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Article

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Reagent Controlled Reversal of Regioselectivity in Nucleophilic Fluorination of Spiro-epoxyoxindole: Synthesis of 3-Fluoro-3-hydroxymethyloxindole and 3-Aryl-3-fluoromethyloxindole

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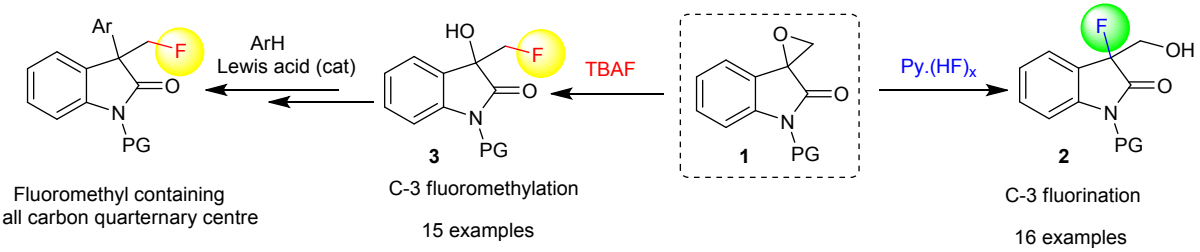
Abstract

A convenient, as well as metal/catalyst-free approach for the reversal of regioselectivity in nucleophilic fluorination of a wide range of spiro-epoxyoxindoles has been reported simply by altering the nucleophilic fluoride reagents. Py·$(HF)_x$ mediated fluorination at tertiary sp^3-C-center of spiro-epoxyoxindole furnishes 3-fluoro-3-hydroxymethyl oxindoles whereas TBAF mediated fluoride addition at primary sp^3-C-center renders 3-fluoromethyl-3-hydroxy oxindoles, which have been utilized for the synthesis of 3-aryl-3-fluoromethyl oxindole.



Introduction

The presence of a fluorine atom in an organic molecule has an immense impact on their physico-chemical as well as biological properties; thus transforming these molecules to potentially more promising scaffolds than those of the nonfluorinated analogues.[1] Because of the ubiquity of the fluorinated compounds in pharmaceutical, agrochemical and radio-chemicals, methods for the incorporation of a fluorine atom in an organic molecule are tremendously demanding.[2] However, the inclusion of a single fluorine atom does not alter the steric factor of the molecule; rather it refines the electronic factors, which are especially important for the proper tuning of biological activity. Since, the 3,3-disubstituted oxindole ring is a prevalent motif in numerous natural products and drug molecules, its fluorinated analogues may enhance the pharmaceutical efficacy and medicinal potency. For example, MaxiPost (**A**) developed by Bristol-Myers Squibb is a promising potassium channel opener for the treatment

of stroke,[3] whereas compound **B** is reported to be a corticotropin-releasing factor receptor antagonist for the treatment of anxiety[4] and compound **C** is an antipsychotic drug candidate (Figure 1).[5] On the otherhand, introduction of a fluoromethyl unit to the C-3 position of oxindole may unveil amazingly potential bioactivity since -CH_2F is the isosteric correspondence to a –CH_3 group.[6]

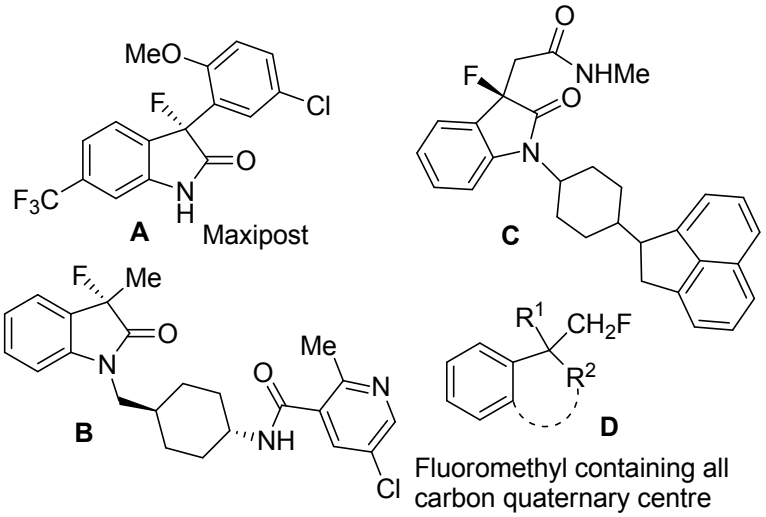


Figure 1. Representative fluorine containing oxindole compounds.

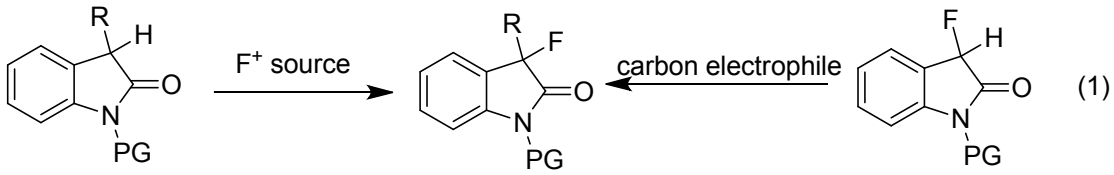
These fascinating properties of the fluorinated oxindoles lure the synthetic fraternity to develop efficient methods to introduce the fluorine atom to oxindoles. One conventional approach of C-F bond formation is electrophilic fluorination of 3-substituted oxindole employing proper electrophilic fluorinating agents (Scheme 1, eq 1).[7] Another synthetic route implicating the C-C bond forming reaction of pre-installed 3-fluorooxindole was delineated in recent time (Scheme 1, eq 1).[8] Despite of the progress in this area, nucleophilic fluorination[9] is more advantageous due to the low cost of the fluoride reagent as well as the substrate. Moreover, the paramount significance of the fluorine chemistry is PET (Positron Emmision Tomography), a nuclear medicine functional imaging technique to recognize the progress of disease and to evaluate therapeutic efficacy. To prepare the radioactive tracers, nucleophilic fluoride ($^{18}F^-$) is the most desirable as well as readily available source due to its high specific activity. Hence nucleophilic fluorination is more effective than electrophilic methods regarding the application in PET. To the best of our knowledge, there is hardly any report of nucleophilic fluorination at sterically congested C-3-carbon centre of oxindole.[9d] Besides these, incorporation of a monofluoromethyl group to C-3 position of oxindole is still a formidable challenge;[6d] specifically the synthesis of fluoromethyl containg all carbon quaternary center[5] is infrequent in the literature. Even though such difficulties, diverse as well as pioneering work in this field

suggested that epoxides and aziridines are familiar substrates for nucleophilic fluorination.[2a, 2c, 9b, 10] Moved by the challenges and inspired by these reports and our recent outcome on ring opening reactions of spiro-compounds,[11] we envisaged that spiro-epoxyoxindole can provide both the functionality by proper tuning of fluorinating reagent and the reaction conditions. Herein, we successfully narrate the reagent dependent reversal of regioselectivity in nucleophilic fluorination of spiro-epoxyoxindole which inturn bestows 3-fluoro-3-substituted oxindole as well as 3-fluoromethyl-3-substituted oxindole concurrently (Scheme 1, eq 2).

Scheme 1. Previous reports and the present work

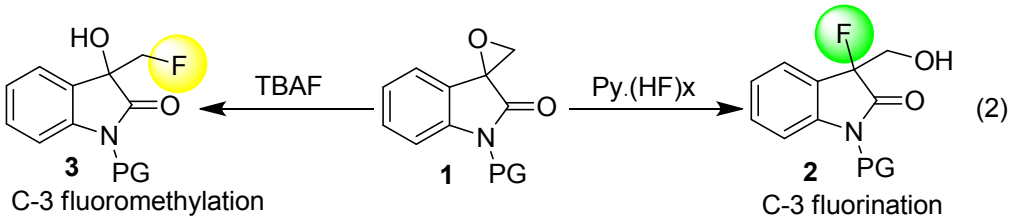
Previous works

Electrophilic fluorination and C-C bond-forming reaction for the synthesis of 3-fluoro-3-substituted oxindoles[7, 8]



Our work

Reversal of regioselectivity in nucleophilic fluorination of spiro-epoxyoxindole

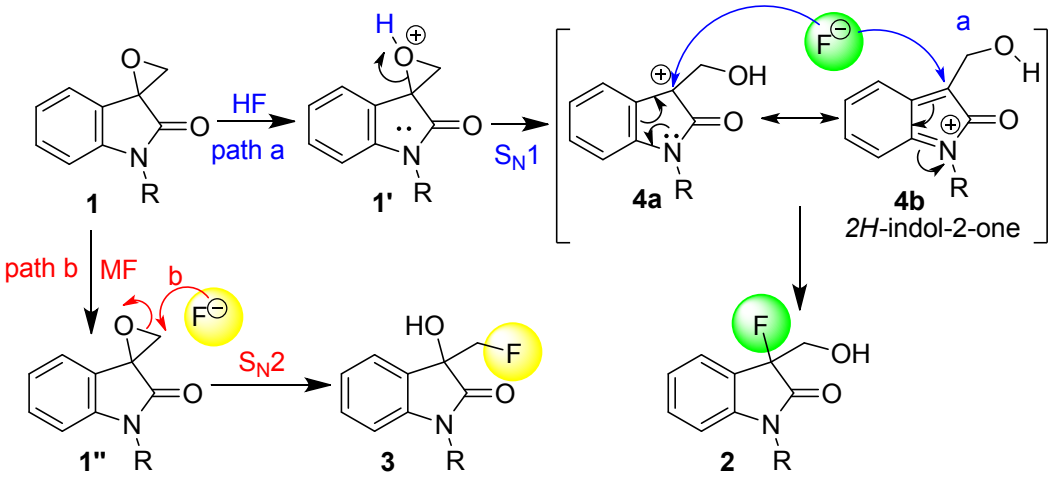


Proposed Reactivity Pattern of Spiro-epoxyoxindole

If we deeply look into the reactivity pattern of the spiro-epoxide, it can easily protonate under acidic condition and formed the protonated structure **1′** (Scheme 2).[11h] This protonated structure can be opened up via S_N1 fashion to form the benzylic carbocationic intermediate **4a** or its canonical form *2H*-indol-2-one intermediate **4b**. At that moment, fluoride ion can add to the C-3 center of the reactive intermediate **4** to form 3-fluoro-3-hydroxymethyloxindole **2** (Scheme 2, path a). Alternatively, in the absence of any acid, fluoride ion[12] can directly add to the primary sp^3-C center of epoxide **1** via S_N2 mechanism to furnish 3-fluoromethyl-3-

hydroxyoxindole **3** (Scheme 2, path b). Therefore, nucleophilic fluorinating reagents along with solvent may play a crucial role in defining the regioselectivity.[2g]

Scheme 2. Proposed reactivity pattern of spiro-epoxyoxindole for nucleophilic fluorination reaction

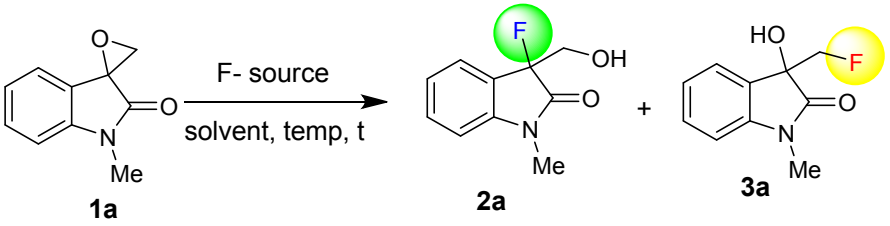


Results and Discussion

To gain a proof of concept, we embarked on a research endeavour by exploiting different nucleophilic fluorinating agents on our candidate substrate *N*-methyl spiro-epoxyoxindole **1a**. To the onset, when the most familiar acidic nucleophilic fluorinating agent, Py·$(HF)_x$ (Olah's reagent) was applied in DCE at rt, desired 3-fluoro-3-hydroxymethyl oxindole **2a** was solely achieved in 55% isolated yield within 2 h, which was confirmed by the crude ^{19}F NMR (Table 1, entry 1). Lowering the temperature to 0 °C retarded the reaction with a trace yield. However, changing the solvent to CH_2Cl_2, eventually increased the yield up to 70% within 1.5 h at rt (Table 1, entry 3). While the fluorination reaction in $CHCl_3$ produced comparable yield, reactions in THF, ether, dioxane, MeCN or DMF were sluggish and mostly afforded low yields with incomplete conversions (Table 1, entries 4-9). We further applied other acidic fluorinating agents like $Et_3N{\cdot}3HF$, but it did not exhibit promising result than Py·$(HF)_x$ (Table 1, entry 10). To expose the fluoride ion for the S_N2 reaction, when we investigated the fluorination reaction by applying other metal fluorides like KF, CsF or NaF in polar aprotic DMF solvent, initially we were disheartened not to afford any product with the full recovery of starting material (Table 1, entries 11-13). Eventually we were delighted to isolate 38% of the desired opposite regioisomer 3-fluoromethyl-3-hydroxyoxindole **3a** when we employed tetrabutylammonium fluoride (TBAF, 1M solution in THF) in DMF at rt which was also confirmed by the crude ^{19}F NMR (Table 1, entry 14). We also obtained **3a** with 30% isolated yield with TBAF in CH_2Cl_2

at rt. Varying the solvent to DCE, THF or MeCN did not improve the yield. (Table 1, entries 15-18). Finally, increasing the temperature to 50 °C in DMF, we were pleased to isolate 63%

Table 1. Optimization of reaction conditions[a]



entry	fluoride source	solvent	temp (°C)	t (h)	yield[b] (%) **2a**	**3a**
1	$Py{\cdot}(HF)_x$	DCE	25	2	55	-
2	$Py{\cdot}(HF)_x$	DCE	0	6	trace	-
3	**$Py{\cdot}(HF)_x$**	**CH_2Cl_2**	**25**	**1.5**	**70**	**-**
4	$Py{\cdot}(HF)_x$	$CHCl_3$	25	2	50	-
5	$Py{\cdot}(HF)_x$	THF	25	6	12	-
6	$Py{\cdot}(HF)_x$	Et_2O	25	6	10	-
7	$Py{\cdot}(HF)_x$	dioxane	25	6	trace	-
8	$Py{\cdot}(HF)_x$	MeCN	25	6	15	-
9	$Py{\cdot}(HF)_x$	DMF	25	6	trace	-
10	$Et_3N{\cdot}3HF$	CH_2Cl_2	25	6	15	-
11	KF	DMF	25	6	-	-
12	CsF	DMF	25	6	-	-
13	NaF	DMF	25	6	-	-
14	TBAF	DMF	25	6	-	38
15	TBAF	CH_2Cl_2	25	6	-	30
16	TBAF	DCE	25	6	-	22
17	TBAF	THF	25	6	-	25
18	TBAF	MeCN	25	6	-	trace
19	**TBAF**	**DMF**	**50**	**6**	**-**	**63**
20	TBAF	DMF	80	6	-	58
21	TBAF	DMSO	25	12	-	60
22	TBAF	DMSO	50	6	-	messy
23	TBAF	CH_2Cl_2	50	6	-	42

[a]*N*-methyl spiro-epoxyoxindole **1a** (0.285 mmol), fluoride reagent (3 equiv) in 2 mL solvent was stirred at specified temperature. [b]Isolated yield. TBAF: 1M solution in THF

of 3-fluoromethyl-3-hydroxyoxindole **3a** within 6 h (Table 1, entry 19). Further hike of temperature did not boost the yield or decrease the reaction time. Reaction in DMSO at rt imparted comparable yield although it required longer reaction time for full conversion (Table 1, entry 21). Other attempts mostly rendered lower yield with incomplete conversion as well as unclean reaction (Table 1, entries 22-23). Thus acidic Olah's reagent in CH_2Cl_2 at rt was manifested to be the superior condition for C-3 fluorination; whereas the C-3 fluoromethylation was obtained in polar aprotic solvent DMF utilizing TBAF at 50 °C which also supported our presumption.

Substrate Scope for C-3 Fluorination Reaction

We instigated to explore the generality of the fluorination reactions with the armoury of the optimized studies. At first, we executed the C-3 fluorination reaction, which was conveniently applied to a wide range of spiro-epoxides (Figure 2). All the *N*-methyl, *N*-benzyl, *N*-allyl and *N*-phenyl spiro-epoxides underwent smooth reaction while employing Olah's reagent in CH_2Cl_2 and afforded the desired 3-fluoro-3-hydroxymethyl oxindoles **2** with good to excellent

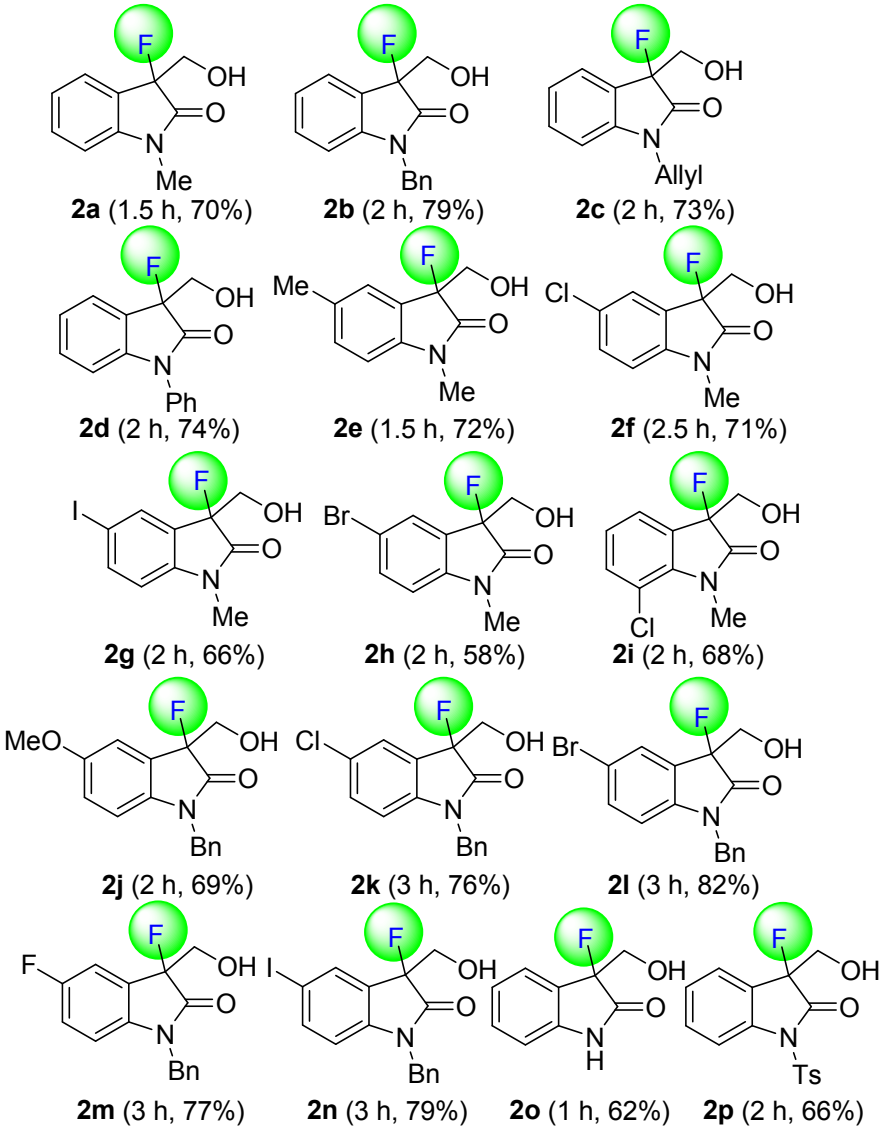


Figure 2. Substrate scope for C-3 fluorination reaction.

yields. Subsequently, substituted spiro-epoxyoxindoles also participated in this transformation with good yields. Electron donating as well as electron withdrawing groups on the oxindole ring did not interrupt in the nucleophilic fluorination reactions; even if the electron deficient substituents required a little longer reaction time for completion. Even the unprotected spiro-epoxyxoxindole imparted good yield of **2o** under the optimized conditions. Finally, we performed the C-3 fluorination reaction of the spiro-epoxide bearing an electron withdrawing group on nitrogen atom. Under the optimised conditions, it also offered the desired 3-fluoro-3-hydroxymethyl oxindole **2p** with good yield within 2 h.

Substrate Scope for C-3 Fluoromethylation Reaction

Afterwards efforts were invested in exploring the scope and limitation of the synthesis of opposite regio-isomer, i.e. C-3 fluoromethylation reaction utilizing TBAF in DMF (Figure 3).

Irrespective of the *N*-protection on spiro-epoxide, we acquired 3-fluoromethyl-3-hydroxyoxindoles **3** with moderate to good yields in all the cases. In striking contrast, unprotected spiro-epoxyxoxindole did not undergo fluoromethylation reaction. This might be due to the fact that the fluoride anion immediately quenched by the –NH proton of unprotected spiro-epoxyoxindole; thus lost its nucleophilicity along with the elctrophilicity of the deprotonated epoxide. Although substituted spiro-epoxyoxindoles experienced smooth reaction and furnished corresponding 3-fluoromethyl -3-hydroxy oxindoles **3** with good yields. However, electron withdrawing protecting group on the *N*-atom of spiro-epoxide impeded the fluorination reaction.

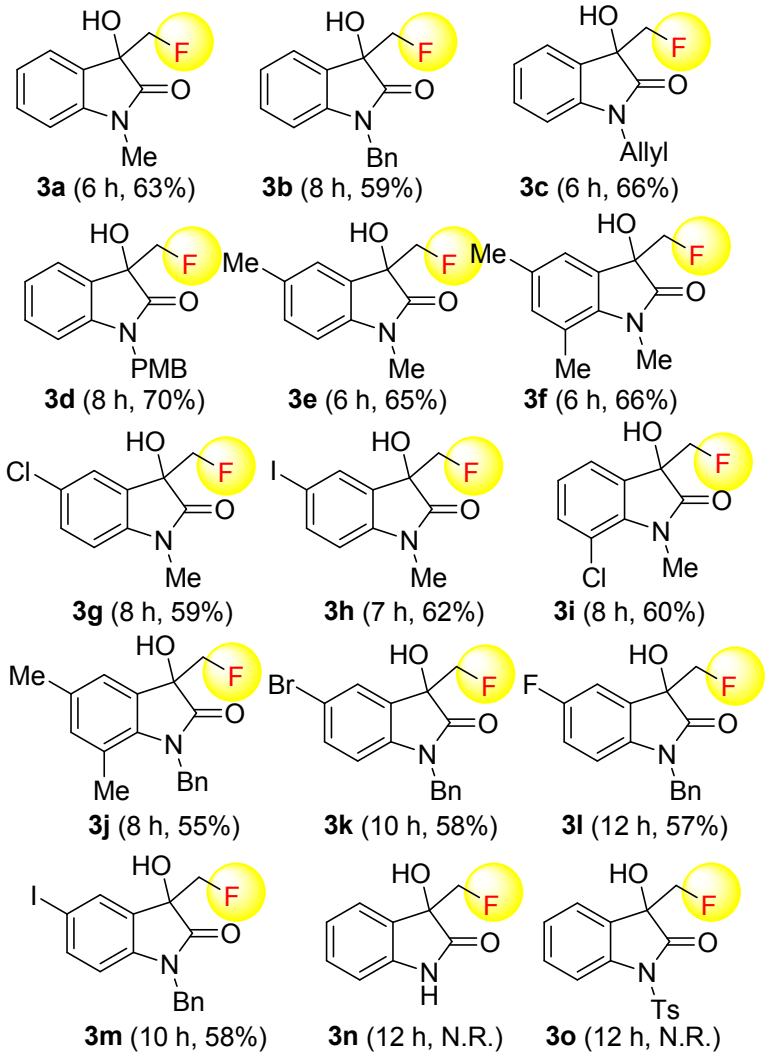
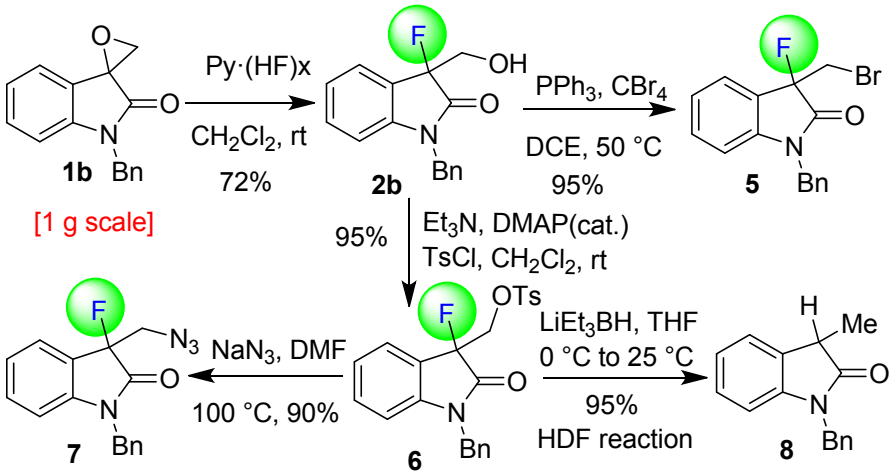


Figure 3. Substrate scope for C-3 fluoromethylation reaction; N.R. = No Reaction.

Application of the Methodology

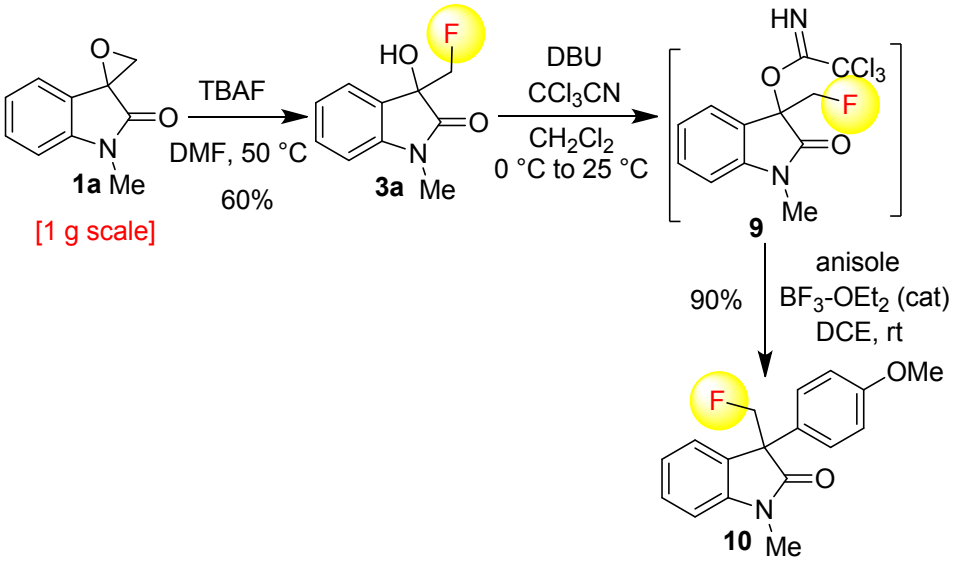
Next, we elaborated our work towards the synthetic potential and effectiveness of the method. In this process, to show the general utility of the methodology, both the fluorination reactions were performed on gram scale; albeit a little erosion of yield in both the cases. To demonstrate the application, we subjected both the fluorinated compounds (**2b** and **3a**) to a variety of transformations (Scheme 3 and 4). An initial effort was devoted towards the Appel reaction of 3-fluoro-3-hydroxymethyl oxindole **2b** which furnished the corresponding bromide **5** in a quantitative yield. Later we were pleased to convert **2b** to corresponding tosylate **6** by tosylation of the primary hydroxyl group of 3-fluoro-3-hydroxymethyl oxindole. Subsequent treatment of the tosylate **6** with sodium azide bestowed the *β*-fluoroazide **7** with excellent yield. Furthermore, to synthesize the compound **B** like structure (Figure 1), we treated the tosylate **6** with super hydride, $LiEt_3BH$; but it only manifested 3-methyl oxindole **8** in excellent yield. Here super hydride not only removed –OTs group but also displaced fluoride by hydride via hydrodefluorination (HDF) reaction[13] to furnish compound **8** (Scheme 3).

Scheme 3. Gram scale C-3-fluorination reaction and selective transformations



Since, construction of fluoromethyl containing all carbon quaternary center is really challenging, as an appended application, 3-fluoromethyl-3-hydroxyoxindole **3a** was initially converted to trichloroacitimidate **9** with trichloroacetonitrile in the presence of DBU. Subsequent Lewis acid catalyzed addition of nucleophile to the corresponding imidate rendered the 3,3′-disubstituted oxindoles. $BF_3.OEt_2$ was found to be the superior catalyst for anisole rendering compound **10** in excellent yield (Scheme 4).

Scheme 4. Gram scale C-3-fluoromethylation reaction and synthesis of 3-aryl-3-fluoromethyl oxindoles



Conclusion

In conclusion, an efficient as well as inexpensive strategy for the reagent dependent reversal of regioselectivity in nucleophilic fluorination of a range of spiro-epoxyoxindoles has been reported. This method thus furnishes 3-fluoro-3-hydroxymethyloxindole as well as 3-fluoromethyl-3-hydroxyoxindole through fine-tuning of reaction conditions. The gram-scale reactions followed by further transformations prove its applicability. This method is also found to be worthy for the synthesis of fluoromethyl containing all carbon quaternary center. Hence, we believe that the present development paves a new way for the nucleophilic fluorination chemistry and unfolds a new avenue in fluorine containing oxindole based drug discovery as well as medicinal chemistry research.

Experimental Section

General Information: All the reactions were carried out using oven dried glassware under an atmosphere of argon (Ar). All reagents were used as purchased from commercial supplier without further purification. Solvents were dried and distilled following usual protocols. Heating reactions were performed in silicon oil bath at the specified temperature. Flash column chromatography was performed in all cases using the indicated solvent system on silica gel (230-400 mesh) purchased. Analytical thin layer chromatography was performed using 60 F254 precoated silica gel plate (0.2 mm thickness) and compounds were visualized by irradiation of UV light. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were measured with 400 (400 MHz) using $CDCl_3$ and DMSO-d_6. Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS.

Melting points were measured with a Stuart SMP30 apparatus and are uncorrected. Spiro-epoxides **1** were prepared by common literature procedures.[11a,b]

General procedure for ring-opening reaction spiro-epoxyoxindoles with Py·(HF)$_x$: To a stirring solution of spiro-epoxy oxindole **1a** (0.100 g, 0.570 mmol) in a teflon vial in dry dichloromethane (4 mL) at 25 °C, Py·(HF)$_x$ (0.154 g, 1.712 mmol) was added. The resulting solution was stirred at the same temperature and monitored by TLC. On completion (1 h), the reaction mixture was concentrated and purified by silicagel flash chromatography using EtOAc/hexane (2:3) to afford the desire product **2a** (0.076 g, 68%).

3-Fluoro-3-(hydroxymethyl)-1-methylindolin-2-one (2a): The compound was prepared by following general procedure and was obtained as gummy liquid (0.082 g, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (dt, J = 7.4, 1.3 Hz, 1H), 7.44 (tt, J = 7.8, 1.5 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.23 (s, 3H), 2.42 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.8 (d, $J_{C\text{-}F}$ = 21 Hz), 144.3 (d, $J_{C\text{-}F}$ = 5 Hz), 131.60 (d, $J_{C\text{-}F}$ = 3 Hz), 125.3, 123.9 (d, $J_{C\text{-}F}$ = 19 Hz), 123.4 (d, $J_{C\text{-}F}$ = 2 Hz), 108.9, 91.5 (d, $J_{C\text{-}F}$ = 189 Hz), 64.4 (d, $J_{C\text{-}F}$ = 30 Hz), 26.3. **^{19}FNMR** ($CDCl_3$, 376 MHz): δ -169.5. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_{10}FNO_2Na$ 218.0588; found 218.0563.

1-Benzyl-3-fluoro-3-(hydroxymethyl)indolin-2-one (2b): The compound was prepared by following general procedure and was obtained as white solid (0.087 g, 79%), **mp** 128−130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 1H), 7.38 – 7.24 (m, 6H), 7.11 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 4.98 (d, J = 15.7 Hz, 1H), 4.85 (d, J = 15.7 Hz, 1H), 4.16 (dd, J = 16.3, 4.6 Hz, 2H), 2.38 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.9 (d, $J_{C\text{-}F}$ = 21 Hz), 143.5 (d, $J_{C\text{-}F}$ = 5 Hz), 134.8, 131.5 (d, $J_{C\text{-}F}$ = 3 Hz), 128.9, 127.9, 127.1, 125.34, 124.0 (d, $J_{C\text{-}F}$ = 19 Hz), 123.4 (d, $J_{C\text{-}F}$ = 2 Hz), 109.94, 91.5 (d, $J_{C\text{-}F}$ = 189 Hz), 64.5 (d, $J_{C\text{-}F}$ = 31 Hz), 43.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}FNO_2Na$ 294.0901; found 294.0875.

1-Allyl-3-fluoro-3-(hydroxymethyl)indolin-2-one (2c): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.080 g, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (dt, J = 7.4, 1.6 Hz, 1H), 7.40 (tt, J = 7.8, 1.6 Hz, 1H), 7.18 – 7.08 (m, 1H), 6.88 (d, J = 7.9 Hz, 1H), 5.84 (ddt, J = 17.3, 10.3, 5.2 Hz, 1H), 5.31 – 5.21 (m, 2H), 4.34 (qdt, J = 16.4, 5.2, 1.6 Hz, 2H), 4.05 – 4.17 (m, 2H) (dd, J = 16.9, 5.0 Hz, 2H), 2.34

(br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.6 (d, J_{C-F} = 21 Hz), 143.5 (d, J_{C-F} = 5 Hz), 131.5 (d, J_{C-F} = 3 Hz), 130.5, 125.4, 123.9 (d, J_{C-F} = 18 Hz), 123.4 (d, J_{C-F} = 2 Hz), 118.1, 109.8, 91.5 (d, J_{C-F} = 189 Hz), 64.4 (d, J_{C-F} = 31 Hz), 42.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.4. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{12}H_{12}FNO_2Na$ 244.0744; found 244.0727.

3-Fluoro-3-(hydroxymethyl)-1-phenylindolin-2-one (2d): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.077 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.50 (m, 3H), 7.50 – 7.40 (m, 3H), 7.37 (tt, *J* = 7.8, 1.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.28 – 4.12 (m, 2H), 2.41 (dd, *J* = 7.0, 4.4 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.1 (d, J_{C-F} = 21 Hz), 144.4 (d, J_{C-F} = 4 Hz), 133.3, 131.5 (d, J_{C-F} = 3 Hz), 129.8, 128.6, 126.3, 125.6, 123.9 (d, J_{C-F} = 3 Hz), 123.7, 110.2, 91.6 (d, J_{C-F} = 189 Hz), 64.6 (d, J_{C-F} = 30 Hz). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -168.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{15}H_{12}FNO_2Na$ 280.0744; found 280.0727.

3-Fluoro-3-(hydroxymethyl)-1,5-dimethylindolin-2-one (2e): The compound was prepared by following general procedure and was obtained as white solid (0.080 g, 72%), **mp** 120−122 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (br. s, 1H), 7.23 (dtt, *J* = 8.0, 1.8, 0.8 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.01 - 4.13 (m, 2H), 3.20 (s, 3H), 2.49 (br. s, 1H), 2.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.7 (d, J_{C-F} = 21 Hz), 141.8 (d, J_{C-F} = 5 Hz), 133.2 (d, J_{C-F} = 2 Hz), 131.7 (d, J_{C-F} = 3 Hz), 126.0, 123.9 (d, J_{C-F} = 19 Hz), 108.6, 91.6 (d, J_{C-F} = 189 Hz), 64.4 (d, J_{C-F} = 30 Hz), 26.3, 21.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.5. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{11}H_{12}FNO_2Na$ 232.0744; found 232.0731.

5-Chloro-3-fluoro-3-(hydroxymethyl)-1-methylindolin-2-one (2f): The compound was prepared by following general procedure and was obtained as yellow solid (0.079 g, 71%), **mp** 103−105 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (t, *J* = 2.0 Hz, 1H), 7.41 (dt, *J* = 8.3, 1.9 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.3 Hz, 1H), 4.14 (dd, *J* = 14.9, 12.4 Hz, 1H), 4.07 – 3.92 (m, 1H), 3.21 (s, 3H), 2.41 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.3 (d, J_{C-F} = 20 Hz), 142.7 (d, J_{C-F} = 5 Hz), 131.3 (d, J_{C-F} = 3 Hz), 128.9 (d, J_{C-F} = 3 Hz), 126.1, 125.6 (d, J_{C-F} = 18 Hz), 109.8, 91.5 (d, J_{C-F} = 190 Hz), 64.1 (d, J_{C-F} = 31 Hz), 26.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.7. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9ClFNO_2Na$ 252.0198; found 252.0180.

3-Fluoro-3-(hydroxymethyl)-5-iodo-1-methylindolin-2-one (2g): The compound was prepared by following general procedure and was obtained as white solid (0.068 g, 66%), **mp**

128−130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (t, *J* = 1.8 Hz, 1H), 7.74 (dt, *J* = 8.2, 1.8 Hz, 1H), 6.67 (dd, *J* = 8.2, 1.3 Hz, 1H), 4.12 (dd, *J* = 14.6, 12.4 Hz, 1H), 3.99 (dd, *J* = 19.1, 12.3 Hz, 1H), 3.19 (s, 3H), 2.54 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.0 (d, $J_{C\text{-}F}$ = 20 Hz), 143.9 (d, $J_{C\text{-}F}$ = 5 Hz), 140.2 (d, $J_{C\text{-}F}$ = 3 Hz), 134.2, 126.2 (d, $J_{C\text{-}F}$ = 18 Hz), 110.8, 91.2 (d, $J_{C\text{-}F}$ = 190 Hz), 85.7 (d, $J_{C\text{-}F}$ = 3 Hz), 64.1 (d, $J_{C\text{-}F}$ = 30 Hz), 26.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.7. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9FINO_2Na$ 343.9554; found 343.9539.

5-Bromo-3-fluoro-3-(hydroxymethyl)-1-methylindolin-2-one (2h): The compound was prepared by following general procedure and was obtained as white solid (0.063 g, 58%), **mp** 128−129 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 – 7.61 (m, 1H), 7.64 – 7.46 (m, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 4.14 (t, *J* = 13.6 Hz, 1H), 4.01 (dd, *J* = 19.3, 12.4 Hz, 1H), 3.21 (s, 3H), 2.36 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.1 (d, $J_{C\text{-}F}$ = 20.5 Hz), 143.3 (d, $J_{C\text{-}F}$ = 5.0 Hz), 134.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 128.8, 125.9 (d, $J_{C\text{-}F}$ = 18.5 Hz), 116.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 110.3, 91.3 (d, $J_{C\text{-}F}$ = 190.0 Hz), 64.2 (d, $J_{C\text{-}F}$ = 30.1 Hz), 26.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.6. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9BrFNO_2Na$ 295.9693; found 295.9674.

7-Chloro-3-fluoro-3-(hydroxymethyl)-1-methylindolin-2-one (2i): The compound was prepared by following general procedure and was obtained as gummy liquid (0.073 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (ddd, *J* = 7.3, 2.1, 1.2 Hz, 1H), 7.36 (dt, *J* = 8.3, 1.4 Hz, 1H), 7.06 (ddd, *J* = 8.2, 7.3, 0.9 Hz, 1H), 4.15 – 3.99 (m, 2H), 3.59 (s, 3H), 2.29 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.0 (d, $J_{C\text{-}F}$ = 20 Hz), 140.1 (d, $J_{C\text{-}F}$ = 5 Hz), 133.8 (d, $J_{C\text{-}F}$ = 3 Hz), 126.7 (d, $J_{C\text{-}F}$ = 18 Hz), 124.3 (d, $J_{C\text{-}F}$ = 2.6 Hz), 123.9, 116.4, 90.7 (d, $J_{C\text{-}F}$ = 188 Hz), 64.4 (d, $J_{C\text{-}F}$ = 30 Hz), 29.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -168.5. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9ClFNO_2Na$ 252.0198; found 252.0182.

1-Benzyl-3-fluoro-3-(hydroxymethyl)-5-methoxyindolin-2-one (2j): The compound was prepared by following general procedure and was obtained as brown solid (0.073 g, 69%), **mp** 148−149 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.27 (m, 3H), 7.13 (t, *J* = 2.3 Hz, 1H), 6.82 (dt, *J* = 8.6, 2.1 Hz, 1H), 6.64 (dd, *J* = 8.6, 1.3 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.83 (d, *J* = 15.7 Hz, 1H), 4.20 – 4.07 (m, 2H), 3.78 (s, 3H), 2.35 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.7 (d, $J_{C\text{-}F}$ = 20 Hz), 156.4 (d, $J_{C\text{-}F}$ = 3 Hz), 136.6 (d, $J_{C\text{-}F}$ = 5 Hz), 134.9, 128.9, 127.9, 127.2, 125.0 (d, $J_{C\text{-}F}$ = 19 Hz), 116.0 (d, $J_{C\text{-}F}$ = 3 Hz), 112.4, 110.6,

91.8 (d, J_{C-F} = 190 Hz), 64.6 (d, J_{C-F} = 31 Hz), 55.9, 43.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.3. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}FNO_3Na$ 324.1006; found 324.0983.

1-Benzyl-5-chloro-3-fluoro-3-(hydroxymethyl)indolin-2-one (2k): The compound was prepared by following general procedure and was obtained as white solid (0.081 g, 76%), **mp** 171−172 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 2.0 Hz, 1H), 7.42 – 7.22 (m, 6H), 6.66 (dd, *J* = 8.4, 1.3 Hz, 1H), 4.96 (d, *J* = 15.8 Hz, 1H), 4.84 (d, *J* = 15.8 Hz, 1H), 4.27 – 4.00 (m, 2H), 2.25 (dd, *J* = 8.5, 4.5 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 171.4 (d, J_{C-F} = 20.4 Hz), 141.9 (d, J_{C-F} = 4.9 Hz), 134.3, 131.3 (d, J_{C-F} = 2.8 Hz), 129.0, 128.9, 128.1, 127.1, 126.1, 125.6 (d, J_{C-F} = 18.4 Hz), 111.0, 91.4 (d, J_{C-F} = 190.0 Hz), 64.2 (d, J_{C-F} = 30.9 Hz), 44.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}ClFNO_2Na$ 328.0511; found 328.0508.

1-Benzyl-5-bromo-3-fluoro-3-(hydroxymethyl)indolin-2-one (2l): The compound was prepared by following general procedure and was obtained as white solid (0.09 g, 82%), **mp** 159−160 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 2.0 Hz, 1H), 7.42 (dt, *J* = 8.3, 1.8 Hz, 1H), 7.36 – 7.25 (m, 5H), 6.61 (dd, *J* = 8.3, 1.3 Hz, 1H), 4.96 (d, *J* = 15.8 Hz, 1H), 4.84 (d, *J* = 15.8 Hz, 1H), 4.25 – 4.04 (m, 2H), 2.25 (d, *J* = 5.0 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.3 (d, J_{C-F} = 20 Hz), 142.5 (d, J_{C-F} = 5 Hz), 134.3, 134.2 (d, J_{C-F} = 3 Hz), 129.0, 128.8, 128.1, 127.1, 125.9 (d, J_{C-F} = 19 Hz), 116.1 (d, J_{C-F} = 3 Hz), 111.4, 91.4 (d, J_{C-F} = 190 Hz), 64.2 (d, J_{C-F} = 31 Hz), 43.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}BrFNO_2Na$ 372.0006; found 371.9989.

1-Benzyl-3,5-difluoro-3-(hydroxymethyl)indolin-2-one (2m): The compound was prepared by following general procedure and was obtained as white solid (0.084 g, 77%), **mp** 161−163 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 6H), 7.00 (tdd, *J* = 8.8, 2.6, 1.7 Hz, 1H), 6.66 (ddd, *J* = 8.6, 4.0, 1.3 Hz, 1H), 4.97 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 15.8 Hz, 1H), 4.21 (ddd, *J* = 14.2, 12.2, 4.3 Hz, 1H), 4.09 (ddd, *J* = 18.6, 12.3, 8.6 Hz, 1H), 2.31 (dd, *J* = 8.7, 4.4 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.6 (d, J_{C-F} = 21 Hz), 160.5 (d, J_{C-F} = 3 Hz), 158.1 (d, J_{C-F} = 3 Hz), 139.2 (q, J_{C-F} = 5 Hz), 134.5, 129.0, 128.0, 127.1, 125.5 (q, J_{C-F} = 19 Hz), 117.8 (d, J_{C-F} = 3 Hz), 117.6 (d, J_{C-F} = 3 Hz), 113.8 (d, J_{C-F} = 26 Hz), 110.7 (d, J_{C-F} = 8 Hz), 91.6 (dd, J_{C-F} = 190, 1.6 Hz), 64.3 (d, J_{C-F} = 30 Hz), 44.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -118.7, -169.4. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}F_2NO_2Na$ 312.0807; found 312.0781.

1-Benzyl-3-fluoro-3-(hydroxymethyl)-5-iodoindolin-2-one (2n): The compound was prepared by following general procedure and was obtained as white solid (0.085 g, 79%), **mp** 158−160 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (t, J = 1.8 Hz, 1H), 7.61 (dt, J = 8.3, 1.8 Hz, 1H), 7.38 – 7.21 (m, 5H), 6.51 (dd, J = 8.3, 1.3 Hz, 1H), 4.95 (d, J = 15.8 Hz, 1H), 4.83 (d, J = 15.8 Hz, 1H), 4.30 – 3.94 (m, 2H), 2.42 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.1 (d, $J_{C\text{-}F}$ = 20 Hz), 143.1 (d, $J_{C\text{-}F}$ = 5 Hz), 140.2 (d, $J_{C\text{-}F}$ = 3 Hz), 134.3 (d, $J_{C\text{-}F}$ = 3 Hz), 129.0, 128.0, 127.1, 126.2 (d, $J_{C\text{-}F}$ = 19 Hz), 111.9, 91.2 (d, $J_{C\text{-}F}$ = 190 Hz), 85.9 (d, $J_{C\text{-}F}$ = 3 Hz), 64.2 (d, $J_{C\text{-}F}$ = 31 Hz), 43.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -169.0. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}FINO_2Na$ 419.9867; found 419.9850.

3-Fluoro-3-(hydroxymethyl)indolin-2-one (2o): The compound was prepared by following general procedure and was obtained as colourless gummy liquid (0.070 g, 62%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 7.48 (dt, J = 7.4, 1.6 Hz, 1H), 7.34 (tt, J = 7.8, 1.7 Hz, 1H), 7.04 (tt, J = 7.5, 1.0 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 5.38 (t, J = 5.7 Hz, 1H), 3.94 (ddd, J = 11.2, 8.8, 5.0 Hz, 1H), 3.75 (ddd, J = 17.8, 11.2, 6.2 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ 172.9 (d, $J_{C\text{-}F}$ = 19.4 Hz), 143.2 (d, $J_{C\text{-}F}$ = 5.8 Hz), 131.2 (d, $J_{C\text{-}F}$ = 3.2 Hz), 125.9, 124.9 (d, $J_{C\text{-}F}$ =18.2 Hz), 122.1 (d, $J_{C\text{-}F}$ = 2.8 Hz), 110.2, 92.6 (d, $J_{C\text{-}F}$ = 184.1 Hz), 62.1 (d, $J_{C\text{-}F}$ = 33.2 Hz). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -164.8. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_9H_8FNO_2Na$ 204.0431; found 204.0425.

3-fluoro-3-(hydroxymethyl)-1-tosylindolin-2-one (2p): The compound was prepared by following general procedure and was obtained as white solid (0.068 g, 66%) **mp** 117−119 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 7.90 (m, 3H), 7.51 (td, J = 7.4, 1.7 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.30 – 7.23 (m, 1H), 4.09 – 3.96 (m, 2H), 2.44 (s, 3H), 1.96 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.1(d, $J_{C\text{-}F}$ = 21 Hz), 146.2, 140.0 (d, $J_{C\text{-}F}$ = 5 Hz), 134.5, 132.3, 130.0, 128.0, 125.7, 125.5 (d, $J_{C\text{-}F}$ = 2 Hz), 123.1 (d, $J_{C\text{-}F}$ = 19 Hz), 114.1, 91.2 (d, $J_{C\text{-}F}$ = 192 Hz), 64.4 (d, $J_{C\text{-}F}$ = 32 Hz), 21.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -163.9. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}FNO_4SNa$ 358.0520; found 358.0523.

General procedure for ring-opening reaction Spiro-epoxyoxindoles with TBAF: To a stirring solution of spiro-epoxy oxindole **1a** (0.100 g, 0.570 mmol) in dry DMF (4 mL), TBAF (1M in THF) (1.71 mL, 1.712 mmol) was added and the reaction mixture was allowed to heat at 50 °C at oil bath. The resulting solution was stirred at the same temperature and monitored

by TLC. On completion (6 h), the reaction was diluted with water, extracted with EtOAc (3×5 mL), washed with brine solution and dried over anhydrous Na_2SO_4. Combined organic layers were concentrated and purified by silicagel flash chromatography using EtOAc/hexane (1:4) to afford the desired product **3a** (0.069 g, 62%).

3-(Fluoromethyl)-3-hydroxy-1-methylindolin-2-one (3a): The compound was prepared by following general procedure and was obtained as white solid (0.072 g, 63%), **mp** 143−145 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 1H), 7.40 (td, *J* = 7.8, 1.3 Hz, 1H), 7.15 (td, *J* = 7.6, 1.0 Hz, 1H), 6.89 (dt, *J* = 7.8, 0.7 Hz, 1H), 4.67 (br. s, 1H), 4.55 (d, *J* = 0.9 Hz, 1H), 3.48 – 3.34 (m, 1H), 3.23 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.5 (d, $J_{C\text{-}F}$ = 3.5 Hz), 143.8, 130.6, 126.6 (d, $J_{C\text{-}F}$ = 2 Hz), 124.6, 123.4, 108.7, 84.7 (d, $J_{C\text{-}F}$ = 179 Hz), 74.9 (d, $J_{C\text{-}F}$ = 20 Hz), 26.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.9. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_{10}FNO_2Na$ 218.0588; found 218.0602.

1-Benzyl-3-(fluoromethyl)-3-hydroxyindolin-2-one (3b): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.061 g, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.35 – 7.24 (m, 6H), 7.13 – 7.08 (m, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 5.03 (d, *J* = 15.8 Hz, 1H), 4.84 – 4.69 (m, 2H), 4.62 (q, *J* = 9.2 Hz, 1H), 3.65 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.7 (d, $J_{C\text{-}F}$ = 3 Hz), 143.0, 135.0, 130.5, 128.9, 127.8, 127.1, 126.7, 124.6, 123.5, 109.8, 84.7 (d, $J_{C\text{-}F}$ = 180 Hz), 74.9 (d, $J_{C\text{-}F}$ = 21 Hz), 43.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}FNO_2Na$ 294.0901; found 294.0903.

1-Allyl-3-(fluoromethyl)-3-hydroxyindolin-2-one (3c): The compound was prepared by following general procedure and was obtained as orange solid (0.075 g, 66%), **mp** 93−94 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.36 (td, *J* = 7.8, 1.3 Hz, 1H), 7.14 (td, *J* = 7.6, 1.0 Hz, 1H), 6.87 (dt, *J* = 7.9, 0.7 Hz, 1H), 5.84 (ddt, *J* = 17.3, 10.3, 5.2 Hz, 1H), 5.31 – 5.16 (m, 2H), 4.75 – 4.64 (m, 1H), 4.63 – 4.52 (m, 1H), 4.42 (ddt, *J* = 16.5, 5.2, 1.8 Hz, 1H), 4.26 (ddt, *J* = 16.4, 5.2, 1.7 Hz, 1H), 3.48 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.3 (d, $J_{C\text{-}F}$ = 3 Hz), 143.1, 130.5 (d, $J_{C\text{-}F}$ = 12 Hz), 126.7 (d, $J_{C\text{-}F}$ = 2 Hz), 124.7, 123.4, 117.8, 109.7, 84.7 (d, $J_{C\text{-}F}$ = 180 Hz), 74.8 (d, $J_{C\text{-}F}$ = 21 Hz), 42.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.3. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{12}H_{12}FNO_2Na$ 244.0744; found 244.0751.

3-(Fluoromethyl)-3-hydroxy-1-(4-methoxybenzyl)indolin-2-one (3d): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.08 g, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.27 (td, *J* = 8.0, 1.3 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.10 (td, *J* = 7.6, 1.0 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.95 (d, *J* = 15.5 Hz, 1H), 4.78 – 4.68 (m, 2H), 4.61 (q, *J* = 9.2 Hz, 1H), 3.77 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.7 (d, $J_{C\text{-}F}$ = 3 Hz), 159.2, 143.0, 130.4, 128.5, 127.0, 126.8, 124.6, 123.4, 114.3, 109.9, 84.7 (d, $J_{C\text{-}F}$ = 180 Hz), 74.9 (d, $J_{C\text{-}F}$ = 21 Hz), 55.2, 43.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}FNO_3Na$ 324.1006; found 324.1025.

3-(Fluoromethyl)-3-hydroxy-1,5-dimethylindolin-2-one (3e): The compound was prepared by following general procedure and was obtained as red solid (0.079 g, 65%), **mp** 118−120 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (br. S, 1H), 7.19 (ddd, *J* = 7.9, 1.8, 0.9 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 4.66 (d, *J* = 1.3 Hz, 1H), 4.54 (d, *J* = 1.6 Hz, 1H), 3.68 (s, 1H), 3.25 – 3.15 (m, 3H), 2.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.5 (d, $J_{C\text{-}F}$ = 3 Hz), 141.4, 133.1, 130.7, 126.6 (d, $J_{C\text{-}F}$ = 2 Hz), 125.4, 108.5, 84.7 (d, $J_{C\text{-}F}$ = 179 Hz), 75.0 (d, $J_{C\text{-}F}$ = 20 Hz), 26.4, 21.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.8. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{11}H_{12}FNO_2Na$ 232.0744; found 232.0752.

3-(Fluoromethyl)-3-hydroxy-1,5,7-trimethylindolin-2-one (3f): The compound was prepared by following general procedure and was obtained as orange solid (0.073 g, 66%), **mp** 154−155 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.92 (s, 1H), 4.62 (q, *J* = 9.2 Hz, 1H), 4.54 – 4.45 (m, 1H), 3.46 (s, 3H), 3.35 (s, 1H), 2.53 (s, 3H), 2.30 (3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 176.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 139.0, 134.7, 133.0, 127.3 (d, $J_{C\text{-}F}$ = 1.7 Hz), 123.2, 120.2, 84.9 (d, $J_{C\text{-}F}$ = 179.6 Hz), 74.2 (d, $J_{C\text{-}F}$ = 20.6 Hz), 29.7, 20.7, 18.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.3. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{12}H_{14}FNO_2Na$ 246.0901; found 246.0913.

5-Chloro-3-(fluoromethyl)-3-hydroxy-1-methylindolin-2-one (3g): The compound was prepared by following general procedure and was obtained as yellow solid (0.067 g, 59%), **mp** 132−134 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.66 (s, 1H), 4.54 (s, 1H), 3.21 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.1 (d, $J_{C\text{-}F}$ = 4 Hz)142.3, 130.4, 129.0, 128.4, 125.3, 109.8, 84.5 (d, $J_{C\text{-}F}$ = 180 Hz), 74.9 (d, $J_{C\text{-}F}$ = 21 Hz), 26.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -230.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9ClFNO_2Na$ 252.0198; found 252.0177.

3-(Fluoromethyl)-3-hydroxy-5-iodo-1-methylindolin-2-one (3h): The compound was prepared by following general procedure and was obtained as yellow solid (0.064 g, 62%), **mp** 179−181 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.65 (m, 2H), 6.67 (d, J = 8.1 Hz, 1H), 4.64 (s, 1H), 4.53 (s, 1H), 3.34 (s, 1H), 3.20 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.8 (d, $J_{C\text{-}F}$ = 3 Hz), 143.5, 139.3, 133.6, 129.0, 110.8, 85.9, 84.5 (d, $J_{C\text{-}F}$ = 180 Hz),, 74.7 (d, $J_{C\text{-}F}$ = 21 Hz), 26.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.9. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9FINO_2Na$ 343.9554; found 343.9570.

7-Chloro-3-(fluoromethyl)-3-hydroxy-1-methylindolin-2-one (3i): The compound was prepared by following general procedure and was obtained as yellow solid (0.064 g, 60%), **mp** 115−117 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (ddd, J = 15.2, 7.8, 1.1 Hz, 2H), 7.06 (dd, J = 8.2, 7.4 Hz, 1H), 4.69 – 4.58 (m, 1H), 4.58 – 4.47 (m, 1H), 3.67 (s, 1H), 3.58 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.9 (d, $J_{C\text{-}F}$ = 3 Hz), 139.7, 132.8, 129.6, 124.3, 123.2, 116.2, 84.6 (d, $J_{C\text{-}F}$ = 180 Hz), 74.3 (d, $J_{C\text{-}F}$ = 21 Hz), 29.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.7. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{10}H_9ClFNO_2Na$ 252.0198; found 252.0200.

1-Benzyl-3-(fluoromethyl)-3-hydroxy-5,7-dimethylindolin-2-one (3j): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.061 g, 55%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 3H), 7.19 – 7.11 (m, 3H), 6.89 – 6.81 (m, 1H), 5.23 (d, J = 16.8 Hz, 1H), 5.09 (d, J = 16.9 Hz, 1H), 4.67 (ddd, J = 47.0, 33.5, 9.0 Hz, 2H), 3.65 (s, 1H), 2.30 (s, 3H), 2.20 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 176.8 (d, $J_{C\text{-}F}$ = 2 Hz), 138.5, 136.8, 134.9, 133.3, 128.9, 127.5, 127.3, 125.5, 123.2, 120.3, 84.9 (d, $J_{C\text{-}F}$ = 179 Hz), 74.1 (d, $J_{C\text{-}F}$ = 21 Hz), 45.1, 20.7, 18.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -228.3. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{18}H_{18}FNO_2Na$ 322.1214; found 322.1223.

1-Benzyl-5-bromo-3-(fluoromethyl)-3-hydroxyindolin-2-one (3k): The compound was prepared by following general procedure and was obtained as red gummy liquid (0.062 g, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.3, 2.0 Hz, 1H), 7.36 – 7.21 (m, 5H), 6.60 (d, J = 8.4 Hz, 1H), 5.01 (d, J = 15.8 Hz, 1H), 4.83 – 4.67 (m, 2H), 4.65 – 4.55 (m, 1H), 3.54 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.2 (d, $J_{C\text{-}F}$ = 3 Hz), 142.0, 134.4, 133.3, 129.0, 128.7, 128.1, 128.0, 127.0, 116.2, 111.4, 85.5 (d, $J_{C\text{-}F}$ = 180 Hz), 74.8 (d, $J_{C\text{-}F}$ = 21 Hz), 44.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}BrFNO_2Na$ 372.0006; found 372.0009.

1-Benzyl-5-fluoro-3-(fluoromethyl)-3-hydroxyindolin-2-one (3l): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.064 g, 57%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 6H), 6.94 (td, *J* = 8.8, 2.6 Hz, 1H), 6.63 (dd, *J* = 8.6, 4.0 Hz, 1H), 5.01 (d, *J* = 15.8 Hz, 1H), 4.81 – 4.68 (m, 2H), 4.65 – 4.56 (m, 1H), 4.05 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.8 (d, J_{C-F} = 3 Hz), 159.6 (d, J_{C-F} = 242 Hz), 138.7 (d, J_{C-F} = 2 Hz), 134.6, 128.9, 128.6 (d, J_{C-F} = 8 Hz), 127.9, 127.0, 116.7 (d, J_{C-F} = 23 Hz), 113.0 (d, J_{C-F} = 25 Hz), 110.6 (d, J_{C-F} = 8 Hz), 84.6 (d, J_{C-F} = 180 Hz), 75.2 (dd, J_{C-F} = 21, 2 Hz), 44.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -118.9, -229.4. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}F_2NO_2Na$ 312.0807; found 312.0812.

1-Benzyl-3-(fluoromethyl)-3-hydroxy-5-iodoindolin-2-one (3m): The compound was prepared by following general procedure and was obtained as yellow gummy liquid (0.063 g, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.7 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.20 – 7.15 (m, 3H), 6.42 (d, *J* = 8.3 Hz, 1H), 4.91 (d, *J* = 15.8 Hz, 1H), 4.70 (d, *J* = 15.8 Hz, 1H), 4.67 – 4.58 (m, 1H), 4.55 – 4.47 (m, 1H), 3.24 (br. s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.9 (d, J_{C-F} = 3 Hz), 142.7, 139.3, 134.5, 133.6, 129.0, 128.0, 127.0, 111.89, 86.0, 84.5 (d, J_{C-F} = 180 Hz), 74.6 (d, J_{C-F} = 21 Hz), 44.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -229.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}FINO_2Na$ 419.9867; found 419.9860.

1-Benzyl-3-(bromomethyl)-3-fluoroindolin-2-one (5): To a stirring solution of compound **2b** (0.100 g, 0.368 mmol) in dry 1,2-dichloroethane (5 mL), triphenyl phosphine (0.580 g, 2.21 mmol) and carbon tetrabromide (0.732 g, 2.21 mmol) were added sequentially at 0 °C and the resulting solution was heated at 50 °C at oil bath for 4 h. Solvent was evaporated and purified by silicagel flash chromatography using 8% EtOAc/hexane to afford the desire product **5 (** 0.117 g, 95%) as colourless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dt, *J* = 7.4, 1.7 Hz, 1H), 7.40 – 7.21 (m, 6H), 7.13 (tt, *J* = 7.6, 1.0 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 5.06 (d, *J* = 15.8 Hz, 1H), 4.81 (d, *J* = 15.7 Hz, 1H), 4.17 – 3.82 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.6 (d, J_{C-F} = 21 Hz), 143.8 (d, J_{C-F} = 5 Hz), 134.7, 131.9 (d, J_{C-F} = 3 Hz), 128.9, 127.9, 127.2, 127.1, 125.1, 123.7 (d, J_{C-F} = 19 Hz), 123.4 (d, J_{C-F} = 3 Hz), 110.0, 90.6 (d, J_{C-F} = 189 Hz), 44.1, 30.1 (d, J_{C-F} = 36 Hz). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -150.2. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}BrFNONa$ 356.0057; found 356.0080.

(1-Benzyl-3-fluoro-2-oxoindolin-3-yl)methyl 4-methylbenzenesulfonate (6): To a stirring solution of Compound **2b** (0.100 g, 0.368 mmol) in dry dichloromethane (4 mL) at 0°C (immersion bath), triethyl amine (0.102 mL, 0.737 mmol) and tosyl chloride (0.106 g, 0.552 mmol) were added sequentially. Then the resulting solution was stirred at 25°C and monitored by TLC. On completion, solvent was evaporated and the residue was purified by silicagel flash chromatography using EtOAc/hexane (1:9) to afford the desire product **6** (0.15 g, 95%) as gummy liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.66 (m, 2H), 7.48 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.35 – 7.24 (m, 8H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.97 (d, *J* = 15.8 Hz, 1H), 4.78 (d, *J* = 15.8 Hz, 1H), 4.60 (dd, *J* = 10.3, 8.1 Hz, 1H), 4.37 (dd, *J* = 18.8, 10.3 Hz, 1H), 2.46 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.8 (d, $J_{C\text{-}F}$ = 20 Hz), 145.3, 143.4 (d, $J_{C\text{-}F}$ = 5 Hz), 134.5, 131.9 (d, $J_{C\text{-}F}$ = 4 Hz), 130.0, 129.0, 128.0, 127.9, 127.0, 126.2, 123.6, 122.5 (d, $J_{C\text{-}F}$ = 20 Hz), 110.0, 89.5 (d, $J_{C\text{-}F}$ = 191 Hz), 68.6 (d, $J_{C\text{-}F}$ = 36 Hz), 44.0, 21.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -165.2. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}FNO_4S$ 426.1170; found 426.1142.

3-(Azidomethyl)-1-benzyl-3-fluoroindolin-2-one (7): Compound **6** (0.05 g, 0.117 mmol) was dissolved in dry DMF (2 mL) at 25°C. Sodium azide (0.038 g, 0.038 mmol) was added to the mixture and the resulting mixture was heated 100°C for 14 h. On completion cold water was added, extracted with EtOAc (3×5 mL), washed with brine solution and dried over anhydrous Na_2SO_4. Combined organic layers were concentrated and purified by silicagel flash chromatography using EtOAc/hexane (1:10) to afford the desire product **7** (0.031 g, 90%) as colorless gummy liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.44 – 7.20 (m, 6H), 7.17 – 7.07 (m, 1H), 6.83 – 6.69 (m, 1H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.84 (d, *J* = 15.7 Hz, 1H), 4.09 (dd, *J* = 12.7, 8.8 Hz, 1H), 3.72 (dd, *J* = 18.7, 12.7 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.9 (d, $J_{C\text{-}F}$ = 20 Hz), 143.4 (d, $J_{C\text{-}F}$ = 5 Hz), 134.7, 131.8 (d, $J_{C\text{-}F}$ = 3 Hz), 129.0, 128.0, 127.2, 125.7, 123.6, 123.5 (d, $J_{C\text{-}F}$ = 3 Hz), 110.0, 90.9 (d, $J_{C\text{-}F}$ = 191 Hz), 53.7 (d, $J_{C\text{-}F}$ = 33 Hz), 44.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -162.1. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{13}FN_4ONa$ 319.0966; found 319.0960.

1-Benzyl-3-methylindolin-2-one (8): To a stirring solution of compound **6** (0.08 g, 0.188 mmol) in dry THF (2 mL) at 0°C (immersion bath), Super hydride (1M in THF) (0.94 mL, 0.94 mmol) was added. Then the resulting solution was allowed to warm at 25°C and monitored by TLC. On completion (2 h), the reaction was quenched with saturated aqueous solution of NH_4Cl, extracted with EtOAc (3×5 mL), washed with brine solution and dried over anhydrous

Na_2SO_4. Combined organic layers were concentrated and purified by silicagel flash chromatography using EtOAc/hexane (1:4) to afford the desire product **8** (0.042 g, 95%) as white solid, **mp** 115−116 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 – 7.22 (m, 6H), 7.17 (tt, *J* = 7.8, 1.0 Hz, 1H), 7.03 (td, *J* = 7.6, 0.9 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.92 (s, 2H), 3.55 (q, *J* = 7.6 Hz, 1H), 1.55 (d, *J* = 7.6 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ 178.7, 143.0, 135.9, 130.6, 128.7, 127.8, 127.5, 127.2, 123.5, 122.4, 108.9, 43.6, 40.5, 15.6. **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{15}NONa$ 260.1046; found 260.1063.

3-(Fluoromethyl)-3-(4-methoxyphenyl)-1-methylindolin-2-one (10): To a stirring solution of compound **3a** (0.100 g, 0.512 mmol) in dry dichloromethane (2.5 mL) at 0 °C (immersion bath), DBU (0.09 mL, 0.614 mmol) and trichloroacetonitrile (0.1 mL, 0.768 mmol) were added sequential. Then the resulting solution was stirred at 25 °C and monitored by TLC. On completion, the reaction was quenched with saturated aqueous solution of NH_4Cl, extracted with EtOAc (3×5 mL), washed with brine solution and dried over anhydrous Na_2SO_4. Combined organic layers were concentrated. The residue was dissolved in dry 1,2-dichloroethane (2 mL). Anisole (0.24 g, 0.22 mmol) and $BF_3.OEt_2$ (.003 mL, 0.029 mmol) were added sequential. The resulting solution was stirred at 25 °C. On completion (2 h), the reaction was quenched with saturated aqueous solution of $NaHCO_3$, extracted with EtOAc (3×5 mL), washed with brine solution and dried over anhydrous Na_2SO_4. Combined organic layers were concentrated and purified by silicagel flash chromatography using EtOAc/hexane (1:9) to afford the desire product **10** (0.131 g, 90%) as yellow solid, **mp** 116−117 °C. **^{1}H NMR** (400 MHz,) δ 7.41 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.37 – 7.34 (m, 2H), 7.22 – 7.15 (m, 1H), 6.94 (dt, *J* = 7.6, 0.9 Hz, 1H), 6.91 – 6.81 (m, 2H), 5.10 – 4.83 (m, 2H), 3.78 (s, 3H), 3.23 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.8 (d, $J_{C\text{-}F}$ = 4 Hz), 159.3, 144.1, 129.0, 128.9, 128.3, 127.1 (d, $J_{C\text{-}F}$ = 6 Hz), 125.4, 122.8, 114.2, 108.6, 85.7 (d, $J_{C\text{-}F}$ = 179 Hz), 56.7 (d, $J_{C\text{-}F}$ = 20 Hz), 55.3, 26.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -221.2. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}FNO_2$ 286.1238; found 286.1237.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest

Supporting Information

NMR spectra for all new compounds **2**, **3, 5, 6, 7, 8, 10.** This material is available free of charge via the Internet at http://pubs.acs.org.

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