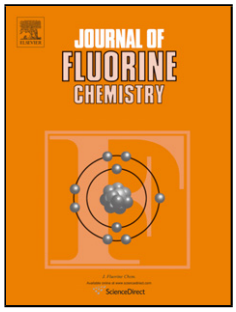

Title: Facile Synthesis of Fluoroalkylated Quinolones Using Fluoroalk-2-ynoates as Fluorinated Building Blocks

Authors: Jun Wu, Hui Zhang, Xiao Ding, Xuefei Tan, Hong C. Shen, Jie Chen, Weimin He, Hongmei Deng, Liping Song, Weiguo Cao

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Facile Synthesis of Fluoroalkylated Quinolones Using Fluoroalk-2-ynoates as Fluorinated Building Blocks

Jun Wu,[‡a,b] Hui Zhang,[‡c,f] Xiao Ding,[c] Xuefei Tan,[b] Hong C. Shen,[b] Jie Chen,[c] Weimin He,[c] Hongmei Deng,[f] Liping Song*[a,c] and Weiguo Cao*[c,d,e]

[a] *School of Materials Science and Engineering, Shanghai University, Shanghai 200444, P. R. China.*

[b] *Medicinal Chemistry Department of Roche Innovation Center Shanghai, Roche R&D Center (China) Ltd., Shanghai 201203, P. R. China.*

[c] *Department of Chemistry, Shanghai University, Shanghai 200444, P. R. China.*

[d] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.*

[e] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.*

[f] *Laboratory for Microstructures, Instrumental Analysis and Research Center of Shanghai University, Shanghai 200444, P. R. China.*

[‡] *Contribute to this work equally.*

* *Corresponding authors.*

E-mail: wgcao@staff.shu.edu.cn; lpsong@shu.edu.cn

Fax: +86-21-66134856

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Facile Synthesis of Fluoroalkylated Quinolones Using Fluoroalk-2-ynoates as Fluorinated Building Blocks

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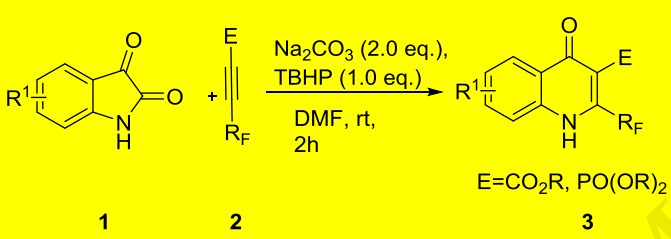
[a] *School of Materials Science and Engineering, Shanghai University, Shanghai 200444, P. R. China.* [b] *Medicinal Chemistry Department of Roche Innovation Center Shanghai, Roche R&D Center (China) Ltd., Shanghai 201203, P. R. China.* [c] *Department of Chemistry, Shanghai University, Shanghai 200444, P. R. China.* [d] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.* [e] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.* [f] *Laboratory for Microstructures, Instrumental Analysis and Research Center of Shanghai University, Shanghai 200444, P. R. China.* [‡] *Contribute to this work equally.*

In the presence of Na_2CO_3, a variety of fluoroalkylated quinolones were efficiently synthesized from isatins and fluoroalk-2-ynoates in good to excellent yields at room temperature. The reaction can proceed *via* two different ways with Michael adduct or isatoic anhydride as the key intermediate.



Highlights

- Facile Synthesis of Fluoroalkylated Quinolones Using Fluoroalk-2-ynoates as Fluorinated Building Blocks
- An efficient and mild access to fluoroalkylated quinolones
- Intramolecular oxidative cyclization

Abstract

In the presence of Na_2CO_3, a variety of fluoroalkylated quinolones were efficiently synthesized from isatins and fluoroalk-2-ynoates in good to excellent yields at room temperature. The reaction can proceed *via* two different ways with Michael adduct or isatoic anhydride as the key intermediate.

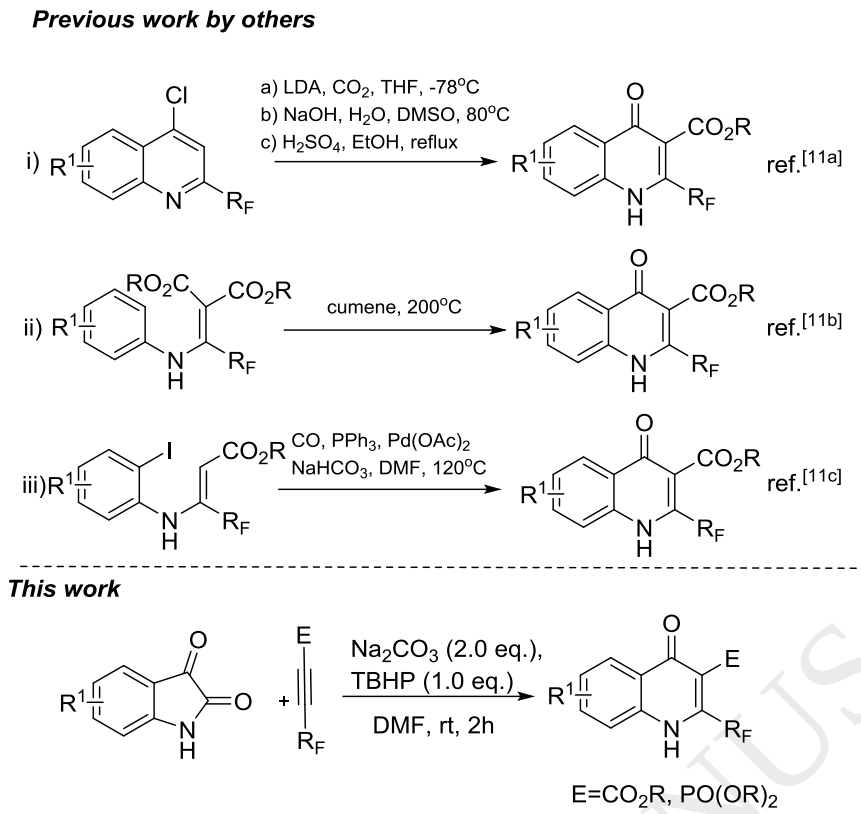
Keywords: oxidative cyclization, fluoroalkylated quinolone, fluoroalkylated

alkyne, nucleophilic addition

1. Introduction

Nalidixic acid, which was firstly discovered as a by-product in the synthesis of chloroquine in 1962 and introduced to clinical use in 1967 as antibiotic [1], led to the beginning of quinolone development in organic chemistry [2] and medicinal chemistry [3-8]. Besides familiar antibacterial activities [3], quinolone and its derivatives have other pharmacologically active profiles for drug discovery since many of them have exhibited excellent biological and pharmacological activities, such as anti-tubercular [4], anti-HIV [5], antimalarial [6], anti-inflammatory [7], anti-tumor [8] activity and so forth.

As is well known, the introduction of fluorine or fluoroalkylated groups into a bioactive molecule has been a common strategy to develop new drugs in medicinal chemistry [9]. Furthermore, the carboxylic acid moiety at 3-position of 4-quilolones has been proved to be essential to antibacterial potency [10]. However, a survey of literatures showed that efficiently building 3-carboxylate-2-perfluoroalkylated 4-quinolones has still less explored [11]. Usually, there are three fundamentally different strategies (**Scheme 1**): (i) introduction of carboxylate and carbonyl groups to 3 and 4 position, respectively [11a]; (ii) intramolecular condensation [11b]; (iii) insertion of carbon monoxide via transition-metal catalyzed reactions [11c]. Yet, due to some limitations in the above methods such as a narrow substrate scope, harsh reaction conditions or dependence on multistep-prepared starting materials et al, it is highly desirable to develop more convenient and efficient approaches for the synthesis of 3-carboxylate-2-fluoroalkylated 4-quinolones from easily available starting materials.



Scheme 1

Recently, with TBHP as the oxidant and Cs_2CO_3 as the base, Wu and his coworkers have developed an efficient transition-metal-free oxidative cyclization reaction using isatins and alkynes for the facile synthesis of non-fluoroalkylated 4-quinolones in DMSO at 100 °C [2b].

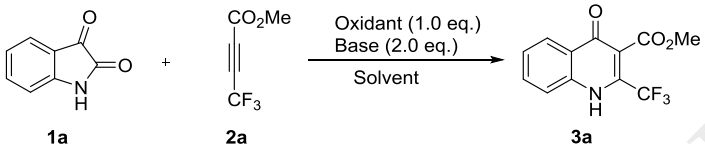
Inspired by their work and based on our previous studies on the synthesis of potentially bioactive fluoroalkylated heterocycles [12], herein, we report an efficient and mild cascade synthesis of 3-carbonyl-2-fluoroalkylated 4-quinolones using fluoroalk-2-ynoates as fluorinated building blocks and commercially available isatins as starting materials without transition-metal catalyst. The reaction proceeded smoothly at room temperature in one pot within a short time to afford structurally diverse desired products; the control experiments demonstrated two possible pathways for their formation.

2. Results and Discussion

At the beginning, we applied Wu's standard conditions to the reaction of

isatin **1a** and methyl 4,4,4-trifluorobut-2-ynoate **2a**, and achieved 28% yield of **3a** (**Table 1**, entry 1). When the reaction temperature was lowered to room temperature, the yield was improved to 43% (**Table 1**, entry 2 *vs* entry 1). Screening of various inorganic and organic bases indicated that Na_2CO_3 was optimal (**Table 1**, entry 3). Further screening of other solvents (**Table 1**, entries 10-16) identified DMF as the best (**Table 1**, entry 13). Other oxidants such as m-CPBA, Oxone, DDQ, $K_2S_2O_8$, NaClO and H_2O_2 all failed to afford better results than TBHP (**Table 1**, entry 13 *vs* entries 17-22).

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	Oxidant	Base	Temp. [°C]	Solvent	Yield (%)[b]
1	TBHP	Cs_2CO_3	100	DMSO	28
2	TBHP	Cs_2CO_3	rt	DMSO	43
3	TBHP	Na_2CO_3	rt	DMSO	79
4	TBHP	K_2CO_3	rt	DMSO	55
5	TBHP	K_3PO_4	rt	DMSO	53
6	TBHP	$KHCO_3$	rt	DMSO	68
7	TBHP	NaOH	rt	DMSO	54
8	TBHP	KOAc	rt	DMSO	17
8	TBHP	DBU	rt	DMSO	ND
9	TBHP	DIEA	rt	DMSO	70
10	TBHP	Na_2CO_3	rt	THF	36
11	TBHP	Na_2CO_3	rt	DCM	Trace
12	TBHP	Na_2CO_3	rt	EtOH	55
13	**TBHP**	**Na_2CO_3**	**rt**	**DMF**	**88, 84**[c]
14	TBHP	Na_2CO_3	rt	MeCN	46
15	TBHP	Na_2CO_3	rt	EtOAc	31
16	TBHP	Na_2CO_3	rt	Acetone	28
17	*m*-CPBA	Na_2CO_3	rt	DMF	21
18	Oxone	Na_2CO_3	rt	DMF	28
19	DDQ	Na_2CO_3	rt	DMF	Trace
20	$K_2S_2O_8$	Na_2CO_3	rt	DMF	Trace
21	NaClO	Na_2CO_3	rt	DMF	Trace
22	H_2O_2	Na_2CO_3	rt	DMF	61

[a] Reaction conditions: isatin **1a** (0.4 mmol), methyl 4,4,4-trifluorobut-2-ynoate **2a** (0.4 mmol), base (0.8 mmol) and TBHP (0.4 mmol) in solvent (4 mL), rt, 2 h.[b] The yields were determined by ^{19}F NMR with $PhCF_3$ as internal standard. [c] Isolated yield. TBHP: *tert*-butyl hydroperoxide; DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

With the optimized condition in hand (**Table 1**, entry 13), we first explored the substrate scope with respect to E and R_F substituents on fluoroalk-2-ynoates **2** (**Table 2**). For this purpose, we used substrates **2a** to **2e** and **2z** to react with isatin **1a**. The reactions proceeded smoothly to afford the desired products **3a**-**3e** and **3z** in 65% to 84% yields.

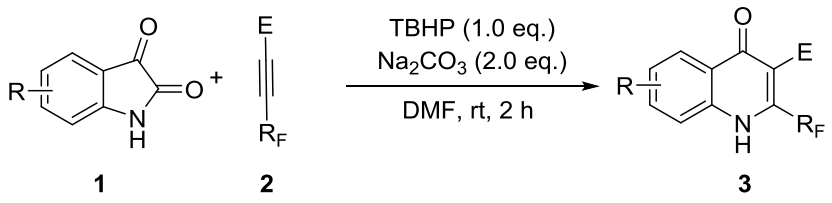
To explore the scope of the protocol with respect to the R substituent on the isatin ring, we used a series of 4-, 5-, 6- or 7- substituted isatins (**1f** to **1v**). Generally, the reaction was not evidently sensitive to the electron density of the phenyl ring in isatin. When R at 4, 5, or 6-position on isatin **1** was either an electron-donating substituent (Me or OMe) or an electron-withdrawing group such as F, Cl, Br, I or CF_3, all the corresponding products were obtained in good yields.

However, when isatin **1** bearing a sterically bulky substituent such as 7-CF_3, 7-CO_2Me or 7-Me, the yield dropped dramatically (**Table 2**, **3t**-**3v**, 47%-54%).

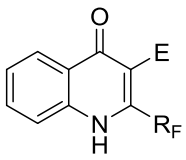
Finally, disubstituted isatins **1** were examined; the yields were satisfying (**Table 2**, **3w**, 85%; **3x** 51%).

To our delight, 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-2,3-dione **1y** could also be tolerated under the optimized conditions, affording 86% yield of methyl 6-bromo-4-oxo-2-(trifluoromethyl)-1,4-dihydro-1,8-naphthyridine-3-carboxylate **3y**.

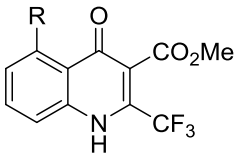
Table 2 Scope of fluoroalkylated 4-quinolones[a,b]



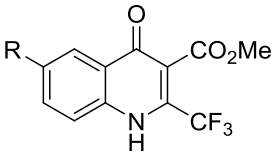
1 **2** **3**



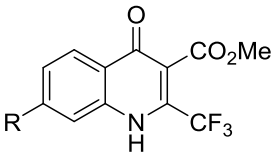
	E	R_F	
3a	CO_2Me	CF_3	84%
3b	CO_2Me	C_2F_5	84%
3c	CO_2Me	C_3F_7	81%
3d	CO_2Me	CF_2H	65%
3e	CO_2Et	CF_3	82%
3z	$PO(OEt)_2$	CF_3	81%



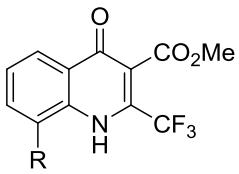
	R	
3f	Cl	91%
3g	Br	89%
3h	Me	76%



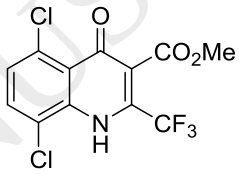
	R	
3i	F	84%
3j	Cl	90%
3k	Br	89%
3l	I	86%
3m	Me	77%
3n	OMe	81%



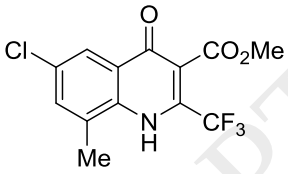
	R	
3o	Br	83%
3p	CF_3	80%
3q	OMe	76%



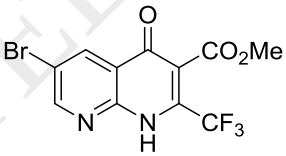
	R	
3r	F	87%
3s	Cl	82%
3t	CF_3	54%
3u	CO_2Me	49%
3v	Me	47%



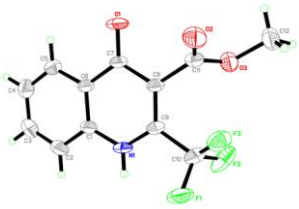
3w 85%



3x 51%



3y 86%



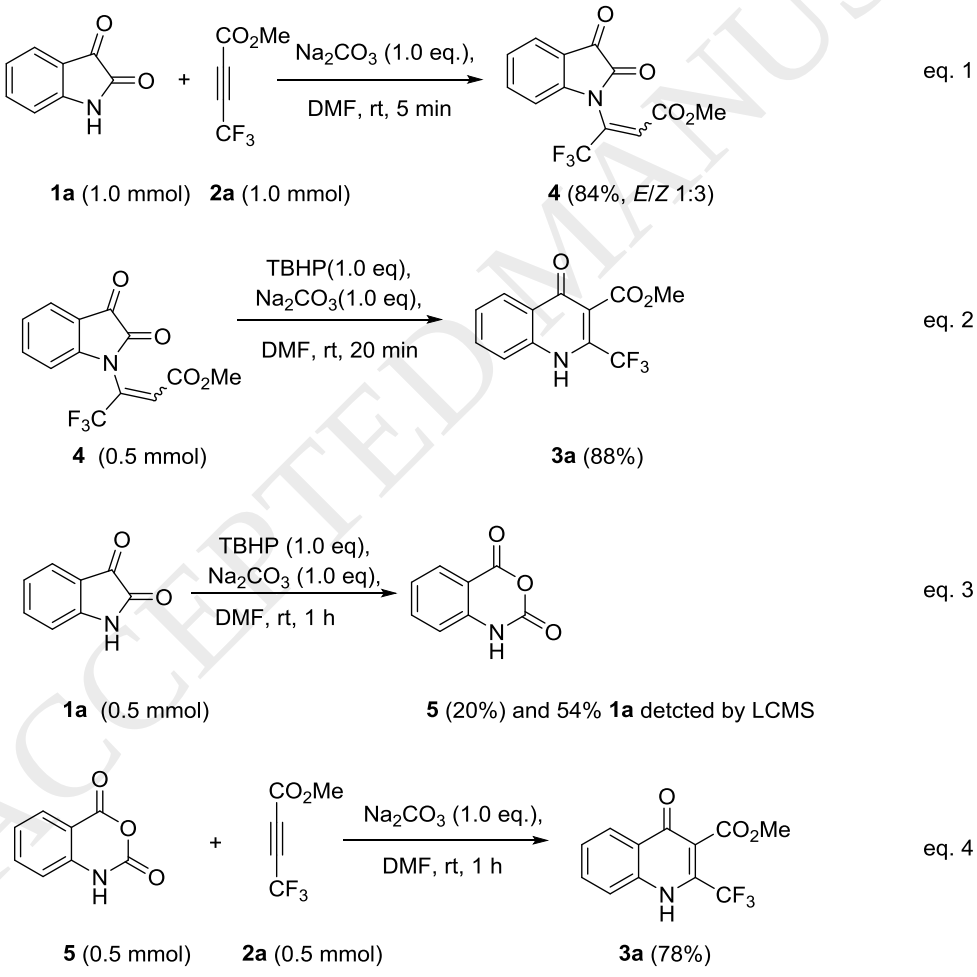
X-ray crystal structure of **3a**[13]

[a] Reactions conditions: isatin divertives **1** (0.4 mmol), fluoroalk-2-ynoates **2** (0.4 mmol), TBHP (0.4 mmol) and Na_2CO_3 (0.8 mmol) in DMF (4 mL), rt, 2 h. [b] Isolated yield.

To gain insight into the mechanism, we conducted two-step control experiments (**Scheme 2**, eq.1 and eq.2). In the presence of Na_2CO_3, treatment of **1a** with **2a** in DMF afforded 84% yield of Michael adduct **4** in 5 min. Then, compound **4** was transformed into **3a** smoothly in 88% yield under our standard conditions, indicating that the desired product formed *via* a process with Michael adduct **4** as a key intermediate.

According to Wu *et al*'s report [2b], however, the final product was generated through a different way. In their work, isatin reacted with TBHP first to give the oxidative intermediate isatoic anhydride which underwent further reaction with methyl 3-phenylpropiolate to achieve the target product. The existence of their key intermediate isatoic anhydride was demonstrated by the fact that a trace of this compound was detected by mass spectroscopy.

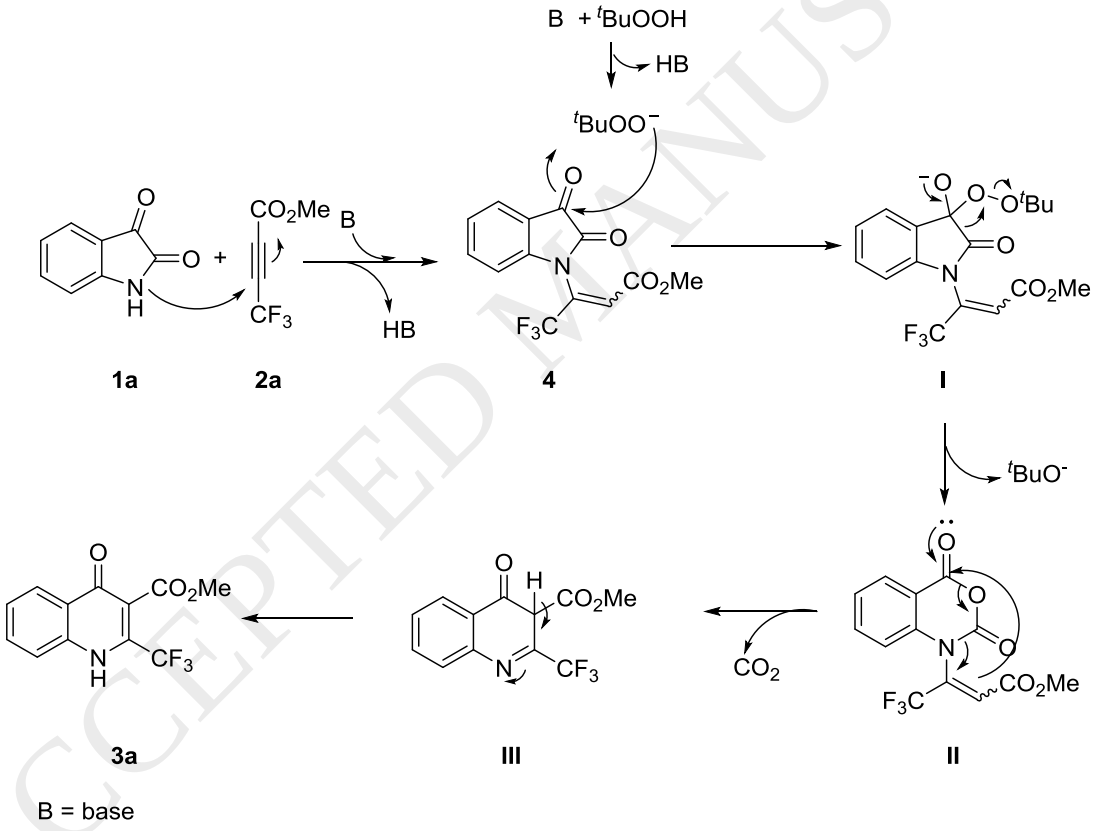
To confirm their results, we carried out more control experiments (**Scheme 2**, eq.3 and eq.4). Under our conditions for 1 h, isatin **1a** can be oxidized by TBHP to give isatoic anhydride **5** in 20% yields. The intermediate **5** reacted with methyl 4,4,4-trifluorobut-2-ynoate **2a** in the presence of base to afford 78% **3a**.



Scheme 2 Control experiments under our standard conditions

The above-described results indicated that the cascade reaction undergoes in two different ways to furnish the same target; one is the isatoic anhydride-mediated path suggested by Wu group [2b], the other here was proposed by us as shown in **Scheme 3**.

Initially, Michael addition of **1a** to **2a** forms **4** in the presence of base. Then, intermolecular nucleophilic attack of TBHP to **4** affords intermediate **I** followed by Baeyer-Villiger type oxidation rearrangement to generate intermediate **II**. The subsequent carbon dioxide elimination and intramolecular cyclization leads to **III** which undergoes isomerization to deliver **3a** as the final product.



Scheme 3 Proposed reaction mechanism

3. Conclusions

We have developed a simple, practical protocol for access to 2-perfluoroalkylated-4-quinolone derivatives. Mechanism study indicated that the cascade reaction undergoes in two different ways to form the same target

product. This protocol, which proceeds at room temperature, opens a new method for transformation of isatin divertives into compounds of medicinal interest. Further exploration of this reaction is underway in our laboratory.

4. Experimental

4.1. General Information

Reagents including anhydride **5** (**Scheme 2**, eq.3) and solvents were purchased from commercially sources and used without further purification. Fluoroalkynoates **2** were prepared according to the known literature [14]. Melting points were recorded on a WRS-1 instrument and are uncorrected. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard: $CFCl_3$ for ^{19}F, TMS for ^{1}H and ^{13}C NMR spectra. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were obtained on a NICOLET iS10 FTIR spectrometer. High-resolution mass spectrometry (HRMS) was conducted on an Agilent Technologies Q-TOF 6530 unit. X-ray analysis was performed on a Bruker Smart Apex2 CCD spectrometer. All the reactions in this paper were monitored by UPLC-MS on a UPLC-MS DW3100 unit. CombiFlash Rf+ was used to purify compounds.

4.2. General procedure for the synthesis of 3a to 3z

A mixture of **1** (0.4 mmol), **2** (0.4 mmol), Na_2CO_3 (0.8 mmol) and TBHP (0.4 mmol) in DMF (4 mL) was stirred at rt for 2 h. Then, the mixture was poured into ice-water, acidified with 1N HCl aq. (6 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by silica gel flash column chromatography to give desired products.

*4.2.1 Methyl 4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3a**).* 91 mg (84% yield), (eluent: PE/EA = 5:1), white solid; mp 207.1-208.3°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.80 (br. s, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.92-7.84 (m, 1H), 7.71-7.63 (m, 1H), 4.06 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.00 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.9, 168.3, 147.2, 145.8 (m), 133.4, 129.9, 128.4, 123.6, 121.1 (q, *J* = 276.7 Hz), 120.5, 101.7, 53.2 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3072, 2964, 1747, 1627, 1576, 1477, 1296, 1188, 1147, 953, 766, 617. HRMS (ESI) calcd. for $C_{12}H_8F_3NO_3$ $[M+H]^+$: 272.0529, found 272.0536.

*4.2.2 Methyl 4-oxo-2-(pentafluoroethyl)-1H-quinoline-3-carboxylate (**3b**).* 108 mg (84% yield), (eluent: PE/EA = 6:1), white solid; mp 146.2-147.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.67 (br. s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.90-7.82 (m, 1H), 7.71-7.64 (m, 1H), 4.06 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -78.86 (s, CF_3), -107.98 (s, CF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.1, 168.0, 146.9, 146.3 (t, *J* = 28.3 Hz, 1H), 133.2, 130.0, 128.6, 123.4, 120.3, 119.5 (qt, *J* = 288.0, 36.4 Hz), 112.7 (tq, *J* = 259.6, 34.3 Hz), 102.3, 53.2 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3076, 2955, 1738, 1628, 1570, 1477, 1290, 1171, 1057, 926, 744, 619. HRMS (ESI) calcd. for $C_{13}H_8F_5NO_3$ $[M+H]^+$: 322.0497, found 322.0502.

*4.2.3 Methyl 4-oxo-2-(heptafluoropropyl)-1H-quinoline-3-carboxylate (**3c**)*. 120 mg (81% yield), (eluent: PE/EA = 6:1), white solid; mp 181.8-183.2°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.43 (br. s, 1H), 8.39-8.35 (m, 1H), 8.08 (d, *J* = 8.3 Hz, 1 H), 7.91-7.85 (m, 1H), 7.72-7.66 (m, 1H), 4.05 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -78.66 (t, *J* = 9.5 Hz, CF_3), -104.19 (q, *J* = 9.5 Hz, CF_2), -120.59 (s, CF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.9, 167.6, 147.0, 146.6 (t, *J* = 27.5 Hz), 133.3, 129.8, 128.6, 123.5, 120.2, 118.6 (m), 111.9 (m), 109.4 (m), 102.8, 53.2 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 2902, 1738, 1535, 1477, 1336, 1217, 1115, 1012, 887, 742, 623. HRMS (ESI) calcd. for $C_{14}H_8F_7NO_3$ $[M+H]^+$: 372.0465, found 372.0463.

*4.2.4 Methyl 4-oxo-2-(difluoromethyl)-1H-quinoline-3-carboxylate (**3d**)*. 66 mg (65% yield), (eluent: PE/EA = 5:1), white solid; mp 219.1-220.4°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.47 (br. s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.88-7.83 (m, 1H), 7.81-7.75 (m, 1H), 7.50-7.43 (m, 1H), 7.26 (t, J = 52.0 Hz, 1H), 3.81 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ: -117.81 (d, J = 51.8 Hz) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 174.2, 165.6, 142.8 (m), 139.4, 133.7, 125.8, 125.5, 119.8, 114.2, 110.9 (t, J = 242.1 Hz), 52.8 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 2831, 1722, 1537, 1479, 1348, 1146, 1068, 974, 752, 685. HRMS (ESI) calcd. for $C_{12}H_9F_2NO_3$ [M+H]$^+$: 254.0623, found 254.0622.

*4.2.5 Ethyl 4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3e**)[11a].* 94 mg (82% yield), (eluent: PE/EA = 5:1), white solid; mp 191.8-193.3°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.94 (br. s, 1H), 8.36 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.92-7.80 (m, 1H), 7.71-7.63 (m, 1H), 4.53 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.34 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.5, 168.4, 147.2, 145.9 (q, J = 35.2 Hz), 133.3, 129.9, 128.4, 123.5, 121.2 (q, J = 275.8 Hz), 120.6, 101.9, 63.1, 13.6 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 2902, 1720, 1533, 1477, 1290, 1153, 1135, 1103, 1016, 762, 617. HRMS (ESI) calcd. for $C_{13}H_{10}F_3NO_3$ [M+H]$^+$: 286.0686, found 286.0688.

*4.2.6 Methyl 5-chloro-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3f**).* 111 mg (91% yield), (eluent: PE/EA = 5:1), white solid; mp 199.0-200.4°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.73 (br. s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.74-7.68 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 3.83 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ: -63.63 (s, CF_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 173.3, 164.9, 142.5, 134.4 (m), 133.8, 132.4, 128.3, 121.7, 120.3 (q, J = 277.8 Hz), 118.9, 117.1, 53.2 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3387, 2750, 1745, 1618, 1558, 1462, 1284, 1203, 1146, 1008, 811, 646. HRMS (ESI) calcd. for $C_{12}H_7ClF_3NO_3$ [M+H]$^+$: 306.0139, found 306.0141.

*4.2.7 Methyl 5-bromo-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3g**)*. 124 mg (89% yield), (eluent: PE/EA = 5:1), pale yellow solid; mp 224.0-225.3°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.26 (br. s, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.67-7.60 (m, 1H), 4.07 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.43 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.9, 168.5, 149.3, 146.2 (q, *J* = 35.5 Hz), 135.6, 132.9, 130.3, 120.8 (q, *J* = 275.8 Hz), 119.3, 118.0, 102.4, 53.5 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3394, 2761, 1743, 1560, 1460, 1301, 1203, 1147, 1002, 810, 627. HRMS (ESI) calcd. for $C_{12}H_7BrF_3NO_3$ $[M+H]^+$: 349.9634, found 349.9638.

*4.2.8 Methyl 5-methyl-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3h**).* 87 mg (76% yield), (eluent: PE/EA = 5:1), white solid; mp 154.2-156.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.23 (br. s, 1H), 8.08-7.75 (m, 1H), 7.77-7.56 (m, 1H), 7.47-7.31 (m, 1H), 4.05 (s, 3H), 2.93 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.14 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.9, 170.5, 148.9, 145.7 (m), 138.2, 132.8, 131.1, 128.3, 121.1 (q, *J* = 275.8 Hz), 119.9, 101.5, 53.2, 24.3 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3567, 2953, 1726, 1624, 1542, 1470, 1303, 1207, 1128, 1080, 970, 802, 669. HRMS (ESI) calcd. for $C_{13}H_{10}F_3NO_3$ $[M+H]^+$: 286.0686, found 286.0694.

*4.2.9 Methyl 6-fluoro-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3i**).* 97 mg (84% yield), (eluent: PE/EA = 6:1), white solid; mp 201.7-202.6°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.77 (br. s, 1H), 8.14-8.09 (m, 1H), 7.97-7.92 (m, 1H), 7.66-7.59 (m, 1H), 4.08 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.99 (s, CF_3), -108.90 (dt, *J* = 8.2, 4.1 Hz, CF) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.8, 167.6 (d, *J* = 5.1 Hz), 161.7 (d, *J* = 251.6 Hz), 145.3 (qd, *J* = 35.3, 3.0 Hz), 144.2, 132.6 (d, *J* = 8.8 Hz), 123.3 (d, *J* = 25.7 Hz), 121.7 (d, *J* = 9.5 Hz), 121.0 (q, *J* = 276.8 Hz), 107.6 (d, *J* = 24.2 Hz), 102.1, 53.4 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3081, 2941, 1745, 1574, 1489, 1292, 1187, 1157, 1134, 1012, 823, 627. HRMS (ESI) calcd. for $C_{12}H_7F_4NO_3$ $[M+H]^+$: 290.0435, found 290.0438.

*4.2.10 Methyl 6-chloro-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3j**).* 110 mg (90% yield), (eluent: PE/EA = 6:1), white solid; mp 205.1-206.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.80 (br. s, 1H), 8.31 (d, *J* = 2.3 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.83-7.77 (m, 1H), 4.08 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.08 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.7, 167.3, 146.0 (q, *J* = 35.2 Hz), 145.6, 134.8, 134.2, 131.5, 122.6, 121.3, 121.0 (q, *J* = 276.7 Hz), 102.4, 53.4 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3091, 2962, 1682, 1566, 1443, 1333, 1144, 1003, 895, 835, 721. HRMS (ESI) calcd. for $C_{12}H_7ClF_3NO_3$ $[M+H]^+$: 306.0139, found 306.0140.

*4.2.11 Methyl 6-bromo-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3k**).* 124 mg (89% yield), (eluent: PE/EA = 5:1), pale yellow solid; mp 203.8-204.9°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.79 (br. s, 1H), 8.50 (s, 1H), 8.02-7.85 (m, *2*H), 4.08 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.11 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.6, 167.2, 146.1 (q, *J* = 35.9 Hz), 145.8, 136.8, 131.5, 126.0, 122.8, 121.7, 120.9 (q, *J* = 275.7 Hz), 102.4, 53.4 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3398, 2901, 1728, 1568, 1470, 1292, 1209, 1145, 1109, 820, 623. HRMS (ESI) calcd. for $C_{12}H_7BrF_3NO_3$ $[M+H]^+$: 349.9634, found 349.9640.

*4.2.12 Methyl 6-iodo-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3l**).* 137 mg (86% yield), (eluent: PE/EA = 5:1), yellow solid; mp 201.0-202.4°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.81 (br. s, 1H), 8.74 (d, *J* = 1.8 Hz, 1H), 8.15-8.09 (m, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 4.08 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.12 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.6, 167.0, 146.2, 146.1 (m), 142.2, 132.5, 131.3, 122.0, 121.0 (q, *J* = 275.8 Hz), 102.4, 94.3, 53.4 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3078, 2950, 1732, 1576, 1525, 1468, 1286, 1182, 1146, 1107, 827, 621. HRMS (ESI) calcd. for $C_{12}H_7F_3INO_3$ $[M+H]^+$: 397.9495, found 397.9505.

*4.2.13 Methyl 6-methyl-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3m**).* 88 mg (77% yield), (eluent: PE/EA = 5:1), white solid; mp 197.0-198.6°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.73 (br. s, 1H), 8.13 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.74-7.68 (m, 1H), 4.06 (s, 3H), 2.59 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.86 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.0, 167.7, 145.7, 144.9 (q, *J* = 35.2 Hz), 139.0, 135.5, 129.6, 122.4, 121.2 (q, *J* = 275.1 Hz), 120.4, 101.7, 53.2, 21.8 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 2881, 1732, 1558, 1531, 1490, 1300, 1186, 1149, 1105, 820, 723, 626. HRMS (ESI) calcd. for $C_{13}H_{10}F_3NO_3$ $[M+H]^+$: 286.0686, found 286.0683.

*4.2.14 Methyl 6-methoxy-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3n**).* 98 mg (81% yield), (eluent: PE/EA = 5:1), white solid; mp 217.7-219.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.68 (br. s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 2.7 Hz, 1 H), 7.53-7.46 (m, 1H), 4.06 (s, 3H), 3.98 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.63 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.1, 166.8, 159.5, 143.3 (q, *J* = 34.5 Hz), 142.9, 131.4, 125.7, 121.6, 121.3 (q, *J* = 275.1 Hz), 101.9, 101.1, 55.8, 53.2 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 2848, 1728, 1531, 1489, 1402, 1292, 1189, 1140, 1026, 829, 723, 625. HRMS (ESI) calcd. for $C_{13}H_{10}F_3NO_4$ $[M+H]^+$: 302.0635, found 302.0636.

*4.2.15 Methyl 7-bromo-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3o**).* 116 mg (83% yield), (eluent: PE/EA = 6:1), pale yellow solid; mp 195.0-195.8°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.87 (br. s, 1H), 8.31 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 4.07 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.21 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.7, 168.3, 147.8, 147.0 (q, *J* = 34.5 Hz), 132.3, 132.0, 128.3, 124.9, 120.8 (q, *J* = 276.6 Hz), 119.3, 102.1, 53.4 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3066, 2912, 1736, 1578, 1454, 1409, 1303, 1161, 1066, 957, 837, 630. HRMS (ESI) calcd. for $C_{12}H_7BrF_3NO_3$ $[M+H]^+$: 349.9634, found 349.9642.

*4.2.16 Methyl 4-oxo-2,7-bis(trifluoromethyl)-1H-quinoline-3-carboxylate (**3p**).* 109 mg (80% yield), (eluent: PE/EA = 5:1), white solid; mp 188.2-189.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.92 (br. s, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 8.43 (s, 1H), 7.89-7.85 (m, 1H), 4.10 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.22

(s, CF_3), -64.25 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.6, 168.1, 147.2 (q, *J* = 35.2 Hz), 146.5, 135.0 (q, *J* = 33.0 Hz), 127.6 (q, *J* = 4.4 Hz), 125.0, 124.2 (q, *J* = 2.9 Hz), 123.6 (q, *J* = 255.5 Hz), 122.4, 120.7 (q, *J* = 257.5 Hz), 103.1, 53.6 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3084, 2908, 1734, 1581, 1544, 1309, 1124, 1064, 846, 731, 634. HRMS (ESI) calcd. for $C_{13}H_7F_6NO_3$ $[M+H]^+$: 340.0403, found 340.0404.

*4.2.17 Methyl 7-methoxy-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3q**).* 92 mg (76% yield), (eluent: PE/EA = 5:1), white solid; mp 204.9-205.7°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.75 (br. s, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 1.3 Hz, 1H), 7.30-7.23 (m, 1H), 4.05 (s, 3H), 3.97 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.03 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.0, 167.8, 164.0, 149.6, 146.5 (q, *J* = 35.0 Hz), 124.8, 121.1, 121.0 (q, J = 275.8 Hz), 114.8, 108.3, 100.5, 55.9, 53.1 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3084, 2966, 1736, 1631, 1556, 1286, 1201, 1161, 995, 845, 719. HRMS (ESI) calcd. for $C_{13}H_{10}F_3NO_4$ $[M+H]^+$: 302.0635, found 302.0640.

*4.2.18 Methyl 8-fluoro-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3r**).* 101 mg (87% yield), (eluent: PE/EA = 6:1), white solid; mp 149.7-151.2°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.25 (br. s, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.84-7.66 (m, 2H), 3.96 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ: -63.68 (s, CF_3), -123.59 (s, CF) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.3, 162.4 (d, *J* = 2.9 Hz), 157.2 (d, *J* = 256.0 Hz), 143.3 (q, *J* = 34.3 Hz), 136.9, 128.5 (d, *J* = 8.1 Hz), 123.8, 121.3 (q, *J* = 275.8 Hz), 119.4 (d, *J* = 4.4 Hz), 117.0 (d, *J* = 18.3 Hz), 112.2, 53.5 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3091, 2964, 1664, 1587, 1490, 1344, 1240, 1149, 974, 791, 760. HRMS (ESI) calcd. for $C_{12}H_7F_4NO_3$ $[M+H]^+$: 290.0435, found 290.0433.

*4.2.19 Methyl 8-chloro-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3s**).* 100 mg (82% yield), (eluent: PE/EA = 6:1), white solid; mp 170.5-171.8°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.90 (br. s, 1H), 8.30-8.25 (m, 1H), 7.99-7.95 (m, 1H), 7.62-7.55 (m, 1H), 4.08 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ:

-64.07 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.8, 168.5, 146.2 (q, *J* = 35.9 Hz), 143.6, 134.6, 133.5, 128.4, 122.4, 122.1, 120.9 (q, *J* = 277.7 Hz), 102.3, 53.5 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3095, 2972, 1670, 1585, 1446, 1344, 1282, 1163, 1126, 953, 793, 746. HRMS (ESI) calcd. for $C_{12}H_7ClF_3NO_3$ $[M+H]^+$: 306.0139, found 306.0142 .

*4.2.20 Methyl 4-oxo-2,8-bis(trifluoromethyl)-1H-quinoline-3-carboxylate (**3t**).* 73 mg (54% yield), (eluent: PE/EA = 6:1), white solid; mp 113.1-114.4°C. ^1H NMR (400 MHz, DMSO-d_6) δ: 12.07 (br. s, 1H), 8.70 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 7.2 Hz, 1H), 7.91-7.86 (m, 1H), 3.96 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ: -59.08 (s, CF_3), -64.16 (s, CF_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.2, 161.6, 144.5 (q, *J* = 33.7 Hz), 143.8, 131.2 (q, *J* = 5.1 Hz), 128.3, 127.6, 126.9 (q, *J* = 29.3 Hz), 124.1 (q, *J* = 272.7 Hz), 122.6, 121.3 (q, *J* = 284.6 Hz), 111.8, 53.5 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 2976, 1670, 1587, 1446, 1396, 1319, 1107, 953, 798, 721. HRMS (ESI) calcd. for $C_{13}H_7F_6NO_3$ $[M+H]^+$: 340.0403, found 340.0411.

*4.2.21 Dimethyl 4-oxo-2-(trifluoromethyl)-1H-quinoline-3,8-dicarboxylate (**3u**).* 65 mg (49% yield), (eluent: PE/EA = 3:1), pale yellow solid; mp 121.0-122.3°C. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.47 (br. s, 1H), 8.60 (d, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 7.5 Hz, 1H), 7.51-7.45 (m, 1H), 4.06 (s, 3H), 3.96 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -65.52 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 168.1, 164.0, 139.1, 136.4, 135.7 (q, *J* = 36.2 Hz), 133.0, 126.5, 124.3, 119.9 (q, *J* = 277.3 Hz), 116.8, 115.7, 53.2 ,53.1 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3188, 2964, 1741, 1601, 1437, 1277, 1151, 1122, 987, 761. HRMS (ESI) calcd. for $C_{14}H_{10}F_3NO_5$ $[M+H]^+$: 330.0584, found 330.0591.

*4.2.22 Methyl 8-methyl-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3v**).* 54 mg (47% yield), (eluent: PE/EA = 8:1), white solid; mp 103.4-104.8°C. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.71 (br. s, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.1 Hz, 1H), 7.57-7.51 (m, 1H), 4.06 (s, 3H), 2.77 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.01 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.2,

168.3, 146.1, 144.3 (q, *J* = 35.2 Hz), 138.5, 133.5, 128.1, 121.2 (q, *J* = 275.1 Hz), 121.1, 120.5, 101.3, 53.1, 17.5 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 2968, 1670, 1583, 1446, 1342, 1284, 1128, 987, 956, 789. HRMS (ESI) calcd. for $C_{13}H_{10}F_3NO_3$ $[M+H]^+$: 286.0686, found 286.0695.

*4.2.23 Methyl 5,8-dichloro-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3w**).* 116 mg (85% yield), (eluent: PE/EA = 8:1), white solid; mp 130.1-131.3°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.94 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ: -63.98 (s, CF_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.2, 164.3, 144.8, 143.9 (q, *J* = 33.7 Hz), 132.1, 131.8, 130.7, 129.3, 121.6, 121.2 (q, *J* = 276.6 Hz), 113.4, 53.6 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3078, 2964, 1670, 1551, 1444, 1338, 1230, 1141, 1009, 962, 890, 817. HRMS (ESI) calcd. for $C_{12}H_7Cl_2F_3NO_3$ $[M+H]^+$: 339.9750, found 339.9747.

*4.2.24 Methyl 6-chloro-8-methyl-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxylate (**3x**).* 65 mg (51% yield), (eluent: PE/EA = 8:1), white solid; mp 143.0-143.8°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.71 (br. s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 4.07 (s, 3H), 2.74 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.08 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.9, 167.4, 144.5, 144.4 (q, *J* = 35.2 Hz), 140.7, 134.2, 134.0, 121.3, 120.1, 121.1 (q, *J* = 275.1 Hz), 102.1, 53.3, 17.3 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3088, 2958, 1668, 1581, 1448, 1381, 1335, 1220, 1140, 966, 814, 714. HRMS (ESI) calcd. for $C_{13}H_9ClF_3NO_3$ $[M+H]^+$: 320.0296, found 320.0302.

*4.2.25 Methyl 6-bromo-4-oxo-2-(trifluoromethyl)-1H-1,8-naphthyridine-3-carboxylate (**3y**).* 121 mg (86% yield), (eluent: PE/EA = 4:1), pale yellow solid; mp 187.4-188.2°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.07 (d, *J* = 2.6 Hz, 1H), 8.65 (d, *J* = 2.6 Hz, 1H), 3.82 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ:

-63.35 (s, CF_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ: 173.0, 164.7, 156.0, 149.6, 137.7 (q, *J* = 37.4 Hz), 136.9, 121.2, 120.4 (q, *J* = 276.6 Hz), 116.8, 116.5, 53.3 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3034, 2874, 1741, 1595, 1437, 1300, 1159, 1003, 918, 621. HRMS (ESI) calcd. for $C_{11}H_6BrF_3N_2O_3$ $[M+H]^+$: 350.9587, found 350.9592.

*4.2.26 3-Diethoxyphosphoryl-2-(trifluoromethyl)-1H-quinolin-4-one (**3z**).* 113 mg (81% yield), (eluent: PE/EA = 5:1), yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 13.78 (br. s, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.91-7.84 (m, 1H), 7.70-7.64 (m, 1H), 4.32-4.15 (m, 4H), 1.38 (t, *J* = 7.0 Hz, 6H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.04 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.8 (d, *J* = 5.9 Hz), 147.8, 147.6 (qd, *J* = 35.4, 5.9 Hz), 133.2, 129.6, 128.4, 123.7, 121.1 (d, *J* = 10.3 Hz), 121.0 (q, *J* = 277.8 Hz), 95.8 (d, *J* = 177.5 Hz), 63.8 (d, *J* = 5.6 Hz), 15.9 (d, *J* = 6.9 Hz) ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 2987, 2646, 1618, 1576, 1487, 1402, 1136, 1014, 964, 768, 642. HRMS (ESI) calcd. for $C_{14}H_{15}F_3NO_4P$ $[M+H]^+$: 350.0764, found 350.0764.

4.3. Procedure for the synthesis of Methyl 3-(2,3-dioxoindolin-1-yl)-4,4,4-trifluorobut-2-enoate (4)

A mixture of **1** (1.0 mmol), **2** (1.0 mmol) and Na_2CO_3 (2.0 mmol) in DMF (10 mL) was stirred at rt for 5 minutes. Then, the mixture was poured into ice-water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by silica gel flash column chromatography to give the desired product *Z*-**4** and *E*-**4**.

*4.3.1 Methyl 3-(2,3-dioxoindolin-1-yl)-4,4,4-trifluorobut-2-enoate **(4**).*

Z-**4**: yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75-7.71 (m, 1H), 7.65-7.59 (m, 1H), 7.26-7.20 (m, 1H), 6.96 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 3.70 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -69.26 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 180.4, 161.5, 157.1, 150.6, 138.8, 133.4 (q, *J* = 37.4 Hz), 127.5 (q, *J* = 3.2 Hz), 126.0, 124.9, 117.9, 120.1 (q, *J* = 277.8 Hz), 111.3, 52.9 ppm. IR

(MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3091, 2964, 1736, 1606, 1470, 1300, 1203, 1140, 1066, 989, 897, 758, 669. HRMS (ESI) calcd. for $C_{13}H_8F_3NO_4$ $[M+H]^+$: 300.0478, found 300.0482.

E-**4**: yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.76-7.62 (m, 2H), 7.29-7.23 (m, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.63 (s, 1H), 3.91 (s, 3H) ppm.^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.39 (s, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 180.3, 161.9, 156.8, 150.1, 139.0, 132.2 (q, *J* = 2.2 Hz), 129.6 (q, *J* = 38.9 Hz), 126.0, 125.2, 119.6 (q, *J* = 277.8 Hz), 117.5, 111.4, 53.1 ppm. IR (MIR-ATR, 4000-600 cm^{-1}): v_{max} = 3070, 2960, 1736, 1608, 1471, 1257, 1140, 1103, 989, 762. HRMS (ESI) calcd. for $C_{13}H_8F_3NO_4$ $[M+H]^+$: 300.0478, found 300.0482.

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[13] CCDC 1886947 (**3a**) contains the supplementary crystallographic details for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/getstructures. Unit cell parameters (**3a**): a: 10.591(11) Å, b: 8.228(9) Å, c: 13.484(14) Å; α: 90.00°, β: 97.776(12)°, γ: 90.00°; space group: P2(1)/c.

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