An efficient approach to 3-oxoisooindoline-1-difluoroalkyl derivatives via metal triflates-catalyzed Mannich/Lactamization cascade reaction

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1. Experiment section

1.1 General

Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were dried before used. Reactions were carried out under nitrogen atmosphere. All commercially available compounds were used without purification. The products were purified by column chromatography over silica gel (100-200 mesh). $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra are recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz, 125 MHz and 470 MHz in CDCl$_3$, respectively, and chemical shifts are reported in ppm. Mass spectra are taken on a Thermo Scientific ISQ LT GC-MS instrument in the electron ionization (EI) mode.

1.2 General procedure for the synthesis of $N$-substituted isoindolinones

2-formylbenzoic 1 (0.1 mmol), amines 2 (0.1 mmol) and In(OTf)$_3$ (10 mol%) in DCM (1.0 mL) were reacted under nitrogen atmosphere at 35 °C for 1h. Then difluoroenoxysilane 3 (0.12 mmol) was added via syringe and the mixture was stirred for 24 h. Upon completion, the mixture was purified by column chromatography over silica gel using petrol ether/ethyl acetate as the eluent.

1.3 Procedure for the synthesis of compound 5a

The solution of compound 4a (196.5 mg, 0.5 mmol) in CH$_3$CN:H$_2$O (4:1) (5 mL) was cooled at 0 °C. The reaction mixture was charged with ceric ammonium nitrate (CAN) (548.2mg, 1.0 mmol) and stirred for 30 min. Upon completion of the reaction (monitored by TLC), diluted with water and quenched with saturated aqueous NaHCO$_3$ solution. The reaction mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/hexanes as eluent to afford compound 5a as white solid (130.6 mg, 91% yield).

2. Characterization data

2.1 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(4-methoxyphenyl)isoindolin-1-one (4a)

The titled compound was isolated as white solid (33.1mg, 84%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.90 (d, $J = 6.7$ Hz, 1H), 7.70 (d, $J = 7.2$ Hz, 2H), 7.63 – 7.48 (m, 4H), 7.32 (t, $J = 7.1$ Hz, 2H), 7.19 – 7.10 (m, 2H), 6.77 (d, $J = 8.7$ Hz, 2H), 6.00 – 5.88 (m, 1H), 3.73 (s, 3H). $^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ −103.42 (d, $J = 285.5$ Hz), −107.30 (d, $J = 285.5$ Hz). $^{13}$C NMR (125 MHz, Chloroform-$d$) $\delta$ 188.75 (t, $J = 285.5$ Hz), 168.45, 158.52, 137.68, 134.63, 133.63, 132.89, 132.41, 130.24, 129.94, 129.81, 129.40, 128.64, 127.79, 124.80, 124.58, 116.45 (t, $J = 25.7$ Hz), 55.55. MS (EI) m/z: 393 [M+].
2.2 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-phenylisoindolin-1-one (4b)

![Chemical Structure]

Chemical Formula: C\textsubscript{22}H\textsubscript{15}F\textsubscript{2}NO\textsubscript{2}

Exact Mass: 363

The titled compound was isolated as white solid (29.0mg, 80%). \textsuperscript{1}H NMR (500 MHz, Chloroform-\textit{d}) \(\delta\) 7.96 (d, \(J = 7.6\) Hz, 1H), 7.76 (d, \(J = 7.5\) Hz, 2H), 7.67 – 7.53 (m, 4H), 7.41 – 7.31 (m, 6H), 7.23 (ddt, \(J = 8.5, 4.4, 2.2\) Hz, 1H), 6.10 (t, \(J = 9.9\) Hz, 1H). \textsuperscript{19}F NMR (470 MHz, Chloroform-\textit{d}) \(\delta\) -103.96 (d, \(J = 286.7\) Hz), -105.01 (d, \(J = 286.7\) Hz). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 188.78 (t, \(J = 28.7\) Hz), 168.09, 137.58, 136.91, 134.65, 132.51, 132.35, 129.97, 129.86, 129.02, 128.67, 126.92, 125.94, 124.76, 124.67, 116.44 (t, \(J = 261.2\) Hz), 62.86 (t, \(J = 26.2\) Hz). MS (EI) \textit{m/z}: 363 [M\textsuperscript{+}].

2.3 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(p-tolyl)isoindolin-1-one (4c)

![Chemical Structure]

Chemical Formula: C\textsubscript{23}H\textsubscript{17}F\textsubscript{2}NO\textsubscript{2}

Exact Mass: 377

The titled compound was isolated as white solid (31.4mg, 83%). \textsuperscript{1}H NMR (500 MHz, Chloroform-\textit{d}) \(\delta\) 7.95 (d, \(J = 6.8\) Hz, 1H), 7.76 (d, \(J = 7.8\) Hz, 2H), 7.60 (dq, \(J = 22.7, 7.4\) Hz, 4H), 7.37 (t, \(J = 7.8\) Hz, 2H), 7.21 (d, \(J = 8.3\) Hz, 2H), 7.12 (d, \(J = 8.2\) Hz, 2H), 6.05 (t, \(J = 10.0\) Hz, 1H), 2.32 (s, 3H). \textsuperscript{19}F NMR (470 MHz, Chloroform-\textit{d}) \(\delta\) -103.84 (d, \(J = 285.8\) Hz), -105.69 (d, \(J = 285.8\) Hz). \textsuperscript{13}C NMR (125 MHz, Chloroform-\textit{d}) \(\delta\) 188.80 (t, \(J = 28.7\) Hz), 168.14, 137.63, 136.85, 134.61, 134.22, 132.97, 132.41, 129.92, 129.85, 129.65, 128.60, 125.97, 124.77, 124.59, 116.51 (t, \(J = 262.6\) Hz), 63.07 (t, \(J = 25.8\) Hz), 21.19. MS (EI) \textit{m/z}: 377 [M\textsuperscript{+}].

2.4 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(4-fluorophenyl)isoindolin-1-one (4d)

![Chemical Structure]

Chemical Formula: C\textsubscript{22}H\textsubscript{14}F\textsubscript{3}NO\textsubscript{2}

Exact Mass: 381

The titled compound was isolated as white solid (28.5mg, 75%). \textsuperscript{1}H NMR (500 MHz, Chloroform-\textit{d}) \(\delta\) 7.96 (d, \(J = 6.9\) Hz, 1H), 7.78 (d, \(J = 7.6\) Hz, 2H), 7.68 – 7.56 (m, 4H), 7.40 (t, \(J = 7.9\) Hz, 2H), 7.30 (dd, \(J = 8.9, 4.8\) Hz, 2H), 7.07 – 6.97 (m, 2H), 6.03 (t, \(J = 9.9\) Hz, 1H). \textsuperscript{19}F NMR (470 MHz,
2.5 2-(4-chlorophenyl)-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4e)

The titled compound was isolated as white solid (30.2mg, 76%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.95 (d, \(J = 7.1\) Hz, 1H), 7.78 (d, \(J = 7.7\) Hz, 2H), 7.66 – 7.56 (m, 4H), 7.39 (t, \(J = 7.9\) Hz, 2H), 7.30 (s, 4H), 6.05 (t, \(J = 9.8\) Hz, 1H). \(^{19}\)F NMR (470 MHz, Chloroform-\(d\)) \(\delta\) -104.27 (d, \(J = 7.2\) Hz).

\(^{13}\)C NMR (125 MHz, Chloroform-\(d\)) \(\delta\) 188.72 (t, \(J = 28.3\) Hz), 167.95, 137.42, 135.52, 134.84, 132.73, 132.55, 132.44, 132.25, 130.08, 129.86, 129.15, 128.76, 127.05, 124.77, 124.74, 116.42 (t, \(J = 262.8\) Hz), 62.81 (t, \(J = 25.7\) Hz). MS (EI) \(m/z\): 397 [M\(^+\)].

2.6 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(4-nitrophenyl)isoindolin-1-one (4f)

The titled compound was isolated as white solid (27.3mg, 67%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 8.26 (d, \(J = 9.1\) Hz, 2H), 7.98 (d, \(J = 8.4\) Hz, 1H), 7.84 (d, \(J = 7.6\) Hz, 2H), 7.70 (d, \(J = 9.1\) Hz, 2H), 7.69 – 7.57 (m, 4H), 7.41 (t, \(J = 7.9\) Hz, 2H), 6.25 (dd, \(J = 12.6, 6.3\) Hz, 1H). \(^{19}\)F NMR (470 MHz, Chloroform-\(d\)) \(\delta\) -99.72 (d, \(J = 290.5\) Hz), -105.55 (d, \(J = 290.5\) Hz). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 187.39 (t, \(J = 7.1\) Hz), 166.65, 143.99, 142.15, 135.99, 134.09, 132.30, 130.90, 129.27, 128.90, 127.83, 123.98, 123.67, 123.41, 115.33 (t, \(J = 262.5\) Hz), 61.04 (t, \(J = 25.0\) Hz). MS (EI) \(m/z\): 408 [M\(^+\)].

2.7 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(m-tolyl)isoindolin-1-one (4g)

The titled compound was isolated as white solid (30.2mg, 76%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) -103.82 (d, \(J = 287.5\) Hz), -105.58 (d, \(J = 287.4\) Hz), -114.57. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 187.63 (t, \(J = 28.75\) Hz), 167.13, 160.16 (d, \(J = 246.9\) Hz), 136.43, 133.75, 131.72, 131.55, 131.15, 128.97, 128.76, 127.68, 126.92, 126.86, 123.72, 123.61, 115.29 (t, \(J = 261.25\) Hz), 114.95, 114.77, 62.02 (t, \(J = 25.0\) Hz). MS (EI) \(m/z\): 381 [M\(^+\)].
The titled compound was isolated as white solid (30.5 mg, 81%). $^1$H NMR (500 MHz, Chloroform- $d$) $\delta$ 7.96 (d, $J = 6.9$ Hz, 1H), 7.75 (d, $J = 7.7$ Hz, 2H), 7.61 (ddd, $J = 26.6, 19.1, 7.4$ Hz, 4H), 7.37 (t, $J = 7.9$ Hz, 2H), 7.29 – 7.18 (m, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 6.14 – 5.98 (m, 1H), 2.26 (s, 3H).

$^{19}$F NMR (470 MHz, Chloroform- $d$) $\delta$ -103.77 (d, $J = 284.6$ Hz), -106.23 (d, $J = 284.6$ Hz).

$^{13}$C NMR (125 MHz, Chloroform- $d$) $\delta$ 188.81 (t, $J = 28.5$ Hz), 168.06, 138.95, 137.66, 135.46, 134.55, 132.95, 132.44, 129.93, 129.84, 128.85, 128.63, 127.84, 126.90, 124.77, 124.61, 123.06, 123.05, 188.81, 188.58, 116.47 (t, $J = 262.8$ Hz), 63.04 (t, $J = 25.8$ Hz), 21.41. MS (EI) $m/z$: 377 [M$^+$].

2.8 2-(3-chlorophenyl)-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4h)

The titled compound was isolated as white solid (28.7 mg, 72%). $^1$H NMR (500 MHz, Chloroform- $d$) $\delta$ 7.96 (d, $J = 7.2$ Hz, 1H), 7.80 (d, $J = 7.7$ Hz, 2H), 7.61 (dt, $J = 15.8, 5.7$ Hz, 4H), 7.45 – 7.37 (m, 3H), 7.29 (d, $J = 5.2$ Hz, 2H), 7.20 (td, $J = 4.6, 2.0$ Hz, 1H), 6.07 (t, $J = 9.7$ Hz, 1H). $^{19}$F NMR (470 MHz, Chloroform- $d$) $\delta$ -103.44 (d, $J = 287.3$ Hz), -104.67 (d, $J = 287.5$ Hz).

$^{13}$C NMR (125 MHz, Chloroform- $d$) $\delta$ 188.68 (t, $J = 28.7$ Hz), 116.41 (t, $J = 263.2$ Hz), 62.74 (t, $J = 25.5$ Hz). MS (EI) $m/z$: 397 [M$^+$].

2.9 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(2-methoxyphenyl)isoindolin-1-one (4i)

The titled compound was isolated as white solid (13.9 mg, 35%). $^1$H NMR (500 MHz, Chloroform- $d$) $\delta$ 7.93 (d, $J = 7.4$ Hz, 1H), 7.69 (d, $J = 7.8$ Hz, 2H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.52 (q, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 7.7$ Hz, 2H), 7.20 (t, $J = 8.8$ Hz, 2H), 6.88 – 6.70 (m, 2H), 6.14 (dd, $J = 14.5, 7.4$ Hz, 1H), 3.63 (s, 3H). $^{19}$F NMR (470 MHz, Chloroform- $d$) $\delta$ -102.94 (d, $J = 296.2$ Hz), -109.77 (d, $J = 286.6$ Hz). $^{13}$C NMR (125 MHz, Chloroform- $d$) $\delta$ 188.35 (t, $J = 29.2$ Hz), 168.78, 155.12, 138.65, 134.36, 133.66, 132.94, 132.42, 132.25, 130.76, 130.25, 129.73, 129.51, 128.58, 124.74, 124.60, 120.85, 116.40 (t, $J = 258.75$), 111.73, 62.12 (t, $J = 26.1$ Hz), 55.49. MS (EI) $m/z$: 393 [M$^+$].

2.10 2-(2-chlorophenyl)-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4j)
The titled compound was isolated as colorless liquid (15.0 mg, 38%). \( ^1H \text{NMR} \) (500 MHz, Chloroform-\( d \)) \( \delta \) 8.00 (d, \( J = 7.2 \) Hz, 1H), 7.80 (d, \( J = 7.2 \) Hz, 2H), 7.62 (dt, \( J = 15.8, 5.8 \) Hz, 4H), 7.47 (d, \( J = 7.9 \) Hz, 1H), 7.42 (t, \( J = 7.8 \) Hz, 2H), 7.37 – 7.27 (m, 2H), 7.25 – 7.18 (m, 1H), 6.28 – 6.08 (m, 1H). \( ^{19}F \text{NMR} \) (470 MHz, Chloroform-\( d \)) \( \delta \) -103.24 (d, \( J = 294.2 \) Hz), -106.72 (d, \( J = 294.5 \) Hz). \( ^{13}C \text{NMR} \) (125 MHz, CDCl\(_3 \)) \( \delta \) 187.19 (t, \( J = 28.7 \) Hz), 167.86, 137.17, 133.70, 133.27, 131.59, 131.16, 129.97, 129.38, 128.78, 127.71, 126.56, 123.75, 115.16 (t, \( J = 261.25 \) Hz), 60.80 (t, \( J = 25.0 \) Hz). MS (EI) \( m/z \): 397 [M\(^+\)].

2.11 2-benzyl-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4k)

The titled compound was isolated as white solid (31.3 mg, 83%). \( ^1H \text{NMR} \) (500 MHz, Chloroform-\( d \)) \( \delta \) 7.87 (t, \( J = 7.0 \) Hz, 3H), 7.58 (t, \( J = 7.4 \) Hz, 1H), 7.52 – 7.46 (m, 2H), 7.40 (t, \( J = 7.8 \) Hz, 3H), 7.30 – 7.22 (m, 5H), 5.48 (d, \( J = 15.2 \) Hz, 1H), 5.16 (dd, \( J = 13.1, 6.6 \) Hz, 1H), 4.38 (d, \( J = 15.2 \) Hz, 1H). \( ^{19}F \text{NMR} \) (470 MHz, Chloroform-\( d \)) \( \delta \) -100.71 (d, \( J = 289.5 \) Hz), -104.22 (d, \( J = 289.5 \) Hz). \( ^{13}C \text{NMR} \) (125 MHz, CDCl\(_3 \)) \( \delta \) 188.48 (t, \( J = 28.7 \) Hz), 169.64, 138.06, 136.54, 134.71, 132.85, 132.40, 132.08, 129.95, 129.68, 128.90, 128.80, 128.43, 127.85, 124.53, 124.37, 117.31 (t, \( J = 261.25 \) Hz), 60.61 (t, \( J = 25.5 \) Hz), 46.02. MS (EI) \( m/z \): 377 [M\(^+\)].

2.12 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(4-methoxy benzyl)isoindolin-1-one (4l)

The titled compound was isolated as white solid (31.3 mg, 83%). \( ^1H \text{NMR} \) (500 MHz, Chloroform-\( d \)) \( \delta \) 7.87 (t, \( J = 7.0 \) Hz, 3H), 7.58 (t, \( J = 7.4 \) Hz, 1H), 7.52 – 7.46 (m, 2H), 7.40 (t, \( J = 7.8 \) Hz, 3H), 7.30 – 7.22 (m, 5H), 5.48 (d, \( J = 15.2 \) Hz, 1H), 5.16 (dd, \( J = 13.1, 6.6 \) Hz, 1H), 4.38 (d, \( J = 15.2 \) Hz, 1H). \( ^{19}F \text{NMR} \) (470 MHz, Chloroform-\( d \)) \( \delta \) -100.71 (d, \( J = 289.5 \) Hz), -104.22 (d, \( J = 289.5 \) Hz). \( ^{13}C \text{NMR} \) (125 MHz, CDCl\(_3 \)) \( \delta \) 188.48 (t, \( J = 28.7 \) Hz), 169.64, 138.06, 136.54, 134.71, 132.85, 132.40, 132.08, 129.95, 129.68, 128.90, 128.80, 128.43, 127.85, 124.53, 124.37, 117.31 (t, \( J = 261.25 \) Hz), 60.61 (t, \( J = 25.5 \) Hz), 46.02. MS (EI) \( m/z \): 407 [M\(^+\)].
The titled compound was isolated as colorless liquid (35.1mg, 86%). $^1$H NMR (500 MHz, Chloroform-d) δ 7.86 (d, $J = 7.7$ Hz, 3H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.52 – 7.45 (m, 2H), 7.17 (d, $J = 8.2$ Hz, 2H), 6.80 (d, $J = 8.2$ Hz, 2H), 5.40 (d, $J = 15.0$ Hz, 1H), 5.14 (dd, $J = 13.0$, 6.7 Hz, 1H), 4.31 (d, $J = 15.0$ Hz, 1H), 3.75 (s, 3H).

$^{19}$F NMR (470 MHz, Chloroform-d) δ -100.79 (d, $J = 289.0$ Hz), -104.00 (d, $J = 288.9$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 188.51 (t, $J = 28.75$ Hz), 169.60, 159.28, 138.09, 134.67, 132.95, 132.43, 132.01, 131.34, 129.95, 129.86, 129.63, 128.77, 128.61, 124.50, 124.31, 117.35 (t, $J = 261.25$ Hz), 114.27, 60.47 (t, $J = 25$ Hz), 55.35, 45.41. MS (EI) m/z: 407 [M$^+$].

### 2.13 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(4-methylbenzyl)isoindolin-1-one (4m)

![Chemical Structure](image)

The titled compound was isolated as colorless liquid (33.1mg, 85%). $^1$H NMR (500 MHz, Chloroform-d) δ 7.82 (d, $J = 8.7$ Hz, 3H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.49 – 7.41 (m, 2H), 7.35 (t, $J = 7.8$ Hz, 3H), 7.13 – 6.99 (m, 4H), 5.39 (d, $J = 15.1$ Hz, 1H), 5.10 (dd, $J = 13.1$, 6.6 Hz, 1H), 4.28 (d, $J = 15.1$ Hz, 1H), 2.24 (s, 3H).

$^{19}$F NMR (470 MHz, Chloroform-d) δ -100.72 (d, $J = 289.1$ Hz), -104.15 (d, $J = 296.6$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 188.50 (t, $J = 28.75$ Hz), 169.61, 138.10, 137.54, 135.06, 134.65, 133.46, 132.93, 132.43, 132.01, 129.96, 129.56, 128.75, 128.46, 124.50, 124.33, 117.34 (t, $J = 260.0$ Hz), 60.52 (t, $J = 25.0$ Hz), 45.74, 21.18. MS (EI) m/z: 391 [M$^+$].

### 2.14 2-(4-chlorobenzyl)-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4n)

![Chemical Structure](image)

The titled compound was isolated as white solid (32.9mg, 80%). $^1$H NMR (500 MHz, Chloroform-d) δ 7.86 (d, $J = 15.7$ Hz, 3H), 7.69 – 7.54 (m, 1H), 7.56 – 7.47 (m, 2H), 7.46 – 7.31 (m, 3H), 7.28 – 7.09 (m, 4H), 5.32 (dd, $J = 15.2$, 4.2 Hz, 1H), 5.26 – 5.03 (m, 1H), 4.42 (dd, $J = 15.0$, 4.3 Hz, 1H). $^{19}$F NMR (470 MHz, Chloroform-d) δ -101.29 (d, $J = 289.1$ Hz), -104.15 (d, $J = 296.6$ Hz). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 188.50 (t, $J = 28.75$ Hz), 169.61, 138.10, 137.54, 135.06, 134.65, 133.46, 132.93, 132.43, 132.01, 129.96, 129.56, 128.75, 128.46, 124.50, 124.33, 117.34 (t, $J = 260.0$ Hz), 60.52 (t, $J = 25.0$ Hz), 45.74, 21.18. MS (EI) m/z: 411 [M$^+$].
2.15 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(3-methylbenzyl)isoindolin-1-one (4o)

![Chemical Structure]

The titled compound was isolated as yellow liquid (32.9mg, 84%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.87 (t, $J = 8.0$ Hz, 3H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.55 – 7.46 (m, 2H), 7.40 (t, $J = 7.8$ Hz, 3H), 7.16 (t, $J = 7.8$ Hz, 1H), 7.03 (d, $J = 5.2$ Hz, 3H), 5.43 (d, $J = 15.1$ Hz, 1H), 5.16 (dd, $J = 12.9$, 6.7 Hz, 1H), 4.34 (d, $J = 15.1$ Hz, 1H), 2.27 (s, 3H).

$^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -100.78 (d, $J = 289.1$ Hz), -104.06 (d, $J = 289.0$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.48 (d, $J = 260.0$ Hz), 60.65 (d, $J = 26.25$ Hz), 45.95, 21.46. MS (EI) m/z: 391 [M$^+$.]

2.16 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(2-methylbenzyl)isoindolin-1-one (4p)

![Chemical Structure]

The titled compound was isolated as yellow liquid (31.8mg, 81%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.86 (dd, $J = 21.0$, 7.4 Hz, 3H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.49 (p, $J = 7.3$ Hz, 2H), 7.38 (q, $J = 6.9$, 6.2 Hz, 3H), 7.13 (q, $J = 8.3$, 6.2 Hz, 4H), 5.45 (d, $J = 15.5$ Hz, 1H), 5.13 (dd, $J = 14.1$, 5.6 Hz, 1H), 4.50 (d, $J = 15.5$ Hz, 1H), 2.22 (s, 3H). $^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -99.89 (d, $J = 288.0$ Hz), -105.84 (d, $J = 288.0$ Hz). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.48 (d, $J = 28.75$ Hz), 169.38, 137.94, 136.75, 134.69, 134.22, 132.79, 132.36, 132.02, 130.82, 129.92, 129.70, 128.66, 128.86, 127.89, 126.29, 124.50, 124.42, 117.34 (d, $J = 260.0$ Hz), 60.61 (d, $J = 26.25$ Hz), 45.95, 19.30. MS (EI) m/z: 391 [M$.]

2.17 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(furan-2-ylmethyl)isoindolin-1-one (4q)

![Chemical Structure]

The titled compound was isolated as yellow liquid (31.8mg, 81%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.86 (dd, $J = 21.0$, 7.4 Hz, 3H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.49 (p, $J = 7.3$ Hz, 2H), 7.38 (q, $J = 6.9$, 6.2 Hz, 3H), 7.13 (q, $J = 8.3$, 6.2 Hz, 4H), 5.45 (d, $J = 15.5$ Hz, 1H), 5.13 (dd, $J = 14.1$, 5.6 Hz, 1H), 4.50 (d, $J = 15.5$ Hz, 1H), 2.22 (s, 3H). $^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -99.89 (d, $J = 288.0$ Hz), -105.84 (d, $J = 288.0$ Hz). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.48 (d, $J = 28.75$ Hz), 169.38, 137.94, 136.75, 134.69, 134.22, 132.79, 132.36, 132.02, 130.82, 129.92, 129.70, 128.66, 128.86, 127.89, 126.29, 124.50, 124.42, 117.34 (d, $J = 260.0$ Hz), 60.61 (d, $J = 26.25$ Hz), 45.95, 19.30. MS (EI) m/z: 391 [M$.]

2.17 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-(furan-2-ylmethyl)isoindolin-1-one (4q)
The titled compound was isolated as white liquid (30.2mg, 82%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.93 (d, \(J = 7.7\) Hz, 2H), 7.85 (dd, \(J = 5.9, 2.7\) Hz, 1H), 7.60 (t, \(J = 7.4\) Hz, 1H), 7.53 – 7.39 (m, 5H), 7.31 – 7.27 (m, 1H), 6.35 – 6.23 (m, 2H), 5.37 (d, \(J = 15.8\) Hz, 1H), 5.28 (dd, \(J = 13.5, 6.4\) Hz, 1H), 4.46 (d, \(J = 15.8\) Hz, 1H).

\(^{19}\)F NMR (470 MHz, Chloroform-\(d\)) \(\delta\) -100.71 (d, \(J = 290.1\) Hz), -104.88 (d, \(J = 290.1\) Hz).

\(^{13}\)C NMR (125 MHz, Chloroform-\(d\)) \(\delta\) 188.51 (t, \(J = 29.2\) Hz), 149.95, 142.74, 138.07, 134.77, 132.70, 132.41, 132.14, 130.01, 129.64, 128.85, 124.48, 124.39, 117.30 (t, \(J = 261.7\) Hz), 110.46, 109.27, 77.39, 60.95 (t, \(J = 25.5\) Hz), 39.04.

MS (EI) \(m/z\): 367 [M\(^+\)].

2.18 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-phenethylisoindolin-1-one (4r)

The titled compound was isolated as white solid (33.1mg, 85%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.93 (d, \(J = 7.7\) Hz, 2H), 7.84 (d, \(J = 4.7\) Hz, 1H), 7.61 (t, \(J = 7.3\) Hz, 1H), 7.45 (dd, \(J = 18.2, 10.4\) Hz, 5H), 7.24 (dd, \(J = 20.2, 6.9\) Hz, 5H), 5.22 (dd, \(J = 12.4, 7.7\) Hz, 1H), 4.25 (ddd, \(J = 14.6, 9.7, 5.7\) Hz, 1H), 3.76 – 3.46 (m, 1H), 3.11 (ddd, \(J = 15.4, 9.8, 6.4\) Hz, 1H), 2.86 (ddd, \(J = 13.7, 9.3, 5.8\) Hz, 1H).

\(^{19}\)F NMR (470 MHz, Chloroform-\(d\)) \(\delta\) -101.80 (d, \(J = 290.0\) Hz), -105.04 (d, \(J = 290.0\) Hz).

\(^{13}\)C NMR (125 MHz, Chloroform-\(d\)) \(\delta\) 188.80 (t, \(J = 29.5\) Hz), 169.45, 138.59, 137.86, 134.87, 133.14, 132.35, 131.91, 130.05, 129.64, 128.91, 128.73, 126.67, 124.43, 124.05, 117.07 (t, \(J = 25.6\) Hz), 44.33, 34.38. MS (EI) \(m/z\): 391 [M\(^+\)].

2.19 2-butyl-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4s)

The titled compound was isolated as black liquid (26.1mg, 76%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.93 (d, \(J = 7.6\) Hz, 2H), 7.83 (d, \(J = 4.7\) Hz, 1H), 7.61 (t, \(J = 7.3\) Hz, 1H), 7.45 (dd, \(J = 18.2, 10.4\) Hz, 5H), 7.24 (dd, \(J = 20.2, 6.9\) Hz, 5H), 5.22 (dd, \(J = 12.4, 7.7\) Hz, 1H), 4.25 (ddd, \(J = 14.6, 9.7, 5.7\) Hz, 1H), 3.76 – 3.46 (m, 1H), 3.11 (ddd, \(J = 15.4, 9.8, 6.4\) Hz, 1H), 2.86 (ddd, \(J = 13.7, 9.3, 5.8\) Hz, 1H).

\(^{19}\)F NMR (470 MHz, Chloroform-\(d\)) \(\delta\) -101.96 (d, \(J = 290.1\) Hz), -105.05 (d, \(J = 290.0\) Hz).

\(^{13}\)C NMR (125 MHz, Chloroform-\(d\)) \(\delta\) 188.94 (t, \(J = 28.76\) Hz), 169.42, 137.87, 134.79, 133.30, 132.45, 131.78, 130.01, 129.61, 128.87, 124.46, 124.07, 117.19 (t, \(J = 48.75\) Hz), 61.02 (t, \(J = 25\) Hz), 42.19, 29.96, 20.11, 13.82. MS (EI) \(m/z\): 343 [M\(^+\)].

2.20 3-(1,1-difluoro-2-oxo-2-phenylethyl)-2-dodecylisoindolin-1-one (4t)
The titled compound was isolated as brown liquid (35.9mg, 79%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.94 (s, 2H), 7.82 (dd, $J = 5.7$, 2.4 Hz, 1H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.49 (dt, $J = 6.1$, 2.8 Hz, 3H), 7.43 (t, $J = 7.9$ Hz, 2H), 5.38 (dd, $J = 12.4$, 7.8 Hz, 1H), 4.02 (ddd, $J = 14.3$, 9.3, 7.0 Hz, 1H), 3.30 (ddd, $J = 14.0$, 9.1, 4.8 Hz, 1H), 1.25 (d, $J = 20.2$ Hz, 20H), 0.87 (t, $J = 7.0$ Hz, 3H). $^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -102.04 (d, $J = 290.2$ Hz), -105.02 (d, $J = 285.7$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.91 (t, $J = 28.75$ Hz), 169.40, 137.87, 134.79, 133.31, 132.45, 131.77, 130.01, 129.60, 128.87, 124.45, 124.06, 117.09 (t, $J = 260.0$ Hz), 61.04 (t, $J = 25.0$ Hz), 42.51, 32.03, 29.73, 29.60, 29.45, 29.36, 27.90, 26.91, 22.80, 14.23. MS (EI) m/z: 455 [M$^+$].

2.21 2-cyclohexyl-3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (4u)

The titled compound was isolated as colorless liquid (25.8mg, 67%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.97 (d, $J = 7.7$ Hz, 2H), 7.81 (d, $J = 6.9$ Hz, 1H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.45 (ddt, $J = 12.1$, 8.6, 5.3 Hz, 4H), 7.34 (d, $J = 7.3$ Hz, 1H), 5.40 (dd, $J = 15.4$, 5.0 Hz, 1H), 3.70 (tt, $J = 12.0$, 2.9 Hz, 1H), 2.31 (td, $J = 12.3$, 8.6 Hz, 1H), 2.14 – 1.98 (m, 1H), 1.84 (dd, $J = 23.7$, 10.4 Hz, 4H), 1.36 – 1.20 (m, 4H). $^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -97.89 (d, $J = 288.8$ Hz), -107.50 (d, $J = 288.8$ Hz). $^{13}$C NMR (125 MHz, Chloroform-$d$) $\delta$ 189.31 (t, $J = 28.75$ Hz), 169.82, 138.53, 134.79, 134.37, 132.53, 131.58, 130.05, 129.48, 128.88, 124.13, 123.81, 116.66 (t, $J = 275$ Hz), 62.26 (t, $J = 24.0$ Hz), 57.14, 30.04, 29.89, 26.49, 26.21, 25.46. MS (EI) m/z: 369[M$^+$].

2.22 3-(1,1-difluoro-2-(4-fluorophenyl)-2-oxoethyl)-2-(4-methoxyphenyl)isoindolin-1-one (4w)
The titled compound was isolated as white solid (34.5mg, 84%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.93 (d, $J = 6.9$ Hz, 1H), 7.79 (dd, $J = 8.5, 5.5$ Hz, 2H), 7.69 – 7.54 (m, 3H), 7.19 (d, $J = 8.9$ Hz, 2H), 7.02 (t, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.9$ Hz, 2H), 5.97 (dd, $J = 11.9, 8.3$ Hz, 1H), 3.75 (s, 3H).

$^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -101.36, -102.93 (d, $J = 284.6$ Hz), -107.55 (d, $J = 284.6$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 186.12 (t, $J = 28.75$ Hz), 167.14, 166.49, 164.43, 157.38, 136.49, 131.76, 131.33, 128.88, 128.27, 127.71, 126.60, 123.72, 123.43, 115.43 (t, $J = 261.25$ Hz), 114.97, 114.80, 113.18, 62.18 (t, $J = 26.25$ Hz), 54.44. MS (EI) m/z: 411$[^{1+}]$.

3-(2-(4-bromophenyl)-1,1-difluoro-2-oxoethyl)-2-(4-methoxyphenyl)isoindolin-1-one (4x)

The titled compound was isolated as white solid (34mg, 72%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.95 (d, $J = 7.0$ Hz, 1H), 7.72 (d, $J = 7.8$ Hz, 2H), 7.60 (dq, $J = 13.2, 7.2$ Hz, 3H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.19 – 5.86 (m, 1H), 3.78 (s, 3H).

$^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -103.70 (d, $J = 285.7$ Hz), -107.00 (d, $J = 285.7$ Hz).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 187.89 (t, $J = 28.75$ Hz), 167.23, 157.38, 148.47, 136.62, 132.37, 131.86, 131.27, 128.80, 128.45, 127.47, 126.65, 123.69, 123.45, 115.39 (t, $J = 261.25$ Hz), 113.23, 62.25 (t, $J = 26.25$ Hz), 54.45. MS (EI) m/z: 471$[^{1+}]$.

2.24 3-(1,1-difluoro-2-(3-fluorophenyl)-2-oxoethyl)-2-(4-methoxyphenyl)isoindolin-1-one (4y)

The titled compound was isolated as white solid (32mg, 78%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.85 (d, $J = 7.2$ Hz, 1H), 7.59 – 7.45 (m, 4H), 7.32 – 7.23 (m, 2H), 7.21 – 7.14 (m, 1H), 7.09 (d, $J = 8.9$ Hz, 2H), 6.73 (d, $J = 8.9$ Hz, 2H), 5.88 (dd, $J = 12.4, 7.6$ Hz, 1H), 3.69 (s, 3H). $^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -102.79 (d, $J = 284.9$ Hz), -108.62 (d, $J = 285.0$ Hz), -111.09. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 186.63 (t, $J = 30.0$ Hz), 167.12, 162.30, 160.33, 157.50, 136.37, 133.06, 131.78, 131.37, 129.33, 128.95, 128.09, 126.69, 124.46, 123.72, 123.49, 120.73, 120.56, 115.52 (t, $J = 225.0$ Hz), 115.33, 113.25, 62.21 (t, $J = 25.0$ Hz), 54.46. MS (EI) m/z: 411$[^{1+}]$.
2.22 3-(1,1-difluoro-2-oxo-2-phenylethyl)isoindolin-1-one (5a)

![Chemical Structure]

Chemical Formula: C_{16}H_{11}F_{2}NO_{2}
Exact Mass: 287

The titled compound was isolated as white solid (130.6mg, 91%). {\textsuperscript{1}}H NMR (500 MHz, Chloroform-\text{d}) \(\delta\) 8.12 (d, \(J = 8.0\) Hz, 2H), 7.91 (d, \(J = 7.4\) Hz, 1H), 7.65 (dq, \(J = 14.8, 7.2\) Hz, 3H), 7.57 (t, \(J = 7.3\) Hz, 1H), 7.51 (t, \(J = 7.7\) Hz, 2H), 6.93 (s, 1H), 5.36 (dd, \(J = 17.5, 5.9\) Hz, 1H). {\textsuperscript{19}}F NMR (470 MHz, Chloroform-\text{d}) \(\delta\) -105.16 (d, \(J = 306.4\) Hz), -111.73 (d, \(J = 306.3\) Hz). {\textsuperscript{13}}C NMR (125 MHz, CDCl_{3}) \(\delta\) 187.71 (t, \(J = 31.25\) Hz), 170.15, 138.56, 134.14, 132.35, 131.89, 131.32, 130.29, 129.36, 128.56, 127.89, 123.70, 123.22, 115.04 (t, \(J = 260.0\) Hz), 56.70 (t, \(J = 25.0\) Hz). MS (EI) \(m/z\): 287[M-].

3. Spectral Graphics

![Graphical Representation]

{\textsuperscript{1}}H NMR (500 MHz, CDCl_{3}) of compound (4a)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4a)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4a)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4b)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4b)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4b)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4c)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4c)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4c)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4d)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4d)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4d)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4e)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4e)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4e)
$^1$H NMR (470 MHz, CDCl$_3$) of compound (4f)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4f)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4f)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4g)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4g)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4g)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4h)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4h)
$^{13}$C NMR ($125$ MHz, CDCl$_3$) of compound (4h)

$^1$H NMR ($500$ MHz, CDCl$_3$) of compound (4i)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4i)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4i)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4j)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4j)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4j)

$^1$H NMR (125 MHz, CDCl$_3$) of compound (4k)
$^{19}\text{F NMR (125 MHz, CDCl}_3\text{)}$ of compound (4k)

$^{13}\text{C NMR (125 MHz, CDCl}_3\text{)}$ of compound (4k)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4I)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4I)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4i)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4m)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4m)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4m)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4n)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4n)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4n)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4o)
$^{19\text{F}}$ NMR (470 MHz, CDCl$_3$) of compound (4o)

$^{13\text{C}}$ NMR (125 MHz, CDCl$_3$) of compound (4o)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4p)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4p)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4p)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4q)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4q)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4q)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4r)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4r)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4r)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4r)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4s)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4s)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4s)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4t)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4t)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4t)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4u)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4u)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4u)
\(^1\text{H NMR (500 MHz, CDCl}_3\text{)}\) of compound (4w)

\(^1\text{F NMR (470 MHz, CDCl}_3\text{)}\) of compound (4w)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4w)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (4x)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4x)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4x)
$^1$H NMR (500 MHz, CDCl$_3$) of compound (4y)

$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (4y)
$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (4y)

$^1$H NMR (500 MHz, CDCl$_3$) of compound (5a)
$^{19}$F NMR (470 MHz, CDCl$_3$) of compound (5a)

$^{13}$C NMR (125 MHz, CDCl$_3$) of compound (5a)