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SYNTHETIC STUDIES ON THE FLUORINATED ANALOGS FOR THE PUTATIVE OXINDOLE-TYPE METABOLITES OF 5-HALOTRYPTAMINES

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Abstract – The suitably protected precursors for direct fluorination, N^b-Boc di-protected 5-fluorotryptamine (**13**), N^b-acetyl-N^b-Boc protected 5-halotryptamines (**15a–c**), were treated with Selectfluor™ in MeCN/water in the presence of $NaHCO_3$ to give the corresponding 3-fluorooxindoles **14** and **16a–c** in good yields. Removal of the protecting groups of **14** and **16a–c** produced (3,5-difluorooxindol-3-yl)ethylamine (**8**) and *N*-acetyl-(3-fluoro-5-halooxindol-3-yl)ethylamines (**9a–c**) in excellent yields, respectively. These compounds are potentially non-epimerizable analogs for the putative metabolites of 5-fluorotryptamine (**6**) and N^b-acetyl-5-halotryptamines (**7a–c**).

INTRODUCTION

The 3-fluorooxindole derivatives **1** have received much attention as a synthetic target for development of novel medicinal agents since BMS-204532 (Maxipost, **2**)[1] was discovered as an effective calcium-dependent potassium channel opener. Fluorinated biomolecules and medicinals can be recognized by enzymes and receptors as well as the nonfluorinated molecules because the replacement of a hydrogen with a fluorine brings about the minimal steric alterations of the molecules.[2] It should be noted that the fluorinated derivatives can be non-epimerizable analogs when the labile proton at the stereogenic center is replaced by a fluorine. Indeed we previously reported the synthesis of 3'-fluorothalidomide as a non-epimerizable analog of thalidomide.[3] Since the stereoelectronic properties of fluorine are also similar to those of hydroxy group, isosteric analogs of prototype molecules can be

† Dedicated to the memory of Dr. John Daly who made many lasting contributions to the wide area of chemistry.

obtained by substituting the hydroxy group with fluorine.[2] Moreover, such substitution will prevent further metabolization which would be subjected otherwise.[2] Thus 3-fluorooxindole derivatives **1** can be employed as mimics for both oxindoles **3** and 3-hydroxyoxindoles **4**, which are often found in natural products and as metabolites of some indole-containing biomolecules. As a part of our studies on the design, synthesis, and biological evaluation of chiral fluorinated bioorganic molecules,[3,4] we synthesized 3-(3-fluorooxindol-3-yl)-L-alanine (**5**).[5] Here we report the synthesis of (3,5-difluorooxindol-3-yl)ethylamine (**8**) and *N*-acetyl-(3,5-difluorooxindol-3-yl)ethylamine (**9a–c**) as potential analogs for the putative oxindole-type metabolites of 5-fluorotryptamine (**6**) and N^b-acetyl-5-halotryptamines (**7a–c**), which have agonistic activities toward serotonin 5-HT_3 receptor and melatonin MT_1 and MT_2 receptors, respectively.[6] It should be noted that oxindoles **3** may epimerize under physiological conditions.[7] Therefore, compounds **8** and **9a–c** can be the non-epimerizable analogs, which are effective tools for investigating the relationship between the biological behavior and the stereochemistry of the metabolites.

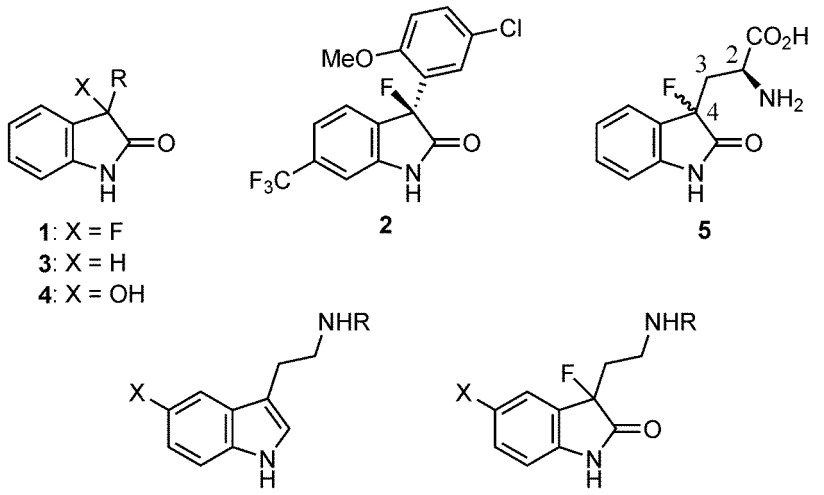


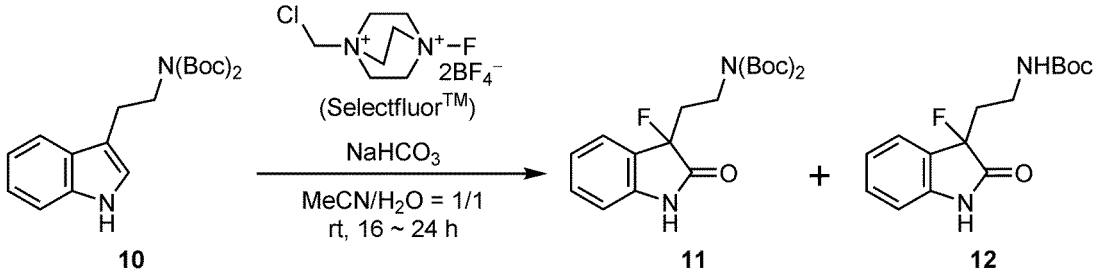
Figure 1. Structures of compounds **1**–**9**.

RESULTS AND DISCUSSION

We previously reported the direct fluorination using Selectfluor™ for preparation of the tryptophan isostere **5**. In this procedure we found that use of the precursor with di-protected α-amino moiety is essential for successful fluorination. For synthesis of the fluorooxindole-containing ethylamine **8**, we employed N^b,N^b-di-(*tert*-butoxycarbonyl)tryptamine (**10**) as a model compound in order to examine the optimum reaction conditions for the fluorination. The suitably protected precursor **10**, prepared from

tryptamine according to the literature,[5,8] was treated with 3 equiv of Selectfluor™ in MeCN/water (1/1) at rt for 16–24 h[9] to produce the corresponding 3-fluorooxindole **11**. However, the yield of **11** was quite low owing to the formation of mono-deprotected product **12** (Table 1, entry 1). This was presumably due to the rather acidic conditions employed for the reaction. We then attempted the fluorination in the presence of a base.[10] Fluorination of **10** in the presence of 3 equiv of $NaHCO_3$ gave 3-fluorooxindole **11** in 58% yield without formation of **12** (entry 2). Use of increased or decreased amount of $NaHCO_3$ did not give any better results (entries 3–6). Excess amount of Selectfluor™ led to increase of the yield of **11** (entry 7). The best result was obtained when the fluorination was carried out using 4 equiv of Selectfluor™ and 4 equiv of $NaHCO_3$ to afford **11** in 73% yield (entry 7).

Table 1. Fluorination of N^b,N^b-di-(*tert*-butoxycarbonyl)tryptamine (**10**)

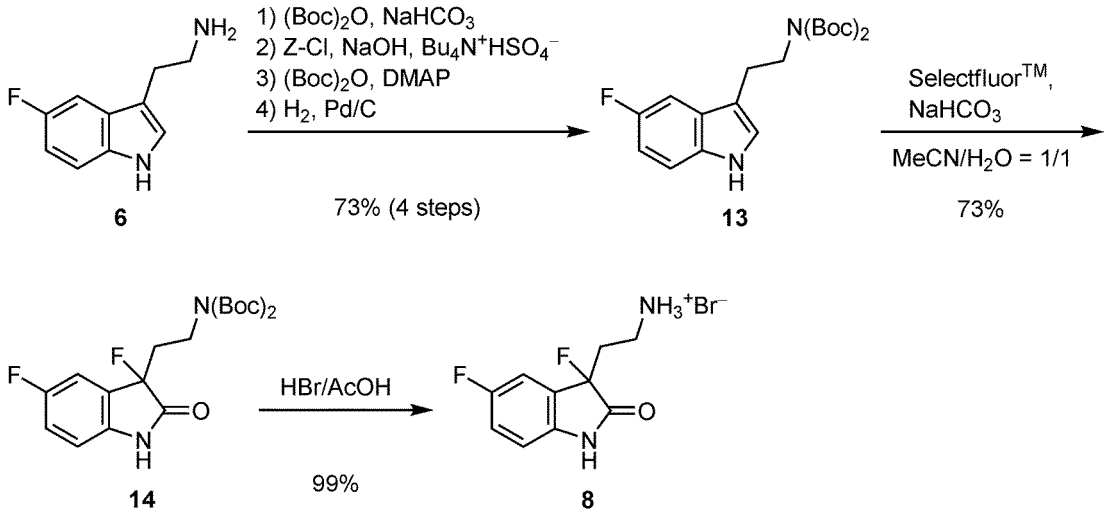


10 **11** **12**

Entry	Selectfluor™ (equiv)	$NaHCO_3$ (equiv)	Yield of **11** (%)[a]	Yield of **12** (%)[a]
1	3	0	20	51
2	3	3	58	0
3	3	0.5	43	29
4	3	1.5	56	11
5	3	4.5	47	0
6	3	6	38	0
7	4	4	73	0

[a]Isolated yield.

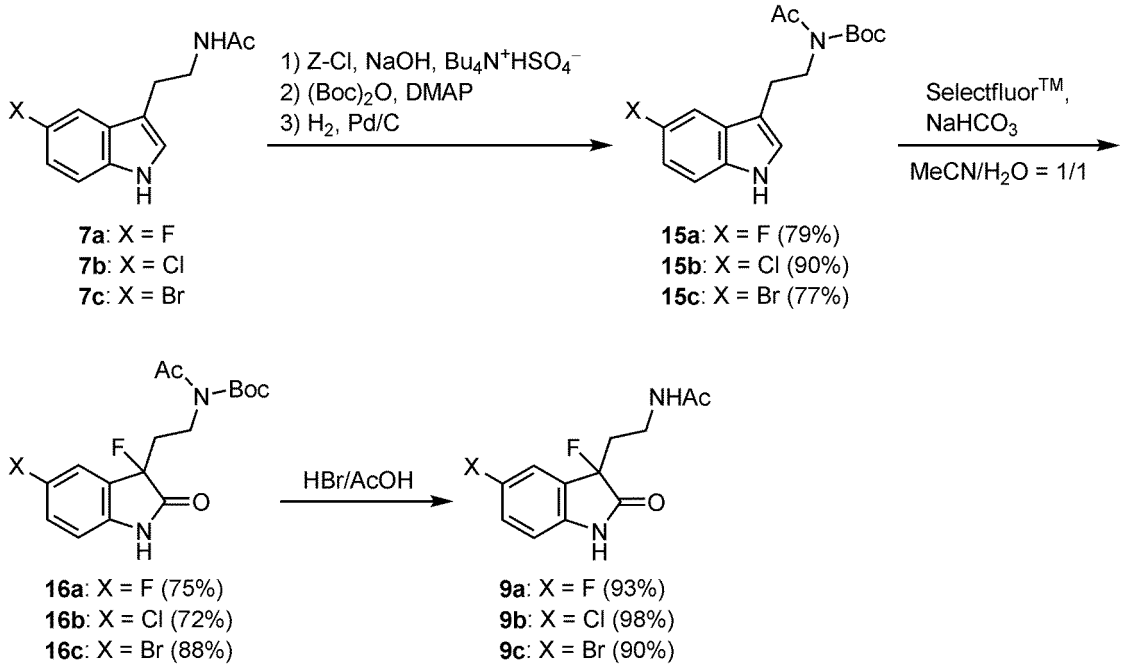
The 5-fluoro analog **13** was prepared from **6** according to the literature.[5,8] We employed above reaction conditions for direct fluorination of **13** and the corresponding 3-fluorooxindole **14** was successfully obtained in 73% yield (Scheme 1).[11] Treatment of **14** with HBr/AcOH smoothly produced the deprotected ethylamine **8** as HBr salt in excellent yield.[12]



Scheme 1. Synthesis of (3,5-difluorooxindol-3-yl)ethylamine (**8**)

We next attempted synthesis of N^b-acetyl protected fluorooxindole-containing ethylamine **9a–c**. Although direct fluorination of **7b** with Selectfluor™ gave **9b**, the yield was unsatisfactory owing to concomitant formation of side products.[13] We then focused on the N^b-di-protected structure. The precursors **15a–c**, prepared in a similar manner to the synthesis of **13**, were treated with Selectfluor™ in the presence of $NaHCO_3$ to give the corresponding 3-fluorooxindoles **16a–c** in good yields (Scheme 2). Removal of the Boc groups of **16a–c** with HBr/AcOH successfully produced the N^b-acetyl protected fluorooxindole-containing ethylamine **9a–c** in excellent yields.[14]

Preparation of the individual enantiomers of **8** and **9a–c** is in progress for investigation of the relationship between the biological behavior and the stereochemistry.



Scheme 2. Synthesis of *N*-acetyl-(3-fluoro-5-halooxindol-3-yl)ethylamines (**9a–c**)

In summary, we achieved the synthesis of fluorooxindole-containing ethylamine **8** as a metabolic analog of **6** by fluorination of the N^b-di-protected tryptamine derivative **13** with Selectfluor™ in the presence of $NaHCO_3$ followed by deprotection. Similarly, N^b-acetyl protected fluorooxindole-containing ethylamine **9a–c** were successfully synthesized as metabolic analogs of **7a–c**.

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11. General procedure for the fluorination of the protected tryptamines: Selectfluor™ (283.4 mg, 0.800 mmol) was added to a solution of N^b,N^b-di-(*tert*-butoxycarbonyl)-5-fluorotryptamine (**13**) (75.7 mg,

0.200 mmol) in a mixture of MeCN and water (1:1, 4 mL) at rt. After stirring for 20 h, the mixture was concentrated and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; hexane/EtOAc = 3/1) to give the corresponding 3-fluorooxindole **14** (60.5 mg, 0.147 mmol, 73%) as a colorless glass, together with the corresponding oxindole derivative (4.1 mg, 0.010 mmol, 5%) as a colorless oil: IR (KBr) ν 3430, 3315, 2979, 2933, 1759, 1734, 1701, 1676, 1631, 1487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (18H, s), 2.35–2.50 (2H, m), 3.71–3.78 (2H, m), 6.88 (1H, ddd, *J* = 8.5, 4.1, 0.9 Hz), 7.05 (1H, tt, *J* = 9.2, 2.3 Hz), 7.16 (1H, dt, *J* = 7.3, 2.3 Hz), 8.62 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ –119.46 (1F, dddd, *J* = 9.2, 7.3, 4.1, 1.8 Hz), –159.14 (1F, t, *J* = 16.2 Hz); MS (EI) *m/z*: 412 (M^+), 356 (M^+–C_4H_8), 300 (M^+–C_8H_{16}); HRMS (EI) calcd for $C_{20}H_{26}F_2N_2O_5$ (M^+): 412.1810; found 412.1794.

12. Synthesis of **8**: To a solution of **14** (23.7 mg, 0.058 mmol) in AcOH (0.5 mL) was added 25% HBr/AcOH (0.5 mL) at 0 °C. After stirring at rt for 10 min, the mixture was concentrated in vacuo to give HBr salt of **8** (16.7 mg, 0.057 mmol, 99%) as a pale yellow solid: mp 136 °C (decomp.); IR (KBr) ν 3700–3100 (br), 3215, 3033, 1739, 1634, 1490 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.31 (1H, dddd, *J* = 27.0, 14.9, 7.8, 6.9 Hz), 2.58 (1H, dddd, *J* = 14.9, 13.5, 7.8, 6.9 Hz), 3.29 (2H, br m), 6.94 (1H, ddd, *J* = 8.5, 4.1, 1.4 Hz), 7.17 (1H, dddd, *J* = 9.2, 8.7, 2.7, 1.8 Hz), 7.31 (1H, dt, *J* = 7.8, 2.7 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –119.67 (1F, dddd, *J* = 9.2, 7.8, 4.1, 1.8 Hz), –160.00 (1F, m); MS (FAB^+) *m/z*: 213 (M^+–Br); HRMS (FAB^+) calcd for $C_{10}H_{11}F_2N_2O$ (M^+–Br): 213.0840; found 213.0854, (FAB^-) calcd for $C_{10}H_{10}BrF_2N_2O$ (M^+–H): 290.9945; found 290.9942.
13. The N^b-acetyl moiety will be subjected to electrophilic fluorination thus giving unidentified oxidized products.
14. General procedure for the acid deprotection of the Boc group of **16a**–**c**: To a solution of **16a** (19.9 mg, 0.056 mmol) in AcOH (1 mL) was added 25% HBr/AcOH (1 mL) at 0 °C. After stirring for 10 min at rt, the mixture was poured into saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; EtOAc/MeOH = 40/1) to give **9a** (13.2 mg, 0.052 mmol, 93%) as a colorless solid: mp 170–172 °C; IR (KBr) ν 3441, 3353, 1732, 1722, 1653, 1636, 1554, 1489 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.82 (3H, s), 2.34 (2H, dt, *J* = 15.1, 7.3 Hz), 3.20 (1H, dt, *J* = 13.7, 7.3 Hz), 3.25 (1H, dt, *J* = 13.7, 7.3 Hz), 6.90 (1H, dd, *J* = 7.8, 3.7 Hz), 7.11 (1H, tt, *J* = 8.7, 1.8 Hz), 7.27 (1H, dt, *J* = 7.8, 1.8 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –120.28 (1F, m), –155.90 (1F, t, *J* = 15.3 Hz); MS (EI) *m/z*: 254 (M^+), 192 (M^+–F–CH_3CO); HRMS (EI) calcd for $C_{12}H_{12}F_2N_2O_2$ (M^+): 254.0867; found 254.0869.