Supporting Information

For

Synthesis of trifluoromethyl-containing isoindolinones from tertiary enamides via cascade radical addition and cyclization process

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(A) General Methods

Commercially available reagents were used as received without further purification unless otherwise indicated. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Silica Gel 60 F254 plates and were visualized by fluorescence quenching at 254 nm. For chromatographic purifications, analytically pure solvents were used and the silica gel 300-400 mesh was used as the solid support. $^1$H NMR and $^{13}$C NMR chemical shifts were reported in $\delta$ units, parts per million (ppm) relative to the chemical shift of residual solvent. Reference peaks for chloroform in $^1$H NMR and $^{13}$C NMR spectra were set at 7.26 ppm and 77.0 ppm, respectively.

(B) Analytical data for the products

Typical experimental procedure for the synthesis of trifluoromethyl-containing isoindolinones 2 and 4

In a 25 mL sealed tube, a mixture of $N$-butyl-$N$-(prop-1-en-2-yl)benzamide 1a (43.4mg, 0.2 mmol), KHF$_2$ (12.4 mg, 1.0 equiv), TMSCF$_3$ (113.8 mg, 4 equiv), PhI(OAc)$_2$ (257.7mg, 4 equiv), EtOAc (2mL) was stirred at 80$^\circ$C under N$_2$ for 12h. The reaction mixture was quenched with saturate brine, dried over anhydrous Na$_2$SO$_4$, and evaporated in vacuum. The residue was purified by flash chromatography on silica gel by gradient elution (ethyl acetate in petroleum ether, 4:1) to obtain the corresponding product 2a.

2-butyl-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid, 75 % yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.84 (d, $J$ = 7.5 Hz, 1H), 7.56 (t, $J$ = 7.4 Hz, 1H), 7.47 (t, $J$ = 7.4 Hz, 1H), 7.42 (d, $J$ = 7.6 Hz, 1H), 3.67-3.69 (m, 1H), 3.21-3.07 (m, 1H), 2.76 (q, $J$ = 10.1 Hz, 2H), 1.96-1.79 (m, 1H), 1.59 (d, $J$ = 10.9 Hz, 4H), 1.43 (dd, $J$ = 13.4, 8.8 Hz, 2H), 0.98 (t, $J$ = 7.3 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 167.77, 147.62, 131.62, 131.35, 128.70, 124.23(q, $J_{CF}$ = 278.4Hz), 123.72, 121.21, 61.87, 40.36 (q, $J_{CF}$ = 27.3 Hz), 40.08, 31.18, 26.43, 20.71, 13.82.
$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -61.60 (s).

HRMS (ESI-TOF) m/z = 308.1233 [M + Na]$^+$, calcd for C$_{15}$H$_{18}$F$_3$NaO: 308.1238

2-butyl-3, 7-dimethyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow solid , 72 % yield ; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.40 (t, $J$ = 7.6 Hz, 1H), 7.20 (t, $J$ = 8.0 Hz, 2H), 3.64-3.66 (m, 1H), 3.10-3.12 (m, 1H), 2.81-2.67 (m, 5H), 1.91-1.80 (m, 1H), 1.63-1.56 (m, 1H), 1.55 (d, $J$ = 6.7 Hz, 3H), 1.45-1.39 (m, 2H), 0.98 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 167.57, 147.20, 136.70, 129.97, 129.63, 127.26, 123.54 (q, $J_{CF} = 278.4$ Hz), 117.54, 59.90, 39.60 (q, $J_{CF} = 27.1$ Hz), 38.93, 30.18, 25.71, 19.75, 16.24, 12.79.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.60 (s).

HRMS (ESI-TOF) m/z =322.1377 [M + Na]$^+$, calcd for C$_{16}$H$_{20}$F$_3$NaO:322.1395

2-butyl-3, 6-dimethyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid , 66 % yield ; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.64 (s, 1H), 7.36 (d, $J$ = 7.7 Hz, 1H), 7.29 (d, $J$ = 7.7 Hz, 1H), 3.72-3.61 (m, 1H), 3.20-3.08 (m, 1H), 2.73 (q, $J$ = 10.1 Hz, 2H), 2.43 (d, $J$ = 13.7 Hz, 3H), 1.90-1.79 (m, 1H), 1.65-1.53 (m, 4H), 1.46-1.38 (m, 2H), 0.97 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 167.89, 144.87, 138.77, 132.53, 131.43, 124.56 (q, $J_{CF} = 278.4$ Hz), 123.92, 120.96, 61.68, 40.56 (q, $J_{CF} = 27.2$ Hz), 40.05, 31.17, 26.49, 21.32, 20.70, 13.83.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.59 (s).

HRMS (ESI-TOF) m/z =322.1389 [M + Na]$^+$, calcd for C$_{16}$H$_{20}$F$_3$NaO: 322.1395
2-butyl-3, 5-dimethyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

White solid, 73 % yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.71 (d, $J = 7.7$ Hz, 1H), 7.29-7.25 (m, 1H), 7.20 (s, 1H), 3.65-3.67 (m, 1H), 3.18-3.06 (m, 1H), 2.81-2.67 (m, 2H), 2.46 (s, 3H), 1.90-1.80 (m, 1H), 1.57 (d, $J = 13.3$ Hz, 4H), 1.46-1.38 (m, 2H), 0.97 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 167.85, 148.01, 142.23, 129.65, 128.79, 124.53 (q, $J_{CF} = 278.4$ Hz), 123.47, 121.63, 61.64, 40.55 (q, $J_{CF} = 27.3$ Hz), 40.02, 31.22, 26.49, 21.99, 20.70, 13.84.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -61.58 (s).

HRMS (ESI-TOF) m/z = 322.1389 [M + Na]$^+$, calcd for C$_{16}$H$_{20}$F$_3$NNaO: 322.1395

2-butyl-3, 5, 7-trimethyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid, 68 % yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.50 (s, 1H), 7.12 (s, 1H), 3.61 (ddd, $J = 14.3$, 11.1, 5.3 Hz, 1H), 3.14-3.16 (m, 1H), 2.92-2.94 (m, 1H), 2.80-2.82 (m, 1H), 2.44 (s, 3H), 2.39 (s, 3H), 1.90-1.83 (m, 1H), 1.65-1.56 (m, 4H), 1.45-1.39 (m, 2H), 0.98 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 167.92, 141.48, 138.77, 135.09, 132.19, 131.61, 124.46 (q, $J_{CF} = 278.5$ Hz), 121.75, 62.33, 39.68, 38.03 (q, $J_{CF} = 27.1$ Hz), 31.06, 24.48, 21.05, 20.75, 18.67, 13.82.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -62.69 (s).

HRMS (ESI-TOF) m/z = 336.1546 [M + Na]$^+$, calcd for C$_{17}$H$_{22}$F$_3$NNaO: 336.1551

2-butyl-5-fluoro-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one
Yellow solid, 67% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.82 (dd, $J$ = 8.3, 5.0 Hz, 1H), 7.17 (td, $J$ = 8.8, 2.0 Hz, 1H), 7.10 (dd, $J$ = 8.1, 1.8 Hz, 1H), 3.65-3.67 (m, 1H), 3.16-3.09 (m, 1H), 2.82-2.67 (m, 2H), 1.89-1.80 (m, 1H), 1.64-1.55 (m, 4H), 1.46-1.38 (m, 2H), 0.98 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 166.68, 165.95, 164.28, 150.04, 125.76, 124.36 (q, $J_{CF}$ = 278.3 Hz), 116.53, 108.88, 61.55, 40.47 (q, $J_{CF}$ = 27.5 Hz), 40.18, 31.17, 26.39, 20.67, 13.81.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.65 (s), -106.97 (s).

HRMS (ESI-TOF) m/z = 326.1119 [M + Na]$^+$, calcd for C$_{15}$H$_{17}$F$_4$NNaO: 326.1144

2-butyl-5-chloro-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

White solid, 60% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.77 (d, $J$ = 8.1 Hz, 1H), 7.48-7.37 (m, 2H), 3.66-3.68 (m, 1H), 3.10-3.12 (n, 1H), 2.87-2.65 (m, 2H), 1.91-1.78 (m, 1H), 1.59 (d, $J$ = 11.5 Hz, 4H), 1.48-1.35 (m, 2H), 0.97 (t, $J$ = 7.3 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 166.71, 149.21, 137.97, 129.82, 129.36, 125.03, $\delta$ 124.33 (q, $J_{CF}$ = 278.2 Hz), 121.76, 61.65, 40.43 (q, $J_{CF}$ = 27.4 Hz), 40.20, 31.09, 26.37, 20.68, 13.81.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -61.61 (s).

HRMS (ESI-TOF) m/z = 342.0877 [M + Na]$^+$, calcd for C$_{15}$H$_{17}$ClF$_3$NNaO: 342.0848

5-bromo-2-butyl-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one
2-butyl-7-chloro-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow solid, 71% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.70 (t, $J$ = 6.7 Hz, 1H), 7.63-7.59 (m, 1H), 7.57 (s, 1H), 3.66-3.68 (m, 1H), 3.15-3.08 (m, 1H), 2.83-2.68 (m, 2H), 1.89-1.80 (m, 1H), 1.62-1.54 (m, 4H), 1.45-1.38 (m, 2H), 0.97 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 166.77, 149.41, 132.20, 130.30, 126.24, 125.21, 124.70, 124.32 (q, $J_{CF}$ = 278.4 Hz), 61.63, 40.41 (q, $J_{CF}$ = 27.5 Hz), 40.18, 31.07, 26.37, 20.67, 13.81.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.62 (s).

HRMS (ESI-TOF) m/z = 386.0336 [M + Na]$^+$, calcd for C$_{15}$H$_{17}$BrF$_3$NNaO: 386.0343

2-butyl-5,7-dichloro-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

White solid, 70% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.47 (t, $J$ = 7.7 Hz, 1H), 7.40 (d, $J$ = 7.9 Hz, 1H), 7.32 (d, $J$ = 7.5 Hz, 1H), 3.73-3.61 (m, 1H), 3.21-3.05 (m, 1H), 2.88-2.68 (m, 2H), 1.92-1.81 (m, 1H), 1.64-1.54 (m, 4H), 1.46-1.38 (m, 2H), 0.97 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 165.36, 150.12, 132.30, 131.48, 130.38, 127.33, 124.36 (q, $J_{CF}$ = 278.4 Hz), 119.79, 60.79, 40.47 (q, $J_{CF}$ = 27.4 Hz), 40.21, 30.95, 26.64, 20.70, 13.77.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.58 (s).

HRMS (ESI-TOF) m/z = 342.0829 [M + Na]$^+$, calcd for C$_{15}$H$_{17}$ClF$_3$NNaO: 342.0848
Yellow solid, 36% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 7.43$ (d, $J = 1.5$ Hz, 1H), 7.30 (d, $J = 1.5$ Hz, 1H), 3.64-3.66 (m, 1H), 3.08-3.10 (m, 1H), 2.81-2.68 (m, 2H), 1.90-1.82 (m, 1H), 1.58 (s, 1H), 1.56 (s, 3H), 1.40-1.42 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 164.44, 151.20, 138.05, 132.43, 130.54, 126.04, 124.28 (q, $J_{CF} = 278.7$ Hz), 120.42, 60.73, 40.45 (q, $J_{CF} = 27.6$ Hz), 40.32, 30.92, 26.57, 26.09, 13.77.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta = -61.55$ (s).

HRMS (ESI-TOF) m/z = 376.0453 [M + Na]$^+$, calcd for C$_{15}$H$_{16}$Cl$_2$F$_3$NNaO: 376.0459

2-butyl-3-methyl-5-nitro-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

White solid, 67% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 8.38$ (dd, $J = 8.3, 1.7$ Hz, 1H), 8.31 (d, $J = 1.0$ Hz, 1H), 8.00 (d, $J = 8.3$ Hz, 1H), 3.71-3.73 (m, 1H), 3.22-3.13 (m, 1H), 2.92-2.82 (m, 2H), 1.94-1.81 (m, 1H), 1.65 (d, $J = 13.3$ Hz, 3H), 1.63-1.57 (m, 1H), 1.49-1.39 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 165.38, 150.20, 148.59, 136.68, 124.91, 124.57, 124.17 (q, $J_{CF} = 278.5$ Hz), 117.03, 62.10, 40.55, 40.27 (d, $J_{CF} = 27.6$ Hz), 30.90, 26.34, 20.66, 13.76.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta = -61.65$ (s).

2-butyl-3-methyl-3-(2, 2, 2-trifluoroethyl)-2,3-dihydro-1H-benzo[e]isoindol-1-one
Yellow liquid, 60 % yield; \(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 9.25 (d, J = 8.4 \text{ Hz}, 1\text{H}), 8.03 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.92 (d, J = 8.2 \text{ Hz}, 1\text{H}), 7.67 (t, J = 8.0 \text{ Hz}, 1\text{H}), 7.58 (t, J = 7.9 \text{ Hz}, 1\text{H}), 7.48 (d, J = 8.4 \text{ Hz}, 1\text{H}), 3.74-3.76 (m, 1\text{H}), 3.20-3.22 (m, 1\text{H}), 2.84 (q, J = 10.1 \text{ Hz}, 2\text{H}), 1.94-1.90 (m, 1\text{H}), 1.69-1.64 (m, 1\text{H}), 1.62 (d, J = 9.8 \text{ Hz}, 3\text{H}), 1.49-1.42 (m, 2\text{H}), 1.00 (t, J = 7.4 \text{ Hz}, 3\text{H}).\

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta = 168.73, 147.72, 133.31, 132.54, 129.27, 128.14, 128.11, 126.81, 125.80 (q, J_{CF} = 278.4 \text{ Hz}), 125.25, 124.22, 118.20, 61.22, 40.17 (q, J_{CF} = 27.2 \text{ Hz}), 40.08, 31.25, 26.28, 20.80, 13.87.

\(^{19}\)F NMR (565 MHz, CDCl\(_3\)) \(\delta = -61.69 \text{ (s)}.\)

HRMS (ESI-TOF) m/z = 358.1392 \([M + Na]^+\), calcd for C\(_{19}\)H\(_{20}\)F\(_3\)NNaO: 358.1395

3-methyl-2-propyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

![Structural formula of 3-methyl-2-propyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one](image)

White solid, 64 % yield; \(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 7.84 (d, J = 7.5 \text{ Hz}, 1\text{H}), 7.56 (td, J = 7.5, 1.1 \text{ Hz}, 1\text{H}), 7.47 (td, J = 7.5, 0.9 \text{ Hz}, 1\text{H}), 7.42 (d, J = 7.6 \text{ Hz}, 1\text{H}), 3.64-3.66 (m, 1\text{H}), 3.09-3.11 (m, 1\text{H}), 2.82-2.70 (m, 2\text{H}), 1.94-1.85 (m, 1\text{H}), 1.71-1.63 (m, 1\text{H}), 1.58 (s, 3\text{H}), 1.00 (t, J = 7.4 \text{ Hz}, 3\text{H}).\)

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta = 167.76, 147.57, 131.61, 131.31, 128.68, 124.50 (q, J_{CF} = 278.4 \text{ Hz}), 123.70, 121.20, 41.91, 40.52 (q, J_{CF} = 27.3 \text{ Hz}), 26.45, 22.31, 11.81.

\(^{19}\)F NMR (565 MHz, CDCl\(_3\)) \(\delta = -61.64 \text{ (s)}.\)

HRMS (ESI-TOF) m/z = 294.1067 \([M + Na]^+\), calcd for C\(_{14}\)H\(_{16}\)F\(_3\)NNaO: 294.1082

2-hexyl-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

![Structural formula of 2-hexyl-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one](image)
Yellow liquid, 55 % yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.84 (d, $J$ = 7.5 Hz, 1H), 7.56 (t, $J$ = 7.5 Hz, 1H), 7.47 (t, $J$ = 7.8 Hz, 1H), 7.42 (d, $J$ = 7.6 Hz, 1H), 3.66-3.68 (m, 1H), 3.12-3.14 (m, 1H), 2.83-2.69 (m, 2H), 1.94-1.82 (m, 1H), 1.67-1.54 (m, 4H), 1.39 (dd, $J$ = 14.1, 7.9 Hz, 2H), 1.33 (d, $J$ = 3.4 Hz, 4H), 0.90 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 167.71, 147.57, 131.59, 131.33, 128.67, 124.39 (q, $J_{CF}$ = 277.8 Hz), 123.69, 121.18, 61.83, 40.51 (q, $J_{CF}$ = 27.2 Hz), 40.30, 31.52, 29.00, 27.14, 26.45, 22.61, 14.05.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.62 (s).

HRMS (ESI-TOF) m/z =336.1537 [M + Na]$^+$, calcd for C$_{17}$H$_{22}$F$_3$NaO: 336.1551

2-cyclopropyl-3-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

White solid, 65 % yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.82 (d, $J$ = 7.5 Hz, 1H), 7.57 (t, $J$ = 7.5 Hz, 1H), 7.47 (t, $J$ = 7.4 Hz, 1H), 7.41 (d, $J$ = 7.7 Hz, 1H), 3.00 (dq, $J$ = 15.7, 10.1 Hz, 1H), 2.79 (dq, $J$ = 15.7, 10.0 Hz, 1H), 2.50-2.43 (m, 1H), 1.63 (s, 3H), 1.16-1.11 (m, 1H), 1.07-1.03 (m, 1H), 1.00-0.92 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 168.90, 147.14, 131.83, 131.28, 128.68, 124.63 (q, $J_{CF}$ = 278.4 Hz), 123.88, 121.35, 63.15, 40.52 (q, $J_{CF}$ = 27.1 Hz), 26.90, 21.99, 5.07, 4.70.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -61.24 (s).

HRMS (ESI-TOF) m/z =292.0902 [M + Na]$^+$, calcd for C$_{14}$H$_{14}$F$_3$NaO: 292.0925

2-butyl-3-propyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid, 57 % yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.83 (d, $J$ = 7.4 Hz, 1H), 7.55 (t, $J$ = 7.4 Hz, 1H), 7.46 (t, $J$ = 7.3 Hz, 1H), 7.35 (d, $J$ = 7.5 Hz, 1H), 3.52-3.43 (m, 1H), 3.27-3.18 (m, 1H), 2.83-2.70
(m, 2H), 1.96-1.85 (m, 2H), 1.83-1.76 (m, 1H), 1.60-1.62 (m, 1H), 1.43-1.45 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H), 0.94-0.86 (m, 1H), 0.76 (t, $J = 7.2$ Hz, 3H), 0.54 (dd, $J = 14.6$, 7.9 Hz, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 168.57$, 145.63, 132.26, 131.52, 128.57, 124.52 (q, $J_{CF} = 278.2$ Hz), 123.59, 121.25, 65.07, 40.47 (q, $J_{CF} = 27.2$ Hz), 40.16, 39.93, 30.71, 20.84, 15.48, 13.85, 13.57.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta = -60.85$ (s).

HRMS (ESI-TOF) m/z =336.1556 [M + Na]$^+$, calcd for C$_{17}$H$_{22}$F$_3$NaO: 336.1551

(2-butyl-3-oxo-1-(2, 2, 2-trifluoroethyl)isoindolin-1-yl)methyl benzoate

Yellow liquid, 42% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 7.88$ (t, $J = 6.4$ Hz, 3H), 7.59 (dd, $J = 16.3$, 7.2 Hz, 2H), 7.55-7.48 (m, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 4.53 (s, 2H), 3.77-3.79 (m, 1H), 3.24-3.26 (m, 1H), 2.95-2.97 (m, 2H), 1.95-1.85 (m, 1H), 1.60-1.53 (m, 1H), 1.46-1.35 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 168.24$, 165.60, 143.35, 133.72, 132.08, 131.78, 129.51, 129.46, 128.80, 128.69, 124.51 (q, $J_{CF} = 278.8$Hz), 123.89, 121.94, 67.66, 63.86, 40.94, 36.17 (q, $J_{CF} = 24.2$ Hz), 31.01, 20.67, 13.72.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta = -60.71$ (s).

HRMS (ESI-TOF) m/z =428.1444 [M + Na]$^+$, calcd for C$_{22}$H$_{22}$F$_3$NaO$_3$: 428.1449

2'-butyl-2-(trifluoromethyl)spiro[cyclohexane-1,1'-isoindolin]-3'-one
Yellow liquid, 57 % yield; The major isomer: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.88 (dd, $J$ = 6.0, 2.6 Hz, 1H), 7.73 (dd, $J$ = 6.1, 2.0 Hz, 1H), 7.55-7.46 (m, 2H), 3.62-3.64 (m, 1H), 3.11-3.13 (m, 1H), 2.71-2.73 (m, 1H), 2.23-1.83 (m, 8H), 1.60-1.54 (m, 2H), 1.46-1.39 (m, 2H), 0.98 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 167.65, 145.96, 132.28, 130.55, 128.46, 125.77 (q, $J_{CF}$ = 281.9 Hz), 124.09, 123.82, 64.44, 45.48 (q, $J_{CF}$ = 24.2 Hz), 40.12, 36.36, 31.14, 24.05, 22.83, 22.04, 20.80, 13.81.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -67.20 (s).

HRMS (ESI-TOF) m/z =348.1546 [M + Na]$^+$, calcd for C$_{18}$H$_{22}$F$_3$NNaO: 348.1551

(E)-$N$-butyl-$N$-(3, 3, 3-trifluoro-1-phenylprop-1-enyl)benzamide

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.45 (d, $J$ = 7.3 Hz, 2H), 7.39 (dd, $J$ = 10.5, 4.2 Hz, 2H), 7.35 (d, $J$ = 5.9 Hz, 4H), 7.28 (t, $J$ = 7.6 Hz, 2H), 5.33 (q, $J$ = 8.3 Hz, 1H), 3.66-3.54 (m, 2H), 1.64 (dd, $J$ = 15.5, 7.5 Hz, 2H), 1.31 (dd, $J$ = 15.1, 7.5 Hz, 2H), 0.90 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 171.45, 151.21 (q, $J_{CF}$ = 6.0 Hz), 135.89, 133.76, 130.44, 130.31, 129.05, 129.04, 128.47, 128.20, 127.71, 113.75 (q, $J_{CF}$ = 35.2 Hz), 48.24, 30.06, 20.11, 13.75.

HRMS (ESI-TOF) m/z =370.1384 [M + Na]$^+$, calcd for C$_{20}$H$_{20}$F$_3$NNaO: 370.1395

(E)-$N$-butyl-$N$-(3, 3, 3-trifluoroprop-1-enyl)benzamide

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.95 (dd, $J$ = 6.0 Hz, 2H), 7.39 (dd, $J$ = 10.5, 4.2 Hz, 2H), 7.35 (d, $J$ = 5.9 Hz, 4H), 7.28 (t, $J$ = 7.6 Hz, 2H), 5.33 (q, $J$ = 8.3 Hz, 1H), 3.66-3.54 (m, 2H), 1.64 (dd, $J$ = 15.5, 7.5 Hz, 2H), 1.31 (dd, $J$ = 15.1, 7.5 Hz, 2H), 0.90 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 171.45, 151.21 (q, $J_{CF}$ = 6.0 Hz), 135.89, 133.76, 130.44, 130.31, 129.05, 129.04, 128.47, 128.20, 127.71, 113.75 (q, $J_{CF}$ = 35.2 Hz), 48.24, 30.06, 20.11, 13.75.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -55.30 (s).

HRMS (ESI-TOF) m/z =370.1384 [M + Na]$^+$, calcd for C$_{20}$H$_{20}$F$_3$NNaO: 370.1395
Yellow liquid, 64% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.56-7.43 (m, 5H), 7.39 (d, $J = 13.5$ Hz, 1H), 5.09 (dd, $J = 14.2$, 6.2 Hz, 1H), 3.82-3.69 (m, 2H), 1.72-1.61 (m, 2H), 1.40 (dd, $J = 15.0$, 7.4 Hz, 2H), 0.97 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 171.10, 136.86, 133.89, 131.21, 128.79, 128.01, 124.36 (q, $J_{CF} = 267.4$ Hz), 96.52 (d, $J_{CF} = 34.3$ Hz), 43.81, 28.46, 20.20, 13.76.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -59.97 (s).

HRMS (ESI-TOF) m/z = 294.1082 [M + Na]$^+$, calcd for C$_{14}$H$_{16}$F$_3$NNaO: 294.1082

(E)-N-propyl-N-(3,3,3-trifluoroprop-1-enyl)benzamide

Yellow liquid, 72% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.52 (dd, $J = 10.8$, 4.2 Hz, 1H), 7.50-7.44 (m, 4H), 7.39 (d, $J = 7.5$ Hz, 1H), 5.08-5.10 (m, 1H), 3.76-3.69 (m, 2H), 1.74-1.67 (m, 2H), 0.98 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 171.12, 136.84, 133.86, 131.20, 128.78, 128.00, 124.33 (q, $J_{CF} = 267.4$ Hz), 96.54 (q, $J_{CF} = 34.7$ Hz), 45.49, 19.69, 11.29.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -60.03 (s).

HRMS (ESI-TOF) m/z = 280.0922 [M + Na]$^+$, calcd for C$_{13}$H$_{14}$F$_3$NNaO: 280.0925

(E)-N-cyclohexyl-N-(3,3,3-trifluoroprop-1-enyl)benzamide
Yellow liquid, 47% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.55-7.40 (m, 5H), 7.10 (d, $J = 14.5$ Hz, 1H), 5.40 (m, 1H), 3.97 (m, 1H), 2.06 (m, 2H), 1.88 (d, $J = 13.3$ Hz, 2H), 1.81 (d, $J = 11.1$ Hz, 2H), 1.39-1.19 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 171.92, 136.10, 135.09, 131.11, 128.71, 127.92, 124.40 (q, $J_{CF} = 267.8$ Hz), 99.48 (q, $J_{CF} = 34.3$ Hz), 57.66, 29.42, 26.19, 25.27.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -60.50 (s).

HRMS (ESI-TOF) m/z = 320.1221 [M + Na]$^+$, calcd for C$_{16}$H$_{18}$F$_3$NNaO: 320.1238

(E)-N-butyl-4-methoxy-N-(3, 3, 3-trifluoroprop-1-enyl)benzamide

Colorless liquid, 68% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.44 (t, $J = 9.0$ Hz, 3H), 6.96 (d, $J = 8.7$ Hz, 2H), 5.06 (m, 1H), 3.87 (s, 3H), 3.80-3.71 (m, 2H), 1.64 (dd, $J = 14.5$, 7.0 Hz, 2H), 1.39 (m, 2H), 0.97 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 170.85, 162.02, 137.42, 130.45, 125.79, 124.50 (q, $J_{CF} = 267.3$ Hz), 114.04, 95.85 (q, $J_{CF} = 34.3$ Hz), 55.46, 43.99, 28.46, 20.23, 13.76.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -59.75 (s).

HRMS (ESI-TOF) m/z = 324.1155 [M + Na]$^+$, calcd for C$_{15}$H$_{18}$F$_3$NNaO$_2$: 324.1187

2-butyl-5-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid, 33% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.73 (d, $J = 8.3$ Hz, 1H), 7.30 (d, $J = 7.1$ Hz, 2H), 4.70 (dd, $J = 6.6$, 3.4 Hz, 1H), 4.07-4.09 (m, 1H), 3.11-3.13 (m, 1H), 2.78-2.68 (m, 1H), 2.54-2.56 (m, 1H), 2.47 (s, 3H), 1.64-1.57 (m, 2H), 1.35 (dd, $J = 15.0$, 7.5 Hz, 2H), 0.95 (t, $J = 7.4$ Hz, 3H).
$^1$C NMR (151 MHz, CDCl$_3$) $\delta$ = 168.13, 144.37, 142.58, 129.81, 129.37, 125.74 (q, $J_{CF}$ = 277.8 Hz), 123.60, 123.07, 53.42, 39.57, 36.66 (q, $J_{CF}$ = 28.1 Hz), 30.09, 21.99, 20.07, 13.75.

$^{19}$F NMR (565 MHz, CDCl$_3$) $\delta$ = -62.59 (s).

HRMS (ESI-TOF) m/z = 308.1241 [M + Na]$^+$, calcd for C$_{15}$H$_{18}$F$_3$NNaO: 308.1238

(E)-N-butyl-4-methyl-N-(3, 3, 3-trifluoroprop-1-enyl)benzamide

\[
\text{Me} \quad \text{\underline{N}} \quad \text{O} \quad \text{C} \quad \underline{\text{F}}_3
\]

Yellow liquid, 36% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.41 (d, $J$ = 13.9 Hz, 1H), 7.36 (d, $J$ = 8.0 Hz, 2H), 7.26 (d, $J$ = 7.9 Hz, 2H), 5.06-5.08 (m, 1H), 3.80-3.69 (m, 2H), 2.41 (s, 3H), 1.67-1.61 (m, 2H), 1.39 (dd, $J$ = 15.1, 7.5 Hz, 2H), 0.97 (t, $J$ = 7.3 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 171.21, 141.75, 137.17, 130.89, 129.38, 128.23, 124.44 (q, $J_{CF}$ = 267.4 Hz), 96.09 (q, $J_{CF}$ = 35.3 Hz), 43.81, 28.45, 21.51, 20.22, 13.76.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -59.84 (s).

HRMS (ESI-TOF) m/z = 308.1203 [M + Na]$^+$, calcd for C$_{15}$H$_{18}$F$_3$NNaO: 308.1238

2-butyl-7-methyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

\[
\text{Me} \quad \text{\underline{N}} \quad \text{O} \quad \text{C} \quad \underline{\text{F}}_3
\]

Yellow liquid, 70% yield; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.43 (t, $J$ = 7.6 Hz, 1H), 7.32 (d, $J$ = 7.6 Hz, 1H), 7.23 (d, $J$ = 7.5 Hz, 1H), 4.69 (dd, $J$ = 6.3, 3.5 Hz, 1H), 4.04-4.06 (m, 1H), 3.10-3.12 (m, 1H), 2.77-2.65 (m, 4H), 2.63-2.50 (m, 1H), 1.66-1.60 (m, 1H), 1.56-1.58 (m, 1H), 1.40-1.33 (m, 2H), 0.95 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 168.83, 144.54, 137.85, 131.28, 130.81, 128.89, 125.70 (q, $J_{CF}$ = 277.8 Hz), 119.89, 53.02, 39.54, 36.91 (q, $J_{CF}$ = 28.1 Hz), 30.09, 20.14, 17.25, 13.73.
$^{19}\text{F NMR (565 MHz, CDCl}_3\text{) }\delta = -62.55 \text{ (s).}$

HRMS (ESI-TOF) m/z = 308.1218 [M + Na]$^+$, calcd for C$_{15}$H$_{18}$F$_3$NNaO: 308.1238

2-butyl-5-chloro-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid, 63 % yield; $^1\text{H NMR (600 MHz, CDCl}_3\text{) }\delta = 7.78 \text{ (d, } J = 8.1 \text{ Hz, 1H), 7.52 (s, 1H), 7.49 (dd, } J = 8.1, 1.6 \text{ Hz, 1H), 4.73 (dd, } J = 6.9, 3.2 \text{ Hz, 1H), 4.07-4.09 (m, 1H), 3.17-3.08 (m, 1H), 2.76 (dqd, } J = 19.0, 11.2, 3.3 \text{ Hz, 1H), 2.63-2.52 (m, 1H), 1.66-1.61 (m, 1H), 1.61-1.56 (m, 1H), 1.35 (dd, } J = 15.0, 7.5 \text{ Hz, 2H), 0.95 (t, } J = 7.4 \text{ Hz, 3H).}$

$^{13}\text{C NMR (101 MHz, CDCl}_3\text{) }\delta = 166.95, 145.38, 138.26, 130.46, 129.52, 125.42 \text{ (d, } J_{CF} = 277.3 \text{ Hz), 125.05, 123.19, 53.37, 39.75, 36.27 \text{ (q, } J_{CF} = 28.4 \text{ Hz), 30.01, 20.04, 13.68.}$

$^{19}\text{F NMR (565 MHz, CDCl}_3\text{) }\delta = -62.51 \text{ (s).}$

HRMS (ESI-TOF) m/z = 328.0697 [M + Na]$^+$, calcd for C$_{14}$H$_{15}$ClF$_3$NNaO: 328.0692

5-bromo-2-butyl-3-(2, 2, 2-trifluoroethyl)isoindolin-1-one

Yellow liquid, 54 % yield; $^1\text{H NMR (600 MHz, CDCl}_3\text{) }\delta = 7.72 \text{ (d, } J = 8.0 \text{ Hz, 1H), 7.68 (s, 1H), 7.65 (dd, } J = 8.0, 1.5 \text{ Hz, 1H), 4.73 (dd, } J = 6.8, 3.2 \text{ Hz, 1H), 4.12-4.03 (m, 1H), 3.15-3.07 (m, 1H), 2.82-2.70 \text{ (m, 1H), 2.57-2.59 (m, 1H), 1.66-1.56 (m, 2H), 1.35 (dd, } J = 15.0, 7.5 \text{ Hz, 2H), 0.95 (t, } J = 7.4 \text{ Hz, 3H).}$

$^{13}\text{C NMR (151 MHz, CDCl}_3\text{) }\delta = 167.08, 145.57, 132.41, 130.88, 126.56, 126.14, 125.42 \text{ (q, } J_{CF} = 277.4 \text{ Hz), 125.27, 77.26, 77.05, 76.84, 53.29, 39.71, 36.21 \text{ (q, } J_{CF} = 28.4 \text{ Hz), 29.99, 20.04, 13.72.}$

$^{19}\text{F NMR (565 MHz, CDCl}_3\text{) }\delta = -62.51 \text{ (s).}$
HRMS (ESI-TOF) m/z = 372.0169 [M + Na]⁺, calcd for C₁₄H₁₅BrF₃NNaO: 372.0187

(E)-N-butyl-N-(3, 3, 3-trifluoroprop-1-enyl)furan-2-carboxamide

Yellow liquid, 60 % yield; ¹H NMR (400 MHz, CDCl₃) δ = 7.96 (d, J = 14.2 Hz, 1H), 7.60 (s, 1H), 7.16 (d, J = 3.3 Hz, 1H), 6.62-6.50 (m, 1H), 5.17-5.19 (m, 1H), 3.85-3.63 (m, 2H), 1.73-1.61 (m, 2H), 1.46-1.33 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 159.17, 146.49, 145.57, 136.19, 124.54 (q, JCF = 268.7 Hz), 119.47, 111.96, 97.35 (q, JCF = 34.4 Hz), 44.38, 28.67, 20.16, 13.71.

¹⁹F NMR (377 MHz, CDCl₃) δ = -59.93 (s).

HRMS (ESI-TOF) m/z = 284.0877 [M + Na]⁺, calcd for C₁₂H₁₄F₃NNaO₂: 284.0874

(E)-N-butyl-N-(4,4,4-trifluorobut-2-en-2-yl)furan-2-carboxamide

Yellow liquid, 60 % yield; ¹H NMR (600 MHz, CDCl₃) δ = 7.44 (s, 1H), 7.05 (d, J = 3.5 Hz, 1H), 6.46 (dd, J = 3.4, 1.7 Hz, 1H), 5.40 (q, J = 7.9 Hz, 1H), 3.63-3.56 (m, 2H), 2.16 (s, 3H), 1.59 (dd, J = 15.5, 7.8 Hz, 2H), 1.38 (dd, J = 15.1, 7.5 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ = 158.57, 149.51 (q, JCF = 6.0 Hz), 147.52, 144.26, 122.87 (q, JCF = 270.1 Hz), 117.05 (q, JCF = 34.7 Hz), 117.10, 111.60, 46.77, 29.87, 20.08, 18.24, 13.77.

¹⁹F NMR (565 MHz, CDCl₃) δ = -58.22 (s).

HRMS (ESI-TOF) m/z = 298.1055 [M + Na]⁺, calcd for C₁₃H₁₆F₃NNaO₂: 298.1031
(C) Spectra

2a. $^1$H NMR

2a. $^{13}$C NMR
2b. $^{1}H$ NMR

![1H NMR spectrum](image)

2b. $^{13}C$ NMR

![13C NMR spectrum](image)
2c. $^1$H NMR

![$^1$H NMR spectrum](image)

2c. $^{13}$C NMR

![$^{13}$C NMR spectrum](image)
2d. $^1$H NMR

![1H NMR spectrum](image1)

2d. $^{13}$C NMR

![13C NMR spectrum](image2)
2e. $^1$H NMR

![$^1$H NMR spectrum]

2e. $^{13}$C NMR

![$^{13}$C NMR spectrum]
2f. $^1$H NMR

![H NMR spectrum](image)

2f. $^{13}$C NMR

![$^{13}$C NMR spectrum](image)
2g. $^1$H NMR

![1H NMR spectrum](image)

2g. $^{13}$C NMR

![$^{13}$C NMR spectrum](image)
2h. $^1$H NMR

2h. $^{13}$C NMR
2i. $^1$H NMR

2i. $^{13}$C NMR
2j. $^1$H NMR

![1H NMR spectrum with chemical shifts and peaks labeled](image)

2j. $^{13}$C NMR

![$^{13}$C NMR spectrum with chemical shifts and peaks labeled](image)
2k. $^1$H NMR

![H NMR spectrum](image)

2k. $^{13}$C NMR

![C NMR spectrum](image)
21. $^1$H NMR

21. $^{13}$C NMR
2m. $^1$H NMR

![1H NMR spectrum](image)

2m. $^{13}$C NMR

![13C NMR spectrum](image)
2n. $^1$H NMR

2n. $^{13}$C NMR
2o. $^1$H NMR

![H NMR spectrum](image1)

2o. $^{13}$C NMR

![C NMR spectrum](image2)
2p. $^1$H NMR

2p. $^{13}$C NMR
2q. $^1$H NMR

![H NMR spectrum]

2q. $^{13}$C NMR

![C NMR spectrum]
2r. $^1$H NMR

![1H NMR spectrum](image1)

2r. $^{13}$C NMR

![13C NMR spectrum](image2)
2s. $^1$H NMR

![1H NMR spectrum]

2s. $^{13}$C NMR

![13C NMR spectrum]
4a’. \(^1\)H NMR

4a’. \(^{13}\)C NMR
4b’. $^1$H NMR

4b’. $^{13}$C NMR
4c’. $^1$H NMR

4c’. $^{13}$C NMR
4d’. $^1$H NMR

![NMR Spectrum](image)

4d’. $^{13}$C NMR

![NMR Spectrum](image)
4e. $^1$H NMR

4e. $^{13}$C NMR
4e'. $^1$H NMR

[Chemical structure image]

4e'. $^{13}$C NMR

[Chemical structure image]
4f. $^1$H NMR

4f. $^{13}$C NMR
4g. $^1$H NMR

![H NMR Spectrum](attachment:image1.png)

4g. $^{13}$C NMR

![C NMR Spectrum](attachment:image2.png)
4h. $^1$H NMR

![$^1$H NMR spectrum]

4h. $^{13}$C NMR

![$^{13}$C NMR spectrum]
6a. $^1$H NMR

![H NMR spectrum](image)

6a. $^{13}$C NMR

![C NMR spectrum](image)
6b. $^1$H NMR

6b. $^{13}$C NMR