Pharmaceutical-oriented methoxylation of aryl C(sp^2)–H bonds using copper catalysts

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General Information:

Methanol was dried by Sodium, distilled under reduced pressure. Unless otherwise noted all commercial materials were used without further purification. All benzoic acids were purchased from Aladdin reagent Co., LTD (Shanghai). Column chromatography was performed with silica gel (300-400 mesh) produced by Qingdao Marine Chemical Factory, Qingdao (China). NMR spectra were recorded on Bruker AVANCE III 500MHz instrument with TMS as internal standard. Coupling constants were reported in Hertz (Hz).

Experimental Sections

General Procedure for the Preparation of Starting Materials

To a 100 mL three-necked flask, acid (20 mmol), DMF (3 drops), and anhydrous CH$_2$Cl$_2$ (30 mL) were added. Oxalyl chloride (40 mmol, 2 equiv) was added dropwise at 0°C resulting in vigorous bubbling. The mixture was stirred for 3 h at room temperature, and the solvent was then removed in vacuo. The resulting acid chloride was used immediately without further purification. The acid chloride was then re-dissolved in 25 mL dry CH$_2$Cl$_2$ and added dropwise to a 30 mL dry CH$_2$Cl$_2$ solution containing amine (24 mmol) and Et$_3$N (30 mmol) at 0 °C. After stirring for 6 h at room temperature, the resulting mixture was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired product.

Characterization Data for Starting Materials

The title compound 1a was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.79 – 7.67 (m, 2H), 7.44 – 7.36 (m, 2H), 6.85 (s, 1H), 3.55 – 3.42 (m, 2H), 2.57 – 2.49 (m, 2H), 2.27 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.36, 137.51, 133.07, 128.72, 128.47, 57.64, 45.16, 37.23.

The title compound 1b was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.79 – 7.67 (m, 2H), 7.44 – 7.36 (m, 2H), 6.85 (s, 1H), 3.55 – 3.42 (m, 2H), 2.57 – 2.49 (m, 2H), 2.27 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.36, 137.51, 133.07, 128.72, 128.47, 57.64, 45.16, 37.23.
The title compound 1b was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.69 – 7.65 (m, 2H), 7.58 – 7.54 (m, 2H), 6.92 (s, 1H), 3.51 (q, $J = 5.3$ Hz, 2H), 2.56 – 2.50 (m, 2H), 2.28 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.49, 133.42, 131.68, 128.69, 125.96, 57.67, 45.12, 37.17.

![Structure 1c](image)

The title compound 1c was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.94 (d, $J = 8.2$ Hz, 2H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.15 (s, 1H), 3.56 (q, $J = 5.3$ Hz, 2H), 2.63 – 2.55 (m, 2H), 2.31 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.26, 137.92, 133.06 ($q$, $J = 32.5$ Hz), 127.59, 125.53 ($q$, $J = 3.6$ Hz), 122.64 ($q$, $J = 273.4$ Hz, 272.1Hz), 57.78, 45.13, 37.35.

![Structure 1d](image)

The title compound 1d was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.82 – 7.78 (m, 2H), 7.52 – 7.47 (m, 1H), 7.43 (t, $J = 7.4$ Hz, 2H), 6.89 (s, 1H), 3.57 – 3.46 (m, 2H), 2.58 – 2.50 (m, 2H), 2.28 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 167.48, 134.68, 131.31, 128.48, 127.01, 57.78, 45.16, 37.17.

![Structure 1e](image)

The title compound 1e was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.84 – 7.72 (m, 2H), 7.58 – 7.48 (m, 2H), 6.97 (s, 1H), 3.57 – 3.44 (m, 2H), 2.62 – 2.52 (m, 2H), 2.31 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.69, 137.69, 133.91, 128.73, 98.29, 57.74, 45.05, 37.01.

![Structure 1f](image)

The title compound 1f was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.31 – 8.25 (m, 2H), 8.01 – 7.95 (m, 2H), 7.13 (s, 1H), 3.61 – 3.51 (m, 2H), 2.61 – 2.54 (m, 2H), 2.31 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 165.38, 149.53, 140.14, 128.28, 123.73, 57.52, 45.08, 37.27.
The title compound 1g was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.84 – 7.77 (m, 2H), 7.14 – 7.05 (m, 2H), 6.88 (s, 1H), 3.54 – 3.46 (m, 2H), 2.57 – 2.49 (m, 2H), 2.28 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.41 , 164.65 (d, $J$ = 251.1 Hz), 130.83 (d, $J$ = 3.1 Hz), 129.33 (d, $J$ = 8.9 Hz), 115.47 (d, $J$ = 21.9 Hz), 57.71 , 45.15 , 37.21 .

The title compound 1h was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.91 (d, $J$ = 8.4 Hz, 2H), 7.74 (d, $J$ = 8.5 Hz, 2H), 7.02 (s, 1H), 3.68 – 3.25 (m, 2H), 2.68 – 2.46 (m, 2H), 2.29 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 165.59 , 138.53 , 132.38 , 127.77 , 118.12 , 114.92 , 57.45 , 45.09 , 37.25 .

The title compound 1i was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.70 (d, $J$ = 8.2 Hz, 2H), 7.22 (d, $J$ = 8.0 Hz, 2H), 6.86 (s, 1H), 3.52 (q, $J$ = 5.5 Hz, 2H), 2.52 (t, $J$ = 5.9 Hz, 2H), 2.39 (s, 3H), 2.27 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 167.46 , 141.65 , 131.79 , 129.12 , 127.02 , 57.84 , 45.14 , 37.12 , 21.43 .

The title compound 1j was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.77 (d, $J$ = 8.8 Hz, 2H), 6.92 (d, $J$ = 8.6 Hz, 2H), 6.82 (s, 1H), 3.84 (s, 3H), 3.51 (q, $J$ = 5.5 Hz, 2H), 2.52 (t, $J$ = 5.9 Hz, 2H), 2.27 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 167.03 , 162.05 , 128.81 , 126.95 , 113.63 , 57.89 , 55.37 , 45.15 , 37.12 .

The title compound 1k was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.08 (s, 1H), 7.98 (d, $J$ = 7.8 Hz, 1H), 7.74 (d, $J$ = 7.8 Hz, 1H), 7.56 (t, $J$ = 7.8 Hz, 1H), 7.02 (s, 1H), 3.55 (q, $J$ = 5.3 Hz, 2H), 2.61 – 2.52 (m, 2H), 2.30 (s, 6H). $^{13}$C NMR (126 MHz,
Chloroform-\(d\) δ 166.07, 135.48, 131.08 (q, \(J = 32.7\) Hz), 130.24, 129.10, 127.93 (q, \(J = 3.2\) Hz), 124.22 (q, \(J = 3.6\) Hz), 123.79 (q, \(J = 272.3\) Hz), 57.65, 45.11, 37.28.

The title compound 1l was prepared according to the General Procedure. \(^1\)H NMR (500 MHz, Chloroform-\(d\)) δ 8.13 (t, \(J = 1.6\) Hz, 1H), 7.81 (d, \(J = 7.7\) Hz, 1H), 7.74 (d, \(J = 7.8\) Hz, 1H), 7.16 (t, \(J = 7.8\) Hz, 1H), 6.86 (s, 1H), 3.51 (q, \(J = 5.4\) Hz, 2H), 2.57 – 2.48 (m, 2H), 2.27 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) δ 165.90, 140.18, 136.68, 136.11, 129.13, 126.16, 94.22, 57.64, 45.17, 37.30.

The title compound 1m was prepared according to the General Procedure. \(^1\)H NMR (500 MHz, Chloroform-\(d\)) δ 7.30 (s, 2H), 7.05 – 6.98 (m, 1H), 6.92 (s, 1H), 3.84 (s, 3H), 3.51 (q, \(J = 5.5\) Hz, 2H), 2.51 (t, \(J = 6.0\) Hz, 2H), 2.26 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) δ 167.33, 159.73, 136.14, 129.44, 118.87, 117.38, 112.47, 57.76, 55.39, 45.15, 37.26.

The title compound 1n was prepared according to the General Procedure. \(^1\)H NMR (500 MHz, Chloroform-\(d\)) δ 7.78 (t, \(J = 1.9\) Hz, 1H), 7.66 (dt, \(J = 7.8, 1.4\) Hz, 1H), 7.44 (dt, \(J = 8.1, 1.8\) Hz, 1H), 7.35 (t, \(J = 7.8\) Hz, 1H), 6.99 (s, 1H), 3.55 – 3.44 (m, 2H), 2.58 – 2.47 (m, 2H), 2.27 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) δ 166.16, 136.41, 134.58, 131.31, 129.77, 127.41, 125.14, 57.67, 45.12, 37.27.

The title compound 1o was prepared according to the General Procedure. \(^1\)H NMR (500 MHz, Chloroform-\(d\)) δ 7.62 – 7.49 (m, 2H), 7.44 – 7.35 (m, 1H), 7.17 (td, \(J = 8.3, 2.6\) Hz, 1H), 7.02 (s, 1H), 3.51 (q, \(J = 5.6\) Hz, 2H), 2.52 (t, \(J = 6.0\) Hz, 2H), 2.27 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) δ 166.19 (d, \(J = 2.0\) Hz), 162.73 (d, \(J = 247.3\) Hz), 136.97 (d, \(J = 5.9\) Hz), 130.11 (d, \(J = 7.2\) Hz), 122.53 (d, \(J = 3.4\) Hz), 118.25 (d, \(J = 20.9\) Hz), 114.41 (d, \(J = 23.1\) Hz), 57.65, 45.16, 37.32.
The title compound 1p was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.94 (t, $J = 1.8$ Hz, 1H), 7.71 (dt, $J = 7.8$, 1.4 Hz, 1H), 7.60 (dt, $J = 8.1$, 1.4 Hz, 1H), 7.33 – 7.23 (m, 1H), 6.96 (s, 1H), 3.51 (q, $J = 5.3$ Hz, 2H), 2.60 – 2.44 (m, 2H), 2.27 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 165.99, 136.62, 134.21, 130.26, 130.00, 125.55, 122.63, 57.63, 45.11, 37.26.

The title compound 1q was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.45 – 7.37 (m, 1H), 7.32 (dd, $J = 6.7$, 1.6 Hz, 2H), 7.02 (d, $J = 9.0$ Hz, 2H), 3.84 (s, 4H), 3.52 (q, $J = 5.5$, 5.0 Hz, 2H), 2.54 (t, $J = 5.8$ Hz, 2H), 2.28 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 167.34, 159.75, 136.13, 129.46, 118.89, 117.42, 112.48, 57.77, 55.43, 45.12, 37.19.

The title compound 1r was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.66 (d, $J = 1.8$ Hz, 2H), 7.46 (t, $J = 1.8$ Hz, 1H), 6.91 (s, 1H), 3.50 (q, $J = 5.4$ Hz, 2H), 2.52 (t, $J = 5.9$ Hz, 2H), 2.28 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 164.87, 137.59, 135.34, 131.15, 125.72, 57.52, 45.15, 37.40.

The title compound 1s was prepared according to the General Procedure. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.89 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.63 – 7.57 (m, 2H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.3$ Hz, 1H), 7.01 (s, 1H), 3.56 (q, $J = 5.3$ Hz, 2H), 2.57 (t, $J = 5.9$ Hz, 2H), 2.31 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 167.21, 144.12, 140.13, 133.26, 128.89, 127.91, 127.57, 127.19, 127.15, 57.82, 45.12, 37.12.
## Optimization of Reaction Conditions

Optimization of reaction conditions using copper(II) as the catalyst and various bases and additives. The conditions are outlined in the table below:

<table>
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<tr>
<th>Entry</th>
<th>[Cu](X mol%)</th>
<th>Base[equiv]</th>
<th>Additive[X mol%]</th>
<th>T[°C]</th>
<th>t [h]</th>
<th>Yield(%)</th>
</tr>
</thead>
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<td>24</td>
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<tr>
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<td>4</td>
</tr>
<tr>
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<td>24</td>
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<td>Cu2(OH)2CO3(5)</td>
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<tr>
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<td>90</td>
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<tr>
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<td>120</td>
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<tr>
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<td>71</td>
</tr>
<tr>
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<td>C6H12N4(20)</td>
<td>120</td>
<td>24</td>
<td>95(90)</td>
</tr>
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</table>

*aReaction condition: 1a (0.2 mmol), [Cu] X mol%, Base(Y equiv), O2 (1 atm), in MeOH(2ml). b 1H NMR yield using CH2Br2 as the internal standard. c Isolated yields. d using air(1 atm) as the atmosphere. e using N2 (1 atm) as the atmosphere. f methenamine.

## Characterization Data for Products of Alkoxylation

**General Procedure for Cu(II)-Catalyzed Alkoxylation**

Cu2(OH)2CO3(0.04 mmol), KOCN (0.40 mmol), methenamine (0.04 mmol), 1 (0.20 mmol), CH3OH (2 mL) were introduced into a 15 mL seal tube equipped with a...
magnetic stirrer in O₂. The mixture was fiercely stirred at 120 °C for 24 h. After cooling to room temperature, the solvent was evaporated under vacuum. The residue was dissolved in mixed solvent of dichloromethane(30ml) and edetate tetrasodium saturated aqueous solution(30ml). After separated, the aqueous phase was extracted twice with dichloromethane(15ml).and the organic layers were combined and evaporated under vacuum and the crude product was purified by column chromatograph using silica gel with n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) as eluent.

The title compound 2a was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2a as a white solid (46.2 mg, 90%). ¹H NMR (500 MHz, Chloroform-d) δ 8.33 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 6.97 (dd, J = 8.4, 1.8 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 3.92 (s, 3H), 3.66 (q, J = 5.9 Hz, 2H), 2.87 – 2.80 (m, 2H), 2.50 (s, 6H).¹³C NMR (126 MHz, Chloroform-d) δ 164.84, 158.08, 138.54, 133.11, 121.34, 119.82, 112.04, 57.77, 56.29, 44.68, 36.56. HRMS (ESI) m/z calcd for C₁₂H₁₈ClN₂O₂ [M]+ 257.1051; found 257.1062.

The title compound 2b was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2b as a white solid (54.2 mg, 90%). ¹H NMR (500 MHz, Chloroform-d) δ 8.21 (s, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.5, 1.7 Hz, 1H), 7.04 (d, J = 1.7 Hz, 1H), 3.89 (s, 3H), 3.53 (q, J = 5.9 Hz, 2H), 2.59 (t, J = 6.1 Hz, 2H), 2.33 (s, 6H).¹³C NMR (126 MHz, Chloroform-d) δ 163.63, 156.91, 132.35, 125.53, 123.43, 119.70, 113.96, 56.79, 55.27, 44.04, 36.14. HRMS (ESI) m/z calcd for C₁₂H₁₇BrN₂NaO₂ [M]+ 323.0366; found 323.0367.

The title compound 2c was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2c as a white solid (54.0 mg, 93%). ¹H NMR (500 MHz, Chloroform-d) δ 8.49 (s, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 4.05 (s, 3H), 3.74 (q, J = 5.8 Hz, 2H), 2.88 (t, J = 6.0 Hz, 2H), 2.56 (s, 6H).¹³C NMR (126 MHz, Chloroform-d) δ 163.49, 156.65, 133.35 (q, J = 32.7 Hz), 131.74, 122.48 (q, J = 273.1, 272.4 Hz), 116.73 (q, J = 3.6 Hz), 107.42 (q, J = 3.6 Hz), 56.75, 55.32, 43.77, 35.74. HRMS (ESI) m/z calcd for C₁₃H₁₈F₃N₂O₂ [M]+ 291.1315; found 291.1319.
The title compound 2d was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2d as a Colorless oil (22.2 mg, 50%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.49 (s, 1H), 8.16 (d, $J = 7.8$ Hz, 1H), 7.53 – 7.38 (m, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 8.3$ Hz, 1H), 4.00 (s, 3H), 3.79 (q, $J = 5.8$ Hz, 2H), 2.97 (t, $J = 4.9$ Hz, 2H), 2.62 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 165.94, 157.79, 133.05, 132.04, 121.13, 111.38, 57.77, 55.98, 44.68, 36.51. HRMS (ESI) m/z calcd for C$_{12}$H$_{19}$N$_2$O$_2$ [M]$^+$ 223.1441; found 223.1444.

The title compound 2e was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2a as a white solid (57.1 mg, 82%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.38 (s, 1H), 7.83 (d, $J = 8.3$ Hz, 1H), 7.42 (d, $J = 6.8$ Hz, 1H), 7.30 (s, 1H), 3.98 (s, 3H), 3.71 (q, $J = 5.9$ Hz, 2H), 2.86 (t, $J = 6.1$ Hz, 2H), 2.55 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 165.07, 157.67, 133.26, 130.55, 120.86, 99.01, 57.78, 56.35, 44.78, 36.71. HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$IN$_2$O$_2$ [M]$^+$ 349.0407; found 349.0404.

The title compound 2f was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2f as a light yellow solid (27.8 mg, 52%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.72 (s, 1H), 8.27 (d, $J = 8.6$ Hz, 1H), 7.90 (d, $J = 10.6$ Hz, 1H), 7.84 (s, 1H), 4.14 (s, 3H), 3.88 (q, $J = 5.8$ Hz, 2H), 3.14 (t, $J = 5.9$ Hz, 2H), 2.76 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 164.22, 158.03, 150.52, 133.05, 126.64, 115.70, 106.77, 58.01, 56.90, 44.50, 36.21. HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$N$_3$O$_4$ [M]$^+$ 268.1292; found 268.1219.

The title compound 2g was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2g as a white solid or Colorless oil (35.1 mg, 73%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.45 (s, 1H), 8.13 –
7.96 (m, 1H), 6.67 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 11.7 Hz, 1H), 3.94 (s, 3H), 3.81 (q, J = 6.0 Hz, 2H), 3.10 (t, J = 6.1 Hz, 2H), 2.70 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) δ164.69 (d, J = 252.3 Hz), 164.29, 158.34 (d, J = 10.6 Hz), 132.96 (d, J = 10.6 Hz), 116.10, 106.96 (d, J = 21.1 Hz), 98.54 (d, J = 26.5 Hz), 56.80 , 55.42 , 43.37 , 34.98 . HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$FN$_2$O$_2$ [M]$^+$ 241.1347; found 241.1359.

The title compound 2h was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2h as a white solid (19.8 mg, 40%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.31 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.33 – 7.28 (m, 1H), 3.97 (s, 3H), 3.64 (q, J = 5.9 Hz, 2H), 2.73 (t, J = 6.1 Hz, 2H), 2.45 (s, 6H).$^{13}$C NMR (126 MHz, Chloroform-$d$) δ 164.89 ,157.61, 133.32 , 130.59 , 121.26 , 120.83 , 98.81 , 57.79 , 56.29 , 44.98 , 37.01 . HRMS (ESI) m/z calcd for C$_{13}$H$_{18}$N$_3$O$_2$ [M]$^+$ 248.1394; found 248.1386.

The title compound 2i was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2a as a white solid (23.6 mg, 50%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.51 (s, 1H), 8.02 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.78 (s, 1H), 4.00 (s, 3H), 3.88 (q, J = 6.0 Hz, 2H), 3.16 (t, J = 5.4 Hz, 2H), 2.76 (s, 6H), 2.39 (s, 3H).$^{13}$C NMR (126 MHz, Chloroform-$d$) δ 166.28, 157.83 , 144.24 , 131.96 , 121.97 , 117.93 , 112.10 , 57.64 , 55.95 , 44.36 , 36.01 , 21.80 . HRMS (ESI) m/z calcd for C$_{13}$H$_{21}$N$_2$O$_2$ [M]$^+$ 237.1598; found 237.1599.

The title compound 2j was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/ triethylamine (v/v/v 1:2:0.03) gave 2j as a white solid (24.7 mg, 49%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.43 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 6.58 (dd, J = 8.8, 2.2 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 3.99 (s, 3H), 3.90 – 3.83 (m, 5H), 3.15 (t, J = 6.2 Hz, 2H), 2.76 (s, 6H).$^{13}$C NMR (126 MHz, Chloroform-$d$) δ 164.98, 162.76 , 158.27 , 132.61 , 112.67 , 104.32 , 97.43 , 56.69 , 55.01 , 54.53 , 43.33 , 34.95 . HRMS (ESI) m/z calcd for C$_{13}$H$_{21}$N$_2$O$_3$ [M]$^+$ 253.1547; found 253.1556.
The title compound 2k was prepared according to General Procedure. A purification by flash chromatography in \( n \)-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2k as a Colorless oil (41.8 mg, 72%). \(^1\)H NMR (500 MHz, Chloroform-\( d \)) \( \delta \) 8.43 (s, 1H), 8.26 (d, \( J \) = 8.1 Hz, 1H), 7.37 – 7.25 (m, 1H), 7.19 (s, 1H), 4.03 (s, 3H), 3.68 (q, \( J \) = 5.8 Hz, 2H), 2.77 (t, \( J \) = 6.0 Hz, 2H), 2.48 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\( d \)) \( \delta \) 163.33, 156.60, 133.25 (q, \( J \) = 32.6 Hz), 131.76, 123.77, 122.50 (q, \( J \) = 272.9 Hz), 116.76 (q, \( J \) = 3.6 Hz), 107.41 (q, \( J \) = 3.6 Hz), 56.75, 55.28, 43.90, 35.98. HRMS (ESI) m/z calc'd for C\(_{13}\)H\(_{18}\)F\(_3\)N\(_2\)O\(_2\) \([M]^+\) 291.1315; found 291.1326.

The title compound 2l was prepared according to General Procedure. A purification by flash chromatography in \( n \)-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2l as a white solid (37.6 mg, 54%). \(^1\)H NMR (500 MHz, Chloroform-\( d \)) \( \delta \) 8.44 (d, \( J \) = 2.4 Hz, 1H), 8.27 (s, 1H), 7.70 (dd, \( J \) = 8.7, 2.4 Hz, 1H), 6.73 (d, \( J \) = 8.7 Hz, 1H), 3.94 (s, 3H), 3.59 (q, \( J \) = 6.0 Hz, 2H), 2.62 (t, \( J \) = 6.1 Hz, 2H), 2.37 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\( d \)) \( \delta \) 163.98, 157.44, 141.12, 140.59, 123.78, 113.72, 83.54, 57.78, 56.10, 45.12, 37.28. HRMS (ESI) m/z calc'd for C\(_{12}\)H\(_{18}\)IN\(_2\)O\(_2\) \([M]^+\) 349.0407; found 349.0406.

The title compound 2m was prepared according to General Procedure. A purification by flash chromatography in \( n \)-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2m as a Colorless oil (25.7 mg, 51%). \(^1\)H NMR (500 MHz, Chloroform-\( d \)) \( \delta \) 8.71 (d, \( J \) = 6.1 Hz, 1H), 7.67 (d, \( J \) = 3.2 Hz, 1H), 7.03 (dd, \( J \) = 8.8, 3.2 Hz, 1H), 6.93 (d, \( J \) = 8.9 Hz, 1H), 3.99 (s, 5H), 3.81 (s, 3H), 3.32 (t, \( J \) = 6.3 Hz, 2H), 2.88 (s, 6H). \(^{13}\)C NMR (126 MHz, Chloroform-\( d \)) \( \delta \) 166.20, 153.69, 152.24, 120.74, 119.87, 115.48, 112.79, 57.43, 56.47, 55.82, 44.09, 35.72. HRMS (ESI) m/z calc'd for C\(_{13}\)H\(_{21}\)N\(_2\)O\(_3\) \([M]^+\) 253.1547; found 253.1545.

The title compound 2n was prepared according to General Procedure. A purification by flash chromatography in \( n \)-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2n as a
Colorless oil (22.6 mg, 44%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.40 (t, $J = 5.6$ Hz, 1H), 7.93 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.51 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 1H), 3.94 (s, 3H), 3.82 (q, $J = 6.2$ Hz, 2H), 3.00 (t, $J = 6.2$ Hz, 2H), 2.65 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 164.43, 132.83, 128.76, 127.47, 127.00, 124.18, 60.93, 56.26, 43.08, 34.88. HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$ClN$_2$O$_2$ [M]$^+$ 257.1051; found 257.1058.

The title compound 2o was prepared according to General Procedure. A purification by flash chromatography in $n$-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2o as a Colorless oil (25.0 mg, 52%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.41 (s, 1H), 7.88 (dt, $J = 7.9$, 1.7 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.11 (td, $J = 7.9$, 4.7 Hz, 1H), 4.03 (d, $J = 2.0$ Hz, 3H), 3.66 (q, $J = 5.8$ Hz, 2H), 2.72 (t, $J = 6.1$ Hz, 2H), 2.45 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 164.48, 155.30 (d, $J = 247.5$ Hz), 146.15 (d, $J = 12.5$ Hz), 127.18, 126.45 (d, $J = 3.1$ Hz), 123.79 (d, $J = 7.1$ Hz), 119.84 (d, $J = 19.6$ Hz), 61.99 (d, $J = 6.9$ Hz), 57.57, 44.83, 36.87. HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$F$_2$N$_2$O$_2$ [M]$^+$ 241.1347; found 241.1336.

The title compound 2p was prepared according to General Procedure. A purification by flash chromatography in $n$-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2p as a Colorless oil (30.7 mg, 51%). $^1$H NMR (500 MHz, Methanol-$d_4$) $\delta$ 8.04 (d, $J = 2.6$ Hz, 1H), 7.63 (dd, $J = 8.8$, 2.7 Hz, 1H), 7.11 (d, $J = 8.9$ Hz, 1H), 3.98 (s, 3H), 3.61 (t, $J = 6.4$ Hz, 2H), 2.80 (t, $J = 6.4$ Hz, 2H), 2.51 (s, 6H). $^{13}$C NMR (126 MHz, Methanol-$d_4$) $\delta$ 166.99, 158.38, 136.75, 134.70, 124.78, 115.22, 114.07, 59.07, 56.93, 45.17, 38.04. HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$BrN$_2$O$_2$ [M]$^+$ 301.0546; found 301.0550.

The title compound 2q was prepared according to General Procedure. A purification by flash chromatography in $n$-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2q as a Colorless oil (37.4 mg, 61%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.49 (s, 1H), 8.06 (d, $J = 3.1$ Hz, 1H), 7.38 – 7.29 (m, 1H), 6.99 (d, $J = 9.1$ Hz, 1H), 4.01 (s, 3H), 3.71 (q, $J = 5.8$ Hz, 2H), 2.81 (t, $J = 6.1$ Hz, 2H), 2.51 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 164.18, 156.10, 142.95, 125.44, 124.95, 122.70, 112.53, 57.84, 56.50, 44.91, 36.91. HRMS (ESI) m/z calcd for C$_{13}$H$_{18}$ClN$_2$O$_3$ [M]$^+$ 307.1264; found 307.1256.
The title compound 2r was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2r as a white solid (32.1 mg, 55%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.39 (s, 1H), 7.92 (d, $J = 2.7$ Hz, 1H), 7.49 (d, $J = 2.7$ Hz, 1H), 3.91 (s, 3H), 3.73 (q, $J = 5.9$ Hz, 2H), 2.87 (t, $J = 6.1$ Hz, 2H), 2.55 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 163.63, 152.98, 132.99, 130.22, 129.88, 129.34, 129.20, 62.00, 57.38, 44.56, 36.64. HRMS (ESI) m/z calcd for C$_{12}$H$_{17}$Cl$_2$N$_2$O$_2$ [M]$^+$ 291.0662; found 291.0671.

The title compound 2s was prepared according to General Procedure. A purification by flash chromatography in n-hexane/ethyl acetate/triethylamine (v/v/v 1:2:0.03) gave 2s as a white solid (28.6 mg, 48%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.63 (s, 1H), 8.19 (d, $J = 8.1$ Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.28 (d, $J = 4.2$ Hz, 1H), 7.17 (s, 1H), 4.09 (s, 3H), 3.94 (q, $J = 6.0$ Hz, 2H), 3.23 (t, $J = 5.8$ Hz, 2H), 2.80 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.09, 158.16, 146.42, 140.04, 132.47, 128.93, 128.26, 127.25, 119.89, 119.39, 110.17, 57.68, 56.13, 44.33, 36.00. HRMS (ESI) m/z calcd for C$_{18}$H$_{23}$N$_2$O$_2$ [M]$^+$ 299.1754; found 299.1767.
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