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Synthesis of ^{14}C-Labelled (S)-(+)-2-[4-(p-Fluorobenzoyl)-1-piperidyl]-1-naphthylethanol Hydrochloride

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SUMMARY

^{14}C-labelled (S)-(+)-2-[4-(p-fluorobenzoyl)-1-piperidyl]-1-naphthylethanol hydrochloride (5), an anti-ischemic drug, was synthesized for studying the pharmacokinetic profiles of the compound in four steps using 2-[carbonyl-^{14}C]acetonaphthone (1) as a labelled starting material.

Key words: Anti-ischemic drug, Ischemia-induced neuronal cell damage, 2-[4-(p-Fluorobenzoyl)-piperidin-1-yl]-2'-acetonaphthone, BINAL-H, (S)-(+)-2-[4-(p-Fluorobenzoly)-1-piperidyl]-1-naphthyl-[1-^{14}C]ethanol

INTRODUCTION

In the previous paper, we reported the sythesis of ^{14}C-labelled 2-[4-(p-fluorobenzoyl)-piperidin-1-yl]-2'-acetonaphthone hydrochloride (E 2001)$^{1)}$, an anti-ischemic drug$^{2)}$. We also found, in the subsequent studies, that

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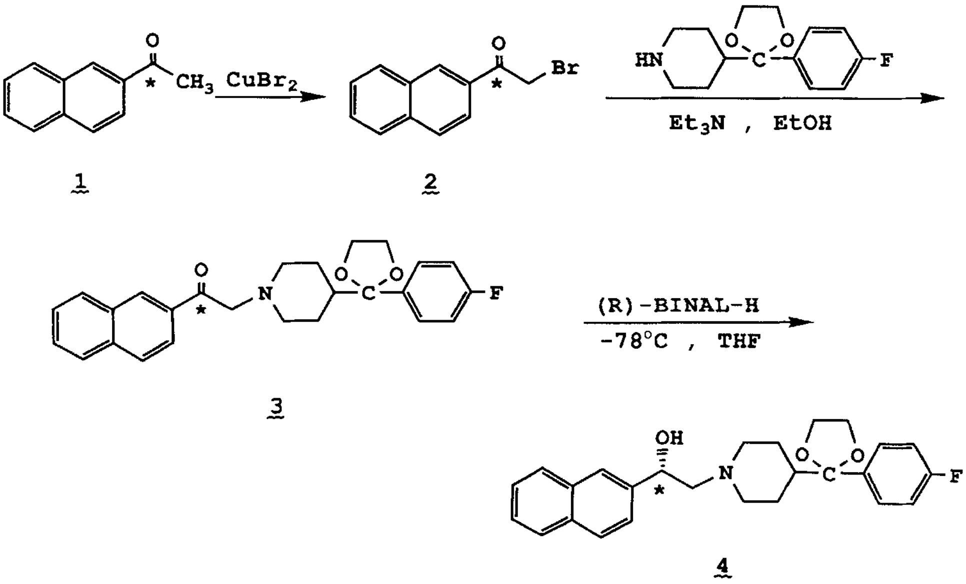
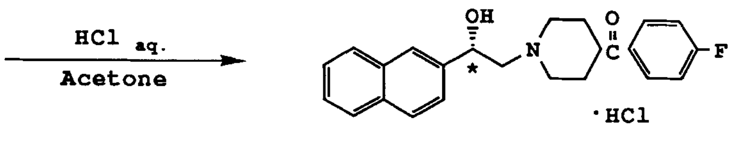
(S)-(+)-2-[4-(p-fluorobenzoyl)-1-piperidyl]-1-naphthylethanol hydrochloride (5) prevented the ischemia-induced neuronal cell damage3).

This paper describes the synthesis of ^{14}C-labelled (S)-(+)-2-[4-(p-fluorobenzoyl)-1-piperidyl]-1-naphthylethanol hydrochloride for the study of its pharmacokinetics. ^{14}C-labelled-(5) was prepared from 2-[carbonyl-^{14}C]-acetonaphthone (1) in four steps (Scheme 1). 2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (2) was prepared, by bromination with copper (II) bromide, from 2-[carbonyl-^{14}C]-acetonaphthone (1)4). The labelled compound (2) was reacted with 4-[2-(p-fluorophenyl)-1-dioxolan-2-yl]piperidine in the presence of triethylamine and potassium iodide to afford 2-{4-[2-(p-fluorophenyl)-1,3-dioxolan-2-yl]-1-piperidyl}-2'-[carbonyl-^{14}C]acetonaphthone (3). Since the labelled compound (3) was extremely unstable in solution, it was precipitated as its hydrochloride immediately after purification by column chromatography.





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Scheme 1. Synthesis of (S)-(+)-2-[4-(p-Fluorobenzoyl)-1-piperidyl]-1-naphthyl-[1-^{14}C]ethanol hydrochloride (5)

2-{4-[2-(p-Fluorophenyl)-1,3-dioxolan-2yl]-1-piperidyl}-2'-[carbonyl-^{14}C]acetonaphthone hydrochloride (3) was obtained in 58 % yield from 1. In order to reduce the compound (3) enantioselectively, the compound (3) was treated with aqueous $NaHCO_3$, followed by reaction with (R)-BINAL-H in dry THF at -78°C according to the method of R. Noyori et al$^{5)}$.

In the preliminary experiments using unlabelled compoud (3), this procedure gave a desired product having a optical purity of 96.3 % e.e. which was analyzed by HPLC using "Chiral Cel OD" column$^{3)}$. But in the case of labelled compound (3), the optical purity was about 60 % e.e.. Thus, the labelled compound (4) was further purified by HPLC on a preparative "Chiral Cel OD" column. (S)-(+)-2-{4-[2-(p-Fluorophenyl)-1,3-dioxolan-2-yl]-1-piperidyl}-1-naphthyl-[1-^{14}C]ethanol (4) was obtained in 63.1 % yield and had an optical purity of 97.6 % e.e.. Deprotection of labelled-(4) in aqueous HCl and acetone gave (S)-(+)-2-[4-(p-fluorobenzoyl)-1-piperidyl]-1-naphthyl-[1-^{14}C]ethanol hydrochloride (5) in 73.4 % yield. The structure of labelled-(5) was confirmed by comparison (TLC) with unlabelled authentic specimen of 5. The labelled compound (5) had a specific activity of 132 μCi per mg (4.88 MBq per mg), a radiochemical purity of >99 %, and an optical purity of 100 % e.e. which was analyzed by HPLC using "Chiral Cel OJ" column.

EXPERIMENTAL

Measurements of radioactivity were carried out using an Aloka LSC-9000 type Liquid Scintillation Spectrometer.
Thin-layer radio chromatography was performed using a Berthold LB-2842 Automatic TLC Linear Analyzer.
Thin-layer chromatography was developed using Kieselgel 60 F_{254} Plate (Merck). High-performance liquid chromatography analyses were carried out on a Waters 510 pump with a JASCO 875-UV detector using a Daicel "Chiral Cel OD" column.

2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (2)

The labelled starting material (2) was prepared from 2-[carbonyl-^{14}C]acetonaphthone using the method of King and Ostrum[4].

2-{4-[2-(p-Fluorophenyl)-1,3-dioxolan-2-yl]-1-piperidyl}-2'-[carbonyl-^{14}C]acetonaphthone hydrochloride (3)

2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (2) [1.13 g; 4.54 mM, 258 mCi (9.55 GBq)], 4-[2-(p-Fluorophenyl)-1,3-dioxolan-2-yl]piperidine (1.33 g; 4.6 mM), triethylamine (1.37 g; 13.6 mM) and potassium iodide (2 mg) were added to ethanol and the mixture was refluxed for 30 min.
The solvent was evaporated and the residue was dissolved in dichloromethane (60 ml). The organic layer was washed with water and dried over magnesium sulfate. After the removal of the solvent, the residue was purified by silica gel column choromatography (toluene/ethyl acetate). Immediately, after the chromatography, hydrogen chloride-ethanol was added to the

pure fractions. Concentration gave a gum product, which was reprecipitated from acetone. The precipitate was collected to give the ^{14}C-labelled-(**3**) crystals [1.20 g; 2.63 mM, 150 mCi (5.55 GBq), 58 % yield].

(S)-(+)-2-{4-[2-(p-Fluorophenyl)-1,3-dioxolan-2-yl]-1-piperidyl}-1-naphthyl-[1-^{14}C]ethanol (**4**)

Asymmetric reduction was conducted under argon atmosphere in a flame-dried flask equipped with a rubber septum. (R)-BINAL-H reagent was prepared according to the method of R. Noyori5) using 1 M lithium aluminium hydride in THF (Aldrich), ethanol distilled from magnesium-iodine and (R)-1,1-Bi-2-naphthol (Aldrich). Tetrahydrofuran was distilled from sodium benzophenone ketyl.

Dichloromethane (50 ml) was added to the ^{14}C-labelled-(**3**) HCl [1.20 g; 2.63 mM, 150 mCi (5.55 GBq)] and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo.

After tetrahydrofuran (12 ml) was added to the resulting foam, the solution was cooled down to -78°C and which was added to the (R)-BINAL-H reagent (8 mM) at -78°C by double ended needle. The resulting mixture was stirred for an additional 16 hr at the same temperature and the reaction was quenched by addition of methanol (6 ml) at -78°C. The mixture was stirred with ether (30 ml) and water (1.5 ml) for 30 min at room temperature and poured into ether (300 ml). The resulting suspension was filtered through Celite. The filtrate was evaporated, dissolved in benzene (80 ml), and washed with 3 N NaOH solution

(40 ml) to remove binaphthol. The benzene layer was dried over, and evaporated. The resulting oil was purified by silica gel column chromatography (MeOH : CH_2Cl_2, 1:10) and HPLC on silica gel (Hexane : AcOEt : Et_3N, 25:25:1). Optical purity of the resulting product was analyzed by HPLC on "Chiral Cel OD" column (iso-octane : iso-propanol : Et_3N, 500:500:2) and it was found that about 80 % of the product was the (+)-^{14}C-labelled-(4) and about 20 % was another enantiomer. Further purification of the product by HPLC on a preparative "Chiral Cel OD" column gave the ^{14}C-labelled-(4) as white crystals [705 mg; 1.66 mM, 95 mCi (3.52 GBq), 63.1 % yield, optical purity, 97.6 %e.e.].

(S)-(+)-2-[4-(p-Fluorobezoyl)-1-piperidyl]-1-naphthyl-[1-^{14}C]-ethanol Hydrochloride (5)

(S)-(+)-2-{4-[2-(p-Fluorobenzoyl)-1,3-dioxolan-2-yl]-1-piperidyl}-1-naphtyl-[1-^{14}C]ethanol (4) [593.7 mg; 1.4 mM, 80 mCi (2.96 GBq)] and 3 N aqueous hydrogen chloride solution were added to acetone (30 ml), and the mixture was refluxed for 5 hr. The solvent was evaporated in vacuo, and ethanol was added to the residue. The resulting precipitate was collected and purified by recrystallization from hot ethanol to give the ^{14}C-labelled-(5) as colorless needles [427 mg; 56.7 mCi (2.1 GBq), 73.4 % yield, specific activity, 132 μCi/mg (4.9 MBq/mg), radiochemical purity, >99.0 %, optical purity, 100 %e.e. (HPLC-"Chiral Cel OJ", Hexane : iso-propanol : Et_3N, 600:400:1)]. Identification of (5) was confirmed by comparison of its RF-values with those of an unlabelled authentic sample on TLC developed by three different solvent systems. RF-values of the compound (5) were 0.68 in chloroform/methanol (10:1, v/v);

(Figure 1), 0.62 in chloroform/methanol/diethylamine (100:10:1) and 0.78 in benzene/methanol/acetic acid (50:50:1).

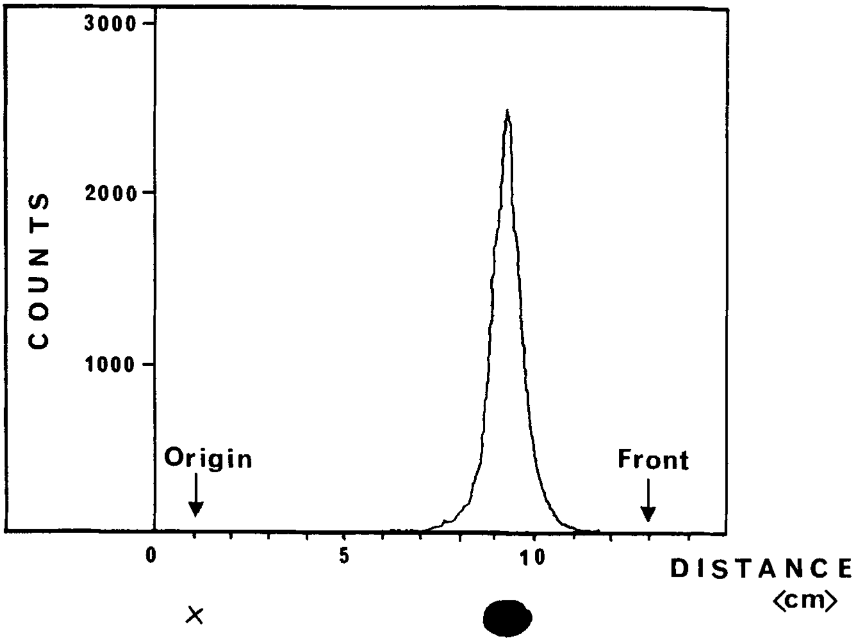

Fig. 1. Radioscans of (5) on TLC developed with chloroform/methanol (10:1)

REFERENCES

1. Karibe N., Nakamura T., Mishima M., Sugimoto H.- J. Labelled Comp. Radiopharm. 27(4): 417-421 (1989).
2. Karibe N., Nakamura T., Higurashi K., Yonaga M., Kaneko T., Sugimoto H.- The Japanese-United States Congress of Pharmaceutical Science, POSTER ABSTRACTS P. S159, Honolulu, Hawaii, December 2-7, 1987.

3. Karibe N., Sugimoto H., Kaneko T., Nakazawa T., Ueno M., Yamastu K.,- JP 89/186628, July 19, 1989.
4. King L. C., Ostrum G. K.- J. Org. Chem. 29: 3459-3461 (1964).
5. Noyori R., Tomino I., Yamada M., Nishizawa M.- J. Am. Chem. Soc. 106: 6717-6725 (1984).