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Iron-catalyzed three-component tandem process: a novel and convenient synthetic route to quinoline-2,4-dicarboxylates from arylamines, glyoxylic esters, and α-ketoesters

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ABSTRACT

A new and convenient iron-catalyzed three-component tandem reaction of aromatic amines, glyoxylic esters, and α-ketoesters has been developed for the synthesis of quinoline-2,4-dicarboxylates under mild conditions. The present protocol, which utilizes cheap catalysts, readily-available starting materials and mild reaction conditions, provides an attractive approach to a series of functionalized quinoline derivatives with promising unique pharmaceutical, biological, and fluorescence-labeling applications.

1. Introduction

Quinolines and their derivatives are ubiquitous in various natural products, and many of them have been widely recognized as important structural motifs to design tremendous synthetic drug candidates since they possess a broad spectrum of biological properties of antimalarials, antibacterial, antipsychotic activity, antiinflammatory, anticancer, anti-HIV, and antituberculosis, etc.[1] In particular, quinoline-2,4-dicarboxylate derivatives are of great importance as pharmaceutical and synthetic materials, because their carboxyl groups could additionally play a pivotal role in endowing the unique bioactivities of quinolines.[2] For example, quinoline 2,4-dicarboxylic acids (QDCs) **I** and **II** can be used as inhibitors against the vesicular glutamate transport (VGLUT) protein (Fig. 1).[2a,b] Compounds **III** were discovered to be promising moieties of new fluorescent tags for monitoring of biomolecules (Fig. 1).[3]

Generally, quinoline-2,4-dicarboxylates were synthesized by a modified Doebner–von Miller pathway prepared by the condensation of dimethyl ketoglutaconate (DKG) with substituted anilines.[2–4] Alternatively, the selective conjugate reaction of the preformed *N*-arylphosphazenes to α,β-unsaturated carbonyl compounds has also been developed.[5] However, both methods suffer from some disadvantages, such as the need of extra steps to prepare active starting materials, a large amount of promoters, the low yield. Therefore, the development of simple, convenient, efficient and, especially, environmentally friendly synthetic methodologies for the construction of quinoline-2,4-dicarboxylates still remains highly desirable.

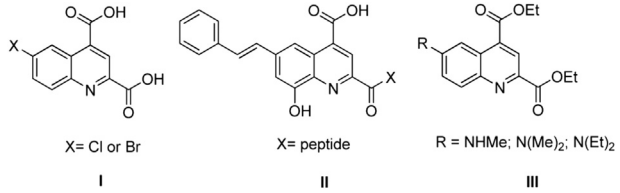

Fig. 1. Structures of some biologically important quinoline-2,4-dicarboxylate derivatives.

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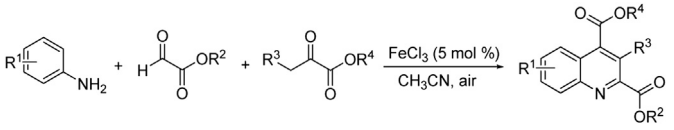
Recently, iron salts as an alternative and promising transition-metal catalysts, have drawn much attention for various organic transformations and synthesis of heterocyclic compounds due to their cost-effectiveness, ready availability, sustainability, and environmentally friendly properties.[6,7] Over the past few years, several examples of iron-catalyzed coupling reactions for the construction of quinoline compounds have been reported.[8–11] For example, Fan et al. described an iron-catalyzed A^3-reaction of aldehydes, amines, and alkynes via a tandem process for preparing 2,4-disubstituted quinolines.[9] Li et al. reported an iron-catalyzed cascade reaction of ynone with *o*-aminoaryl compounds leading to 3-carbonyl quinolines.[10] Wang et al. presented the iron-promoted (25 mol %) tandem reaction of anilines with styrene oxides for the synthesis of 3-substituted quinolines.[11] However, quinoline-2,4-dicarboxylates could not be afforded by the reported iron-catalyzed procedures. Herein, we wish to report a new and convenient iron-catalyzed three-component tandem reaction of aromatic amines, glyoxylic esters, and α-ketoesters for the construction of a serial of quinoline-2,4-dicarboxylates under mild conditions (Scheme 1). The present protocol provides an attractive and environmentally friendly approach to a variety of functionalized quinoline-2,4-dicarboxylates in a simple and one-pot procedure.

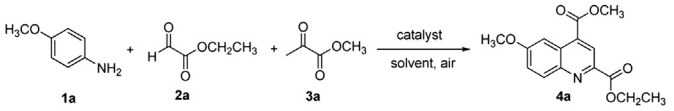


Scheme 1. Iron-catalyzed three-component reaction for the synthesis of quinoline-2,4-dicarboxylates.

2. Results and discussion

Initially, the reaction for the synthesis of quinoline-2,4-dicarboxylate **4a** from *p*-anisidine **1a**, ethyl glyoxylate **2a**, and methyl pyruvate **3a** was conducted to examine the catalytic activity of various simple metal complexes, such as Cu, Ag, Bi, Pd, Zn, Fe, and In salts (10 mol %) in CH_3CN at room temperature. As shown in Table 1, among various metal salts screened, $FeCl_3$ was found to be the most effective catalyst that afforded the desired product **4a** in 88% yield (Table 1, entry 8). Further optimization showed that $FeCl_3$ could still maintain high activity even when the catalyst loading was reduced to 5 mol % (Table 1, entry 11). A relatively lower yield was obtained with the further reduction of the catalyst loading (Table 1, entries 12 and 13). No product was observed in the absence of catalyst (Table 1, entry 1). The screening of a range of solvents using $FeCl_3$ as catalyst demonstrated that CH_3CN was the optimal reaction medium while others, such as toluene, 1,4-dioxane, DME, DMSO, CH_2Cl_2, EtOAc, THF, and CH_3OH gave lower yields of the quinolines (entries 14–21). Moreover, the reaction was accelerated when the model reaction was carried out under 60 °C, but the yield was not improved as expected (Table 1, entry 22).

Table 1
Reaction of *p*-anisidine **1a**, ethyl glyoxylate **2a**, and methyl pyruvate **3a** under various reaction conditions[a]

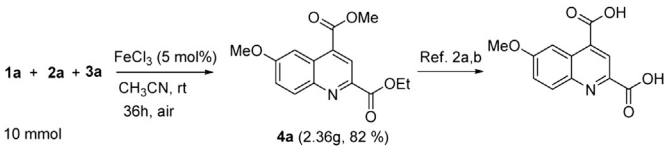


Entry	Catalyst (mol %)	Solvent	Yield (%)[b]
1	None	CH_3CN	0
2	$Cu(OTf)_2$ (10)	CH_3CN	61
3	AgOTf (10)	CH_3CN	62
4	$Bi(OTf)_3$(10)	CH_3CN	66
5	$Pd(OAc)_2$ (10)	CH_3CN	0
6	$Zn(OTf)_2$ (10)	CH_3CN	58
7	$CuBr_2$ (10)	CH_3CN	68
8	$FeCl_3$ (10)	CH_3CN	88
9	$InCl_3$(10)	CH_3CN	80
10	$FeCl_3$ (15)	CH_3CN	89
11	$FeCl_3$ (5)	CH_3CN	88
12	$FeCl_3$ (2)	CH_3CN	79
13	$FeCl_3$ (1)	CH_3CN	76
14	$FeCl_3$ (5)	Toluene	60
15	$FeCl_3$ (5)	1,4-Dioxane	62
16	$FeCl_3$ (5)	DME	64
17	$FeCl_3$ (5)	DMSO	40
18	$FeCl_3$ (5)	CH_2Cl_2	65
19	$FeCl_3$ (5)	EtOAc	45
20	$FeCl_3$ (5)	THF	60
21	$FeCl_3$ (5)	CH_3OH	40
22	$FeCl_3$ (5)	CH_3CN	72[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), **3a** (0.75 mmol), catalyst (1–10 mol %), CH_3CN (3 mL), room temperature, under air, 30 h.
[b] Isolated yields based on **1a**.
[c] 60 °C, 12 h.

Under the optimized conditions, the scope and generality of this process were tested with respect to various aromatic amines, and a series of substituted quinoline-2,4-dicarboxylates were obtained in moderate to good yields (Table 2). Both electron-rich and electron-withdrawing aromatic amines were suitable for this protocol. In general, aromatic amines containing electron-rich groups showed the better activities than those bearing electron-withdrawing groups (**4a**–**l**). Long chain alkyl substituted aromatic amine, such as 4-butylaniline and cycloalkyl substituted aromatic amine, such as 4-cyclohexylaniline could be transformed into the desired products in 72% and 71% yields, respectively, (**4e** and **f**). It is noteworthy that a wide range of functionalities, such as halogen, hydroxyl, cyano, and carbonyl groups were compatible with this reaction leading to the products **4g**–**l**, which could be used for further transformations. Furthermore, (2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl 2-oxoacetate was also compatible with this reaction, affording the desired product **4n** in 62% yield. In addition, α-alkyl substituted ketoester, such as methyl 2-oxo-4-phenylbutanoate was tolerated in this process, but a relatively low yield was obtained presumably because of the steric effect (**4o**).

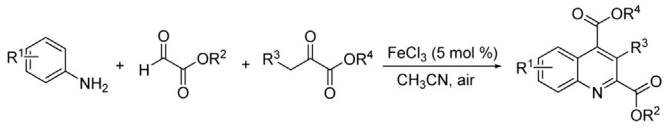
To examine the feasibility of a large-scale reaction, the reaction of *p*-anisidine **1a**, ethyl glyoxylate **2a**, and methyl pyruvate **3a** was investigated. The reaction could afford 2.36 g of **4a** in 82% yield without any significant loss of its efficiency (Scheme 2). Therefore, this protocol could be used as a practical method to synthesize the precursors of some important bioactive molecules, such as quinoline 2,4-dicarboxylic acid (QDC), which can be employed as inhibitor against the vesicular glutamate transport (VGLUT).[2a,b]

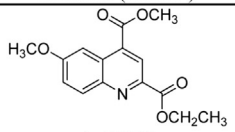
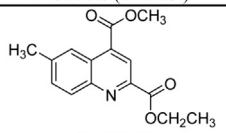
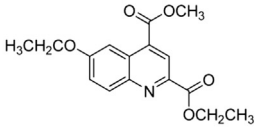
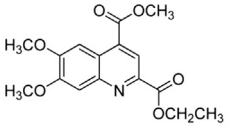
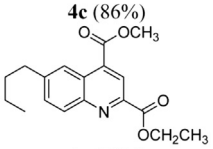
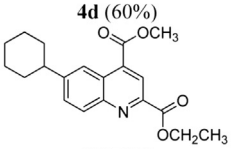
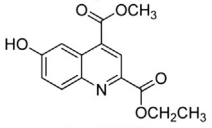
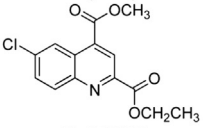
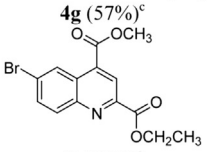
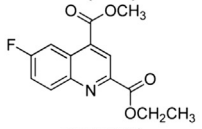
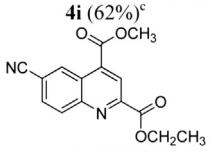
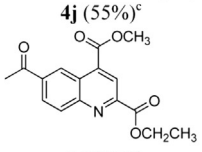
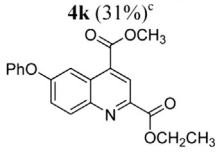
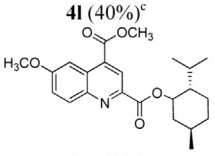
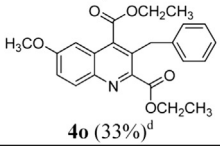


Scheme 2. The large-scale reaction for the construction of quinoline-2,4-dicarboxylates.

To gain further insights into this reaction, several control experiments were conducted (Schemes 3–6). When the reaction of ethyl glyoxylate **2a** with methyl pyruvate **3a** was performed in the standard conditions, only a trace amount of **10** was detected (Scheme 3), suggesting that this reaction mechanism might be

Table 2
Iron-catalyzed three-component tandem reaction of aromatic amines, glyoxylic esters, and α-ketoesters[a]



Products (Yields[b])	Products (Yields[b])
 **4a** (88%)	 **4b** (80%)
 **4c** (86%)	 **4d** (60%)
 **4e** (72%)	 **4f** (71%)
 **4g** (57%)[c]	 **4h** (71%)[c]
 **4i** (62%)[c]	 **4j** (55%)[c]
 **4k** (31%)[c]	 **4l** (40%)[c]
 **4m** (52%)	 **4n** (62%)
 **4o** (33%)[d]	

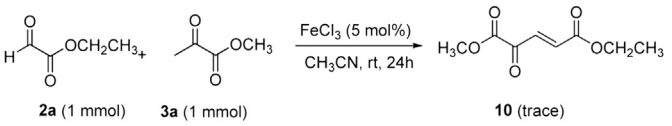
[a] Reaction conditions: arylamine (0.5 mmol), ethyl glyoxylate (0.55 mmol), α-ketoesters (0.75 mmol), $FeCl_3$ (5 mol %), CH_3CN (3 mL), room temperature, under air, 30-36h.

[b] Isolated yields based on arylamine.

[c] 60°C, 36h.

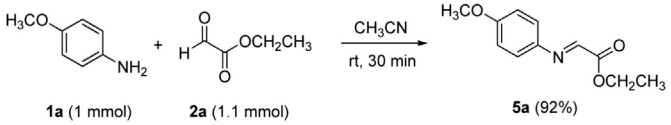
[d] $FeCl_3$ (10 mol %), 60°C, 36h.

different from the modified Doebner–von Miller reaction.[2] On the other hand, imine **5a** could be isolated in 92% yield when *p*-methoxyaniline **1a** reacted with ethyl glyoxylate **2a** in the absence of catalyst (Scheme 4). Furthermore, treatment of **5a** with methyl pyruvate **3a** under the standard procedure led to the formation of the desired product **4a** in 86% yield (Scheme 5). Nevertheless, the desired product **4a** was not detected when the reaction of **5a** with methyl pyruvate **3a** was conducted in absence of catalyst (Scheme 6). The above results indicated that imine complex might be the key intermediate and $FeCl_3$ played an important role in the formation of quinoline-2,4-dicarboxylates.Based on the above experimental results and previous studies,[9,12,13] a postulated reaction pathway was proposed as shown in Scheme 7. Firstly, aromatic amine **1** reacted with ethyl glyoxylate **2** to generate the imine intermediate **5**, which was followed by addition of the enolate **6** that quickly formed from the tautomerization of ketoester in the presence of iron salts, and produced intermediate **7**.[12] Subsequently, the nucleophilic attack of phenyl ring to keto group led to the formation of intermediate **8**. Next, water elimination and following proton shift with help of chloride ion would produce the 1,2-dihydroquinolines intermediate **9**.[12b,13] Finally, the dihydroquinoline intermediate **9** was oxidized by air oxygen to give the desired quinoline **4**.[13]



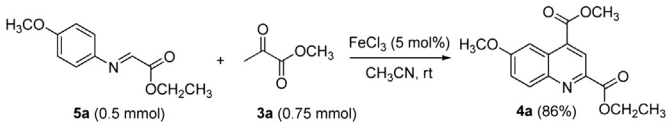
2a (1 mmol) **3a** (1 mmol) **10** (trace)

Scheme 3. The reaction of **2a** with **3a** in the standard conditions.



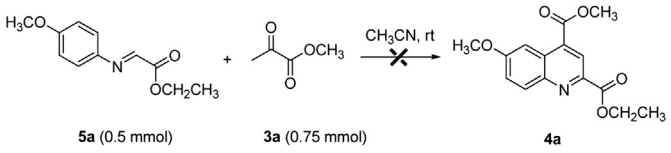
1a (1 mmol) **2a** (1.1 mmol) **5a** (92%)

Scheme 4. The reaction of **1a** with **2a** in the absence of catalyst.



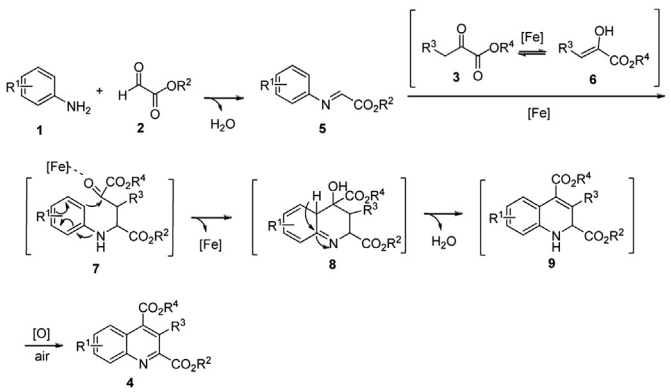
5a (0.5 mmol) **3a** (0.75 mmol) **4a** (86%)

Scheme 5. The reaction of imine **5a** with **3a** in the presence of $FeCl_3$ (5 mol %).



5a (0.5 mmol) **3a** (0.75 mmol) **4a**

Scheme 6. The reaction of imine **5a** with **3a** in the absence of catalyst.



Scheme 7. Postulated reaction pathway.

3. Conclusions

In summary, a simple and convenient method has been developed for the preparation of substituted quinoline-2,4-dicarboxylates via a new one-pot three-component tandem process of aromatic amines, glyoxylic esters, and α-ketoesters by employing cheap iron salts as the catalysts. The present protocol, which possesses some advantages of cheap catalysts, readily-available starting materials, and mild reaction conditions over the common methods, paves a new way towards the synthesis of versatile quinoline building blocks potentially for constructing a variety of drug candidates, biofunctional molecules and fluorescent tags. The detailed scope, mechanism, and synthetic application of this reaction are under investigation.

4. Experimental section

4.1. General

All commercially available reagent grade chemicals were purchased from Aldrich, Acros and Alfa Aesar Chemical Company and used as received without further purification unless otherwise stated. All solvents were dried according to standard procedures. The NMR data were collected in $CDCl_3$ with TMS as internal standard on a Bruker Avance 600 spectrometer (600 MHz ^1H, 150 MHz ^{13}C) at room temperature. The following abbreviations were used to express the multiplicities: s=singlet; d=doublet; t=triplet; q=quartet; quint=quintet; m=multiplet; br=broad, and the chemical shifts (δ) were described in parts per million and J values were given in Hertz. High-resolution mass spectra was obtained in a Bruker Daltonics Data Analysis 3.2. All reactions were carried out in oven-dried glasswares with magnetic stirring and monitored by thin-layer chromatography on TLC plates. The products were purified by flash column chromatography on silica gel (200–300 mesh).

4.2. Experimental procedures

*4.2.1. General procedures for preparation of quinoline-2,4-dicarboxylates **4**.* The reaction mixture of arylamine **1** (0.5 mmol), ethyl glyoxylate **2** (0.55 mmol), α-ketoesters **3** (0.75 mmol), $FeCl_3$ (5 mol %) and CH_3CN (3 mL) was stirred at room temperature or 60 °C for the indicated time until complete consumption of the starting material, which was monitored by TLC analysis (30–36 h). Then the solvents were removed by rotary evaporation to provide crude products. The residue was purified by flash chromatography on silica gel to give the desired product **4**.

*4.2.2. Reaction of **1a** and **2a** in the absence of catalyst.* The reaction mixture of *p*-methoxyaniline **1a** (1 mmol), ethyl glyoxylate **2a** (1.1 mmol), and CH_3CN (3 mL) was stirred at room temperature for 30 min. Then the solvents were removed by rotary evaporation to provide crude products. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give the desired imine **5a** as a yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ=1.40 (t, J=7.1 Hz, 3H), 3.83 (s, 3H), 4.41 (q, J=7.1 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.9 Hz, 2H), 7.93 (s, 1H).

*4.2.3. Reaction of imine **5a** and **3a** in the presence of catalyst.* The isolated **5a** (0.5 mmol) was immediately added into a mixture of methyl pyruvate **3a** (0.75 mmol), $FeCl_3$ (5 mol %), and CH_3CN (3 mL). The reaction mixture was stirred at room temperature for 30 h. After the completion of the reaction, the solvents were removed by rotary evaporation to provide crude products. Then the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 7:1) to give the desired product **4a** in 86% yield.

*4.2.4. Reaction of imine **5a** and **3a** in the absence of catalyst.* The reaction mixture of imine **5a** (0.5 mmol), methyl pyruvate **3a** (0.75 mmol), and CH_3CN (3 mL) was stirred at room temperature for 30 h. The solution was concentrated in vacuum, no desired product was detected.

Compound **4a** was obtained in 88% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.36; ^1H NMR (600 MHz, $CDCl_3$): δ=1.48 (t, J=7.1 Hz, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 4.55 (q, J=7.1 Hz, 2H), 7.45 (dd, J=2.7, 9.3 Hz, 1H), 8.22 (d, J=9.2 Hz, 1H), 8.26 (d, J=2.7 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.4, 52.7, 55.7, 62.3, 103.0, 123.1, 123.8, 128.3, 132.8, 133.1, 145.0, 145.2, 161.0, 165.0, 166.3; HRMS calcd for $C_{15}H_{15}NO_5Na$ $(M+Na)^+$, 312.0842; found, 312.0837.

Compound **4b** was obtained in 80% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.39; ^1H NMR (600 MHz, $CDCl_3$): δ=1.48 (t, J=7.1 Hz, 3H), 2.59 (s, 3H), 4.05 (s, 3H), 4.56 (q, J=7.1 Hz, 2H), 7.65 (d, J=1.5, 8.6 Hz, 1H), 8.23 (d, J=8.7 Hz, 1H), 8.57 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.4, 22.3, 52.8, 62.4, 122.3, 124.2, 126.3, 131.0, 132.8, 135.1, 141.0, 146.9, 147.4, 164.9, 166.3; HRMS calcd for $C_{15}H_{15}NO_4Na$ $(M+Na)^+$, 296.0893; found, 296.0901.

Compound **4c** was obtained in 86% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.36; ^1H NMR (600 MHz, $CDCl_3$): δ=1.47–1.51 (m, 6H), 4.03 (s, 3H), 4.22 (q, J=7.0 Hz, 2H), 4.55 (q, J=7.2 Hz, 2H), 7.44 (d, J=2.8, 9.2 Hz, 1H), 8.21 (d, J=9.2 Hz, 1H), 8.24 (d, J=2.7 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.4, 14.6, 52.7, 62.2, 64.1, 103.6, 123.0, 124.0, 128.4, 132.8, 133.1, 144.8, 145.1, 160.4, 165.0, 166.3; HRMS calcd for $C_{16}H_{17}NO_5Na$ $(M+Na)^+$, 326.0999; found, 326.0993.

Compound **4d** was obtained in 60% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.31; ^1H NMR (600 MHz, $CDCl_3$): δ=1.51 (t, J=10.6 Hz, 3H), 4.07 (s, 6H), 4.11 (s, 3H), 4.58 (q, J=10.6 Hz, 2H), 7.68 (s, 1H), 8.36 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.4, 52.7, 56.3, 56.3, 62.3, 103.0, 109.3, 121.1, 123.5, 132.5, 145.2, 146.6, 153.0, 165.1, 166.5; HRMS calcd for $C_{16}H_{17}NO_6$ Na $(M+Na)^+$, 342.0954; found, 342.0958.

Compound **4e** was obtained in 72% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.40; ^1H NMR (600 MHz, $CDCl_3$) δ=0.95 (t, J=1.4 Hz, 3H), 1.38–1.44 (m, 2H), 1.49 (t, J=7.1 Hz, 3H), 1.68–1.75 (m, 2H), 2.85 (t, J=7.7 Hz, 2H), 4.06 (s, 3H), 4.57 (q, J=7.1 Hz, 2H), 7.68 (dd, J=1.7, 8.7 Hz, 1H), 8.27 (d, J=8.6 Hz, 1H), 8.60 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ=13.9, 14.4, 22.4, 33.2, 36.3, 52.8, 62.4, 122.3, 123.7, 126.4, 131.1, 132.1, 135.1, 145.8, 146.9, 147.6, 165.0, 166.3; HRMS calcd for $C_{18}H_{21}NO_4Na$ $(M+Na)^+$, 338.1363; found, 338.1373.

Compound **4f** was obtained in 71% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.50; ^1H NMR (600 MHz, $CDCl_3$): δ=1.27–1.33 (m, 1H), 1.42–1.46 (m, 2H), 1.48 (t, J=7.1 Hz, 3H), 1.51–1.58 (m, 2H), 1.78 (d, J=12.8 Hz, 1H), 1.89 (d, J=12.9 Hz, 2H), 1.97 (d, J=12.0 Hz, 2H), 2.74–2.78 (m, 1H), 4.06 (s, 3H), 4.56 (q, J=7.1 Hz, 2H), 7.72 (dd, J=1.6, 8.8 Hz, 1H), 8.27 (d, J=8.8 Hz, 1H), 8.62 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.4, 26.0, 26.7, 34.1, 45.1, 52.8, 62.4, 122.1, 122.3, 126.5, 130.8, 131.1, 135.2, 146.9, 147.8, 150.7, 165.0, 166.3; HRMS calcd for $C_{20}H_{23}NO_4Na$ $(M+Na)^+$, 364.1519; found, 364.1518.

Compound **4g** was obtained in 57% yield according to the general procedure (60 °C, 36 h). TLC (*n*-hexane/EtOAc, 2:1 v/v): R_f=0.33; ^1H NMR (600 MHz, $CDCl_3$): δ=1.36 (t, J=7.1 Hz, 3H), 3.97 (s, 3H), 4.40 (q, J=7.0 Hz, 2H), 7.47 (dd, J=2.6, 9.1 Hz, 1H), 8.03 (s, 1H), 8.09 (d, J=9.1 Hz, 1H), 8.41 (s, 1H), 10.79 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.7, 53.3, 62.0, 106.7, 122.5, 124.2, 128.0, 133.1, 133.2, 144.1, 144.2, 159.9, 164.8, 166.2; HRMS calcd for $C_{14}H_{14}NO_5$ $(M+H)^+$, 276.0866; found, 276.0869.

Compound **4h** was obtained in 71% yield according to the general procedure (60 °C, 36 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.39; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.49 (t, *J*=7.1 Hz, 3H), 4.06 (s, 3H), 4.57 (q, *J*=7.0 Hz, 2H), 7.76 (d, *J*=8.9 Hz, 1H), 8.28 (d, *J*=9.0 Hz, 1H), 8.68 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.3, 53.0, 62.6, 123.2, 124.7, 126.8, 131.6, 132.7, 134.8, 136.9, 147.1, 148.1, 164.5, 165.6; HRMS calcd for $C_{14}H_{12}ClNO_4Na$ $(M+Na)^+$, 316.0347; found, 316.0349.

Compound **4i** was obtained in 62% yield according to the general procedure (60 °C, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.39; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.49 (t, *J*=7.1 Hz, 3H), 4.07 (s, 3H), 4.57 (q, *J*=7.1 Hz, 2H), 7.89 (d, *J*=2.0, 9.0 Hz, 1H), 8.20 (d, *J*=9.0 Hz, 1H), 8.67 (s, 1H), 9.07 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.3, 53.0, 62.6, 123.2, 125.5, 127.1, 128.0, 132.7, 134.2, 134.8, 147.3, 148.2, 164.5, 165.6; HRMS calcd for $C_{14}H_{12}BrNO_4Na$ $(M+Na)^+$, 359.9842; found, 359.9839.

Compound **4j** was obtained in 55% yield according to the general procedure (60 °C, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.38; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.49 (t, *J*=7.1 Hz, 3H), 4.06 (s, 3H), 4.57 (q, *J*=7.1 Hz, 2H), 7.61 (dd, *J*=2.8, 7.9 Hz, 1H), 8.36 (dd, *J*=5.6, 9.2 Hz, 1H), 8.57 (dd, *J*=2.8, 10.6 Hz, 1H), 8.71 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.3, 52.9, 62.5, 109.6, 109.7, 121.0, 121.2, 123.2, 127.5, 127.6, 133.9, 134.0, 135.0, 146.0, 147.3, 162.1, 163.8, 164.6, 165.7; HRMS calcd for $C_{14}H_{12}FNO_4Na$ $(M+Na)^+$, 300.0643; found, 300.0654.

Compound **4k** was obtained in 31% yield according to the general procedure (60 °C, 36 h). TLC (*n*-hexane/EtOAc, 2:1 v/v): R_f=0.52; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.51 (t, *J*=7.1 Hz, 3H), 4.11 (s, 3H), 4.60 (q, *J*=7.1 Hz, 2H), 7.96 (dd, *J*=1.6, 8.7 Hz, 1H), 8.45 (d, *J*=8.8 Hz, 1H), 8.77 (s, 1H), 9.36 (d, *J*=1.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.3, 53.3, 63.0, 113.9, 118.2, 123.8, 125.5, 131.0, 132.2, 132.6, 136.2, 149.3, 150.7, 164.1, 165.1; HRMS calcd for $C_{15}H_{12}N_2O_4Na$ $(M+Na)^+$, 307.0689; found, 307.0691.

Compound **4l** was obtained in 40% yield according to the general procedure (60 °C, 30 h). TLC (*n*-hexane/EtOAc, 2:1 v/v): R_f=0.50; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.51 (t, *J*=7.1 Hz, 3H), 2.78 (s, 3H), 4.11 (s, 3H), 4.59 (q, *J*=7.1 Hz, 2H), 8.37 (dd, *J*=1.7, 8.8 Hz, 1H), 8.41 (d, *J*=8.8 Hz, 1H), 8.73 (s, 1H), 9.53 (d, *J*=1.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.3, 26.8, 53.1, 62.8, 111.8, 123.1, 127.5, 128.4, 130.8, 131.8, 137.6, 150.0, 150.3, 164.5, 165.6, 197.5; HRMS calcd for $C_{16}H_{15}NO_5Na$ $(M+Na)^+$, 324.0842; found, 324.0846.

Compound **4m** was obtained in 52% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.34; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.49 (t, *J*=7.1 Hz, 3H), 3.96 (s, 3H), 4.56 (q, *J*=7.1 Hz, 2H), 7.14 (dd, *J*=0.9, 8.5 Hz, 2H), 7.23 (t, *J*=7.4 Hz, 3H), 7.42–7.45 (m, 2H), 7.57 (dd, *J*=2.7, 9.2 Hz, 1H), 8.29 (d, *J*=2.6 Hz, 1H), 8.32 (d, *J*=9.2 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=14.4, 52.7, 62.4, 110.3, 120.0, 120.2, 123.1, 123.7, 124.8, 127.7, 130.1, 133.3, 134.3, 145.6, 146.1, 155.5, 159.2, 164.8, 166.0; HRMS calcd for $C_{20}H_{17}NO_5Na$ $(M+Na)^+$, 374.0999; found, 374.1004.

Compound **4n** was obtained in 62% yield according to the general procedure (rt, 30 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.44; ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.83 (d, *J*=6.9 Hz, 3H), 0.93 (t, *J*=5.3 Hz, 6H), 1.14–1.30 (m, 3H), 1.59–1.60 (m, 1H), 1.66–1.76 (m, 3H), 1.99–2.03 (m, 1H), 2.21 (d, *J*=11.8 Hz, 1H), 3.97 (s, 3H), 4.04 (s, 3H), 5.07–5.14 (m, 1H), 7.43 (d, *J*=9.3 Hz, 1H), 8.22 (s, 1H), 8.23 (d, *J*=8.9 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=16.5, 20.7, 22.0, 23.6, 26.5, 31.5, 34.3, 40.8, 47.0, 52.7, 55.7, 76.2, 102.9, 122.9, 123.6, 128.2, 132.9, 133.1, 145.2, 145.3, 160.9, 164.4, 166.4; HRMS calcd for $C_{23}H_{29}NO_5Na$ $(M+Na)^+$, 422.1943; found, 422.1946.

Compound **4o** was obtained in 33% yield according to the general procedure (60 °C, 36 h). TLC (*n*-hexane/EtOAc, 3:1 v/v): R_f=0.40; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.17 (t, *J*=7.1 Hz, 3H), 1.31 (t, *J*=7.1 Hz, 3H), 3.92 (s, 3H), 4.27 (q, *J*=7.1 Hz, 2H), 4.41–4.44 (m, 4H), 7.00 (s, 1H), 7.09 (d, *J*=7.4 Hz, 2H), 7.15 (t, *J*=7.1 Hz, 1H), 7.21 (t, *J*=7.3 Hz, 2H), 7.41 (dd, *J*=2.2, 9.1 Hz, 1H), 8.10 (d, *J*=9.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=13.9, 14.1, 35.5, 55.6, 62.1, 102.1, 123.1, 126.0, 126.3, 128.3, 128.8, 129.0, 131.6, 139.0, 139.7, 141.9, 148.6, 159.8, 166.3, 167.4; HRMS calcd for $C_{23}H_{24}NO_5$ $(M+H)^+$, 394.1649; found, 394.1656.

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