[4,5]imidazo[2,1-a]isoquinolin derivatives via visible-light-induced radical cascade cyclization is described. By using N-methacryloyl-2-phenylbenzoimidazoles and diverse radical precursors, various benzo[4,5]imidazo[2,1-a]isoquinolin derivatives containing $CH_2CN/CF_2COOEt/CF_3$ can be formed in good to excellent yields under mild reaction conditions. The method exhibits good functional group tolerance and a wide range of substrate scope.

INTRODUCTION

Nitrogen-containing heterocyclic compounds are a class of very important organic compounds, especially those having a benzo[4,5]imidazo[2,1-a]isoquinoline tetracyclic core skeleton, which are not only an important part of privileged synthetic intermediates but also present in some bioactive molecules as well as functional materials.[1] Some pharmaceutically active molecules and functionalized material molecules having a benzimidazole tetracyclic core skeleton are shown in **Fig 1**. Such as **A** (Modulating the potassium ion flux),[2] **B** (Antitumor),[3] **C** (Agent for hemoglobinopathies)[4] and **D** (Candidates for organic electronics).[5] In the past decade, several synthetic methods for the benzo[4,5]imidazo[2,1-a]isoquinoline tetracyclic skeleton have been proposed, such as palladium-catalyzed intramolecular cyclization of benzimidazoles,[6] dehydrogenative coupling of 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]aniline derivatives,[7] TEMPO-promoted C(sp_3)–H amination,[8] Cp*Rh^{III}-catalyzed [4+2] annulation of 2-arylimidazoles and α-diazoketoesters,[9] silver-catalyzed decarboxylative radical cascade cyclization,[10] and oxidative radical relay functionalization for the synthesis of benzimidazo[2,1-a]iso-quinolin-6(5*H*)-ones,[11] etc. Although these methods have synthesized benzo[4,5]imidazo[2,1-a]isoquinoline tetracyclic core skeleton, there are still some limitations, such as the difficulty in preparing starting materials, the use of explosive peroxides, the unitary functional group and high reaction temperatures.

Therefore, it is necessary to develop more environmentally friendly, mild and efficient methods to construct benzo[4,5]imidazo[2,1-a]isoquinoline tetracyclic skeleton with diversified functional groups. In recent years, visible-light-induced photoredox catalysis has attracted extensive attention in organic synthesis due to its inherent green and sustainable features, and some landmark achievements have been achieved.[12-15] Some examples have been reported where C–X covalent bonds are activated by visible-light catalysis to form corresponding free radical intermediates, which are then subjected to radical addition or cyclization.[16-18] However, there are very few reports on the construction of the benzo[4,5]imidazo[2,1-a]isoquinoline skeleton through visible light catalysis. As far as we know, only

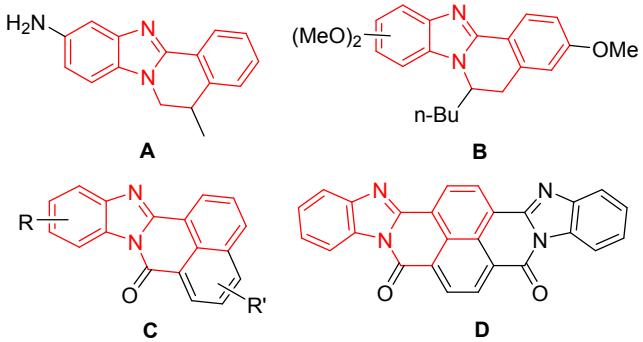


Fig 1. Representative examples of benzoxazines.

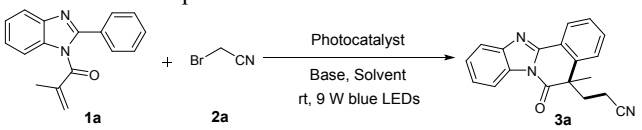
Yu's group has reported a method of constructing the benzo[4,5]imidazo[2,1-a]isoquinoline skeleton via visible light catalysis.[19] Although Yu et.al. synthesized benzo[4,5]imidazo[2,1-a]isoquinoline by visible light catalysis, this method used only one free radical precursor and the product yield is not high. Inspired by these works, we designed a visible-light-induced photocatalyzed radical cascade cyclization to construct benzo[4,5]imidazo[2,1-a]isoquinoline tetracyclic skeleton. This is the first work for the synthesis of benzo[4,5]imidazo[2,1-a]isoquinolines containing $CH_2CN/CF_2COOEt/CF_3$ from N-methacryloyl-2-phenylbenzoimidazoles and $BrCH_2CN/BrCF_2COOEt/CF_3(SO_2)Cl$ under visible-light-induced photocatalysis. This strategy not only avoids cumbersome preparation of raw materials, stoichiometric oxidants and high reaction temperatures, but also introduces a variety of valuable functional groups such as $CN/CF_2/CF_3$ to benzo[4,5]imidazo[2,1-a]isoquinoline with excellent yield (up to 98%).

RESULTS AND DISCUSSION

Initially, we chose N-methacryloyl-2-phenylbenzoimidazole **1a** and bromoacetonitrile **2a** as model substrates (**1a**/**2a** = 1:2, molar ratio) to access the target product **3a**. In the presence of *fac*-Ir(ppy)$_3$ (3% mol), Na_2CO_3 (1.5 equiv) and CH_3CN (1 mL), the desired product **3a** was obtained in 84% isolated yield by irradiation of 9 W blue LEDs at room temperature for 24 hours (**Table 1**, entry 1). Next, some parameters affecting the reaction were screened, such as photocatalyst, base andsolvent. It was found that some commonly used photocatalysts, such as Eosin Y, $Ru(bpy)_3Cl_2\cdot 6H_2O$ and $[Ir(dtbbpy)(ppy)_2][PF_6]$ did not show catalytic activity (**Table 1**, entries 2-4). After comparing the reduction potentials of Eosin Y ($E_{1/2}$* = -1.06 V vs. SCE in CH_3CN),[20] $Ru(bpy)_3Cl_2\cdot 6H_2O$ ($E_{1/2}$* Ru^{II}/Ru^{III} = -0.81 V vs. SCE in CH_3CN)[21] and $[Ir(dtbbpy)(ppy)_2][PF_6]$ ($E_{1/2}$* Ir^{III}/Ir^{IV} = -0.89 V vs. SCE in CH_3CN)[21] with bromoacetonitrile ($E_{1/2}$ = -1.63 V vs. SCE in CH_3CN) (**Fig. S8**), it can be seen that their reducibility is insufficient to reduce bromoacetonitrile. A series of bases were also screened, such as KOAc, $NaHCO_3$, K_2HPO_4 and NEt_3, and an excellent yield of 91% can be satisfactorily obtained when using KOAc (**Table 1**, entries 5-8). Meanwhile, a set of solvents including DMF, DCM, acetone, and isopropanol were tested, but they were not as good as CH_3CN (**Table 1**, entries 9-12). Additionally, control experiments revealed that the photocatalyst and continuous illumination were necessary for the reaction, and the base as well as argon atmosphere greatly improved the reaction yield (**Table 1**, entries 13-16).

Under the optimized reaction conditions, using **2a** as the cyanomethylation reagent, the scope and limitations of visible-light-induced cyanomethylation/cyclization of N-methacryloyl-2-phenylbenzoimidazoles (**1**) were evaluated. It can be seen from **Table 2** that when the para-position/ortho-position of the 2-benzene ring of benzimidazole was substituted with an electron-donating group (-Me, -OMe or -OEt), the desired products **3b-3e** could be obtained in excellent yields (79-92%). However, when the para-position of the 2-benzene ring was substituted with an electron-withdrawing group (-F, -Cl or -Br), the corresponding products **3f-3h** were only obtained in moderate yields (63-74%). This indicates that electron-donating groups conducive to the improvement of the reaction yield, which may be because the electron-donating group increases the density of the electron cloud of the molecule, so that its intermediate is more easily oxidized by the oxidized photocatalyst (as shown in **Scheme 2**). In addition, when the ortho and meta positions of

Table 1. Optimization of reaction conditions.[a]



Entry	Photocatalyst	Base	Solvent	Yield[b] (%)
1	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	84
2	Eosin Y	Na_2CO_3	CH_3CN	Trace
3	$Ru(bpy)_3Cl_2\cdot 6H_2O$	Na_2CO_3	CH_3CN	Trace
4	$[Ir(dtbbpy)(ppy)_2][PF_6]$	Na_2CO_3	CH_3CN	Trace
5	*fac*-Ir(ppy)$_3$	KOAc	CH_3CN	91
6	*fac*-Ir(ppy)$_3$	$NaHCO_3$	CH3CN	84
7	*fac*-Ir(ppy)$_3$	K_2HPO_4	CH_3CN	54
8	*fac*-Ir(ppy)$_3$	Et_3N	CH_3CN	55
9	*fac*-Ir(ppy)$_3$	KOAc	DMF	48
10	*fac*-Ir(ppy)$_3$	KOAc	DCM	51
11	*fac*-Ir(ppy)$_3$	KOAc	acetone	86
12	*fac*-Ir(ppy)$_3$	KOAc	isopropanol	Trace
13[c]	-	Na_2CO_3	CH_3CN	Trace
14[d]	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	Trace
15[e]	*fac*-Ir(ppy)$_3$	-	CH_3CN	32
16[f]	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	68

[a]Unless otherwise noted, reaction conditions: the mixture of **1a** (1.0 equiv, 0.2 mmol), **2a** (2.0 equiv, 0.4 mmol), photocatalyst (3 mol%) and base (1.5 equiv, 0.3 mmol) in degassed dry solvent (1 mL) was irradiated by 9 W blue LEDs under Ar atmosphere at rt for 14-24 h. [b]Isolated yield by flash chromatography. [c]No photocatalyst. [d]In the dark. [e]No base. [f]Under air atmosphere.

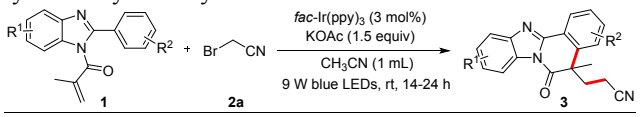
2-benzene ring were both substituted by -Cl, the reaction could still proceed smoothly, giving the desired product **3i** in moderate yield (58%). As expected, when the benzene ring of benzimidazole was substituted or both benzene rings in the substrate (**1**) were substituted, the desired products still could be successfully obtained (**3j-3l**, 63-98% yields).

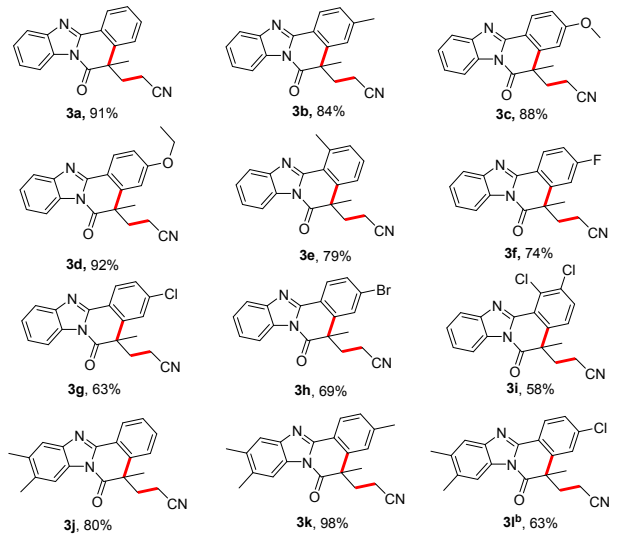
To verify the versatility of this method, we expanded the source of free radicals for the reaction. Due to the importance of fluorine-containing compounds, we introduced F-containing groups into benzo[4,5]imidazo[2,1-a]isoquinoline. We tried to replace bromoacetonitrile **2a** with ethyl difluorobromobromoacetate **2b** to react with 1a under the optimal reaction conditions used in **Table 2**. It is gratifying that the difluoroalkylated product **4a** was successfully obtained in 87% yield (**Table 3**). In addition, the structure of **4a** was determined by X-ray crystallography analysis (**Fig. S9**). Next, the effects of different substituents on the reaction were explored. It was found that substrates (**1**) with either electron-

donating groups (-Me, -OMe, -OEt) or electron-withdrawing groups (-F, -Cl, -Br) could be converted into corresponding products **4a-4g** in good yields (76-91%). In addition, when two benzene rings in the substrate (**1**) were substituted, the reaction could still proceed smoothly, giving the desired products in satisfactory yields (**4h-4i**, 65-85%).

This reaction can also be easily used for the synthesis of trifluoromethylated products. The reaction of trifluoromethanesulfonyl chloride with **1a** proceeded smoothly to give the desired product **5a** in 56% isolated yield (**Table 4**). The exploration of the substrate scope showed that substrates containing electron-donating or electron-withdrawing groups were suitable for the reaction. By using this method, various CF_3-containing benzo[4,5]imidazo[2,1-a]isoquinolin-6(5*H*)-ones (**5a-5f**) could be obtained in moderate yields (46-67%).

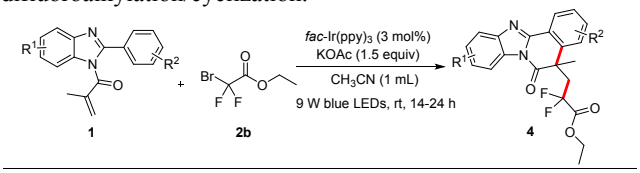
Table 2. Substrate scope of photoredox-catalyzed cyanomethylation/cyclization.[a]

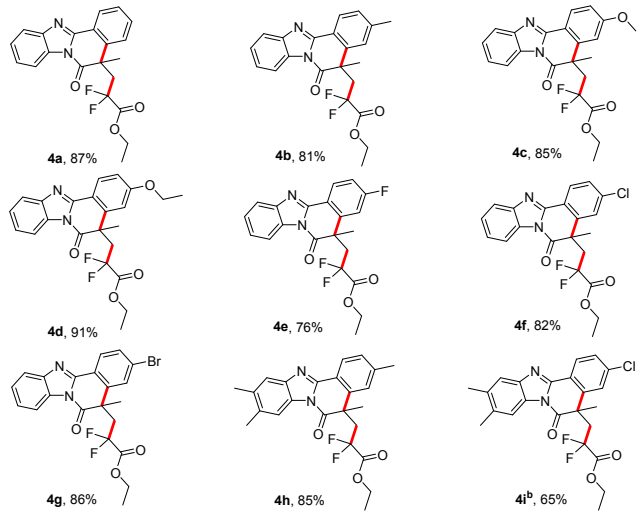




[a]Unless otherwise noted, reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), KOAc (1.5 equiv), CH_3CN (1.0 mL), 9 W blue LEDs, at rt under argon atmosphere, 14-24 h. Isolated yield. [b]DCM instead of CH_3CN.

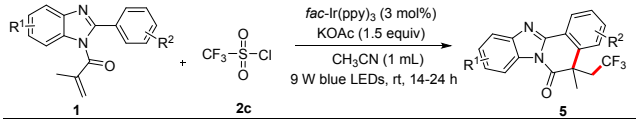
Table 3. Substrate scope of photoredox-catalyzed difluoroalkylation/cyclization.[a]

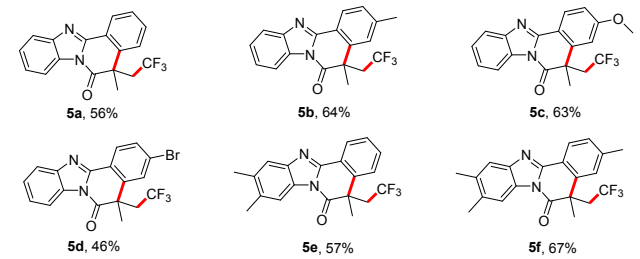




[a]Unless otherwise noted, reaction conditions: **1** (0.2 mmol), **2b** (0.4 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), KOAc (1.5 equiv), CH_3CN (1.0 mL), 9 W blue LEDs, at rt under argon atmosphere, 14-24 h. Isolated yield. [b]DCM instead of CH_3CN.

Table 4. Substrate scope of photoredox-catalyzed trifluoroalkylation/cyclization.[a]

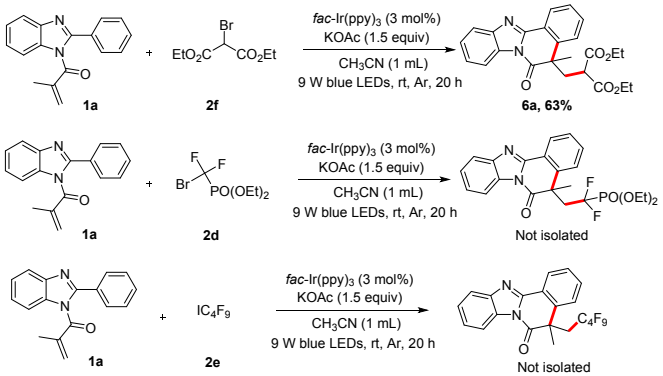




[a]Unless otherwise noted, reaction conditions: **1** (0.2 mmol), **2c** (0.4 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), KOAc (1.5 equiv), CH_3CN (1.0 mL), 9 W blue LEDs, at rt under argon atmosphere, 14-24 h. Isolated yield.

In addition, we explored the reaction of **1a** with other free radical precursors, such as diethyl bromide difluoromethane diphosphonate **2d**, perfluoroiodide **2e**, and diethyl bromomalonate **2f**. It was found that **1a** can react with **2f** to produce **6a**, but the reaction between **1a** and **2d**/**2e** is not obvious, and a large amount of raw materials remain. The above experimental results show that **1a** can react with a variety of free radical precursors, but there are still some limitations (**Scheme 1**).

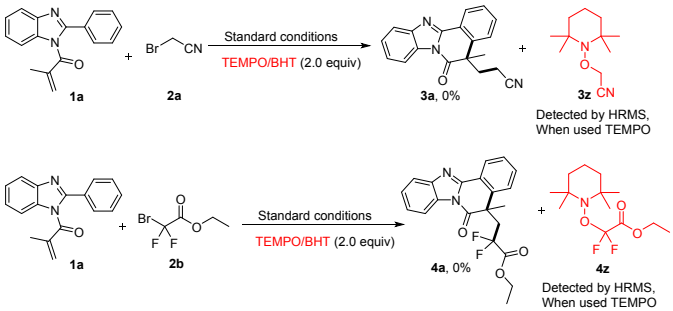
Scheme 1. The reaction of **1a** with other free radical precursors.



In order to investigate the reaction mechanism, a series of control experiments were carried out using the reactions of N-methacryloyl-2-phenylbenzimidazole **1a** with bromoacetonitrile **2a** and ethyl difluorobromoacetate **2b**, respectively (**Scheme 2**). First, when the radical scavengers

2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2.0 eq) and 2,6-ditert-butyl-4-methylphenol (BHT, 2.0 eq) were separately added to the reaction system under standard reaction conditions, the reaction was completely inhibited. Meanwhile, the TEMPO−CH_2CN and TEMPO−CF_2COOEt were detected by high resolution mass spectrometry (HRMS) analysis. The above experimental results indicated that a radical process might be involved in this transformation and • CH_2CN/ • CF_2COOEt radical might be formed. In order to confirm whether a radical chain process existed in this reaction, the light on/off experiments were performed (**Fig. S1**). The experiments results showed that the product yield still increases slightly under dark conditions, indicating a free radical chain propagation process in the reaction. The emission spectrum of the lamp and the ultraviolet-visible absorption spectra of substrates indicated that *fac*-Ir(ppy)$_3$ is the only light-absorbing substance in the reaction (**Fig. S2-S3**). Furthermore, fluorescence quenching experiments showed that the excited *fac*-Ir(ppy)$_3$* can be significantly quenched by **2a/2b** (**Fig. S4-S7**). The CV experimrnts (**Fig. S8**) of **2a** ($E_{1/2}$ = -1.63 V vs. SCE in CH_3CN) and **2b** ($E_{1/2}$ = -1.60 V vs. SCE in CH_3CN) showed that they can oxidize the excited *fac*-Ir(ppy)$_3$* ($E_{1/2}$* Ir^{III}/Ir^{IV} = -1.73 V vs. SCE in CH_3CN)[21] to a higher valence state, which indicates that **2a/2b** may be involved in the oxidative quenching process of the excited *fac*-Ir(ppy)$_3$*.

Scheme 2. Control experiments.

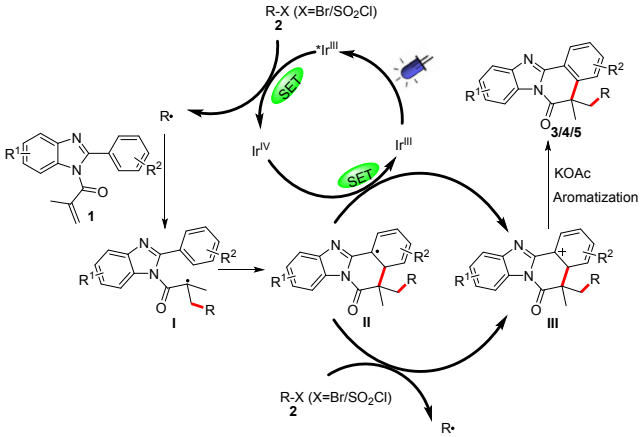


On the basis of the above experiments and previous works,[16-18] a plausible mechanism of this visible-light-induced photocatalytic radical cascade cyclization reaction was described in **Scheme 3**. Initially, the ground-state [*fac*-Ir(ppy)$_3$] is converted into an excited-state [*fac*-Ir(ppy)$_3$*] under the irradiation of visible light, and then excited-state [*fac*-Ir(ppy)$_3$*] undergoes a single electron transfer (SET) process with 2 to form radical • R, halogen anion and [*fac*-Ir(ppy)$^{3+}$]. Subsequently, the radical • R attacks the C−C double bond in the olefinic amide unit of the substrate **1** to form the radical intermediate **I**, which is converted into the radical intermediate **II** by radical addition cyclization to the benzene ring. Next, the radical intermediate **II** undergoes a single electron oxidation to produce the carbocation **III**, during which the [*fac*-Ir(ppy)$_3$] is regenerated. In addition, intermediate **II** may be oxidized by **2** to generate intermediate **III**, with the formation of • R. Finally, the carbocation intermediate **III** is deprotonated under the action of a base to give the eventual product **3**.

CONCLUSIONS

In conclusion, we have disclosed the first visible-light-induced photocatalytic radical cascade cyclization strategy for the synthesis of $CH_2CN/CF_2COOEt/CF_3$ containing benzo[4,5]imidazo[2,1-a]isoquinolin derivatives from N-methacryloyl-2-phenylbenzoimidazoles and readily available various radical precursors. This reaction uses visible light as an energy source with mild, green and sustainable characteristics. In addition, this method has the advantages of simple operation, good functional group compatibility, wide range of substrate scope and good to excellent yields.

Scheme 3. Proposed reaction mechanism.



EXPERIMENTAL SECTION

General Information. Unless otherwise noted, materials obtained from commercial suppliers were used directly without further purification. Flash column chromatography was performed using 200 - 300 mesh silica gel. All ^{1}H NMR spectra, ^{13}C NMR and ^{19}F NMR spectra were respectively recorded on 600 MHz, 150 MHz and 565 MHz NMR spectrometers using deuterochloroform ($CDCl_3$) as solvent at room temperature, all chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows (s = singlet; d = doublet; t = triplet; m = multiplet; q = quartet). The coupling constants, J, are reported in Hertz (Hz). High-resolution mass spectra were obtained by using ESI ionization sources (Varian 7.0T FTICR-MS). Fluorescence emission was determined by fluorescence spectrophotometer (F-320 Gangdong, Tianjin). Melting points were taken on a WPX-4 apparatus and were uncorrected (Yice instrument equipment Co Ltd, Shanghai). The round bottom flask was made of borosilicate glass. The 9 W blue LEDs (Epistar Amou-0708, 220 V, 50 Hz, 420-500 nm) without any filters, and the spectral distribution and intensity of the lamp was shown in **Fig. S2**. The distance from the light source to the irradiation vessel about 4 cm. The starting materials **2** were obtained from commercial suppliers and starting materials **1** were prepared according to the reported procedures.[10,11,22]

General Procedures for Preparation of 1. *Step1*: According to the reported procedures.[22] To a 10 mL test tube was added $CuBr_2$ (1 mol%), *o*-phenylenediamine (0.2 mmol), benzylamine (0.3 mmol) and toluene (2 mL). The reaction mixture was stirred at 100 °C under air for 24 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in vacuo and the residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 5 :1). Finally get the 2-phenylimidazole derivatives.

Step2: According to the reported procedures.[10-11] To the solution of benzimidazole (5 mmol, 1.0 equiv.) and DMAP (1.0 mmol, 0.2 equiv.) in DCM (0.5 M) was added Et_3N (10 mmol, 2.0

equiv.) and methacryloyl chloride (10 mmol, 2.0 equiv.) at 0 °C. The solution was warmed up to room temperature and stirred for 12–24 h. Reaction progress was checked by thin layer chromatography (TLC). The mixture was diluted with DCM (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic and aqueous layers were separated. The aqueous layer was extracted with DCM (20 mL ×2). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue, which was purified by flash chromatography and then recrystallized from n-hexane/EtOAc to afford the product **1**.

General Procedures for Preparation of 3/4/5. A round bottomed flask equipped with a magnetic stirrer bar was charged with *fac*-Ir(ppy)$_3$ (3 mol %), olefinic amide **1** (0.2 mmol), KOAc (0.3 mmol) and bromoacetonitrile **2a** /ethyl bromodifluoroacetate **2b** /trifluoromethane chloride **2c** (0.4 mmol). The flask was evacuated and backfilled with Ar (three times). Then degassed dry CH_3CN (1 mL) was injected under Ar. The resultant mixture was stirred at room temperature under irradiation of 9 W blue LEDs. The reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, water (10 mL) was added into the reaction mixture. The resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (petroleum ether/EtOAc = 3:1 to 10:1, v/v) to give the desired product **3**/**4**/**5**.

Gram-Scale Synthesis of 3a. A round bottomed flask equipped with a magnetic stirrer bar was charged with olefinic amide **1** (5.0 mmol), *fac*-Ir(ppy)$_3$ (0.15 mmol), KOAc (7.5 mmol) and bromoacetonitrile **2a** (10.0 mmol). The flask was evacuated and backfilled with Ar (three times). Then degassed dry CH_3CN (20 mL) was injected under Ar. The resultant mixture was stirred at room temperature under irradiation of two 9 W blue LEDs. The reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, water (20 mL) was added into the reaction mixture. The resulting mixture was extracted with ethyl acetate (40 mL × 3). The organic layers were combined, and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (petroleum ether/EtOAc = 5:1, v/v) to give the desired product **3a** (0.93 g, 62%).

Characterization of products. *3-(5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3a**)*: Isolated yield (54.8 mg, 91%), White solid, Melting range: 114.2-118.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 (d, *J* = 7.8 Hz, 1H), 8.33 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.65-7.62 (m, 1H), 7.56-7.54 (m, 1H), 7.48-7.43 (m, 3H), 2.90-2.85 (m, 1H), 2.42-2.37 (m, 1H), 2.11-2.06 (m,1H), 2.00-1.95 (m, 1H), 1.76 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.6, 149.1, 144.0, 139.1, 132.4, 131.2, 128.6, 126.5, 126.3, 126.0, 125.7, 123.1, 120.0, 118.1, 115.7, 48.7, 36.6, 29.7, 13.6; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}N_3NaO$ 324.1107; Found 324.1106.

*3-(3,5-dimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3b**)*: Isolated yield (53.0 mg, 84%), White solid, Melting range: 148.1-149.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.46-7.41 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 1H), 2.89-2.84 (m, 1H), 2.50 (s, 3H), 2.41-2.36 (m,1H), 2.10-2.05 (m, 1H), 2.00- 1.94 (m, 1H), 1.74 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.7, 149.3, 144.1, 143.2, 139.1, 131.1, 129.7, 126.5, 126.2, 126.1, 125.7, 120.5, 119.8, 118.2, 115.6, 48.7, 36.7, 29.7, 22.0, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}N_3O$ 316.1444; Found 316.1445.

*3-(3-methoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3c**)*: Isolated yield (58.3 mg, 88%), White solid, Melting range: 145.0-148.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.45-7.39 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.94 (s, 1H), 3.94 (s, 3H), 2.90-2.85 (m, 1H), 2.37-2.32 (m,1H), 2.12-2.07 (m, 1H), 2.03-1.98 (m, 1H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.6, 163.1, 149.3, 144.1, 141.2, 131.1, 128.6, 126.2, 125.5, 119.6, 118.1, 115.9, 115.5, 114.2, 111.6, 55.7, 48.9, 36.8, 29.7, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}N_3O_2$ 332.1394; Found 332.1392.

*3-(3-ethoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3d**)*: Isolated yield (63.6 mg, 92%), White solid, Melting range: 117.2-122.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (d, *J* = 8.7 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.44-7.39 (m, 2H), 7.06 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 4.18-4.15 (m, 2H), 2.89-2.84 (m, 1H), 2.37-2.32 (m,1H), 2.12-2.06 (m, 1H), 2.03-1.98 (m, 1H), 1.74 (s, 3H), 1.49 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.7, 162.5, 149.3, 144.0, 141.2, 131.1, 128.6, 126.2, 125.5, 119.6, 118.1, 115.6, 115.6, 114.5, 112.1, 64.1, 48.9, 36.8, 29.7, 14.7, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}N_3O_2$ 346.1550; Found 346.1550.

*3-(1,5-dimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3e**)*: Isolated yield (49.8 mg, 79%), White liquid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36-8.34 (m, 1H), 7.84-7.84 (m, 1H), 7.49-7.42 (m, 3H), 7.37-7.33 (m, 2H), 3.05 (s, 3H), 2.90-2.85 (m, 1H), 2.40-2.35 (m, 1H), 2.09-2.04 (m, 1H), 2.00-1.95 (m, 1H), 1.74 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.7, 149.3, 144.1, 140.6, 140.1, 131.9, 131.0, 130.3, 126.0, 126.0, 123.5, 121.7, 120.3, 118.2, 115.7, 48.7, 36.9, 30.1, 24.6, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}N_3O$ 316.1444; Found 316.1444.

*3-(3-fluoro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3f**)*: Isolated yield (47.2 mg, 74%), White solid, Melting range: 165.5-170.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.32 (d, *J* = 7.1 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.48-7.43 (m, 2H), 7.28-7.27 (m, 1H) 7.18-7.16 (m, 1H) 2.90-2.85 (m, 1H), 2.36-2.31 (m,1H), 2.15-2.10 (m, 1H), 2.04-1.99 (m, 1H), 1.76 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.9, 165.2 (d, *J* = 254.4 Hz), 148.3, 144.0, 141.9 (d, *J* = 7.6 Hz), 131.1, 129.1 (d, *J* = 9.0 Hz), 126.4, 126.0, 120.0, 119.6 (d, *J* = 2.9 Hz), 117.7, 116.7 (d, *J* = 22.4 Hz), 115.6, 112.9 (d, *J* = 23.3 Hz)., 48.9, 36.7, 29.5, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}FN_3O$ 320.1194; Found 320.1194.

*3-(3-chloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3g**)*: Isolated yield (42.3 mg, 63%), White solid, Melting range: 164.0-169.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.46 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.48-7.46 (m,

3H), 2.90-2.85 (m, 1H), 2.38-2.33 (m, 1H), 2.15-2.09 (m, 1H), 2.05-2.00 (m, 1H), 1.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 170.8, 148.2, 143.9, 140.8, 138.7, 131.1, 129.3, 127.9, 126.5, 126.2, 126.0, 121.7, 120.1, 117.7, 115.7, 48.7, 36.6, 29.5, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}ClN_3O$ 336.0898; Found 336.0897.

*3-(3-bromo-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3h**)*: Isolated yield (52.5 mg, 69%), White solid, Melting range: 168.5-170.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41-8.38 (m, 1H), 8.33-8.32 (m, 1H), 7.84-7.81 (m, 1H), 7.70-7.68 (m, 1H), 7.62 (s, 1H) 7.47-7.46 (m, 2H), 2.90-2.85 (m, 1H), 2.38-2.33 (m, 1H), 2.14-2.09 (m, 1H), 2.06-2.01 (m, 1H), 1.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 170.8, 148.2, 143.8, 141.0, 132.2, 131.1, 129.0, 128.1, 127.1, 126.5, 126.3, 122.1, 120.1, 117.8, 115.7, 48.7, 36.7, 29.5, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}BrN_3O$ 380.0393; Found 380.0393.

*3-(1,2-dichloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3i**)*: Isolated yield (42.9 mg, 58%), White solid, Melting range: 231.5-233.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.50-7.49 (m, 2H), 7.37 (d, J = 8.5 Hz, 1H), 2.91-2.86 (m, 1H), 2.38-2.33 (m,1H), 2.16-2.10 (m, 1H), 2.04-1.99 (m, 1H), 1.76 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 170.3, 145.8, 143.8, 140.0, 135.9, 132.5, 130.4, 128.0, 127.1, 126.5, 124.9, 123.3, 121.1, 117.8, 115.7, 48.8, 36.7, 29.8, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{14}Cl_2N_3O$ 370.0508; Found 370.0506.

*3-(5,9,10-trimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3j**)*: Isolated yield (52.7 mg, 80%), White liquid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.49-8.47 (m, 1H), 8.11 (s, 1H), 7.62-7.58 (m, 2H), 7.54-7.51 (m, 1H), 7.46 (d, J = 7.9 Hz, 1H), 2.90-2.85 (m, 1H), 2.43-2.36 (m, 1H), 2.09-2.04 (m, 1H), 1.99-1.94 (m, 1H), 1.75 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.5, 148.3, 142.5, 138.9, 135.4, 135.3, 132.0, 129.5, 128.6, 126.3, 125.7, 123.5, 120.3, 118.1, 116.0, 48.6, 36.8, 29.6, 20.5, 20.4, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}N_3O$ 330.1601; Found 330.1597.

*3-(3,5,9,10-tetramethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3k**)*: Isolated yield (67.3 mg, 98%), White solid, Melting range: 180.5-181.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53 (d, J = 7.2 Hz, 1H), 8.12 (s, 1H), 7.63 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 2.90-2.85 (m, 1H), 2.51-2.30 (m, 10H), 2.09-2.03 (m, 1H), 2.02-1.97 (m, 1H), 1.75 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.6, 148.2, 143.8, 139.3, 136.0, 135.9, 130.0, 128.9, 127.1, 126.2, 119.3, 118.1, 116.0, 48.7, 36.7, 29.8, 22.1, 20.6, 20.4, 13.7; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}N_3O$ 344.1757; Found 344.1757.

*3-(3-chloro-5,9,10-trimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanenitrile (**3l**)*: Isolated yield (45.8 mg, 63%), White solid, Melting range: 194.1-195.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.62 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.44 (s, 1H), 2.90-2.85 (m, 1H), 2.43-2.30 (m,7H), 2.13-2.01 (m, 2H), 1.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 170.7, 147.2, 140.8, 138.9, 136.2, 136.1, 129.4, 129.1, 128.2, 126.1, 121.2, 119.8, 117.7, 116.0, 48.7, 36.7, 29.6, 20.6, 20.5, 13.7; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{19}ClN_3O$ 364.1211; Found 364.1211.

*ethyl-2,2-difluoro-3-(5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanoate (**4a**)*: Isolated yield (66.9 mg, 87%), White solid, Melting range: 116.7-119.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 (d, J = 7.6 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.58-7.55 (m, 1H), 7.52-7.50 (m, 1H), 7.48-7.42 (m, 3H), 3.97-3.85 (m, 2H), 3.45-3.38 (m, 1H), 3.09-3.01 (m, 1H), 1.76 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.4, 163.3 (t, J = 31.8 Hz), 149.3, 144.0, 138.7, 131.5, 131.3, 128.3, 126.8, 126.2, 126.0, 125.7, 122.7, 119.9, 115.7, 114.4 (dd, J_1= 251.2 Hz, J_2 = 255.8 Hz), 63.1, 45.3 (d, J = 4.6 Hz), 44.5 (t, J = 23.6 Hz), 31.3, 13.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ -98.8, -99.3, -103.8, -104.2; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{18}F_2N_2NaO_3$ 407.1177; Found 407.1175.

*ethyl-3-(3,5-dimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)-2,2-difluoropropanoate (**4b**)*: Isolated yield (64.5 mg, 81%), White solid, Melting range: 123.9-126.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 (d, J = 8.0 Hz, 1H), 8.35 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.45-7.40 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.25 (s, 1H), 3.96-3.84 (m, 2H), 3.43-3.36 (m, 1H), 3.08-3.00 (m, 1H), 2.46 (s, 3H), 1.74 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.5, 163.3 (t, J = 31.9 Hz), 149.5, 143.9, 142.0, 138.7, 131.4, 129.3, 127.3, 126.2, 126.0, 125.5, 120.0, 119.7, 115.6, 114.4 (dd, J_1= 249.3 Hz, J_2 = 254.2 Hz), 63.0, 45.2 (d, J = 4.7 Hz), 44.4 (t, J = 22.3 Hz), 31.3, 21.8, 13.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ -98.6, -99.1, -103.9, -104.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}F_2N_2O_3$ 399.1515; Found 399.1514.

*ethyl-2,2-difluoro-3-(3-methoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanoate (**4c**)*: Isolated yield (70.4 mg, 85%), White solid, Melting range: 148.3-156.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.46-7.40 (m, 2H), 7.07 (dd, J_1 = 8.7, J_2 = 2.0 Hz, 1H), 6.93 (d, J =2.0 Hz, 1H), 4.00-3.90 (m, 5H), 3.45-3.38 (m, 1H), 3.06-2.98 (m, 1H), 1.75 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.4, 163.3 (t, J = 32.0 Hz), 162.3, 149.5, 140.8, 131.3, 128.8, 128.2, 125.9, 125.3, 124.7, 119.4, 115.6, 114.3 (dd, J_1 = 251.3 Hz, J_2 = 256.0 Hz), 114.2, 112.5, 63.1, 55.6, 45.5 (d, J = 5.2 Hz), 44.4 (t, J = 23.5 Hz), 31.4, 13.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ -98.5, -98.9, -103.9, -104.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}F_2N_2O_4$ 415.1464; Found 415.1463.

*ethyl-3-(3-ethoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)-2,2-difluoropropanoate (**4d**)*: Isolated yield (78.0 mg, 91%), White solid, Melting range: 128.7-129.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (d, J = 8.7 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.43-7.38 (m, 2H), 7.03 (d, J = 8.7 Hz, 1H), 6.92 (s, 1H), 4.15-4.12 (m, 2H), 4.00-3.90 (m, 2H), 3.44-3.37 (m, 1H), 3.04-2.96 (m, 1H), 1.74 (s, 3H), 1.47 (t, J = 6.5 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.4, 163.3 (t, J = 31.9 Hz), 161.7, 149.6, 144.0, 140.8, 131.4, 130.0, 128.2, 125.9, 125.2, 119.4, 115.6, 115.3, 114.6, 113.0, 114.4 (dd, J_1= 249.5 Hz, J_2 = 253.8 Hz), 63.3, 45.5 (d, J = 4.1 Hz), 44.5 (t, J = 22.4 Hz), 31.4, 14.7, 13.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ -98.6, -99.0, -103.9, -104.4; HRMS (ESI)

m/z: $[M+H]^+$ Calcd for $C_{23}H_{23}F_2N_2O_4$ 429.1620; Found 429.1622.

*ethyl-2,2-difluoro-3-(3-fluoro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanoate (**4e**)*: Isolated yield (61.2 mg, 76%), White solid, Melting range: 130.0-131.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 8.34 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.47-7.42 (m, 2H), 7.25-7.22 (m, 1H), 7.17-7.15 (m, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.47-3.39 (m, 1H), 3.00-2.92 (m, 1H), 1.76 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.8, 164.6 (d, J = 253.2 Hz), 163.1 (t, J = 31.9 Hz), 148.6, 143.9, 141.7 (d, J = 7.8 Hz), 131.4, 128.8 (d, J = 9.1 Hz), 126.2, 125.8, 119.9, 119.1 (d, J = 2.8 Hz), 116.3 (d, J = 22.4 Hz), 115.7, 114.4 (dd, J_1= 250.5 Hz, J_2 = 253.1 Hz), 113.8 (d, J = 23.4 Hz), 63.2, 45.5 (d, J = 3.9 Hz), 44.5 (t, J = 22.8 Hz), 31.2, 13.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ -99.9, -100.4, -102.9, -103.3, -106.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{18}F_3N_2O_3$ 403.1264; Found 403.1264.

*ethyl-3-(3-chloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)-2,2-difluoropropanoate (**4f**)*: Isolated yield (68.7 mg, 82%), White solid, Melting range: 121.0-126.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.45 (d, J = 8.3 Hz, 1H), 8.34 (d, J = 6.9 Hz, 1H), 7.82 (d, J = 7.0 Hz, 1H), 7.49-7.42 (m, 4H), 4.02 (q, J = 7.1 Hz, 2H), 3.46-3.39 (m, 1H), 3.02-2.94 (m, 1H), 1.75 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.7, 163.0 (t, J =32.0 Hz), 148.4, 143.9, 140.5, 137.6, 131.4, 128.9, 127.6, 127.0, 126.2, 126.0, 121.4, 120.0, 115.7, 114.2 (dd, J_1= 250.3 Hz, J_2 = 253.1 Hz), 63.3, 45.3 (d, J = 4.1 Hz), 44.4 (t, J = 23.3 Hz), 31.1, 13.7; ^{19}F NMR (565 MHz, $CDCl_3$): δ -99.3, -99.7, -103.3, -103.8; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{18}ClF_2N_2O_3$ 419.0969; Found 419.0967.

*ethyl-3-(3-bromo-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)-2,2-difluoropropanoate (**4g**)*: Isolated yield (79.7 mg, 86%), White solid, Melting range: 153.8-156.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.45 (d, J = 8.3 Hz, 1H), 8.35-8.34 (m, 1H), 7.83-7.82 (m, 1H), 7.65 (dd, J_1 = 8.4, J_2 = 1.8 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.47-7.43 (m, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.46-3.39 (m, 1H), 3.03-2.95 (m, 1H), 1.76 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.6, 163.0 (t, J =32.0 Hz), 148.5, 143.9, 140.6, 131.8, 131.4, 130.0, 127.7, 126.2, 126.0, 125.9, 121.8, 120.0, 115.7, 114.2 (dd, J_1 = 250.2 Hz, J_2 = 253.4 Hz), 64.0, 63.1, 45.3 (d, J = 4.8 Hz), 44.5 (t, J = 22.5 Hz), 31.1, 13.7; ^{19}F NMR (565 MHz, $CDCl_3$): δ -99.1, -99.6, -103.4, -103.9; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{18}BrF_2N_2O_3$ 463.0463; Found 463.0461.

*ethyl-2,2-difluoro-3-(3,5,9,10-tetramethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)propanoate (**4h**)*: Isolated yield (72.5 mg, 85%), White solid, Melting range: 151.1-152.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 7.57 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 3.94-3.82 (m, 2H), 3.42-3.35 (m, 1H), 3.06-2.98 (m, 1H), 2.45-2.40 (m, 9H), 1.73 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.4, 163.4 (t, J = 31.9 Hz), 148.8, 142.2, 141.6, 138.5, 135.0, 134.8, 129.7, 129.3, 127.3, 126.0, 120.2, 119.9, 116.0, 114.4 (dd, J_1= 249.0 Hz, J_2 = 254.3 Hz), 63.0, 45.1 (d, J = 5.1 Hz), 44.5 (t, J = 23.6 Hz), 31.3, 21.8, 20.5, 20.4, 13.6; ^{19}F NMR (565 MHz, $CDCl_3$): δ -98.4, -98.9, -104.2, -104.7; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{25}F_2N_2O_3$ 427.1828; Found 427.1827.

*ethyl-3-(3-chloro-5,9,10-trimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)-2,2-difluoropropanoate (**4i**)*: Isolated yield (58.1 mg, 65%), White solid, Melting range: 172.0-173.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51-8.50 (m, 1H), 8.13 (s, 1H), 7.61 (s, 1H), 7.49-7.48 (m, 1H), 7.43 (s, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.45-3.38 (m, 1H), 3.02-2.94 (m, 1H), 2.43-2.41 (m, 6H), 1.76 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.5, 163.0 (t, J =32.1 Hz), 147.5, 141.4, 140.4, 137.6, 135.7, 135.5, 129.5, 129.0, 127.8, 127.0, 121.1, 119.9, 116.0, 114.1 (dd, J_1= 249.7 Hz, J_2 = 253.5 Hz), 63.3, 45.2 (d, J = 4.3 Hz), 44.5 (t, J = 23.7 Hz), 31.2, 20.5, 20.4, 13.7; ^{19}F NMR (565 MHz, $CDCl_3$): δ -99.2, -99.6, -103.5, -104.0; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}ClF_2N_2O_3$ 447.1282; Found 447.1281.

*5-methyl-5-(2,2,2-trifluoroethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**5a**)*: Isolated yield (37.0 mg, 56%), White solid, Melting range: 127.6-130.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (d, J = 7.7 Hz, 1H), 8.36 (d, J = 7.3 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.61-7.59 (m, 1H), 7.54-7.52 (m, 1H), 7.48-7.43 (m, 3H), 3.51-3.44 (m, 1H), 2.98-2.91 (m, 1H), 1.76 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.9, 149.2, 143.9, 138.5, 131.6, 131.4, 128.4, 126.4, 126.4, 126.2, 125.8, 125.0 (q, J = 277.0 Hz), 122.4, 119.9, 115.7, , 45.3, 44.0 (q, J = 27.8 Hz), 30.9; ^{19}F NMR (565 MHz, $CDCl_3$): δ -61.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{14}F_3N_2O^+$ 331.1053; Found 331.1051.

*3,5-dimethyl-5-(2,2,2-trifluoroethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**5b**)*: Isolated yield (44.1 mg, 64%), White solid, Melting range: 203.4-208.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 7.4 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.47-7.41 (m, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.25 (s, 1H), 3.49-3.42 (m, 1H), 2.97-2.90 (m, 1H), 2.48 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.1, 149.4, 143.8, 142.4, 138.5, 131.3, 129.6, 129.6, 126.8, 126.4, 126.1, 125.6, 124.9 (q, J = 276.8 Hz), 119.7, 115.6, 45.2, 44.0 (q, J = 27.5 Hz), 30.9, 21.9; ^{19}F NMR (565 MHz, $CDCl_3$): δ -61.3; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{16}F_3N_2O$ 345.1209; Found 345.1209.

*3-methoxy-5-methyl-5-(2,2,2-trifluoroethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**5c**)*: Isolated yield (45.4 mg, 63%), White solid, Melting range: 154.2-156.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.47 (d, J = 8.7 Hz, 1H), 8.32 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.45-7.39 (m, 2H), 7.08-7.07 (m, 1H), 6.94 (s, 1H), 3.92 (s, 3H), 3.50-3.43(m, 1H), 2.94-2.86 (m, 1H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.0, 162.5, 149.4, 144.1, 140.6, 131.3, 128.4, 126.1, 125.4, 124.9 (q, J = 277.1 Hz), 119.5, 115.6, 115.2, 114.0, 112.4, 55.6, 45.4, 44.0 (q, J = 27.7 Hz), 31.1; ^{19}F NMR (565 MHz, $CDCl_3$): δ -61.3; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{16}F_3N_2O_2$ 361.1158; Found 361.1157.

*3-bromo-5-methyl-5-(2,2,2-trifluoroethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**5d**)*: Isolated yield (37.6 mg, 46%), White solid, Melting range: 241.0-244.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (d, J = 8.4 Hz, 1H), 8.35-8.34 (m, 1H), 7.84-7.82 (m, 1H), 7.68-7.66 (m, 1H), 7.62 (s, 1H), 7.49-7.45 (m, 2H), 3.51-3.44 (m, 1H), 2.94-2.86 (m, 1H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.2, 148.4, 143.9, 140.2, 132.0, 131.3, 129.7, 127.8, 126.4, 126.3, 126.2, 124.8 (q, J = 277.2 Hz), 121.5, 120.1, 115.7, 45.2, 44.0 (q, J = 27.9 Hz), 30.8; ^{19}F NMR (565 MHz, $CDCl_3$): δ -

61.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{13}BrF_3N_2O$ 409.0158; Found 409.0156.

*5,9,10-trimethyl-5-(2,2,2-trifluoroethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**5e**):* Isolated yield (40.9 mg, 57%), White solid, Melting range: 170.1-172.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.50 (d, J = 8.5 Hz, 1H), 8.14 (s, 1H), 7.59 (s, 1H), 7.58-7.55 (m, 1H), 7.52-7.49 (m, 1H), 7.45 (d, J = 7.9 Hz, 1H), 3.50-3.42 (m, 1H), 2.96-2.89 (m, 1H), 2.43-2.41 (m, 6H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.9, 148.5, 142.4, 138.3, 135.2, 135.2, 131.3, 129.7, 128.4, 126.4, 126.2, 125.0 (q, J = 277.2 Hz), 122.7, 120.1, 116.0, 45.2, 44.0 (q, J = 27.6 Hz), 30.9, 20.5, 20.4; ^{19}F NMR (565 MHz, $CDCl_3$): δ -61.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}F_3N_2O$ 359.1366; Found 359.1365.

*3,5,9,10-tetramethyl-5-(2,2,2-trifluoroethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**5f**):* Isolated yield (49.9 mg, 67%), White solid, Melting range: 196.2-198.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.57 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 3.48-3.40 (m, 1H), 2.95-2.88 (m, 1H), 2.47 (s, 3H), 2.42-2.40 (m, 6H), 1.73 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.0, 148.8, 142.5, 141.9, 138.3, 135.0, 134.9, 129.7, 129.4, 126.8, 126.1, 125.0 (q, J = 277.2 Hz), 120.0, 116.0, 45.1, 44.0 (q, J = 27.6 Hz), 30.9, 21.9, 20.5, 20.4; ^{19}F NMR (565 MHz, $CDCl_3$): δ -61.4; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}F_3N_2O$ 373.1522; Found 373.1522.

*diethyl 2-((5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)malonate (**6a**):* Isolated yield (53 mg, 63%), White liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52-8.50 (m, 1H), 8.35-8.33 (m, 1H), 7.84-7.83 (m, 1H), 7.60-7.57 (m, 1H), 7.52-7.49 (m, 2H), 7.46-7.43 (m, 2H), 3.97-3.93 (m, 1H), 3.88-3.83 (m, 1H), 3.77-3.69 (m, 2H), 3.10-3.05 (m, 2H), 2.80-2.75 (m, 1H), 1.77 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 172.0, 168.5, 168.4, 149.5, 143.9, 139.9, 131.9, 131.3, 128.2, 126.5, 126.1, 126.0, 125.7, 123.0, 119.8, 115.7, 61.7, 61.6, 48.7, 48.0, 39.3, 30.2, 13.7, 13.6; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{25}N_2O_5$ 421.1758; Found 421.1768.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; mechanistic investigation; characterization data; spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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