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Radiosynthesis of ^{18}F-labeled *N*-desmethyl-loperamide analogues for prospective molecular imaging radiotracers

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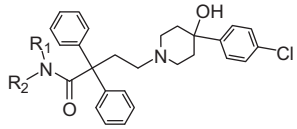
ABSTRACT

A simple procedure for preparing fluoroethyl-desmethyl-loperamide **4** and its analogue **5** was developed. Standard compound **4** was synthesized in useful yields for radiolabeling analysis. [*N*-Ethyl-18F]*N*-desmethyl-loperamide, **3,** was rapidly and efficiently labeled with no-carrier added fluorine-18 ($t_{1/2}$ = 109.7 min) by treatment of readily prepared [^{18}F]1-bromo-2-fluoro ethane with a *N*-desmethyl-loperamide precursor at a consistent 7% radiochemical yield. This procedure was also adapted to the radiosynthesis of **3** by [^{18}F]ethylene tosylate, but at a lower 3% radiochemical yield.

Introduction

Progress in the synthesis of new fluorinated compounds to act as drugs and ^{18}F-labeled analogues as potential imaging agents has grown dramatically.[1,2] Many drugs such as antibiotics, sedatives, antidepressants, and anti-tumor agents, are fluorinated compounds.[3–5] Radiosynthesis methods to introduce fluorine-18 ($t_{1/2}$ = 109.7 min) into organic molecules have become increasingly important for the development of radiotracers for position emission tomography (PET),[6–8] a sensitive and powerful technique that is valuable for both clinical research[9,10] and drug development.[11,12]

Permeability-glycoprotein (P-gp) functions as a drug efflux pump at the blood–brain barrier and at other tissues, including some tumors.[13,14] Radiotracers for imaging P-gp function in vivo could be valuable to assess the role of P-gp in neuropsychiatric disorders and in multi-drug resistance during cancer chemotherapy.[15] Loperamide **1** (Fig. 1) is a potent μ-receptor agonist that acts on the gastrointestinal tract;[16] this molecule is a safe antidiarrheal drug with no undesirable central nervous system effects because it is excluded from the brain by the efflux transporter-glycoprotein (P-gp).[17] Loperamide has been shown to be an avid substrate for P-gp,[18] and its radiolabeled [^{11}C]loperamide has been proven to be a promising radiotracer to study the function of P-gp at the blood–brain barrier.[19] In addition, its primary metabolite, [*N*-methyl-11C]*N*-desmethyl-loperamide **2**, has also been evaluated as a radiotracer for imaging P-gp function[20] and showed a greater promise because of its more favorable metabolic profile.[21] In this Letter, we aimed to synthesize new fluoro derivatives of this metabolite, such as **4** and **5**. We also reported the radiosynthesis of ^{18}F-labeled analogue of *N*-desmethyl-loperamide **3**. We considered that an ^{18}F-labeled analog of [^{11}C]dLop, **3,** might also behave as a prospective radiotracer for imaging P-gp function and potentially offer the advantage of greater availability for a wider range of applications.



Loperamide,**1**, R^1 = Me, R^2 =Me
[^{11}C]dLop, **2**, R^1 = H, R^2 =$^{11}CH_3$
[^{18}F]FEt-dLop, **3**,R^1 = H, R^2 = $^{18}FCH_2CH_2$
FEt-dLop,**4** R^1 = H, R^2 = FCH_2CH_2
FPr-dLop,**5** R^1 = H, R^2 = $FCH_2CH_2CH_2$

Figure 1. The structure of loperamide and its analogs.

Result and discussion

Synthesis of compounds 4 and 5

To establish the reaction conditions for the preparation of **3**, we first tried a simple method to prepare the standard compounds **4** and **5** (Scheme 1). The intermediate compound **b** was prepared

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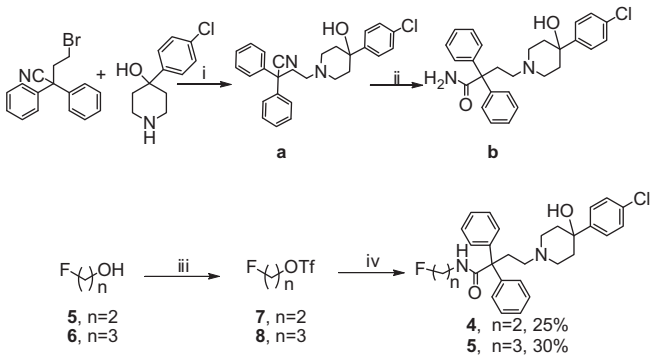
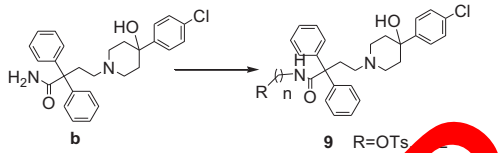


Scheme 1. Synthesis of standard compounds **4** and **5**. Reagents and conditions: (i) DIPEA, CH_3CN, 80 °C, 31 h, 60%; (ii) KOH, ^{t}BuOH, 3 d, reflux, 87%; (iii) $(CF_3SO_2)_2O$, Et_3N CH_2Cl_2, rt, 1 h; (iv) **b**, NaH, DMF, 80 °C, 24 h.

from commercially available 4-(4-chlorophenyl)-4-hydroxyl piperidine and 4-bromo-2, 2-diphenylbutane nitrile as described previously.[20] Compound **7** was prepared without purification by slowly adding triflic anhydride (10 mmol) to a solution of 2-fluoroethanol (10 mmol) and Et_3N (10 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 1 h at room temperature, concentrated, and transferred to a mixture of the amide **b** (0.36 mmol) and NaH (0.39 mmol) in DMF (5 mL). This mixture was then stirred for 12 h at 80 °C. Chromatography (silica gel; hexane/EtOAc, 1:3 v:v; then EtOAc) of the crude mixture, followed by HPLC on a Luna C18 column (250 × 10 mm) eluted at 8 mL/min with 0.025% aq NH_4OH (A)-MeCN (B), with B increased from 30% to 100% over 30 min, gave **4** (t_R = 16.8 min) at a 25% yield with 99% purity. Other attempts to achieve the alkylation of amide **b**, either with 1-bromo-2-fluoroethane, fluoroethyl tosylate, or with 1-fluoro-2-iodoethane, achieved lower yields. The synthesis of compound **5** was analogous to that of compound **4** through the activation of a hydroxyl group on 3-fluoropropan-1-ol with triflic anhydride, followed by coupling with the amide precursor **b** to obtain **5** at a 30% yield with 99% purity. The successful synthesis of **4** and **5** confirmed the susceptibility of amide alkylation of *N*-desmethyl-loperamide. Although **4** was only synthesized at a 25% yield, the amount was adequate to serve as a chromatographic reference material.

Table 1
Synthesis of R$(CH_2)_n$-*N*-desmethyl-loperamide from the amide **b**



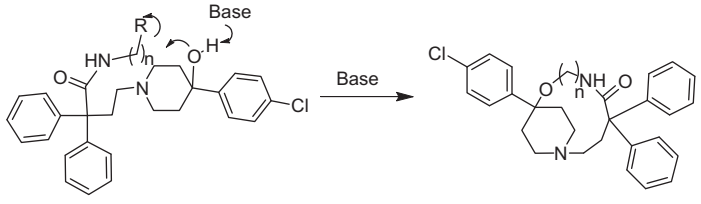
Reagents	Reaction conditions	Product	Yield
TsO–(CH2)2–OTs	NaH, DMF, MW, 110 °C, 15 min	**9**	–
Br–(CH2)2–OTs	NaH, DMF, MW, 110 °C, 15 min	**10**	–
Br–(CH2)2–OTs	NaH, DMF, 80 °C, 12 h	**10**	–
Br–(CH2)2–Br	NaH, DMF, 80 °C, 12 h	**10**	–
Br–(CH2)2–Br	NaH, DMSO, 80 °C, 24 h	**10**	–
Br–(CH2)2–Br	KOH, DMF, 80 °C, 12 h	**10**	–
Br–(CH2)3–Br	NaH, DMF, 80 °C, 12 h	**11**	–
Br–(CH2)2–OTf	K_2CO_3, ^{t}BuOH, 80 °C, 12 h	**11**	–
Br–(CH2)3–OTf	NaH, DMF, 80 °C, 24 h	**11**	–

Synthesis of radiolabeling precursors

An aliphatic nucleophilic substitution reaction with [^{18}F]fluoride ions can be highly efficient if the leaving groups are sulfonates (tosylate, mesylate, or triflate, etc.) or other halides (Cl, Br, or I) and the reaction is performed in a polar aprotic solvent, such as DMF, THF, DMSO, CH_3CN, etc.[12] The aliphatic bromide and tosylate precursors used for the radiolabeling of [^{18}F]**4** and [^{18}F]**5** were designed and tried via a number of reaction conditions, as shown in Table 1. The desired precursors **9, 10,** and **11** were not successfully obtained by a reaction of amide **b** with ethylene ditosylate, 1, 2-dibromoethane, 1-bromoethyl tosylate, or 1-bromopropyl triflate under various reaction conditions (Table 1). The unexpected cyclic byproducts **12** and **13** (Scheme 2) were isolated, and their structures were determined using ^{1}H NMR and HRMS. The failure to prepare the desired precursors probably due to the affection of the hydroxyl group on **b**. This group is also a strong nucleophile under basic conditions and is able to activate product decomposition through cyclization (Scheme 2), as the byproducts **12** and **13** have been detected by MS (Fig. 2) at the mass of the proposed cyclic. Because this approach to prepare the aliphatic bromide and tosylate precursors for aliphatic nucleophilic substitution with [^{18}F]fluoride ions was not feasible, alternate strategies were adopted to achieve radiosynthesis through the use of other conditions and labeling agents, as shown in Scheme 3.

Radiosynthesis of [^{18}F]FEt-dLop

A cyclotron-produced [^{18}F]fluoride ion solution (100–120 mCi) was mixed with kryptofix 2.2.2 (5 mg) and K_2CO_3 (0.5 mg) in MeCN–H_2O (95:5 v:v; 0.1 mL) and then dried by two addition–evaporation cycles of MeCN (2 mL). 2-Bromoethyl tosylate (30 μL) in *t*-butanol plus 1,2-dichlorobenzene (1 mL; 1:9 v:v) was



Scheme 2. Hypothesized decomposition of R$(CH_2)_n$-*N*-desmethyl-loperamide by cyclization.