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Green synthesis of 2-trifluoromethyl quinoline derivatives under metal-free conditions and their antifungal properties

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ABSTRACT

The skeleton of 2-trifluoromethyl quinoline is the core structure of many natural products and pharmaceutical molecules. The synthesis of this scaffold is limited by metal catalysis, harsh conditions, toxic or hazardous reagents and solvents, and lower atom-economy. Herein, a novel method for the synthesis of 2-trifluoromethyl quinolines *via* the [4 + 2] cyclization of β-keto esters or 1,3-diketones with various substituted *o*-aminobenzaldehydes using the metal free catalyst in EtOH is reported. This atom- and step-economical protocol features simple operation, broad substrate scope, and good functional-group compatibility. The synthetic utility of this methodology was highlighted by easy gram-scale synthesis and late-stage functionalization, which would promote the vigorous development of quinoline chemistry. Moreover, the in vitro antifungal activities of the 2-trifluoromethyl quinolines against *F. graminearum* (from wheat), *F. graminearum* (from corn), *F. moniliforme, F. oxysporum*, and *R. solani* were investigated to further potential utility of these compounds.

1. Introduction

In the context of the global energy crisis and environmental problems, developing green and sustainable synthetic methods is one of the most urgent tasks [1–3]. To achieve this goal, some factors should be mentioned in the process of developing synthetic new methods or synthetizing new products, such as maximization of resource efficiency, minimization of energy consumption, high product selectivity, operational simplicity, and environmental friendliness. Obviously, the barrier that affect the accomplishment of a green earth is lack of an efficient sustainable approach to devise strategies. Therefore, in order to overcome this limitation, the concept of green chemistry came into being. Green chemistry aims to reduce or eliminate the use of harmful chemicals in chemical production, including starting materials, catalyzers, and solvents, and realize the green integration of raw materials, reactions, and products [4]. Different from the traditional treatment method of "abatement after pollution", green chemistry reduces the generation and discharge of pollutants from the source. Among these, finding benign reaction media for the production of chemicals is one of the leading areas in this field. To date, numerous green solvents have been developed and used in chemical synthesis, such as water (H_2O), ethanol (EtOH), dimethyl carbonate (DMC), ionic liquids (ILs), and poly (ethylene glycol)s (PEGs) [5,6].

Quinoline, one of the privileged *N*-heterocyclic motifs, is widely found in many natural products, pharmaceuticals, functional materials, and bioactive molecules [7–9]. Among these, 2-trifluoromethyl quinolines are prominent and valuable structural subunits that exhibit a variety of pharmaceutical activities (Scheme 1), such as antimalarial, antibacterial, antituberculosis, antihypertensive, and anti-inflammatory [10–12]. Moreover, 2-trifluoromethyl quinoline scaffolds have also been used as organic ligands [13,14] and fluorescence probes [15,16]. Considering the importance of their biological activity and broad applications, it is of continuous and great interest in the development of efficient and straightforward methods for the synthesis of 2-trifluoromethyl quinolines. Over the past decades, substantial synthetic methods for accessing 2-trifluoromethtyl quinolines have been established, including Skraup – Doebner – von Miller quinoline synthesis [17–19], direct 2-trifluoromethylations of the quinoline core with various CF_3 reagents [20–23], intramolecular cyclization of trifluoroacetimidoyl chlorides [24–26], and intermolecular [5 + 1] reactions [27–29], [4 + 2] reactions [25,30–32], and [3 + 3] reactions [33,34]. For detail of [4 + 2] reactions, in 2001, Uneyama and co-

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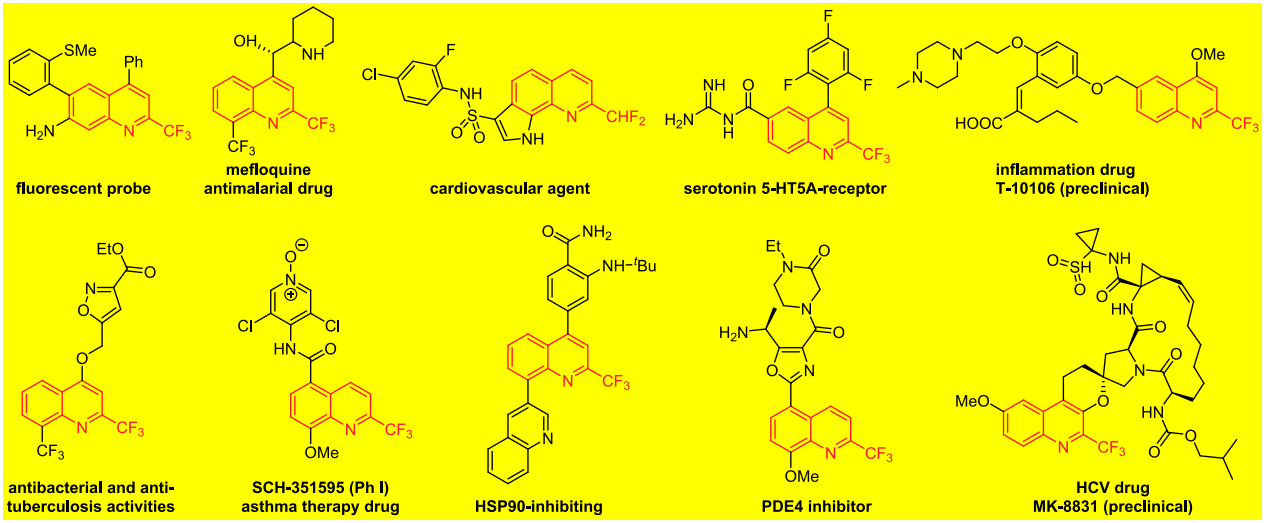
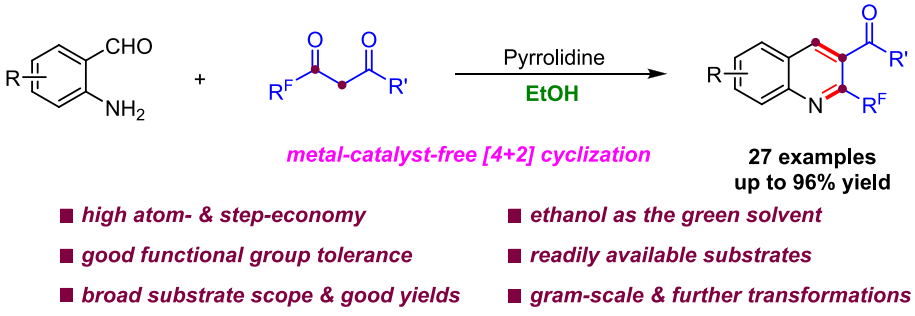


Scheme 1. Representative examples bearing the 2-trifluoromethyl quinoline core structure.



Scheme 2. Metal-catalyst-free synthesis of 2-trifluoromethyl quinoline derivatives in EtOH.

workers successfully disclosed an elegant method for the synthesis of 2-trifluoromethyl quinoline derivatives through Rh-catalyzed [4 + 2] annulation of *N*-aryl trifluoroacetimidoyl chlorides with alkynes [25]. Zhou and co-workers reported a [4 + 2] reaction between trifluoroacetimidoyl chlorides and alkynes in 2013 in the presence of visible-light [30]. In 2019, Zhang and co-workers disclosed base promoted cascade Knoevenagel and aza-Wittig reactions of *o*-azidobenzaldehyde and fluorinated 1,3-diketones to various 2-fluoroalkylated quinolines [31]. Soon after, a similar work was reported by Zhang's group [32]. Despite these tremendous achievements, the further use of these methods is limited by complicated starting materials, multiple synthetic steps, transition metal catalyzed, harsh reaction conditions, toxic or hazardous reagents and solvents, lower atom- and step-economy, as well as poor regioselectivities. Thus, it still remains highly challenging and attractive to develop new efficient methods to synthesize 2-trifluoromethyl quinolines from readily available materials under eco-friendly conditions from a scientific and practical standpoint [4].

In connection with our interest in heterocyclic chemistry and sustainable chemistry [35–41], here we present an unprecedented metal-catalyst-free [4 + 2] annulation reaction of *o*-aminobenzaldehydes and fluorinated β-keto esters or 1,3-diketones (Scheme 2). This new protocol provides an efficient, simple, and eco-friendly method for the rapidly assemble a myriad of 2-trifluoromethyl quinoline skeletons utilizing ethanol as a green solvent. This method features simple reaction conditions, good functional tolerance, high yields, and excellent atom- and step-economy. Scale-up reaction and late-stage functionalization of 2-trifluoromethylquinolines is feasible. Moreover, the in vitro antifungal activity of the title compounds was also studied.

2. Materials and methods

2.1. Chemicals and instruments

All reactions were carried out in air atmosphere. All reagents were purchased from Tansoole, Leyan, Bide pharmaceutical, Energy Chemical and were directly used without further purification unless otherwise noted. Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (TLC Silica Gel 60 F_{254}); Visualization of the developed chromatogram was performed by fluorescence. Flash chromatography was performed with silica gel (200–300 mesh) using ethyl acetate (EA)/petroleum ether (PE) as eluent. Proton nuclear magnetic resonance (^{1}H NMR) data were acquired at 400 MHz on Bruker Ascend spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as *s*, singlet; *d*, doublet; *t*, triplet; *m*, multiplet. Coupling constants *J* are quoted in Hz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) data were acquired at 100 MHz on Bruker Ascend 400 spectrometer. Chemical shifts are reported in ppm relative to the center line of a triplet at 77.16 ppm for chloroform-*d* and the center line of a septet at 47.6 ppm for MeOD. Fluorine nuclear magnetic resonance (^{19}F NMR) data were acquired at 376 MHz on a Bruker Ascend 400 spectrometer, and the chemical shifts were obtained from the MestReNova software without correction. Mass spectra were acquired on a Bruker Daltonics MicroTof-Q II mass spectrometer. Analytical data of products **3aa** [31], **3fa-3ga** [42], **3oa** [43], **3va** [44], **3ac** [31], and **3ad** [45] are in accordance with the literature values.

2.2. General procedure for the preparation of compounds **3**

In a sealed tube with a Teflon screw cap equipped with a stirring bar, *o*-aminobenzaldehydes **1** (0.5 mmol, 1.0 equiv.), fluorinated β-keto esters 1,3-diketones **2** (0.75 mmol, 1.5 equiv.), pyrrolidine (17.8 mg, 0.25 mmol, 0.5 equiv.) and EtOH (5.0 mL) were added and heated at 90 °C for 5 h. Then, the reaction mixture was cooled to room temperature, filtered on celite and washed with DCM (3 × 5 mL). The solvent of filtrate was removed under reduced pressure to produce crude product, which was purified by silica gel column chromatography to afford the desired product **3**.

2.3. General procedure for the evaluation of fungicidal activities

16.6 mg of the test sample was taken and dissolved in 0.66 mL of DMSO, and then, an aqueous solution containing 1 % Tween 80 was added to it to make 5 mg/mL of the original drug. An appropriate amount of the test drug was pipetted into a conical flask under aseptic conditions and shaken well, and then the same amount was poured into three petri dishes with a diameter of 9 cm to make a 500 μg/mL drug-containing plate. In the abovementioned experiments, the treatment without the drug was set as a blank control, and each treatment was repeated three times. The cultured pathogenic bacteria were cut along the edge of the colony with a hole punch with a diameter of 6.5 mm under aseptic conditions, and the bacterial cake was inoculated in the center of the drug-containing plate with an inoculator. The culture dish was cultured in a constant temperature incubator at 25 °C. When the diameter of the control colony expanded to more than 6 cm, the colony diameter was measured by the cross method, the average value was taken, and the bacteriostatic rate was calculated at the end of the culture.

2.4. Compounds data

2.4.1. Ethyl 2-(trifluoromethyl)quinoline-3-carboxylate (3aa)

(PE:EA = 10:1, R_f = 0.29, White solid, 93 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.00 – 7.87 (m, 2H), 7.78 – 7.70 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 147.0, 144.9 (q, J = 35.2 Hz), 140.3, 132.5, 130.3, 129.7, 128.3, 127.6, 124.2, 121.3 (q, J = 275.8 Hz), 62.6, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.87.

2.4.2. Ethyl 5-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (3ba)

(PE:EA = 10:1, R_f = 0.43, mp = 79–81 ℃, Yellow solid, 89 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.52 (d, J = 7.1 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 2.74 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 147.5, 144.3 (q, J = 35.1 Hz), 136.8, 135.8, 132.2, 130.0, 128.3, 127.1, 123.6, 121.3 (q, J = 275.5 Hz), 62.6, 18.7, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.84 (s, 1H). HRMS (ESI) *m/z* calculated for $C_{14}H_{13}F_3NO_2$ $[M + H]^+$ 284.0898, found 284.0906.

2.4.3. Ethyl 5-fluoro-2-(trifluoromethyl)quinoline-3-carboxylate (3ca)

(PE:EA = 10:1, R_f = 0.50, mp = 68–69 ℃, White solid, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.83 (td, J = 8.2, 6.0 Hz, 1H), 7.39 (t, J = 8.5 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 157.8 (d, J = 258.9 Hz), 147.4, 145.8 (q, J = 35.5 Hz), 134.0 (d, J = 4.0 Hz), 132.3 (d, J = 8.9 Hz), 126.1 (d, J = 4.4 Hz), 124.5 (d, J = 2.4 Hz), 121.1 (q, J = 276.0 Hz), 118.6 (d, J = 16.3 Hz), 113.2 (d, J = 18.9 Hz), 62.8, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.13, −119.93. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}F_4NO_2$ $[M + H]^+$ 288.0648, found 288.0652.

2.4.4. Ethyl 5-chloro-2-(trifluoromethyl)quinoline-3-carboxylate (3da)

(PE:EA = 10:1, R_f = 0.50, mp = 83–85 ℃, White solid, 76 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.85 – 7.67 (m, 2H), 4.49 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 147.6, 145.5 (q, J = 35.6 Hz), 137.2, 132.1, 129.5, 129.3, 126.0, 125.1, 121.1 (q, J = 276.0 Hz), 62.8, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.02. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}ClF_3NO_2$ $[M + H]^+$ 304.0352, found 304.0358.

2.4.5. Ethyl 5-bromo-2-(trifluoromethyl)quinoline-3-carboxylate (3ea)

(PE:EA = 10:1, R_f = 0.49, mp = 91–92 ℃, White solid, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 – 8.89 (m, 1H), 8.18 (dd, J = 9.8, 4.1 Hz, 1H), 8.02 – 7.90 (m, 1H), 7.79–7.66 (m, 1H), 4.50 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 147.6, 145.5 (q, J = 35.6 Hz), 139.8, 133.3, 132.6, 130.0, 127.3, 125.4, 122.4, 119.6, 62.9, 14.1 ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.97. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}BrF_3NO_2$ $[M + H]^+$ 347.9847, found 347.9853.

2.4.6. Ethyl 6-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (3fa)

(PE:EA = 10:1, R_f = 0.48, White solid, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.73 – 7.67 (m, 2H), 4.46 (q, J = 7.2 Hz, 2H), 2.58 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 145.9, 144.2 (q, J = 35.1 Hz), 140.5, 139.7, 135.2, 130.1, 128.0, 127.3, 121.7 (q, J = 275.5 Hz), 62.9, 22.2, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.72.

2.4.7. Ethyl 6-chloro-2-(trifluoromethyl)quinoline-3-carboxylate (3ga)

(PE:EA = 10:1, R_f = 0.38, White solid, 76 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 9.0, 2.2 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 145.1 (q, J = 35.6 Hz), 139.2, 135.9, 133.6, 131.8, 128.3, 126.9, 125.2, 121.1 (q, J = 275.6 Hz), 62.6, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.98.

2.4.8. Ethyl 6-bromo-2-(trifluoromethyl)quinoline-3-carboxylate (3 ha)

(PE:EA = 10:1, R_f = 0.29, White solid, 84 % yield). ^{1}H NMR (400 MHz, Acetone): δ 8.80 (s, 1H), 8.37 (d, J = 1.8 Hz, 1H), 8.06 – 7.97 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 145.2 (q, J = 29.8 Hz), 139.1, 136.1, 131.8, 130.3, 128.7, 125.2, 124.1, 121.1 (q, J = 275.9 Hz), 62.9, 14.1. ^{19}F NMR (376 MHz, Acetone): δ −64.55.

2.4.9. Ethyl 6-nitro-2-(trifluoromethyl)quinoline-3-carboxylate (3ia)

(PE:EA = 10:1, R_f = 0.19, mp = 128–130 ℃, White solid, 48 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 – 8.84 (m, 2H), 8.64 (dd, J = 9.3, 2.5 Hz, 1H), 8.41 (d, J = 9.3 Hz, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.7, 148.0 (d, J = 36.0 Hz), 147.6, 141.9, 132.3, 126.8, 126.1, 125.7, 124.7, 120.7 (d, J = 276.3 Hz), 63.2, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.34. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}F_3N_2O_4$ $[M + H]^+$ 315.0593, found 315.0600.

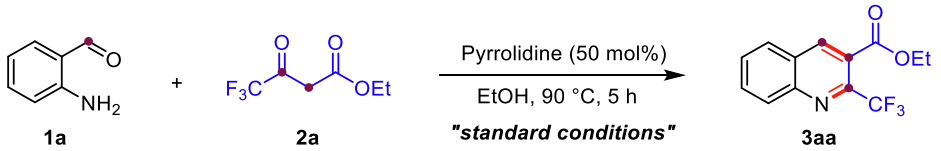
2.4.10. Ethyl 2,6-bis(trifluoromethyl)quinoline-3-carboxylate (3ja)

(PE:EA = 10:1, R_f = 0.43, mp = 93–94 ℃, White solid, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.36 (d, J = 8.9 Hz, 1H), 8.28 (s, 1H), 8.06 (dd, J = 8.9, 1.5 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 147.9, 146.9 (q, J = 35.6 Hz), 141.1, 131.6, 131.5 (q, J = 33.2 Hz), 128.1 (q, J = 2.9 Hz), 126.8, 126.2 (q, J = 4.4 Hz), 125.5, 120.9 (q, J = 260.0 Hz), 63.0, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.90, −64.21. HRMS (ESI) *m/z* calculated for $C_{14}H_{10}F_6NO_2$ $[M + H]^+$ 338.0616, found 338.0619.

2.4.11. Ethyl 7-amino-2-(trifluoromethyl)quinoline-3-carboxylate (3 ka)

(PE:EA = 3:1, R_f = 0.38, mp = 126–128 ℃, Yellow solid, 24 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.27 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 4.42 (dt, J = 19.8, 9.9 Hz, 4H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 150.5, 149.1, 145.4 (q, J = 69.4, 34.8 Hz), 140.0, 129.7, 121.5 (q, J = 280.2 Hz),

Table 1
Optimization of Reaction Conditions.[a]



Entry	Variations from the "standard conditions"	Yield (%)[b]
1	None	93
2	Without pyrrolidine	15
3	*L*-proline instead of pyrrolidine	20
4	Piperazine instead of pyrrolidine	35
5	Morpholine instead of pyrrolidine	42
6	DCM instead of EtOH	trace
7	DMF instead of EtOH	21
8	EA instead of EtOH	18
9	MeOH instead of EtOH	43
10[c]	H_2O instead of EtOH	19
11	**1a:2a** (1:1.2) instead of **1a:2a** (1:1.5)	50
12	Pyrrolidine (30 mol%) instead of pyrrolidine (50 mol%)	80
13	3 h instead of 5 h	60
14	10 h instead of 5 h	93
15	70 °C instead of 90 °C	45
16	0.065 M instead of 0.1 M	75
17	0.2 M instead of 0.1 M	79

[a] Standard conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), and pyrrolidine (50 mol%) in EtOH solvent (5.0 mL) at 90 °C for 5 h under air atmosphere. [b] Isolated yield. [c] TBAB (tetrabutylammonium bromide) was added (0.5 equiv.). DCM = dichloromethane, DMF = *N,N*-dimethylformamide, EA = ethyl acetate.

121.3, 121.2, 119.9, 108.9, 62.2, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.87. HRMS (ESI) *m/z* calculated for $C_{13}H_{12}F_3N_2O_2$ $[M + H]^+$ 285.0851, found 285.0855.

2.4.12. Ethyl 7-fluoro-2-(trifluoromethyl)quinoline-3-carboxylate (3la)

(PE:EA = 10:1, R_f = 0.29, mp = 43–44 ℃, Yellow solid, 66 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.70 (s, 1H), 7.99 (dd, *J* = 9.0, 5.8 Hz, 1H), 7.88 (dd, *J* = 9.5, 2.4 Hz, 1H), 7.54 (td, *J* = 8.7, 2.5 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.4, 164.8 (d, *J* = 255.6 Hz), 148.3 (d, *J* = 13.4 Hz), 146.0 (q, *J* = 35.5 Hz), 140.2, 130.6 (d, *J* = 10.2 Hz), 124.7, 123.7 (d, *J* = 2.7 Hz), 121.1 (q, *J* = 275.9 Hz), 120.6 (d, *J* = 25.7 Hz), 114.1 (d, *J* = 21.0 Hz), 62.7, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.02, −103.68. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}F_4NO_2$ $[M + H]^+$ 288.0648, found 288.0657.

2.4.13. Ethyl 7-chloro-2-(trifluoromethyl)quinoline-3-carboxylate (3ma)

(PE:EA = 10:1, R_f = 0.29, mp = 81-83℃, Pale yellow solid, 60 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.65 (s, 1H), 8.21 (d, *J* = 1.7 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.3, 147.3, 145.9 (q, *J* = 35.5 Hz), 140.1, 138.8, 130.9, 129.4, 129.2, 125.9, 124.4, 121.0 (q, *J* = 275.9 Hz), 62.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.06. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}ClF_3NO_2$ $[M + H]^+$ 304.0352, found 304.0357.

2.4.14. Ethyl 7-bromo-2-(trifluoromethyl)quinoline-3-carboxylate (3na)

(PE:EA = 10:1, R_f = 0.23, mp = 82–85 ℃, Pale yellow solid, 85 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.64 (d, *J* = 3.7 Hz, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 6.9 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.3, 147.3, 145.8 (d, *J* = 35.7 Hz), 140.2, 133.3, 132.5, 129.4, 127.1, 126.2, 124.5, 121.0 (d, *J* = 276.0 Hz), 62.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.05. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}BrF_3NO_2$ $[M + H]^+$ 347.9847, found 347.9850.

2.4.15. Ethyl 8-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (3oa)

(PE:EA = 10:1, R_f = 0.33, White solid, 50 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.63 (s, 1H), 7.73 (dd, *J* = 21.2, 7.5 Hz, 2H), 7.62 – 7.56 (m, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 2.82 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.9, 146.1, 143.5 (q, *J* = 35.0 Hz), 140.3, 138.8, 132.4, 129.4, 127.6, 126.1, 123.7, 121.4 (q, *J* = 275.5 Hz), 62.5, 17.6, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.80.

2.4.16. Ethyl 8-fluoro-2-(trifluoromethyl)quinoline-3-carboxylate (3pa)

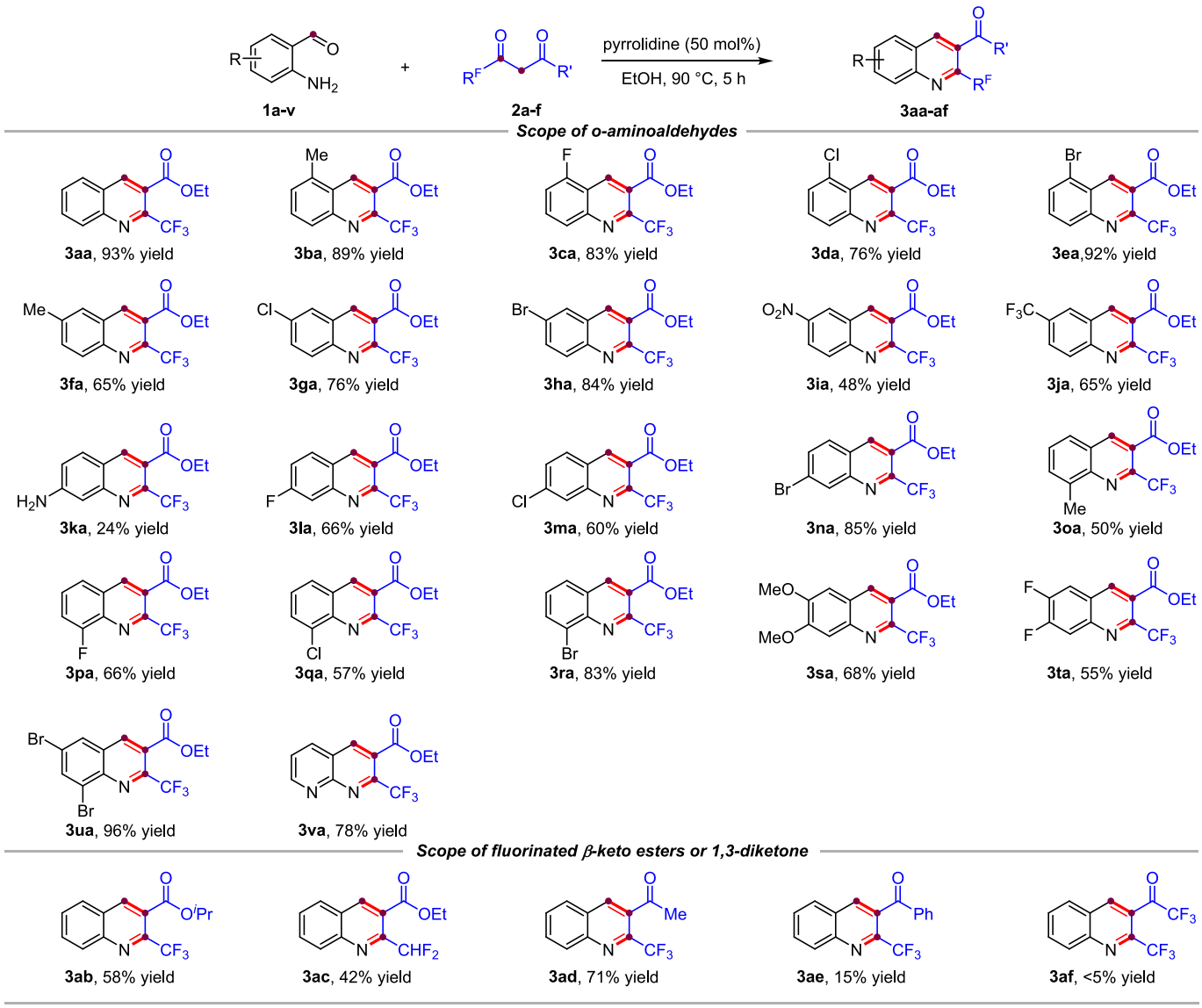
(PE:EA = 10:1, R_f = 0.23, mp = 71–73 ℃, Pale yellow solid, 66 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.69 (s, 1H), 7.69 (ddd, *J* = 14.9, 12.6, 6.5 Hz, 2H), 7.56 (td, *J* = 8.9, 1.2 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.1, 158.0 (d, *J* = 261.9 Hz), 144.8 (q, *J* = 36.3 Hz), 139.9 (d, *J* = 2.7 Hz), 137.1 (d, *J* = 12.1 Hz), 129.8 (d, *J* = 7.9 Hz), 129.0, 125.1, 123.9 (d, *J* = 5.0 Hz), 120.9 (q, *J* = 275.7 Hz), 116.5 (d, *J* = 18.5 Hz), 62.7, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.88, −122.05. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}F_4NO_2$ $[M + H]^+$ 288.0648, found 288.0650.

2.4.17. Ethyl 8-chloro-2-(trifluoromethyl)quinoline-3-carboxylate (3qa)

(PE:EA = 10:1, R_f = 0.29, mp = 79–81 ℃, Yellow solid, 57 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.70 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.3, 145.3 (d, *J* = 35.8 Hz), 143.4, 140.8, 135.0, 132.5, 129.7, 129.0, 127.2 125.1, 121.1 (d, *J* = 275.8 Hz), 62.8, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.88. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}ClF_3NO_2$ $[M + H]^+$ 304.0352, found 304.0358.

2.4.18. Ethyl 8-bromo-2-(trifluoromethyl)quinoline-3-carboxylate (3ra)

(PE:EA = 10:1, R_f = 0.29, mp = 86–87 ℃ Pale White solid, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.69 (s, 1H), 8.20 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.2, 145.4 (q, *J* = 35.8 Hz), 144.3, 140.9, 136.1, 130.1, 128.9, 128.0, 126.0, 125.1, 121.0 (q, *J* = 275.8 Hz), 62.8, 14.1. ^{19}F NMR (376 MHz,



Scheme 3. Scope of *o*-aminobenzaldehydes and fluorinated β-keto esters or 1,3-diketones. Reaction conditions: Unless otherwise specified, reactions are performed under standard condition: **1a-v** (0.5 mmol), **2a-f** (0.75 mmol), and pyrrolidine (50 mol%) in EtOH (5.0 mL) at 90 °C for 5 h under air atmosphere. The yields were given as isolated yields.

$CDCl_3$): δ −63.88. HRMS (ESI) *m/z* calculated for $C_{13}H_{10}BrF_3NO_2$ $[M + H]^+$ 347.9847, found 347.9850.

2.4.19. Ethyl 6,7-dimethoxy-3-(trifluoromethyl)-2-naphthoate (3sa)

(PE:EA = 5:1, R_f = 0.34, mp = 148–149 ℃, White solid, 68 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.51 (s, 1H), 7.52 (s, 1H), 7.14 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.05 (d, *J* = 6.4 Hz, 6H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.0, 155.0, 152.3, 144.6, 142.8 (q, *J* = 35.0 Hz), 137.9, 123.9, 122.4, 121.6 (q, *J* = 275.0 Hz), 108.4, 105.0, 62.4, 56.7, 56.5, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.40. HRMS (ESI) *m/z* calculated for $C_{15}H_{16}F_3NO_4$ $[M + H]^+$ 330.0953, found 330.0955.

2.4.20. Ethyl 6,7-difluoro-2-(trifluoromethyl)quinoline-3-carboxylate (3ta)

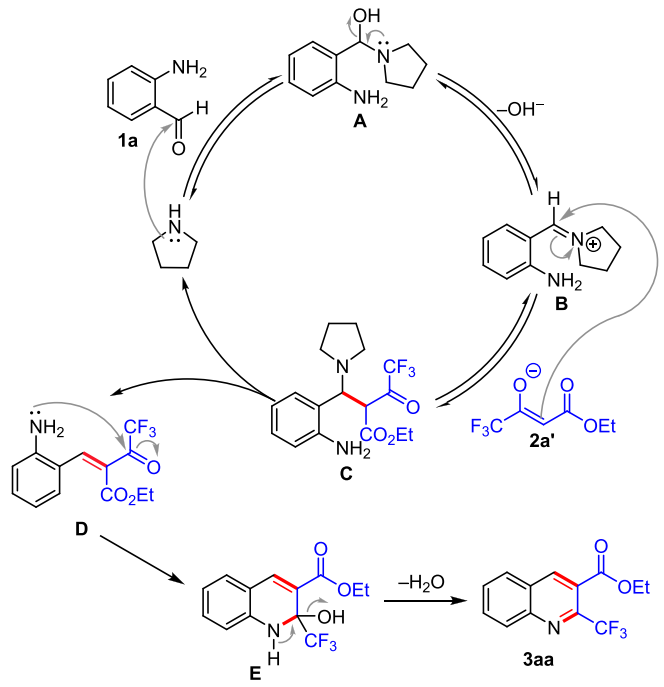
(PE:EA = 10:1, R_f = 0.30, mp = 75–76 ℃, Yellow solid, 55 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.62 (s, 1H), 8.00 (dd, *J* = 10.5, 7.5 Hz, 1H), 7.70 (dd, *J* = 9.3, 8.4 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.2, 154.3 (dd, *J* = 260.2, 16.1 Hz), 152.2 (dd, *J* = 258.7, 16.0 Hz), 145.3 (dd, *J* = 35.5, 3.2 Hz), 144.5 (d, *J* = 11.8 Hz), 139.4 (dd, *J* = 5.4, 1.5 Hz), 125.0 (d, *J* = 8.6 Hz), 124.6 (d, *J* = 2.0 Hz), 121.0 (q, *J* = 275.7 Hz), 116.7 (dd, *J* = 16.9, 1.3 Hz), 113.6 (dd, *J* = 18.1, 1.7 Hz), 62.9, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.04, −125.46, −129.27. HRMS (ESI) *m/z* calculated for $C_{13}H_9F_5NO_2$ $[M + H]^+$ 306.0553, found 306.0559.

2.4.21. Ethyl 6,8-dibromo-2-(trifluoromethyl)quinoline-3-carboxylate (3ua)

(PE:EA = 10:1, R_f = 0.43, mp = 115–116 ℃, White solid, 96 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.57 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 164.7, 145.6 (q, *J* = 36.0 Hz), 143.0, 139.8, 138.8, 129.8, 129.4, 126.9, 125.9, 123.5, 120.8 (q, *J* = 275.9 Hz), 63.0, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.97. HRMS (ESI) *m/z* calculated for $C_{13}H_9Br_2F_3NO_2$ $[M + H]^+$ 425.8952, found 425.8955.

2.4.22. Ethyl 2-(trifluoromethyl)-1,8-naphthyridine-3-carboxylate (3va)

(PE:EA = 2:1, R_f = 0.39, White solid, 78 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.29 (dd, *J* = 4.1, 1.9 Hz, 1H), 8.75 (s, 1H), 8.37 (dd, *J* = 8.2,



Scheme 4. Proposed reaction mechanism.

1.9 Hz, 1H), 7.69 (dd, J = 8.2, 4.2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 156.7, 154.6, 147.9 (q, J = 35.7 Hz), 141.7, 137.5, 125.5, 124.9, 122.6, 120.8 (d, J = 276.3 Hz), 63.0, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.14.

2.4.23. Isopropyl 2-(trifluoromethyl)quinoline-3-carboxylate (3ab)

(PE:EA = 10:1, R_f = 0.51, mp = 51–52 ℃, Yellow solid, 58 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.73 (t, J = 7.5 Hz, 1H), 5.33 (dt, J = 12.5, 6.3 Hz, 1H), 1.42 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 146.9, 144.7 (q, J = 35.3 Hz), 140.1, 132.4, 130.2, 129.6, 128.3, 127.6, 124.7, 121.3 (q, J = 275.6 Hz), 70.6, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.60. HRMS (ESI) m/z calculated for $C_{14}H_{13}F_3NO_2$ $[M + H]^+$ 284.0898, found 284.0906.

2.4.24. Ethyl 2-(difluoromethyl)quinoline-3-carboxylate (3ac)

(PE:EA = 10:1, R_f = 0.30, Yellow oil, 42 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.92 – 7.82 (m, 1H), 7.72 – 7.66 (m, 1H), 7.56–7.24 (m, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 150.6 (t, J = 22.0 Hz), 148.1, 141.0, 132.6, 130.2, 129.0, 128.7, 127.3, 122.7 (t, J = 1.9 Hz), 111.4 (t, J = 241.3 Hz), 62.3, 14.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.28.

2.4.25. 1-(2-(Trifluoromethyl)quinolin-3-yl)ethan-1-one (3ad)

(PE:EA = 5:1, R_f = 0.29, Yellow solid, 71 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.96 – 7.84 (m, 2H), 7.76 – 7.70 (m, 1H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 146.8, 136.9, 132.7, 132.3, 130.2, 129.8, 128.2, 127.6, 121.3 (q, J = 275.7 Hz), 30.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.93.

2.4.26. Phenyl(2-(trifluoromethyl)quinolin-3-yl)methanone (3ae)

(PE:EA = 10:1, R_f = 0.17, Yellow oil, 15 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 – 8.25 (m, 1H), 7.96 – 7.88 (m, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 146.8, 144.8 (q, J = 34.9 Hz), 137.4, 136.3, 134.3, 132.0, 130.7, 130.3, 130.2, 129.7, 128.8, 128.0, 127.3, 121.2 (q, J = 276.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.74. HRMS (ESI) m/z calculated for $C_{17}H_{11}F_3NO$ $[M + H]^+$ 302.0793, found 302.0799.

2.4.27. 2-(Trifluoromethyl)quinoline-3-carbaldehyde (4aa)

(PE:EA = 8:1, R_f = 0.47, White solid, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (d, J = 1.7 Hz, 1H), 8.97 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.98 (dd, J = 11.4, 4.1 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.7 (q, J = 3.7 Hz), 147.8, 146.2 (q, J = 35.6 Hz), 139.8, 133.6, 130.2, 129.85, 129.5, 128.0, 126.4, 121.6 (q, J = 276.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −60.98. HRMS (ESI) m/z calculated for $C_{11}H_7F_3NO$ $[M + H]^+$ 226.0480, found 226.0483.

2.4.28. (2-(Trifluoromethyl)quinolin-3-yl)methanol (5aa)

(PE:EA = 8:1, R_f = 0.15, White solid, mp = 120–121 ℃, 65 % yield). ^{1}H NMR (400 MHz, MeOD): δ 8.67 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.88 – 7.79 (m, 1H), 7.73 (t, J = 7.5 Hz, 1H), 4.96 (s, 2H). ^{13}C NMR (100 MHz, MeOD): δ 145.3, 144.2 (dd, J = 67.8, 33.9 Hz), 136.5, 132.4, 130.3, 129.1, 128.9, 128.8, 127.5, 122.1 (q, J = 275.5 Hz), 58.7 (q, J = 4.2 Hz). ^{19}F NMR (376 MHz, MeOD): δ −66.45. HRMS (ESI) m/z calculated for $C_{11}H_9F_3NO$ $[M + H]^+$ 228.0636, found 228.0642.

2.4.29. 2-(Trifluoromethyl)quinoline-3-carboxylic acid (6aa)

(DCM:MeOH = 8:1, R_f = 0.21, White solid, mp = 197–200 ℃, 99 % yield). ^{1}H NMR (400 MHz, MeOD): δ 8.77 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.90 – 7.82 (m, 1H), 7.70 (t, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, MeOD): δ 166.8, 146.6, 144.3 (q, J = 35.2 Hz), 140.0, 132.3, 129.5, 129.2, 128.3, 127.7, 124.6, 121.2 (q, J = 274.8 Hz). ^{19}F NMR (376 MHz, MeOD): δ −65.33. HRMS (ESI) m/z calculated for $C_{11}H_7F_3NO_2$ $[M + H]^+$ 242.0429, found 242.0432.

2.4.30. Cyclohexyl 2-(trifluoromethyl)quinoline-3-carboxylate (7aa)

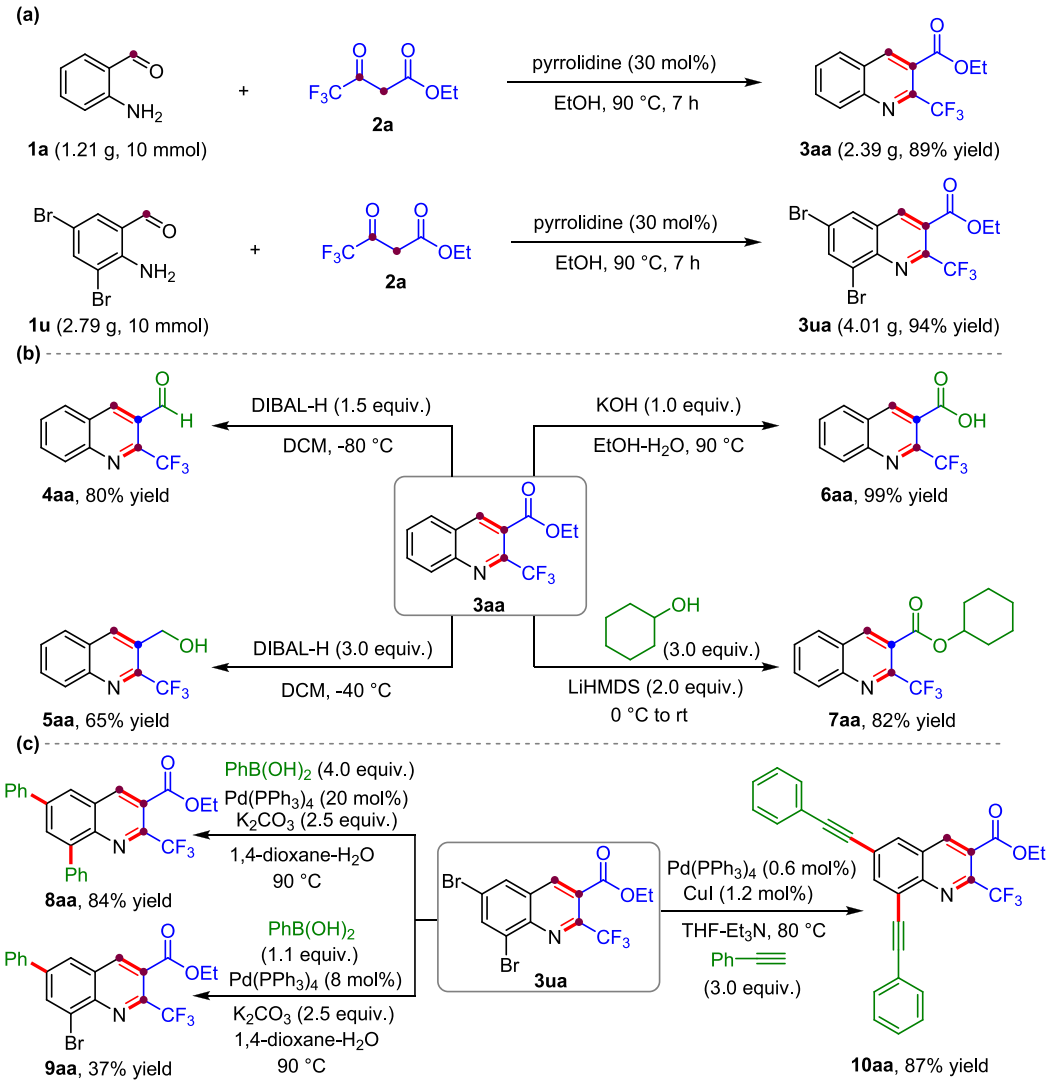
(PE:EA = 10:1, R_f = 0.31, White solid, mp = 73–74 ℃, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.65 (t, J = 7.6 Hz, 1H), 5.09 – 4.97 (m, 1H), 2.02 – 1.90 (m, 2H), 1.80 – 1.68 (m, 2H), 1.60 – 1.47 (m, 3H), 1.45 – 1.30 (m, 2H), 1.22 (ddt, J = 17.9, 14.2, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 146.8, 144.6 (q, J = 35.0 Hz), 140.0, 132.3, 130.1, 129.5, 128.2, 127.5, 124.6, 121.2 (q, J = 275.6 Hz), 75.4, 31.4, 25.3, 23.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.57. HRMS (ESI) m/z calculated for $C_{17}H_{16}F_3NNaO_2$ $[M + Na]^+$ 346.1031, found 346.1031.

2.4.31. Ethyl 6,8-diphenyl-2-(trifluoromethyl)quinoline-3-carboxylate (8aa)

(PE:EA = 8:1, R_f = 0.47, Colorless oil, 84 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.72 (d, J = 7.4 Hz, 2H), 7.63 (d, J = 7.3 Hz, 2H), 7.45 – 7.38 (m, 4H), 7.34 (td, J = 7.2, 4.8 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 143.8 (q, J = 35.6 Hz), 143.7, 142.2, 141.8, 140.6, 139.3, 137.7, 132.7, 131.0, 129.2, 128.6, 128.4, 128.1, 127.6, 125.4, 125.0, 121.3 (q, J = 275.8 Hz), 62.5, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.72. HRMS (ESI) m/z calculated for $C_{25}H_{18}F_3NNaO_2$ $[M + Na]^+$ 444.1187, found 444.1186.

2.4.32. Ethyl 8-bromo-6-phenyl-2-(trifluoromethyl)quinoline-3-carboxylate (9aa)

(PE:EA = 10:1, R_f = 0.38, mp = 97–99 ℃, White solid, 37 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.39 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 1.7 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.42 – 7.35 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 145.0 (q, J = 35.8 Hz), 143.4, 143.1, 140.8, 138.0, 135.6, 129.3, 129.0, 128.9, 127.5, 126.2, 125.3, 125.1, 120.9 (q, J = 275.7 Hz), 62.7, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.79. HRMS (ESI) m/z calculated for $C_{19}H_{13}BrF_3NNaO_2$ $[M + Na]^+$ 445.9979, found 445.9984.



Scheme 5. Scaled-up reaction and synthetic utilization.

2.4.33. Ethyl 6,8-bis(phenylethynyl)-2-(trifluoromethyl)quinoline-3-carboxylate (10aa)

(PE:EA = 8:1, R_f = 0.44, mp = 98–100 °C, Brown solid, 37 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (s, 1H), 8.10 (d, J = 1.7 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H), 7.61 (dd, J = 4.6, 2.3 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.37 – 7.27 (m, 6H), 4.40 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 146.0, 145.1 (q, J = 35.7 Hz), 140.1, 138.0, 132.1, 131.9, 130.5, 129.2, 129.0, 128.6, 128.5, 127.7, 125.2, 125.1, 124.8, 122.9, 122.3, 121.1 (q, J = 275.8 Hz), 98.0, 93.0, 87.6, 85.2, 62.7, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.88. HRMS (ESI) *m/z* calculated for $C_{29}H_{18}F_3NNaO_2$ $[M + Na]^+$ 492.1187, found 492.1185.

3. Results and discussion

3.1. Optimization of the reaction conditions

We commenced our studies with *o*-aminobenzaldehyde **1a** and ethyl 4,4,4-trifluoro-3-oxobutanoate **2a** as the model substrates to explore the reaction conditions (Table 1). After exploring relevant reaction parameters, gratifyingly, we found that pyrrolidine (50 mol%) in EtOH (5 mL) was able to catalyze this novel [4 + 2] annulation efficiently at 90 °C for 5 h under an air atmosphere, and led to desired 2-trifluoromethyl quinoline **3aa** in 93 % yield (Table 1, entry 1). Controlled experiment showed that the pyrrolidine played a vital role in the named process (Table 1, entry 2). Other secondary amines, e.g., *L*-proline, piperazine, and morpholine were also suitable catalyzer for the present transformations (Table 1, entries 3–5). Traces of product was detected in DCM (Table 1, entry 6). Intriguingly, a greatly diminished yield was obtained in polar DMF (Table 1, entry 7). Except for EtOH, several common green solvents such as EA, MeOH, and H_2O were also applicable in this protocol (Table 1, entries 8–10). A smaller amount of **2a** (1.2 equiv.) or pyrrolidine (30 mol%) led to a dramatic decrease in yield (Table 1, entries 11–12). Similarly, lower yields of **3aa** were obtained for shortening the reaction time or reducing the reaction temperature (Table 1, entry 13 and entry 15). Further study by increasing the reaction time did not show an obviously flourishing tendency in yield (Table 1, entry 14). Concentration screening experiments showed that the concentration of **1a** has a significant impact on the reaction performance, and either a higher or a lower concentration gave less product (Table 1, entries 16–17).

3.2. Substrates scope for synthesizing 2-trifluoromethyl quinolines

With the optimized reaction conditions in hand, the substrate scope of *o*-aminobenzaldehydes for the [4 + 2] annulation reaction was first investigated. To our delight, most of the substrates were efficiently converted to the corresponding 2-trifluoromethyl quinolines with good to excellent yields under optimized reaction conditions. The results are

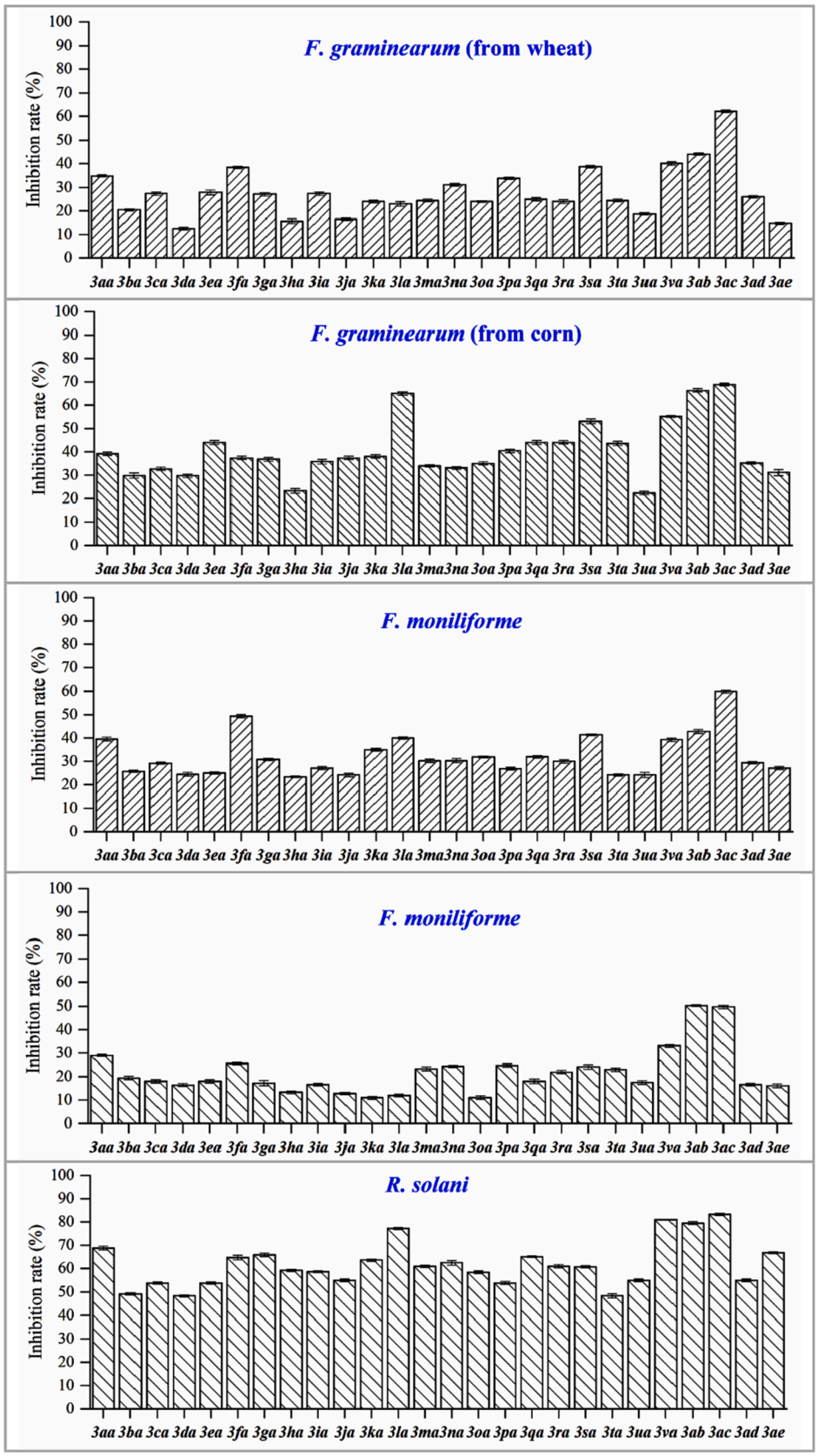


Fig. 1. Antifungal activity of **3aa-3ae.**

summarized in Scheme 3. Regarding the *o*-aminobenzaldehyde, various substituents at any position of benzene ring, including methyl (**1b**, **1f**, and **1o**), halides such as fluorine (**1c**, **1 L**, and **1p**), chlorine (**1d**, **1 g**, **1 m,** and **1q**), bromine (**1e**, **1 h**, **1n,** and **1r**), and strong electron-withdrawing groups such as nitro (**1i**), and trifluoromethyl (**1j**) groups were all tolerated well. Notably, substrate **1 k** with strong electron-donating group (–NH_2) was compatible as well, albeit with a lower yield. Moreover, this reaction was not limited to monosubstituted substrates, disubstituted *o*-aminobenzaldehydes (**1 s**-**1u**) also reacted well to afford the corresponding products **3sa-ua** in 68 %, 55 %, and 96 % yields, respectively. Additionally, it is worth noting that the reaction with pyridine-derived substrate **1v** proceeded smoothy to give desired product in 78 % yield.

We further evaluated the scope of fluorinated β-keto esters or 1,3-diketones. Replacement **2a** with isopropyl 4,4,4-trifluoro-3-oxobutanoate **2b** also reacted smoothy, delivering the desired product in 58 % yield. Except CF_3-substituent β-keto esters, β-keto ester containing CHF_2 (**2c**) group was also well tolerated. Intrigued by the results obtained, we extended the scope of β-keto esters to 1,3-diketones. Among the various 1,3-diketones tested, methyl ketone **2d** and phenyl ketone **2e** reacted smoothly under the standard reaction conditions and gave the desired product **3ad** and **3ae** in 71 % and 15 % yields, respectively. Hexafluoroacetylacetone **2f** showed extremely lower reactivity under the same conditions.

3.3. Proposed reaction mechanism

Based on previous literature reports [46–49] and above experiment results, a plausible catalytic cycle has been proposed for the metal-catalyst-free [4 + 2] annulation described herein, using **1a** and **2a** as representative substrates (Scheme 4). Initially, an active iminium salt **B** was generated from the condense reaction of *o*-aminobenzaldehyde **1a** with pyrrolidine. Next, intermediate **B** reacted with enolate **2a'** to afford nucleophilic adduct **C**, from which pyrrolidine was removed by 1,2-elimination and participated in catalytic cycle. Then the Knoevenagel condensation product **D** was obtained and underwent nucleophilic addition and dehydration, which gave the desired 2-trifluoromethyl quinoline **3aa**.

3.4. Scale-up reactions and further transformations

To illustrate the practicality of this newly established methodology, large scale (10 mmol) synthesis of **3aa** and **3ua** were carried out (Scheme 5). The product was isolated in 89 % and 94 % yields under the standard reaction conditions. Product **3aa** could be converted to corresponding aldehyde **4aa** in 80 % yield with diisobutylaluminum hydride (DIBAL-H) reduction. Similarly, treatment **3aa** with 3.0 equiv. DIBAL-H at −40 °C, corresponding benzylic alcohol **5aa** was obtained in good yield. Then, carboxylic acid **6aa** was observed through hydrolysis of ester group. The treatment of **3aa** with lithium bis(trimethylsilyl)amide (LiHMDS) in cyclohexanol at room temperature for 3 h could afford transesterification product **7aa** in 82 % yield, which is difficult to be obtained through other methods. Next, several transition metal-catalyzed cross coupling reactions were performed with dibrominated product **3ua**. Adjusting the reaction performance by changing the loading of $Pd(PPh_3)_4$ and phenyl boronic acid, we obtained the Suzuki coupling products **8aa** and **9aa** in 84 % and 37 % yields, respectively. Notably, subjecting **3ua** to Sonogashira coupling reaction conditions, alkynylation product **10aa** was isolated in 87 % yield.

3.5. Antifungal activities

To further demonstrate the potential application of 2-trifluoromethyl quinoline scaffolds, the in vitro antifungal activity of target compounds against *F. graminearum* (from wheat), *F. graminearum* (from corn), *F. moniliforme*, *F. oxysporum*, and *R. solani* were performed [50], and the results are summarized in Fig. 1. In general, most of the designed 2-trifluoromethyl quinoline derivatives displayed a certain degree of fungicidal activity against the above mentioned five kinds of fungi at a concentration of 500 μg/mL in DMSO. Among them, the synthesized compounds noticeably were obviously better to *R. solani* than other tested four fungi, with a moderate to good inhibitor rate. Particularly, compound **3ad** exhibited 83.24 % inhibitory index against *R. solani*.

4. Conclusion

In summary, we have successfully developed an environmentally friendly, economical and straightforward [4 + 2] protocol to the synthesis of 2-trifluoromethyl quinoline skeletons from commercially available β-keto esters or 1,3-diketones and various *o*-aminobenzaldehydes. The reaction exhibited good yields, high atom- and step-economy, wide substrate scope, and excellent functional group tolerance. The established method is scalable, simply operable (under air atmosphere), solvent green (EtOH as solvent), and metal-catalyst-free (pyrrolidine as the catalyst). The outstanding synthetic utility of this methodology was highlighted by a series of further transformations and preliminary antifungal activities. Further investigations on the synthesis of novel complex molecules with green methods and their applications are ongoing in our laboratories.

CRediT authorship contribution statement

Liangxin Fan: Conceptualization, Methodology, Investigation, Writing – original draft. **Fangyu He:** Conceptualization, Investigation, Data curation. **Lijun Shi:** Resources, Formal analysis. **Guoyu Yang:** Data curation. **Zhenliang Pan:** Data curation. **Miaomiao Wang:** Investigation, Data curation. **Caixia Wang:** Validation, Visualization. **Lulu Wu:** Resources. **Senyu Han:** Data curation. **Yifang Guo:** Data curation. **Cuilian Xu:** Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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