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A facile procedure for synthesis of 3-[2-(*N*,*N*-dialkylamino)ethyl]-3-fluorooxindoles by direct fluorination of *N*,*N*-dialkyltryptamines

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ABSTRACT

A practical procedure for the synthesis of 3-fluorooxindole derivatives having basic amine moieties was developed, which involves Selectfluor™-mediated oxidative fluorination of *N*,*N*-dialkyltryptamines in the presence of Lewis acid. This procedure was applied to an antimigraine drug, rizatriptan, to afford the corresponding 3-fluorooxindole, which is a potential fluorine-containing drug candidate.

1. Introduction

Fluorine-containing drugs and drug candidates have been synthesized in pharmaceutical research over the last 20 years [1] because introduction of fluorine atoms into bioactive compounds often induces dramatic changes in their chemical, physical, and pharmacological properties [2]. The 3-fluorooxindole compounds **1** have received much attention as synthetic targets for development of novel medicinal agents (Fig. 1). Owing to the steric and electronic similarities of a fluorine to a hydrogen and a hydroxyl group [2], 3-fluorooxindoles are potential mimics of the corresponding oxindoles **2** and 3-hydroxyoxindoles **3** that are often found in natural products [3], biologically active compounds [4], and metabolites of indoles [5]. For example, BMS-204352 (MaxiPost™, **4**) was reported to be effective for the treatment of stroke [6]. As a part of our studies on the design, synthesis, and biological evaluation of fluorine-containing bioactive compounds [7], we have been developing the oxidative fluorination of indoles with Selectfluor™ [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] (**5**) [8] to obtain the corresponding 3-fluorooxindoles [9].

In our recent studies on the application of the above fluorination to N_b-acyl or -acyloxycarbonyl protected tryptamines [10], we noticed that this fluorination is drastically affected by the character of the N_b-amino group of tryptamines. In order to make this fluorination versatile, we focused on a class of *N*,*N*-dialkyltryptamines **6** having the rather basic amino group. Compounds **6** are known to be effective ligands for serotonin receptors [11] and the corresponding 3-fluorooxindoles **7** are expected to be potential analogs for the putative oxindole-type metabolites of **6** and as drug candidates having enhanced, additional and/or altered biological activities. Herein, we report an efficient procedure for the synthesis of 3-fluorooxindoles **7** by direct, oxidative fluorination of **6** with **5** in the presence of Lewis acid.

2. Results and discussion

We first attempted fluorination of *N*,*N*-dimethyltryptamine (**6a**) as a model compound according to our procedure [9,10] which employs 3 equiv of **5** in MeCN/H_2O (1/1). However, unlike the fluorination of N_b-acyl or -acyloxycarbonyl protected tryptamines **8a**–**c** (Table 1, entries 1–3), only a trace amount of 3-fluorooxindole **7a** was obtained (Table 1, entry 4) together with a substantial amount of unidentified products. We then examined fluorination of **6a** in other solvents. Using MeOH/H_2O in place of MeCN/H_2O increased the yield to 13% (entry 5). Further improvement of the yield (24%) was observed when the reaction was performed in a 1/1 mixture of MeCN/MeOH (entry 6). Use of MeOH alone again produced **7a**, in low yield (7%) (entry 7). Interestingly, a trace amount of *N*-methyltryptamine **10** could be isolated under the conditions in entry 7.

Formation of the *N*-demethylated product **10** suggested that the dimethylamino group of **6a** can be oxidized by **5**. The mechanism of this oxidation would involve formation of the iminium ion **12** and carbinolamine **13** (Scheme 1, path A). Path B

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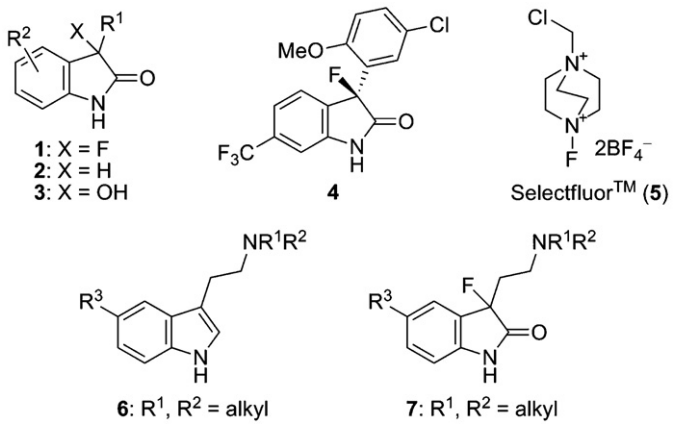


Fig. 1. Structures of compounds **1**–**7**.

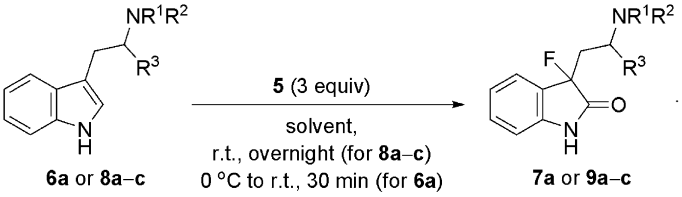
would be an alternative possibility although we could not isolate aldehyde **16**. Actually, similar mechanisms have been proposed for the demethylation of tertiary methylamines using halogenating reagents [12] and heme enzymes [13].

To confirm these reaction pathways, we attempted to trap the intermediates **12** and **14** with a cyanide anion. Reaction of **6a** with **5** and sodium cyanide in MeOH at 0 °C for 30 min produced α-aminonitriles **17** and **18** in 58% and 8% yields, respectively (Scheme 2), which strongly supports the oxidative pathways shown in Scheme 1. It should be noted that oxidation of tertiary amines is known to trigger various transformations including *N*-dealkylation, dimerization, deamination, etc. [14]. Thus, formation of the complex mixture in the reaction of **6a** with **5** is probably due to the high nucleophilicity of the dimethylamino group of **6a**.

With these results in mind, we attempted the fluorination of **6a** in the presence of acid so as to decrease the nucleophilicity of the dimethylamino group. Results are shown in Table 2. Fluorination of **6a** in the presence of 1.1 equiv of BF_3·MeOH in MeCN/MeOH (1/1) produced **7a** in 73% yield (entry 1). Use of a larger or smaller amount of BF_3·MeOH did not improve the results (entries 2 and 3). After screening several Lewis acids for further optimization (entries 4–7), the best result (96% yield) was obtained when the fluorination was carried out using 1.1 equiv of $AlCl_3$ (entry 4). Next, we examined the reaction in the presence of some Brønsted acids. Treatment of **6a** with 1.1 equiv of acetic acid or trifluoroacetic acid furnished 3-fluorooxindole **7a** in moderate yields (entries 8 and 9). We also attempted the fluorination using *N*,*N*-dimethyltryptamine hydrochloride salt (**6a** · HCl) as a substrate. However, the yields of **7a** did not meet our expectation (entries 10–12).

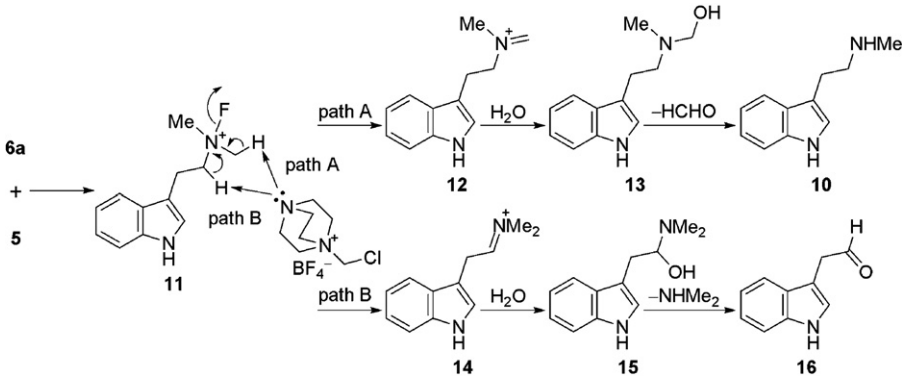
For scope and limitations we applied the newly developed procedure for other *N*,*N*-dialkyltryptamines **6b**–**h** having various acyclic and cyclic amino groups (Table 3). Fluorination of **6b**–**h**

Table 1
Fluorination of tryptamines **6a** and **8a**–**c** with Selectfluor™ (**5**).

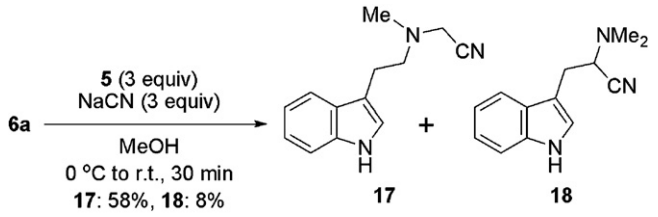


Entry	Substrate	R^1	R^2	R^3	Solvent (ratio)	Product	Yield (%)
1	**8a**[a]	Ac	H	CO_2Me	MeCN/H_2O (1/1)	**9a**	70
2	**8b**[b]	Boc	Boc	CO_2Me	MeCN/H_2O (1/1)	**9b**	71
3	**8c**[c]	Boc	Boc	H	MeCN/H_2O (1/1)	**9c**	71[d]
4	**6a**	Me	Me	H	MeCN/H_2O (1/1)	**7a**	Trace
5	**6a**	Me	Me	H	MeOH/H_2O (1/1)	**7a**	13
6	**6a**	Me	Me	H	MeCN/MeOH (1/1)	**7a**	24
7	**6a**	Me	Me	H	MeOH	**7a**	7 (13)[e]

[a] Ref. [9].
[b] Ref. [10a].
[c] Ref. [10b].
[d] Yields of the N_b-Boc diprotected fluorooxindole and the N_b-Boc monoprotected fluorooxindole are 20% and 51%, respectively.
[e] Yield of the recovered starting material in parenthesis.

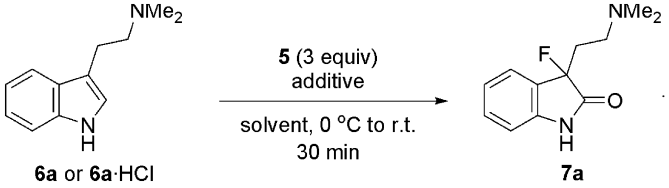


Scheme 1. Possible mechanism for oxidation of tertiary amine **6a** mediated by **5**.



Scheme 2. Trapping of the iminium ion intermediates using sodium cyanide.

Table 2
Fluorination of **6a** and its hydrochloride **6a**·HCl in the presence of various acids.

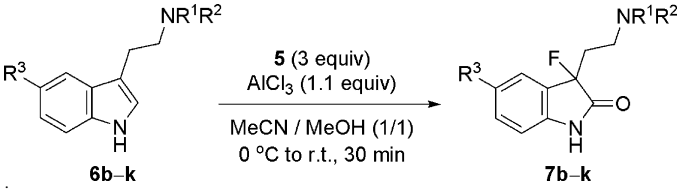


Entry	Substrate	Additive (equiv)	Solvent (ratio)	Yield (%)
1	**6a**	BF_3·MeOH (1.1)	MeCN/MeOH (1/1)	73
2	**6a**	BF_3·MeOH (0.1)	MeCN/MeOH (1/1)	54
3	**6a**	BF_3·MeOH (10)	MeCN/MeOH (1/1)	33
4	**6a**	$AlCl_3$ (1.1)	MeCN/MeOH (1/1)	96
5	**6a**	$SnCl_4$ (1.1)	MeCN/MeOH (1/1)	76
6	**6a**	$ZnCl_2$ (1.1)	MeCN/MeOH (1/1)	13
7	**6a**	$TiCl_4$ (1.1)	MeCN/MeOH (1/1)	75
8	**6a**	AcOH (1.1)	MeCN/MeOH (1/1)	27
9	**6a**	TFA (1.1)	MeCN/MeOH (1/1)	64
10	**6a**·HCl	None	MeCN/H_2O (1/1)	35
11	**6a**·HCl	None	MeOH/H_2O (1/1)	27
12	**6a**·HCl	None	MeCN/MeOH (1/1)	55

with **5**, in the presence of 1.1 equiv of $AlCl_3$, successfully produced the corresponding 3-fluorooxindoles **7b**–**h** in excellent yields (entries 1–7). Fluorination of **6i**–**k** having electron-donating and -withdrawing groups at the 5-position of indole ring also gave satisfactory results (entries 8–10). Thus, we have developed a practical oxidative fluorination of *N*,*N*-dialkyltryptamines **6** with broad applicability.

In order to investigate the effect of $AlCl_3$ on the fluorination, we performed a ^{1}H NMR spectroscopic investigation of **6a** in CD_3CN/CD_3OD (1/1) at room temperature. The original *N*-Me signal of **6a** observed at 2.32 ppm shifted to lower field, appearing at 2.88, upon addition of 1 equiv of $AlCl_3$ (Fig. 2). This result suggested that the nucleophilicity of the dialkylamino group would be decreased by the coordination to $AlCl_3$ in the course of fluorination of **6a**. However, considering that similar low-field shift was observed by addition of 1 equiv of H_2SO_4, the nucleophilicity would be also decreased by protonation with the Lewis-acid-assisted Brønsted acid derived from MeOH and $AlCl_3$ [15].

Table 3
Oxidative fluorination of various *N*,*N*-dialkyltryptamines **6b**–**k** with **5** in the presence of $AlCl_3$.



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**6b**	Et	Et	H	**7b**	90
2	**6c**	*i*-Pr	*i*-Pr	H	**7c**	98
3	**6d**	$-(CH_2)_4-$		H	**7d**	98
4	**6e**	$-(CH_2)_5-$		H	**7e**	99
5	**6f**	Me	Et	H	**7f**	92
6	**6g**	Me	*n*-Pr	H	**7g**	93
7	**6h**	Me	Bn	H	**7h**	90
8	**6i**	Me	Me	Me	**7i**	88
9	**6j**	Me	Me	Br	**7j**	95
10	**6k**	Me	Me	Cl	**7k**	96

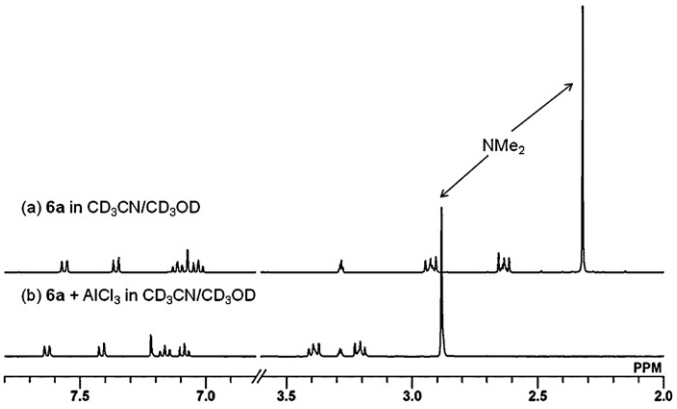
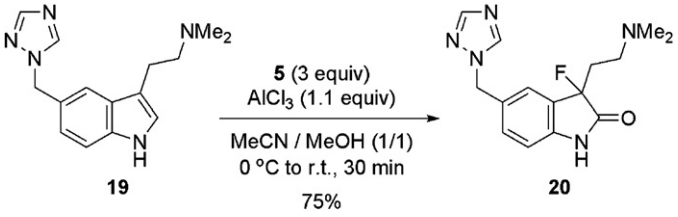


Fig. 2. ^{1}H NMR spectra of **6a** before and after addition of $AlCl_3$.



Scheme 3. Synthesis of 3-fluorooxindole **20** from rizatriptan (**19**).

Finally, we applied this new protocol to a tryptamine-based medicinal, rizatriptan (**19**), which is a potent agonist toward both serotonin 5-HT_{1B} and 5-HT_{1D} receptors, and is currently used for treatment for migraine headache [16]. Reaction of **19** with 3 equiv of **5** in the presence of 1.1 equiv of $AlCl_3$ in MeCN/MeOH (1/1) produced **20** in 75% yield (Scheme 3).

3. Conclusion

We have developed a facile procedure for the synthesis of 3-[2-(*N*,*N*-dialkylamino)ethyl]-3-fluorooxindoles **7** by direct oxidative fluorination of *N*,*N*-dialkyltryptamines **6** with Selectfluor^{TM} (**5**) in the presence of Lewis acid. The new procedure will enable the synthesis of 3-fluorooxindole derivatives having basic amine moieties in only one step from the corresponding tryptamines. Enantiomer separation and biological evaluation of the obtained 3-fluorooxindoles are currently underway.

4. Experimental

4.1. General

Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Spectroscopic measurements were carried out with the following instruments: IR spectra, JASCO FT/IR-460Plus; mass spectra (MS), JEOL JMS-GCmate II; high resolution mass spectra (HRMS), JEOL JMS-GCmate II; ^{1}H NMR spectra, JEOL ECX-400P (400 MHz) in $CDCl_3$ with TMS (=0.00 ppm) as an internal standard; ^{13}C NMR spectra, JEOL ECX-400P

(100 MHz) in $CDCl_3$ with $CDCl_3$ (=77.0 ppm) as an internal standard; ^{19}F NMR spectra, JEOL ECX-400P (376 MHz) in $CDCl_3$ with $CFCl_3$ (=0.00 ppm) as an internal standard. Column chromatography and thin layer chromatography were performed on Merck 9385 silica gel 60 (0.040–0.063 mm) and on Merck 5715, respectively.

4.2. General procedure for the synthesis of 3-fluorooxindole derivatives 7 and 20 by the fluorination of tryptamines 6 and 19 with Selectfluor™ (5) in the presence of $AlCl_3$: 3-[2-(N,N-dimethylamino)ethyl]-3-fluorooxindole (7a)

To a stirred MeCN/MeOH (1/1, 5 ml) solution of **6a** (50 mg, 0.27 mmol) were added $AlCl_3$ (39 mg, 0.29 mmol) and Selectfluor™ (**5**) (282 mg, 0.80 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. Concentration of the mixture gave a residue, which was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH/NH_4OH = 93/7/0.5) to give 3-fluorooxindole **7a** (57 mg, 96%) as a pale yellow oil: IR (neat) ν 2952 (NH), 1735 (C=O) cm^{-1}; ^1H NMR δ 2.14 (6H, s), 2.25–2.36 (3H, m), 2.48 (1H, m), 6.91 (1H, d, J = 7.8 Hz), 7.08 (1H, t, J = 7.8 Hz), 7.32 (1H, tt, J = 7.8, 1.8 Hz), 7.38 (1H, dd, J = 7.8, 1.8 Hz), 9.18 (1H, brs); ^{13}C NMR δ 32.7 (d, J = 27.8 Hz), 45.1, 53.0 (d, J = 7.7 Hz), 93.1 (d, J = 185.0 Hz), 110.6 (d, J = 1.9 Hz), 123.0 (d, J = 2.9 Hz), 124.9 (d, J = 1.9 Hz), 125.9 (d, J = 18.2 Hz), 131.2 (d, J = 3.8 Hz), 141.8 (d, J = 5.8 Hz), 174.9 (d, J = 21.1 Hz); ^{19}F NMR δ –155.74 (1F, dd, J = 13.0, 10.8 Hz); MS (EI) m/z: 222 (M^+), 202 (M^+–HF), 187 (M^+–HF–CH_3); HRMS (EI) calcd for $C_{12}H_{15}FN_2O$ (M^+): 222.1168; found 222.1147.

4.2.1. 3-[2-(N,N-Diethylamino)ethyl]-3-fluorooxindole (7b)

Yield: 90%; colorless oil; IR (neat) ν 3208 (NH), 1737 (C=O) cm^{-1}; ^1H NMR δ 0.84 (6H, t, J = 7.3 Hz), 2.22–2.37 (3H, m), 2.41–2.58 (5H, m), 6.89 (1H, d, J = 7.8 Hz), 7.08 (1H, t, J = 7.8 Hz), 7.32 (1H, tt, J = 7.8, 1.8 Hz), 7.38 (1H, dd, J = 7.8, 1.8 Hz), 8.30 (1H, brs); ^{13}C NMR δ 11.1, 31.5 (d, J = 26.8 Hz), 46.4, 46.6 (d, J = 8.6 Hz), 93.3 (d, J = 183.1 Hz), 110.5, 123.0 (d, J = 2.9 Hz), 125.0 (d, J = 1.9 Hz), 125.9 (d, J = 18.2 Hz), 131.2 (d, J = 2.9 Hz), 141.8 (d, J = 5.8 Hz), 174.5 (d, J = 21.1 Hz); ^{19}F NMR δ –153.70 (1F, brs); MS (EI) m/z: 250 (M^+), 235 (M^+–CH_3), 230 (M^+–HF), 201 (M^+–HF–C_2H_5); HRMS (EI) calcd for $C_{14}H_{19}FN_2O$ (M^+): 250.1481; found 250.1471.

4.2.2. 3-[2-(N,N-Diisopropylamino)ethyl]-3-fluorooxindole (7c)

Yield: 98%; pale yellow solid; mp 119–122 °C; IR (KBr) ν 3170 (NH), 1730 (C=O) cm^{-1}; ^1H NMR δ 0.84 (6H, d, J = 6.4 Hz), 0.89 (6H, d, J = 6.9 Hz), 2.26 (1H, m), 2.41–2.52 (3H, m), 2.96 (2H, sept, J = 6.4 Hz), 6.93 (1H, d, J = 7.8 Hz), 7.10 (1H, t, J = 7.8 Hz), 7.32 (1H, tt, J = 7.8, 1.8 Hz), 7.39 (1H, dd, J = 7.8, 1.8 Hz), 8.91 (1H, brs); ^{13}C NMR δ 19.8, 20.7, 35.6 (d, J = 25.9 Hz), 38.9 (d, J = 9.6 Hz), 48.1, 93.3 (d, J = 184.0 Hz), 110.8 (d, J = 1.9 Hz), 123.0 (d, J = 2.9 Hz), 124.9, 126.1 (d, J = 18.2 Hz), 131.1 (d, J = 3.8 Hz), 141.7 (d, J = 5.8 Hz), 175.2 (d, J = 21.1 Hz); ^{19}F NMR δ –153.65 (1F, brs); MS (EI) m/z: 278 (M^+), 263 (M^+–CH_3), 258 (M^+–HF), 215 (M^+–HF–C_3H_7); HRMS (EI) calcd for $C_{16}H_{23}FN_2O$ (M^+): 278.1794; found 278.1788.

4.2.3. 3-(2-Pyrrolidinoethyl)-3-fluorooxindole (7d)

Yield: 98%; pale yellow oil; IR (neat) ν 3210 (NH), 1738 (C=O) cm^{-1}; ^1H NMR δ 1.65–1.73 (4H, m), 2.31–2.42 (3H, m), 2.44–2.58 (5H, m), 6.91 (1H, d, J = 7.8 Hz), 7.07 (1H, t, J = 7.8 Hz), 7.31 (1H, tt, J = 7.8, 1.4 Hz), 7.38 (1H, dd, J = 7.8, 1.4 Hz), 9.21 (1H, brs); ^{13}C NMR δ 23.4, 34.0 (d, J = 27.8 Hz), 49.5 (d, J = 8.6 Hz), 53.8, 93.2 (d, J = 185.0 Hz), 110.6 (d, J = 1.9 Hz), 122.9 (d, J = 1.9 Hz), 124.9, 126.0 (d, J = 18.2 Hz), 131.1 (d, J = 2.9 Hz), 141.8 (d, J = 5.8 Hz), 175.1 (d, J = 21.1 Hz); ^{19}F NMR δ –155.65 (1F, dd, J = 11.7, 10.3 Hz); MS (EI) m/z: 248 (M^+), 228 (M^+–HF); HRMS (EI) calcd for $C_{14}H_{17}FN_2O$ (M^+): 248.1325; found 248.1316.

4.2.4. 3-(2-Piperidinoethyl)-3-fluorooxindole (7e)

Yield: 99%; pale yellow oil; IR (neat) ν 3063 (NH), 1733 (C=O) cm^{-1}; ^1H NMR δ 1.28–1.34 (2H, m), 1.40–1.46 (4H, m), 2.04–2.09 (2H, m), 2.21–2.35 (5H, m), 2.59 (1H, ddt, J = 20.8, 13.0, 4.7 Hz), 6.92 (1H, d, J = 7.8 Hz), 7.07 (1H, t, J = 7.8 Hz), 7.31 (1H, tt, J = 7.8, 1.4 Hz), 7.36 (1H, dd, J = 7.8, 1.4 Hz), 9.05 (1H, brs); ^{13}C NMR δ 24.1, 25.5, 31.9 (d, J = 26.8 Hz), 52.8 (d, J = 9.6 Hz), 54.3, 93.6 (d, J = 183.1 Hz), 110.5 (d, J = 1.9 Hz), 122.8 (d, J = 2.9 Hz), 124.9, 125.9 (d, J = 18.2 Hz), 131.1 (d, J = 2.9 Hz), 142.0 (d, J = 4.8 Hz), 175.1 (d, J = 21.1 Hz); ^{19}F NMR δ –154.37 (1F, brs); MS (EI) m/z: 262 (M^+), 242 (M^+–HF); HRMS (EI) calcd for $C_{15}H_{19}FN_2O$ (M^+): 262.1481; found 262.1466.

4.2.5. 3-[2-(N-Ethyl-N-methylamino)ethyl]-3-fluorooxindole (7f)

Yield: 92%; pale yellow oil; IR (neat) ν 3207 (NH), 1739 (C=O) cm^{-1}; ^1H NMR δ 0.87 (3H, t, J = 7.3 Hz), 2.11 (3H, s), 2.18–2.42 (5H, m), 2.53 (1H, m), 6.91 (1H, d, J = 7.8 Hz), 7.08 (1H, t, J = 7.8 Hz), 7.32 (1H, tt, J = 7.8, 1.4 Hz), 7.38 (1H, dd, J = 7.8, 1.4 Hz), 9.06 (1H, brs); ^{13}C NMR δ 11.7, 32.1 (d, J = 26.8 Hz), 41.1, 50.8 (d, J = 8.6 Hz), 51.2, 93.4 (d, J = 184.0 Hz), 110.7, 122.9 (d, J = 2.9 Hz), 125.0, 125.9 (d, J = 18.2 Hz), 131.2 (d, J = 2.9 Hz), 142.0 (d, J = 5.8 Hz), 175.1 (d, J = 21.1 Hz); ^{19}F NMR δ –154.82 (1F, t, J = 12.4 Hz); MS (EI) m/z: 236 (M^+), 221 (M^+–CH_3), 216 (M^+–HF), 187 (M^+–HF–C_2H_5); HRMS (EI) calcd for $C_{13}H_{17}FN_2O$ (M^+): 236.1325; found 236.1323.

4.2.6. 3-[2-(N-Methyl-N-propylamino)ethyl]-3-fluorooxindole (7g)

Yield: 93%; pale brown oil; IR (neat) ν 3208 (NH), 1739 (C=O) cm^{-1}; ^1H NMR δ 0.79 (3H, t, J = 7.3 Hz), 1.31 (2H, sex, J = 7.3 Hz), 2.10–2.57 (6H, m), 2.13 (3H, s), 6.91 (1H, d, J = 7.8 Hz), 7.07 (1H, t, J = 7.8 Hz), 7.31 (1H, tt, J = 7.8, 1.4 Hz), 7.37 (1H, dd, J = 7.8, 1.4 Hz), 9.25 (1H, brs); ^{13}C NMR δ 11.7, 19.9, 32.0 (d, J = 26.8 Hz), 41.5, 51.3 (d, J = 8.6 Hz), 59.6, 93.2 (d, J = 184.0 Hz), 110.6, 123.0 (d, J = 2.9 Hz), 124.9, 125.9 (d, J = 18.2 Hz), 131.2 (d, J = 3.8 Hz), 141.8 (d, J = 5.8 Hz), 174.8 (d, J = 21.1 Hz); ^{19}F NMR δ –155.05 (1F, brs); MS (EI) m/z: 250 (M^+), 230 (M^+–HF), 221 (M^+–C_2H_5), 201 (M^+–HF–C_2H_5), 187 (M^+–HF–C_3H_7); HRMS (EI) calcd for $C_{14}H_{19}FN_2O$ (M^+): 250.1481; found 250.1475.

4.2.7. 3-[2-(N-Benzyl-N-methylamino)ethyl]-3-fluorooxindole (7h)

Yield: 90%; colorless oil; IR (neat) ν 3418 (NH), 1733 (C=O) cm^{-1}; ^1H NMR δ 2.08 (3H, s), 2.32–2.63 (4H, m), 3.34 (1H, d, J = 13.3 Hz), 3.40 (1H, d, J = 13.3 Hz), 6.88 (1H, d, J = 7.8 Hz), 7.05 (1H, t, J = 7.8 Hz), 7.15–7.25 (5H, m), 7.29 (1H, tt, J = 7.8, 1.4 Hz), 7.34 (1H, dd, J = 7.8, 1.8 Hz), 8.83 (1H, brs); ^{13}C NMR δ 32.2 (d, J = 27.8 Hz), 41.5, 51.4 (d, J = 8.6 Hz), 62.3, 93.2 (d, J = 185.0 Hz), 110.6 (d, J = 1.9 Hz), 123.0 (d, J = 2.9 Hz), 125.0, 125.9 (d, J = 18.2 Hz), 126.9, 128.1, 128.9, 131.1 (d, J = 2.9 Hz), 138.3, 141.5 (d, J = 5.8 Hz), 174.7 (d, J = 21.1 Hz); ^{19}F NMR δ –154.37 (1F, brs); MS (EI) m/z: 298 (M^+), 283 (M^+–CH_3), 278 (M^+–HF), 207 (M^+–C_7H_7), 187 (M^+–HF–C_7H_7); HRMS (EI) calcd for $C_{18}H_{19}FN_2O$ (M^+): 298.1481; found 298.1481.

4.2.8. 3-[2-(N,N-Dimethylamino)ethyl]-3-fluoro-5-methyloxindole (7i)

Yield: 88%; pale brown oil; IR (neat) ν 2951 (NH), 1737 (C=O) cm^{-1}; ^1H NMR δ 2.15 (6H, s), 2.22–2.33 (3H, m), 2.33 (3H, s), 2.47 (1H, tt, J = 13.3, 5.1 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.11 (1H, d, J = 7.8 Hz), 7.19 (1H, s), 9.05 (1H, brs); ^{13}C NMR δ 21.0, 32.8 (d, J = 27.8 Hz), 45.1, 52.9 (d, J = 8.6 Hz), 93.3 (d, J = 185.0 Hz), 110.4, 125.5, 125.9 (d, J = 18.2 Hz), 131.5 (d, J = 2.9 Hz), 132.6 (d, J = 2.9 Hz), 139.2 (d, J = 5.8 Hz), 175.0 (d, J = 21.1 Hz); ^{19}F NMR δ –155.45 (1F, dd, J = 13.3, 12.6 Hz); MS (EI) m/z: 236 (M^+), 216 (M^+–HF), 201 (M^+–HF–CH_3); HRMS (EI) calcd for $C_{13}H_{17}FN_2O$ (M^+): 236.1325; found 236.1318.

4.2.9. 5-Bromo-3-[2-(N,N-dimethylamino)ethyl]-3-fluorooxindole (7j)

Yield: 95%; pale yellow oil; IR (neat) ν 2953 (NH), 1742 (C=O) cm^{-1}; ^1H NMR δ 2.13 (6H, s), 2.21–2.36 (3H, m), 2.48 (1H, m), 6.81 (1H, dd, J = 8.2, 1.8 Hz), 7.45 (1H, dt, J = 8.2, 1.8 Hz), 7.50 (1H, t, J = 1.8 Hz); ^{13}C NMR δ 32.6 (d, J = 26.8 Hz), 45.0, 52.9 (d, J = 7.7 Hz), 92.9 (d, J = 185.9 Hz), 112.2, 115.4 (d, J = 2.9 Hz), 127.8 (d, J = 18.2 Hz), 128.2, 134.0 (d, J = 2.9 Hz), 140.9 (d, J = 5.8 Hz), 174.4 (d, J = 21.1 Hz); ^{19}F NMR δ –155.81 (1F, dd, J = 13.5, 11.7 Hz); MS (EI) m/z: 302 (M^++2), 300 (M^+), 282 [(M^++2)–HF], 280 (M^+–HF), 267 [(M^++2)–HF–CH_3], 265 (M^+–HF–CH_3); HRMS (EI) calcd for $C_{12}H_{14}BrFN_2O$ (M^+): 300.0274; found 300.0273.

4.2.10. 5-Chloro-3-[2-(N,N-dimethylamino)ethyl]-3-fluorooxindole (7k)

Yield: 96%; pale yellow oil; IR (neat) ν 2949 (NH), 1740 (C=O) cm^{-1}; ^1H NMR δ 2.13 (6H, s), 2.21–2.35 (3H, m), 2.49 (1H, m), 6.85 (1H, dd, J = 8.2, 1.8 Hz), 7.30 (1H, dt, J = 8.2, 1.8 Hz), 7.36 (1H, t, J = 1.8 Hz), 9.29 (1H, brs); ^{13}C NMR δ 32.6 (d, J = 26.8 Hz), 45.0, 52.9 (d, J = 8.6 Hz), 93.0 (d, J = 185.9 Hz), 111.7, 125.4, 127.5 (d, J = 18.2 Hz), 128.3 (d, J = 2.9 Hz), 131.1 (d, J = 3.8 Hz), 140.4 (d, J = 5.8 Hz), 174.5 (d, J = 21.1 Hz); ^{19}F NMR δ –155.92 (1F, dd, J = 13.5, 10.3 Hz); MS (EI) m/z: 258 (M^++2), 256 (M^+), 238 [(M^++2)–HF], 236 (M^+–HF), 223 [(M^++2)–HF–CH_3], 221 (M^+–HF–CH_3); HRMS (EI) calcd for $C_{12}H_{14}ClFN_2O$ (M^+): 256.0779; found 256.0764.

4.2.11. 3-[2-(N,N-Dimethylamino)ethyl]-3-fluoro-5-[(1,2,4-triazol-1-yl)methyl]oxindole (20)

Yield: 75%; pale yellow oil; IR (neat) ν 3119 (NH), 1737 (C=O) cm^{-1}; ^1H NMR δ 2.08 (6H, s), 2.19–2.30 (3H, m), 2.48 (1H, m), 6.88 (1H, d, J = 7.8 Hz), 7.25 (1H, dt, J = 7.8, 1.8 Hz), 7.34 (1H, t, J = 1.8 Hz), 7.98 (1H, s), 8.10 (1H, s), 8.28 (1H, brs); ^{13}C NMR δ 32.6 (d, J = 26.8 Hz), 45.0, 53.0 (d, J = 7.7 Hz), 53.1, 92.7 (d, J = 185.9 Hz), 110.8, 125.0, 126.8 (d, J = 18.2 Hz), 129.4 (d, J = 2.9 Hz), 131.2 (d, J = 2.9 Hz), 142.1 (d, J = 5.8 Hz), 143.0, 152.3, 174.2 (d, J = 21.1 Hz); ^{19}F NMR δ –155.21 (1F, t, J = 12.4 Hz); MS (EI) m/z: 303 (M^+), 283 (M^+–HF), 268 (M^+–HF–CH_3); HRMS (EI) calcd for $C_{15}H_{18}FN_5O$ (M^+): 303.1495; found 303.1491.

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