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Note

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Solvent Effects: Syntheses of 3,3-Difluorooxindoles and 3-Fluorooxindoles from Hydrazonoindolin-2-one by Selectfluor

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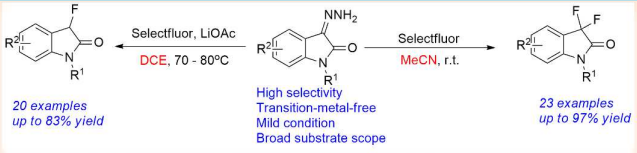
Supporting Information



ABSTRACT: Efficient syntheses of 3,3-difluorooxindoles and 3-fluorooxindoles via fluorination of hydrazonoindolin-2-one with Selectfluor are reported. Under different solvent conditions, this method produced 3,3-difluorooxindoles and 3-fluorooxindoles selectively. The broad substrate scope and mild reaction conditions make this transformation a valuable method in drug discovery and development.

3-Fluorooxindole derivatives are biologically active compounds,[1] which have attracted considerable attention as promising agents for treatments of stroke (Figure 1, **A**),[2] together with other activities, such as corticotropin-releasing factor (CRF) receptor antagonists (Figure 1, **B**),[3] and potential -agents for the treatment of abnormal cell growth (Figure 1, **C**).[4] Introduction of fluorides into the 3-position of indoles represents an important strategy in preparing these compounds.[5]

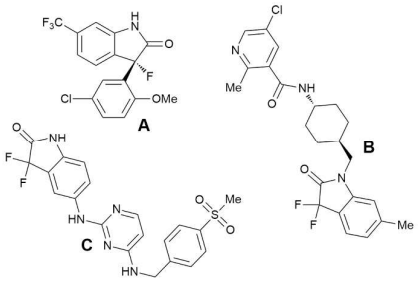
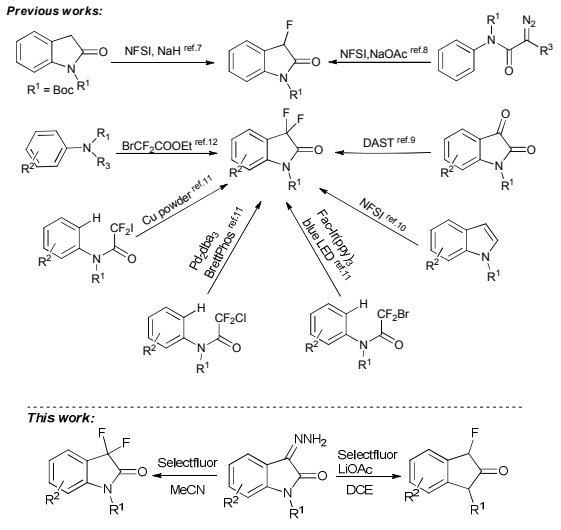


Figure1. Representative examples of bioactive 3-fluorooxindole derivatives

Preparation of functionalized 3-fluorooxindoles has received considerable synthetic interests over the last few decades.[6] Primarily, 3-fluoroinated oxindole was synthesized by nucleophilic addition of fluoride from N-fluorobenzene-sulfonimide (NFSI) under the strong basic condition of sodium hydride (Scheme1).[7] Alternatively, an NSFI-initiated fluoroarylation and ring-cylization of diazoacetamides offered another pathway.[8] However, these methods employed strong base and normally produced moderate yields. In the meanwhile, various methods for the syntheses of 3,3-difluorooxindoles have been developed. These methods generally fall into two categories: a) direct fluorination of indole derivatives, such as nucleophilic fluorination of isatin with thermally unstable diethylaminosulfur trifluoride (DAST)[9] and electrophilic fluorination of indole with NSFI.[10] b) ring-closure strategies to construct pyrole ring of indoles, including transition-metal or photo-catalyzed intramolecular cyclization of halodifluoroacetamides[11] and intermolecular difluoroalkylation/amidation of anilines.[12] While significant progresses have been made in these syntheses, there are still many limitations, such as instability of the fluorinating reagents, poor functional-group tolerance and lengthy synthetic routes. Clearly, a new method that allows the generation of 3-fluoro-2-oxindole derivatives under mild conditions is still

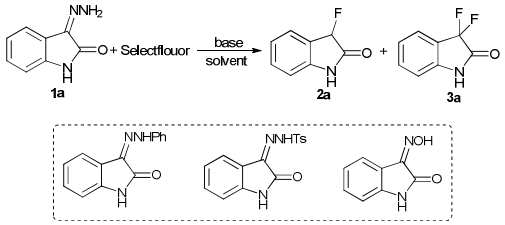
Scheme 1. Different Protocols for Construction of fluoro-2-oxindoles



urgently needed.

Selective incorporation of different numbers of fluorine into the 3-position of oxindoles represents another challenge. None of the previous examples produced both 3-fluorooxindole and 3,3-difluorooxindole under the same strategy. Based on our previous experience in decarboxylative fluorination of carboxylic acids,[13] we set out to develop a general method to synthesize both compounds from commercially available and cost-effective starting material, isatin, through fine tuning of reaction conditions, such as solvent, base and temperature. Herein, we report our progress.

Table 1. Optimization of Reaction Conditions[a]



entry	Solvent	base	2a (%)[b]	3a (%)[b]
1	Cyclohexane	LiOAc	17	23
2	Benzene	LiOAc	16	29
3	Ethyl acetate	LiOAc	38	11
4	MTBE	LiOAc	36	0
5	THF	LiOAc	35	15
6	Dioxane	LiOAc	23	5
7	MeCN	LiOAc	0	49
8	DCE	LiOAc	46	3
9	DCE	Li_2CO_3	38	18
10	DCE	$NaHCO_3$	33	10
11	DCE	NaOAc	11	2
12	DCE	NaOH	0	0
13	DCE	Et_3N	0	0
14	DCE	None	0	0
15[c]	DCE	LiOAc	53	6
16[c,d]	DCE	LiOAc	68	6
17[c,d,e]	DCE	LiOAc	42	3
18[c,d,f]	DCE	LiOAc	51	12
19[g]	DCE	LiOAc	0	0
20	MeCN	None	0	60
21[h]	MeCN	None	0	68
22[i]	MeCN	None	0	76
23[j]	MeCN	None	0	75

[a] Standard conditions: **1a** 0.5 mmol, Selectfluor 1 mmol, base 2 mmol, 3 mL solvent, 70 °C, 15 hours. [b] Yield determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c] base 6 equiv. [d] DCE 13 mL. [e] 60 °C. [f] 80 °C. [g] Other fluorinating reagent NSFI, NFPY, DAST or TBAF. [h] 50 °C. [i] r.t. [j] ice-bath.

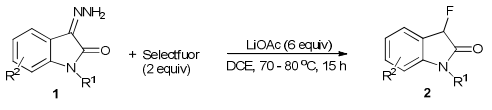
Our initial studies commenced with the model reaction between isatin hydrazone **1a** and Selectfluor (Table 1). We found that simply mixing isatin hydrazone with Selectfluor at 70 °C in cyclohexane for 15 hours, afforded 17% 3-fluorooxindole **2a** and 23% 3,3-difluorooxindole **3a** with lithium acetate (LiOAc) as base (entry 1). This initial result promoted us to improve both yield and selectivity towards either 3-fluorooxindole or 3,3-difluorooxindole. Various hydrophilic and hydrophobic solvents were screened. Dichloroethane (DCE) was demonstrated as the best solvent to afford 3-fluorooxindole with 46% yield and acetonitrile (MeCN) as the best solvent to produce 3,3-difluorooxindole with 49% yield (entries 1 to 8). Further optimization with different bases in DCE, revealed LiOAc as the best base. No fluorinating product was detected in DCE without base (entry 14). After further optimizations of the reagent ratio, concentration and temperature, the reaction of **1a** with Selectfluor (2 equiv)/ LiOAc (6 equiv) at 70 °C in a dilute solution produced **2a** in 68% yield with high selectivity (entry 16). No product **2a** or **3a** was formed when Selectfluor was replaced with the other fluorinating reagents, such as NSFI, 1-fluoropyridium tetrafluoroborate (NFPY), tetranbuylammonium fluoride (TBAF) and DAST (entry 19). On the other hand, the product **3a** was selectively obtained with 60% yield in MeCN without a base at 70 °C (entry 20). Reactions with MeCN as solvent at different temperatures were also tested. Room temperature was proved to be the best temperature for the selective formation of 3,3-difluoroxindole **3a** (entries 21-23). At last, the other isatin hydrazone analogs, such as phenyl-, tosyl-, and oxime-hydrazones were also tested. None of them afforded fluorinated product (inlet of Table 1).

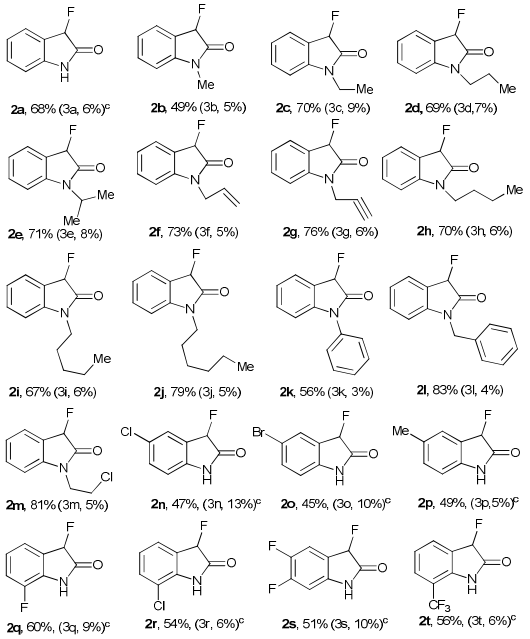
3-Fluorooxindoles are interesting synthetic synthons and tools for elucidating biological processes.[14] Under the optimized condition, the substrate scope of 3-fluorooxindoles formation with different combination of concentration and temperature was investigated. As summarized in Scheme 2, a wide range of N-substituted isatin hydrazones successfully underwent fluorination with Selectfluor at 80 °C in DCE with satisfactory yields. As the size and steric hindrance of the protecting groups increased, the yields also improved (**2l**, **2m** versus **2b**, **2c**). Sensitive functional groups, such as olefin (**2f**), alkyne (**2g**) and chloride (**2m**) were tolerated and thus permitted further functionalization. To minimize 3, 3-difluorooxindole formation, the reactions of unprotected isatin hydrazone derivatives were carried out at the lower concentration and slightly lower temperature (70 °C). The 5-subistituted isatin hydrazones with both electron-rich (**2p**) and electron-deficient functional groups (**2n** and **2o**) afforded moderate yields. Reactions of 7-subtituted isatin hydrazones (**2q**, **2r**, and **2t**) resulted in slightly higher yields than those of 5-subistituted counterparts. The *bis*-substituted istatin hydrazones, such as 5,6-difluoro-3-hydrazonoindolin-2-one, also formed the corresponding 3-fluorooxindole **2s** in 51% yield. Overall, low concentration and optimal temperature were the keys to generate 3-fluorooxindoles selectively.

Replacement of the keto carbonyl (C=O) group of isatins with the bioisoteric analogue moiety difluoromethylene (CF2)

leads to 3,3-difluoro-2-oxindoles, which are of biological significance in the development of medicinally active agents.[15]

Scheme 2. Synthesis of 3-fluorooxindoles[a,b]

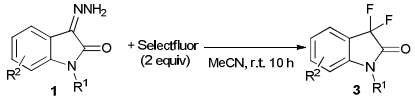


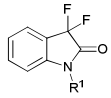


[a] Standard conditions: **1** 0.5 mmol, Selectfluor 1.0 mmol, LiOAc 3.0 mmol, 3 mL DCE, 80 °C. [b] Isolated yield after column chromatography. [c] 13 mL DCE, 70 °C.

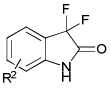
Here we describe a direct fluorination of isatin hydrazones under our optimized condition to synthesize 3,3-difluorooxindole. As shown in Scheme 3, the reaction demonstrated a broad substrate scope readily forming a variety of 3,3-difluorooxindoles in satisfactory yields. A range of isatin hydrazones gave 3, 3-difluoro-2- oxindoles (**3a-3x**) as the exclusive products in 25-97% yields in MeCN at room

Scheme 3. Synthesis of 3,3-Difluoroxindole [a,b]





3a, R^1 = H, 76%
3b, R^1 = Me, 44%
3c, R^1 = Et, 51%
3d, R^1 = *n*-Pr, 40%
3e, R^1 = *i*-Pr, 60%
3f, R^1 = -$CH_2CH{=}CH_2$, 60%
3g, R^1 = -$CH_2C{\equiv}CH$, 95%
3h, R^1 = *n*-Bu, 55%
3i, R^1 = $(CH_2)_4CH_3$, 65%
3j, R^1 = $(CH_2)_5CH_3$, 67%
3k, R^1 = Ph, 85%
3l, R^1 = Bn, 89%
3m, R^1 = CH_2CH_2Cl, 91%



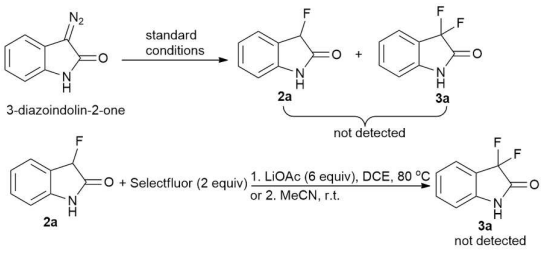
3n, R^2 = 5-Cl, 96%
3o, R^2 = 5-Br, 80%
3p, R^2 = 5-Me, 25%
3q, R^2 = 7-F, 91%
3r, R^2 = 7-Cl, 97%
3s, R^2 = 5,6-2F, 66%
3t, R^2 = 7-CF_3, 95%
3u, R^2 = 5-NO_2 , 70%c
3v, R^2 = 5-F, 94%
3w, R^2 = 7-Br, 83%
3x, R^2 = OMe, 0%

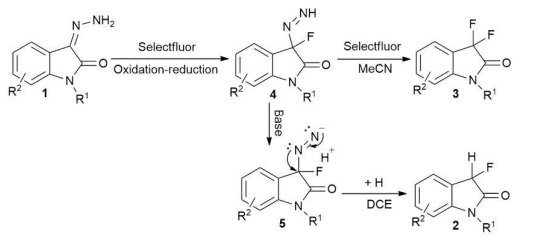
[a] Standard conditions: **1** 0.5 mmol, Selectfluor 1.0 mmol, 3 mL MeCN, r.t. [b] Isolated yield after column chromatography. [c] 50 °C

temperature. For N-substituted isatin hydrazones, the yields improved along with the increase in the size and steric hindrance of the protecting groups (**3l**, **3m** versus **3b**, **3c**). Sensitive functional groups, such as allyl, propargryl and 1-chloroethyl, were tolerated (**3f**, **3g** and **3m**). The aryl-substituted isatin hydrazones, bearing a broad range of functional groups, were also compatible in this transformation. The isatin hydrazones **1** with electron-donating substituents gave higher yields (66%-97%) (**3n, 3o, 3q-3w)** than those of **1** with electron-deficient substituents (**3p, 3x)**. High temperature was required for 5-nitro-3,3-difluoroindolin-2-one **3u,** due to the poor solubility of **1u**.

To gain mechanistic insight into the reaction, several control experiments were carried out. No deutrated product was observed with D_2O or 1,2-dichloroathane-d_4 ($C_2D_4Cl_2$) as solvent under our standard condition. In Murphy's synthesis of aryldihalomethanes by denitrogenative dihalogenation of benzaldehyde hydrazones, diazo intermediate was proposed to be the reaction intermediate.[16] However, when 3-diazoindolin-2-one was subjected to the standard conditions, the desired products was not obtained (scheme 4). Thus, the possibility of involving 3-diazoindolin-2-one as intermediate could be ruled out. No germinal difluorinated product **3a** formed when mono-fluorooxindole **2a** were subjected to the standard condition of scheme 2 or scheme 3. This result implies that **3a** does not come from the further fluorination of **2a**.

Scheme 4. Control Experiments and Plausible Mechanism





A plausible mechanism is proposed in Scheme 4. An oxidation and electrophilic substitution of isatin hydrazone by Selectfluor occurred to generate intermediate **4**. In a solvent such as acetonitrile, intermediate **4** was converted to 3,3-difluorooxindole **3** by oxidation and denitrogenative fluorination.[16] On the other hand, in DCE, with a weak base as LiOAc, dehydrogenation of **4** afforded intermediate **5**. Final denitrogentaion and hydrogen abstraction from HOAc produced 3-fluorooxindole **2**.

In conclusion, we have successfully developed an efficient strategy to synthesize a range of 3-CHF/CF_2-containing

indolin-2-one with Selectfluor under mild conditions. This method has advantage over other methods due to high selectivity and broad substrate scope. A plausible mechanism based on behavior of Selectfluor in different solvents was proposed. The high functional group tolerance and mild reaction conditions make this transformation applicable in drug discovery and development.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out using oven-dried glassware. All reagents were used as received from commercial sources unless specified otherwise or prepared as described in the literature. NMR spectra were recorded on Bruker Avance 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C and 376 MHz for ^{19}F) or Bruker Avance 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C acquisition) with $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The peak information is described as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet(m), and composite (comp, for the overlapped signals). NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard. Column chromatography was performed on silica gel 300-400 mesh. High-resolution mass spectra were obtained on Thermo Fisher LCQ Orbitrap Velos Pro mass spectrometer at Hunan University Mass Spectrometry Facilities.

General procedure for the preparation of 3-hydrazono -2-oxindoles(1a-1x). General procedure for the syntheses of the 3-hydrazono-2-oxindoles **1a-1x**: Isatin (1.0 g, 6.06 mmol, 1 equiv.) was dissolved in methanol (20 mL) and stirred vigorously. To this solution was added hydrazine hydrate (reagent grade 80%, 0.73 mL, 2.0 equiv.) in one portion and the solution was heated to reflux. After consumption of isatin as determined by TLC, the solution was allowed to cool to room temperature. Precipitations formed at this stage was isolated by filtration and washed with a small quantity of cold methanol. Additional portion of product was isolated and purified by column chromatography after concentration.

General procedure A for the synthesis of 3-fluorooxiindoles (2a, and 2n-2t). To a 100 mL round-bottle flask with a magnetic stirring bar were added 3-hydrazono-2-oxindoles (0.5 mmol, 1.0 equiv.), Selectfluor (354 mg, 1 mmol) and LiOAc (198 mg, 3 mmol). Then DCE (13 mL) was added. The reaction mixture was heated to 70 °C in oil bath and stirred for 18 hours. After hydrazone was consumed (monitored by thin layer chromatography), the resulting mixture was cooled, concentrated and purified by flash column chromatography on silica gel (n-hexane: EA=9:1) to give the pure products **2**.

General procedure B for the syntheses of 3fluorooxindoles (2b-2m). To a 25 mL round-bottle flask with a magnetic stirring bar were added 3-hydrazono-2-oxindoles (0.5 mmol, 1.0 equiv.), Selectfluor (354.3 mg, 1 mmol) and LiOAc (198 mg, 3 mmol). Then DCE (3 mL) was added. The reaction mixture was heat to 80°C in oil bath and stirred for 16 hours. After the hydrazones was consumed (monitored by thin layer chromatography), the resulting mixture was cooled, concentrated and purified by flash column chromatography on silica gel (n-hexane: EA=9:1) to give the pure products **2**.

General procedure C for the syntheses of 3, 3-difluoro-oxindoles (3a-3t, 3v-3w). To a 25 mL round-bottle flask with a magnetic stirring bar were added 3-hydrazono-2-oxindoles (0.5 mmol, 1.0 equiv.), and Selectfluor (354 mg, 1 mmol). Then acetonitrile (3 mL) was added. The reaction mixture was stirred at room temperature for 12 hours. After hydrazone was consumed (monitored by thin layer chromatography), the resulting mixture was concentrated and purified by flash column chromatography on silica gel (n-hexane: EA=9:1) to give the pure products **3**.

General procedure D for the syntheses of 3, 3-difluoro-oxindoles (3u). To a 25 mL round-bottle flask with a magnetic stirring bar were added 3-hydrazono-2-oxindoles (0.5 mmol, 1.0 equiv.), and Selectfluor (354 mg, 1 mmol). Then acetonitrile (3 mL) was added. The reaction mixture was heat to 50°C in oil bath and stirred for 12 hours. After the hydrazones was consumed (monitored by thin layer chromatography), the resulting mixture was cooled, concentrated and purified by flash column chromatography on silica gel (n-hexane: EA=9:1) to give the pure products **3u**.

3-Fluoro-2-oxindole **(2a)**[17] (General Procedure A) White solid, 50.1 mg, 68% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.88 (d, $J_{H\text{-}F}$ = 50.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9 (d, J = 18.0 Hz), 143.8 (d, J = 6.0 Hz), 131.8 (d, J = 3.0 Hz), 126.6, 123.8 (d, J = 16.0 Hz), 122.7 (d, J = 2.0 Hz), 110.8 (d, J = 1.0 Hz), 86.5 (d, J = 181.0 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -192.1 (d, $J_{H\text{-}F}$ = 50.8 Hz).

3-Fluoro-1-methylindolin-2-one **(2b)**[14c] (General Procedure B) White solid, 40.5 mg, 49% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.60 (d, $J_{H\text{-}F}$ = 50.8 Hz, 1H), 3.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (d, J = 18.0 Hz), 144.8 (d, J = 5.0 Hz), 131.5 (d, J = 4.0 Hz), 126.0, 123.3 (d, J = 3.0 Hz), 122.8 (d, J = 17.0 Hz), 108.8, 85.5 (d, J = 187.0 Hz), 26.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.4 (d, $J_{H\text{-}F}$ = 50.8 Hz).

3-Fluoro-1-ethylindolin-2-one **(2c)**[14c] (General Procedure B) White solid, 62.6 mg, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.0 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 5.66 (d, $J_{H\text{-}F}$ = 51.0 Hz, 1H), 3.74 (q, J = 7.5 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (d, J = 17.8 Hz), 143.8 (d, J = 5.1 Hz), 131.4 (d, J = 3.3 Hz), 126.2 (d, J = 1 Hz), 123.1 (d, J = 2.9 Hz), 123.0 (d, J = 16.1 Hz), 108.9 (d, J = 1.1 Hz), 85.6 (d, J = 186.8 Hz), 34.8, 12.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.4 (d, $J_{H\text{-}F}$ = 50.8 Hz).

3-Fluoro-1-propylindolin-2-one **(2d)** (General Procedure B) White solid, 66.7 mg, 69% yield, mp 40-42 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 5.66 (d, $J_{H\text{-}F}$ = 50.8 Hz, 1H), 3.58-3.69 (m, 2H), 1.66-1.75 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (d, J = 17.7 Hz), 144.2 (d, J = 5.0 Hz), 131.4 (d, J = 3.3 Hz), 126.2, 123.1 (d, J = 2.7 Hz), 122.9 (d, J = 16.0 Hz), 109.1, 85.5 (d, J = 186.8 Hz), 41.7, 20.8, 11.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.1 (d, $J_{H\text{-}F}$ = 50.8 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H13FNO 194.0976, Found 194.0974.

3-Fluoro-1-isopropylindolin-2-one **(2e)** (General Procedure B) White solid, 68.6 mg, 71% yield, mp 37-38 °C. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 5.60 (d, $J_{H\text{-}F}$ = 51.2 Hz, 1H), 4.50-4.60 (m, 2H), 1.48 (q, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (d, J = 17.5 Hz), 143.5 (d, J = 5.1 Hz), 131.2 (d, J = 3.3 Hz), 126.3, 123.2 (d, J = 16.0 Hz), 122.7 (d, J = 2.7 Hz), 110.4, 85.5 (d, J = 186.3 Hz), 44.2, 19.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -192.9 (d, $J_{H\text{-}F}$ = 51.2 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H13FNO 194.0976, Found 194.0973.

3-Fluoro-1-allylindolin-2-one **(2f)** (General Procedure B) White solid, 69.8 mg, 73% yield, mp 52-53 °C. ^{1}H NMR (500 MHz, CDCl3) δ 7.48 (d, J = 7.0 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.79-5.86 (m, 1H), 5.71 (d, $J_{H\text{-}F}$ = 51.0 Hz, 1H), 5.27 (t, J = 9.3 Hz, 2H), 4.26-4.37 (m, 2H). 13C NMR (125 MHz, $CDCl_3$) δ 170.8 (d, J = 18.7 Hz), 144.0 (d, J = 5.0 Hz), 131.4 (d, J = 3.7 Hz), 130.7, 126.1, 123.3 (d, J = 2.5 Hz), 122.7 (d, J = 16.3 Hz), 118.2, 109.7, 85.5 (d, J = 187.5 Hz), 42.4. 19F NMR (376 MHz, $CDCl_3$) δ -192.8 (d, $J_{H\text{-}F}$ = 51.0 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H11FNO 192.0819, Found 192.0816.

3-Fluoro-1-propargylindolin-2-one **(2g)**[14c] (General Procedure B) White solid, 71.9 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.43 (s, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 5.72 (d, $J_{H\text{-}F}$ = 51.2 Hz, 1H), 4.38-4.59 (m, 2H), 2.71 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (d, J = 18.0 Hz), 142.8 (d, J = 5.0 Hz), 131.5 (d, J = 4.0 Hz), 126.2 (d, J = 1.0 Hz), 123.7 (d, J = 3.0 Hz), 122.6 (d, J = 17.0 Hz), 109.9 (d, J = 2 Hz), 85.4 (d, J = 188.0), 76.1, 72.9, 29.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.1 (d, $J_{H\text{-}F}$ = 51.2 Hz).

3-Fluoro-1-butylindolin-2-one **(2h)** (General Procedure B) White solid, 72.5 mg, 70% yield, mp 41-43 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.48 (m, 2H), 7.08-7.12 (m, 1H), 6.86 (t, J = 8.8 Hz, 1H), 5.68 (d, $J_{H\text{-}F}$ = 51.2 Hz, 1H), 3.66-3.69 (m, 2H), 1.66-1.67 (m, 2H), 1.39-1.42 (m, 2H), 0.94-0.99 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (d, J = 17.9 Hz), 144.3 (d, J = 5.2 Hz), 133.4 (d, J = 3.2 Hz), 126.2, 123.1 (d, J = 2.8 Hz), 122.9 (d, J = 16.2 Hz), 109.1 (d, J = 1.3 Hz), 85.5 (d, J = 186.8), 39.9, 29.3, 20.1, 13.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.2 (d, $J_{H\text{-}F}$ = 51.2 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C12H15FNO 208.1132, Found 208.1130.

3-Fluoro-1-amylindolin-2-one **(2i)** (General Procedure B) White solid, 74.1 mg, 67% yield, mp 39-41 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.2 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.65 (d, $J_{H\text{-}F}$ = 51.2 Hz, 1H), 3.60-3.72 (m, 2H), 1.63-1.71 (m, 2H), 1.33-1.36 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (d, J = 18.0 Hz), 144.2 (d, J = 5.0 Hz), 131.4 (d, J = 3.0 Hz), 126.2, 123.0 (d, J = 3.0Hz), 122.9 (d, J = 16.0 Hz), 85.5 (d, J = 187.0Hz), 40.1, 29.0, 26.9, 22.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.1 (d, $J_{H\text{-}F}$ = 51.2 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C13H17FNO 222.1289, Found 222.1286.

3-Fluoro-1-hexylindolin-2-one **(2j)** (General Procedure B) White solid, 92.9 mg, 79% yield, mp 38-39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.2 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.65 (d, $J_{H\text{-}F}$ = 50.8 Hz, 1H), 3.60-3.72 (m, 2H), 1.64-1.70 (m, 2H), 1.29-1.34 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (d, J = 17.9 Hz), 144.2 (d, J = 5.0 Hz), 131.4 (d, J = 3.0 Hz), 126.2, 123.0 (d, J = 3.0Hz), 122.9 (d, J = 16.0 Hz), 109.1, 85.5 (d, J = 187.0Hz), 40.1, 27.2, 22.5, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -193.2 (d, $J_{H\text{-}F}$ = 50.8 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C14H19FNO 236.1445, Found 236.1442.

3-Fluoro-1-phenylindolin-2-one **(2k)**[14c] (General Procedure B) White solid, 63.6 mg, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 3H), 7.40-7.46 (m, 3H), 7.33 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.85 (d, $J_{H\text{-}F}$ = 51.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (d, J = 18.0 Hz), 144.9 (d, J = 5.0 Hz), 133.5, 131.4 (d, J = 4.0 Hz), 126.3, 123.8 (d, J = 3.0Hz), 122.6 (d, J = 17.0 Hz), 110.1 (d, J = 1.0 Hz), 85.5 (d, J = 187.0Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -191.7 (d, $J_{H\text{-}F}$ = 51.2 Hz).

3-Fluoro-1-benzylindolin-2-one **(2l)**[14c] (General Procedure B) White solid, 100.1 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 1H), 7.28-7.36 (m, 6H), 7.08 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 5.77 (d, $J_{H\text{-}F}$ = 51.2 Hz, 1H), 4.88 (q, J = 24.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (d, J = 18.0 Hz), 143.9 (d, J = 5.0 Hz), 135.0, 131.4 (d, J = 3.0 Hz), 128.9, 127.9, 127.4, 126.2, 123.3 (d, J = 3.0Hz), 122.8 (d, J = 16.0 Hz), 109.8, 85.5 (d, J = 188.0Hz), 43.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -192.6 (d, $J_{H\text{-}F}$ = 51.2 Hz).

3-Fluoro-1-chloroethylindolin-2-one **(2m)** (General Procedure B) White solid, 86.5 mg, 81% yield, mp 70-72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8 Hz, 1H), 5.70 (d, $J_{H\text{-}F}$ = 50.8 Hz, 1H), 3.93-4.12 (m, 2H), 3.76 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (d, J = 18.0 Hz), 143.7 (d, J = 5.0 Hz), 131.5 (d, J = 3.0 Hz), 126.4 (d, J = 1.0 Hz), 123.6 (d, J = 2.0 Hz), 122.7 (d, J = 16.0 Hz), 109.1 (d, J = 1.0 Hz), 86.2 (d, J = 188.0Hz), 42.0, 40.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -192.9 (d, $J_{H\text{-}F}$ = 50.8 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C10H10ClFNO 214.0429, Found 214.0428.

5-Chloro-3-fluoro-indolin-2-one **(2n)** (General Procedure A) White solid, 43.6mg, 47% yield, mp 120-123 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.77 (s, 1H), 7.56 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 5.89 (d, $J_{H\text{-}F}$ = 50.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.5 (d, J = 17.5 Hz), 142.7 (d, J = 6.3 Hz), 131.6 (d, J = 3.8 Hz), 126.8, 126.6 (d, J = 2.5 Hz), 125.7 (d, J = 16.3 Hz), 112.3, 86.2 (d, J = 182.5Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -192.8 (d, $J_{H\text{-}F}$ = 50.0 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H6ClFNO 186.0116, Found 186.0115.

5-Bromo-3-fluoro-indolin-2-one **(2o)** (General Procedure A) White solid, 51.7mg, 45% yield, mp 151-152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 7.67 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 5.89 (d, $J_{H\text{-}F}$ = 50.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.1 (d, J = 18.0 Hz), 147.9 (d, J = 5.0 Hz), 139.2 (d, J = 3.0 Hz), 134.2, 130.8 (d, J = 15.0 Hz), 118.9 (d, J = 3.0 Hz), 117.6, 90.9 (d, J = 183.0Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -192.7 (d, $J_{H\text{-}F}$ = 50.0 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H6BrFNO 229.9611, Found 229.9609.

5-Methyl-3-fluoro-indolin-2-one **(2p)** (General Procedure A) White solid, 40.4 mg, 49% yield, mp 107-109 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 5.65 (d, $J_{H\text{-}F}$ = 50.8 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6 (d, J = 18.0 Hz), 139.4 (d, J = 6.0 Hz), 133.0 (d, J = 3.0 Hz), 131.8 (d, J = 3.0 Hz), 127.0, 123.3 (d, J = 16.0 Hz), 110.5, 86.0 (d, J = 188.0Hz), 21.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -193.4 (d, $J_{H\text{-}F}$ = 50.8 Hz). HRMS (ESI-TOF)

m/z: $[M + H]^+$ Calcd for C9H9FNO 166.0663, Found 166.0660.

7-Fluoro-3-fluoro-indolin-2-one **(2q)** (General Procedure A) Light-yellow solid, 50.7 mg, 60% yield, mp 103-105 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 7.27-7.34 (m, 2H), 7.05-7.10 (m, 1H), 5.95 (d, $J_{H\text{-}F}$ = 50.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6 (d, J = 17.0 Hz), 146.9 (d, J = 242.0 Hz), 130.8 (q, J = 6.0 Hz), 126.5-126.7 (m), 123.7 (q, J = 3.0 Hz), 122.7 (d, J = 3.0 Hz), 118.7-118.9 (m), 86.2 (d, J = 183.0Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -132.3, -192.0 (d, $J_{H\text{-}F}$ = 50.0 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H6F2NO 170.0412, Found 170.0409.

7-Chloro-3-fluoro-indolin-2-one **(2r)** (General Procedure A) White solid, 50.6 mg, 54% yield, mp 119-121 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.08 (t, J = 7.8 Hz, 1H) 5.96 (d, $J_{H\text{-}F}$ = 50.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7 (d, J = 17.0 Hz), 141.5 (d, J = 6.0 Hz), 131.6 (q, J = 3.0 Hz), 121.6 (q, J = 16.0 Hz), 125.3, 124.0 (d, J = 3.0 Hz), 114.9, 86.7 (d, J = 183.0Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -191.8 (d, $J_{H\text{-}F}$ = 50.0 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H6ClFNO 186.0116, Found 186.0113.

5,6-2-Fluoro-3-fluoro-indolin-2-one **(2s)** (General Procedure A) White solid, 47.7 mg, 51% yield, mp 117-119 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 7.69 (t, J = 8.0 Hz, 1H), 6.92-6.96 (m, 1H), 5.86 (d, $J_{H\text{-}F}$ = 50.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8 (d, J = 17.0 Hz), 150.4-153.1 (m), 144.7-147.2 (m), 140.8-141.0 (m), 119.6-119.8 (m), 116.7 (d, J = 21.0 Hz), 101.0 (q, J = 22.0 Hz), 85.9 (d, J = 184.0Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -133.6, -147.2, -192.0 (d, $J_{H\text{-}F}$ = 50.4 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H5F3NO 188.0318, Found 188.0314.

7-Trifluoromethyl-3-fluoro-indolin-2-one **(2t)** (General Procedure A) White solid, 61.3 mg, 56% yield, mp 101-103 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 5.97 (d, $J_{H\text{-}F}$ = 50.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.2 (d, J = 17.5 Hz), 141.2 (d, J = 2.5 Hz), 130.6, 127-128.0 (m), 125.7 (d, J = 16.25 Hz), 122.9 (d, J = 1.2Hz), 123.7 (q, J = 270.6 Hz), 111.9 (q, J = 31.9 Hz), 85.1 (d, J = 182.5Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.2, -193.2 (d, $J_{H\text{-}F}$ = 50.4 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C9H6F4NO 220.0380, Found 220.0379.

3,3-Difluoroindolin-2-one **(3a)**[12b] (General Procedure C) White solid, 64.2 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.60 (m, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (t, J = 29.0 Hz), 143.0 (t, J = 8.0 Hz), 134.7, 125.3, 119.6 (t, J = 23.0 Hz), 112.3, 111.7 (t, J = 247.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.3 (s, 2F).

3,3-Difluoro-1-methylindolin-2-one **(3b)**[12c] (General Procedure C) White solid, 40.3 mg, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.2 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (t, J = 30.0 Hz), 143.9 (t, J = 5.6 Hz), 133.6, 124.6, 123.9, 120.1 (t, J = 23.1 Hz), 110.9 (t, J = 248.1 Hz), 109.5, 26.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.3 (s, 2F).

3,3-Difluoro-1-ethylindolin-2-one **(3c)**[11a] (General Procedure C) White solid, 50.2 mg, 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 3.76 (q, J = 7.4 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 164.9 (t, J = 30.0 Hz), 143.1 (t, J = 7.0 Hz), 133.6 (t, J = 1.5 Hz), 124.8, 123.7 (t, J = 1.5 Hz), 120.3 (t, J = 23.0 Hz), 110.9 (t, J = 247.5 Hz), 109.6, 35.0, 12.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.5 (s, 2F).

3,3-Difluoro-1-propylindolin-2-one **(3d).** (General Procedure C) White solid, 42.2 mg, 40% yield, mp 60-62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.2 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.66 (t, J = 7.2 Hz, 2H), 1.69-1.78 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.4 (t, J = 30.0 Hz), 143.5 (t, J = 7.0 Hz), 133.6 (t, J = 1.5 Hz), 124.7, 123.7 (t, J = 2 Hz), 120.2 (t, J = 23.0 Hz), 110.9 (t, J = 248.0 Hz), 109.8, 41.8, 20.5, 11.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.3 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H12F2NO 212.0881, Found 212.0878.

3,3-Difluoro-1-isopropylindolin-2-one **(3e)**[10] (General Procedure C) White solid, 63.3 mg, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 4.46-4.56 (m, 1H), 1.50 (d, J = 7.2 Hz, 6H). ^{13}C NMR (125MHz, $CDCl_3$) δ 165.0 (t, J = 29.3 Hz), 142.9 (t, J = 7.5 Hz), 133.4, 124.9, 123.4, 120.5 (t, J = 22.5 Hz), 111.0, 110.5 (t, J = 2 Hz), 120.2 (t, J = 23.0 Hz), 110.5 (t, J = 247.5 Hz), 44.8, 19.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (s, 2F).

3,3-Difluoro-1-allylindolin-2-one **(3f)** (General Procedure C) White solid, 62.7 mg, 60% yield, mp 41-42 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 5.79-5.87 (m, 1H), 5.29 (d, J = 12.0 Hz, 2H), 4.33 (d, J = 5.5 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.1 (t, J = 31.0 Hz), 143.2 (t, J = 6.9 Hz), 133.5, 130.1, 124.73, 123.9 (t, J = 1.5 Hz), 120.1 (t, J = 22.5 Hz), 118.6, 110.8 (t, J = 248.5 Hz), 110.4, 42.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.0 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H10F2NO 210.0725, Found 210.0730.

3,3-Difluoro-1-propargylindolin-2-one **(3g)** (General Procedure C) White solid, 98.4 mg, 95% yield, mp 96-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.2 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6Hz, 1H), 4.50 (d, J = 2.4 Hz, 2H), 2.31 (t, J = 2.6 Hz, 1H). ^{13}C NMR (125MHz, $CDCl_3$) δ 164.3 (t, J = 30.6 Hz), 142.1 (t, J = 6.8 Hz), 133.6, 124.7, 124.3, 120.0 (t, J = 23.1 Hz), 110.8 (t, J = 248.7 Hz), 110.6, 75.4, 73.5, 29.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.4 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H8F2NO 208.0568, Found 208.0564.

3,3-Difluoro-1-butylindolin-2-one **(3h)**[10] (General Procedure C) White solid, 61.9 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.2 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.69 (t, J = 7.2 Hz, 2H), 1.63-1.71 (m, 2H), 1.35-1.44 (m, 2H), 0.96 (t, J = 7.4Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 165.3 (t, J = 30.0 Hz), 143.5 (t, J = 6.9 Hz), 133.5, 124.8, 123.7, 120.3 (t, J = 22.5 Hz), 110.9 (t, J = 247.5 Hz), 109.8, 40.0, 29.1, 20.0, 13.6 (d, J = 3.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (s, 2F).

3,3-Difluoro-1-amylindolin-2-one **(3i)** (General Procedure C) White solid, 77.8 mg, 65% yield, mp 37-40 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.67 (t, J = 7.5 Hz, 2H), 1.66-1.71 (m, 2H), 1.34-1.36 (m, 4H), 0.89 (t, J = 6.7Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.3 (t, J = 30.0 Hz), 143.5 (t, J = 7.0 Hz), 133.5, 124.8, 123.7 (t, J = 1.5 Hz), 120.3 (t, J = 23.0 Hz),

110.9 (t, *J* = 247.5 Hz), 109.8, 40.3, 28.9, 26.8, 22.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C13H16F2NO 240.1194, Found 240.1190.

3,3-Difluoro-1-hexylindolin-2-one **(3j)** (General Procedure C) White solid, 84.8 mg, 67% yield, mp 37-39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.6Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 3.68 (t, *J* = 7.4 Hz, 2H), 1.64-1.72 (m, 2H), 1.30-1.34 (m, 6H), 0.88 (t, *J* = 7Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.2 (t, *J* = 30.0 Hz), 143.5 (t, *J* = 7.0 Hz), 133.6, 124.7, 123.7 (t, *J* = 2 Hz), 120.2 (t, *J* = 23.0 Hz), 110.9 (t, *J* = 248.0 Hz), 109.8, 40.3, 31.3, 27.0, 26.4, 22.5, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C14H18F2NO 254.1351,Found 254.1346.

3,3-Difluoro-1-phenylindolin-2-one **(3k)**[10] (General Procedure C) White solid, 104.2 mg, 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.64 (m, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.54 -7.57 (m, 2H), 7.41 -7.48 (m, 4H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125MHz, $CDCl_3$) δ 164.6 (t, *J* = 30.6 Hz), 144.2 (t, *J* = 6.8 Hz), 133.5, 132.7, 130.0, 129.0, 126.2, 125.0, 124.4, 119.9 (t, *J* = 23.7 Hz), 110.8 (t, *J* = 248.1 Hz), 110.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.6 (s, 2F).

3,3-Difluoro-1-benzylindolin-2-one **(3l)**[10] (General Procedure C) White solid, 115.3 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 1H), 7.28 -7.39 (m, 6H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.90 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.5 (t, *J* = 30.0 Hz), 143.1 (t, *J* = 7.0 Hz), 134.3, 133.5, 129.1, 128.2, 127.3, 124.7, 124.0 (t, *J* = 2.0 Hz), 120.2 (t, *J* = 23.0 Hz), 110.0 (t, *J* = 248.0 Hz), 110.6, 44.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.7 (s, 2F).

3,3-Difluoro-1-chloroethylindolin-2-one **(3m)** (General Procedure C) White solid, 105.3 mg, 91% yield, mp 65-67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.77 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.5 (t, *J* = 26.0 Hz), 143.1 (t, *J* = 7.0 Hz), 133.7, 125.0, 124.2, 120.0 (t, *J* = 22.5 Hz), 110.6 (t, *J* = 247.5 Hz), 109.9, 42.1, 40.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.8 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C10H9ClF2NO 232.0335, Found 232.0331.

5-Chloro-3,3-difluoroindolin-2-one **(3n)**[12b] (General Procedure C) Light-yellow solid, 97.7 mg, 96% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (s, 1H), 7.83 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (125MHz, DMSO-d_6) δ 165.9 (t, *J* = 23.5 Hz), 141.9 (t, *J* = 7.5 Hz), 134.5, 127.8, 125.6, 121.2 (t, *J* = 22.5 Hz), 114.0, 111.1 (t, *J* = 248.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.1 (s, 2F).

5-Bromo-3,3-difluoroindolin-2-one **(3o)**[12b] (General Procedure C) White solid, 99.2 mg, 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 7.96 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.2 (t, *J* = 17.0 Hz), 139.9 (t, *J* = 7.0 Hz), 136.6, 128.4, 122.0 (t, *J* = 23.0 Hz), 116.6, 113.1, 110.1 (t, *J* = 250.5 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0 (s, 2F).

5-Methyl-3,3-difluoroindolin-2-one **(3p)**[12b] (General Procedure C) White solid, 22.9 mg, 25% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.48 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.3 (t, *J* = 29.0 Hz), 140.5 (t, *J* = 8.0 Hz), 134.8, 133.2, 125.6, 119.7 (t, *J* = 22.5 Hz), 112.0, 111.9 (t, *J* = 247.0 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.7 (s, 2F).

7-Fluoro-3,3-difluoroindolin-2-one **(3q)** (General Procedure C) White solid, 85.2 mg, 91% yield, mp 102-105 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.47-7.55 (m, 2H), 7.18-7.23 (m, 1H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.0 (t, *J* = 29.0 Hz), 147.35 (d, *J* = 243.0 Hz), 130.2-130.5 (m), 125.0 (d, *J* = 6.0 Hz), 121.8-122.3 (m), 121.7 (d, *J* = 7.0 Hz), 121.3 (d, *J* = 4.0 Hz), 108.5-113.5 (m). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.7, -131.1 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H5F3NO 188.0318, Found 188.0316.

7-Chloro-3,3-difluoroindolin-2-one **(3r)** (General Procedure C) White solid, 98.7 mg, 97% yield, mp 108-110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.62-7.68 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.3 (t, *J* = 29.0 Hz), 140.8 (t, *J* = 7.5 Hz), 134.5, 125.2, 124.0, 121.4 (t, *J* = 23.0 Hz), 116.4, 111.3 (t, *J* = 248.0 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.2 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H5ClF2NO 204.0022, Found 204.0021.

5,6-2-Fluoro-3,3-difluoroindolin-2-one **(3s)** (General Procedure C) White solid, 67.7 mg, 66% yield, mp 107-109 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.03 (t, *J* = 8.5 Hz, 1H), 7.09-7.13 (m, 1H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.2 (t, *J* = 29.0 Hz), 152.2-154.9 (m), 145.3-147.8 (m), 140.3-140.6 (m), 115.8 (d, *J* = 21.0 Hz), 115.0-115.5 (m), 110.9 (t, *J* = 248.0 Hz), 102.8 (d, *J* = 23.0 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.5 (s, 2F), -128.7, -144.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C8H4F4NO 206.0224, Found 206.0220.

7-Trifluoromethyl-3,3-difluoroindolin-2-one **(3t)** (General Procedure C) White solid, 112.6 mg, 95% yield, mp 96-99 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.6 (t, *J* = 29.0 Hz), 140.6 (t, *J* = 7.5 Hz), 130.9 (d, *J* = 4.0 Hz), 129.4, 123.2 (q, *J* = 270.0 Hz), 124.1, 121.3 (t, *J* = 23.0 Hz), 113.3 (q, *J* = 33.5 Hz), 109.9 (t, *J* = 246.5 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.3 (s, 3F), -110.2 (s, 2F). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C9H5F5NO 238.0286, Found 238.0285.

5-Nitryl-3,3-difluoroindolin-2-one **(3u)**[9c] (General Procedure D) White solid, 75.0 mg, 70% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.60 (s, 1H), 8.44 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 13.6 Hz, 1H). ^{13}C NMR (125MHz, DMSO-d_6) δ 166.4 (t, *J* = 28.7 Hz), 149.1 (t, *J* = 7.5 Hz), 143.6, 131.1, 121.5, 120.2 (t, *J* = 23.1 Hz), 112.9, 110.4 (t, *J* = 248.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.6 (s, 2F).

5-Fluoro-3,3-difluoroindolin-2-one **(3v)**[12c] (General Procedure C) White solid, 87.9 mg, 94% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 7.70 (s, 1H), 7.39 (t, *J* = 9.0 Hz, 1H), 7.00-7.03 (m, 1H). ^{13}C NMR (125MHz, DMSO-d_6) δ 166.2 (t, *J* = 28.1 Hz), 158.8 (d, *J* = 238.8 Hz), 139.3 (t, *J* = 7.5 Hz), 121.3 (d, *J* = 22.5 Hz), 120.5-120.9 (m), 113.7 (d, *J* = 7.5 Hz), 113.4 (d, *J* = 26.3Hz), 111.3 (t, *J* = 248.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.6 (s, 2F), -119.0.

5-Bromo-3,3-difluoroindolin-2-one **(3w)**[12c] (General Procedure C) yellow oil, 102.9 mg, 83% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100MHz, DMSO-d_6) δ 166.3 (t, *J* = 29.0 Hz), 142.5 (t, *J* = 7.5 Hz), 137.5, 125.5, 124.5, 121.4 (t, *J* = 23.0 Hz), 111.5 (t, *J* = 248.0 Hz), 104.5.

^{19}F NMR (376 MHz, DMSO-d_6) δ -110.0 (s, 2F).

■ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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