Synthesis of ^{14}C-Labelled 2-[4-(p-Fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone Hydrochloride (E-2001-^{14}C)

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SUMMARY

^{14}C-labelled 2-[4-(p-fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone hydrochloride (4), a glutamate release inhibitor for studying the pharmacokinetic profiles of E-2001, was synthesized in two steps using 2-bromo-2'-[carbonyl-^{14}C]-acetonaphthone (1) as the labelled starting material.

Key words: Glutamate release inhibitor, Carbon-^{14}C, 2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone, 4-(p-Fluorobenzoyl)-piperidine, 2-[4-(p-Fluorobenzoyl)piperidin-1-yl]-2'-[carbonyl-^{14}C]acetonaphthone

INTRODUCTION

2-[4-(p-Fluorobenzoyl)pipieridin-1-yl]-2'-acetonaphthone hydrochloride (E-2001) was observed for the first time in our laboratories during the course of the studies on anti-ischemia drugs[1]. E-2001 showed a potent inhibitory effect on glutamate release and prevented the ischemia-induced neuronal cell damage[2].

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This paper describes the synthesis of ^{14}C-labelled 2-[4-(p-fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone hydrochloride (4). This synthesis was carried out to study the pharmacokinetic profiles of E-2001. ^{14}C-labelled-(4) was prepared from 2-bromo-2'-[carbonyl-^{14}C]-acetonaphthone (1) in two steps.

2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (1) was reacted with 4-(p-fluorobenzoyl)piperidine (2) in the presence of triethylamine and potassium iodide to afford 2-[4-(p-fluorobenzoyl)-piperidin-1-yl]-2'-[carbonyl-^{14}C]acetonaphthone (3). Compound (3) was purified by column chromatography and, immediately, converted to the hydrochloride by the usual method to obtain a precipitate, labelled compound (3) was extremely unstable in solution. 2-[4-(p-Fluorobenzoyl)-piperidin-1-yl]-2'-[carbonyl-^{14}C]acetonaphthone hydrochloride (4) was obtained in 74.5 % yield based on 1.

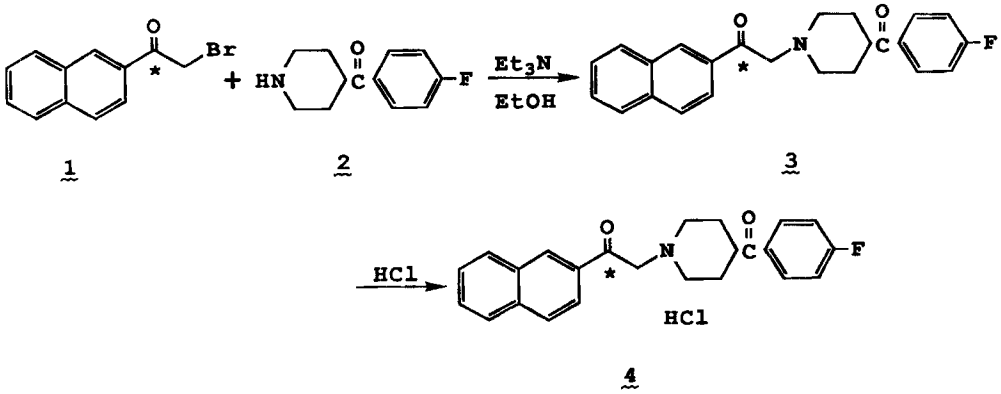

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Fig. 1. Synthesis of 2-[4-(p-Fluorobenzoyl)piperidin-1-yl]-2'-[carbonyl-^{14}C]acetonaphthone hydrochloride (4)

The structure of ^{14}C-labelled-(4) was confirmed by comparison (TLC) with unlabelled authentic specimen of (4).
^{14}C-labelled-(4) had a radiochemical purity of 99.9 % and a specific activity of 109.8 μCi per mg.

EXPERIMENTAL

Measurements of radioactivity were carried out using an Aloka LSC-9000 type Liquid Scintillation Spectrometer. Thin-layer radiochromatography was performed using a Berthold LB-2842 Automatic TLC Linear Analyzer. Thin-layer chromatography was developed using Kieselgel 60 F_{254} plate (Merck). Wakogel C-200 (Wako Chemical Industuries) was used for silica gel chromatograhy.

2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (1)

The labelled starting material (1), which was synthesized from [1-^{14}C]acetyl chloride (6) according to the method outlined in Figure 2, was purchased from Amersham International Ltd.

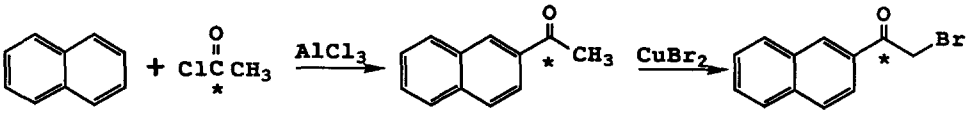

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Fig. 2. Synthesis of 2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (1)

2-[4-(p-Fluorobenzoyl)piperidin-1-yl]-2'-[carbonyl-^{14}C]-acetonaphthone hydrochloride (4)

2-Bromo-2'-[carbonyl-^{14}C]acetonaphthone (1) (396 mg; 1.58 mM, 90 mCi), 4-(p-fluorobenzoyl)piperidine (2) (491 mg; 2.37 mM), triethylamine (319 mg; 3.16 mM) and potassium iodide (1 mg) were added to EtOH (50 ml) and the mixture was refluxed for 30 min. The solvent was evaporated and dichloromethane (60 ml)

was added to the residue. The dichloromethane layer was washed with water and dried over magnesium sulfate. Dichloromethane was evaporated, and the residue was purified by silica gel column chromatography (benzene : AcOEt, 85:15). Immediately, after the chromatography, hydrogen chloride-ethanol was added to the fractions containing the product (3). The resulting precipitate was collected, washed with acetone to give the ^{14}C-labelled-(4) white crystals (486.7 mg, 74.5 % yield from (1); specific activity, 109.8 μ Ci/mg, radiochemical purity, 99.9 %). Identification of (4) 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 (4) were 0.66 in chloroform/methanol (10:1, v/v); (Figure 3), 0.23 in benzene/acetone/acetic acid (80:20:1) and 0.73 in chloroform/methanol/DMF (100:10:1).

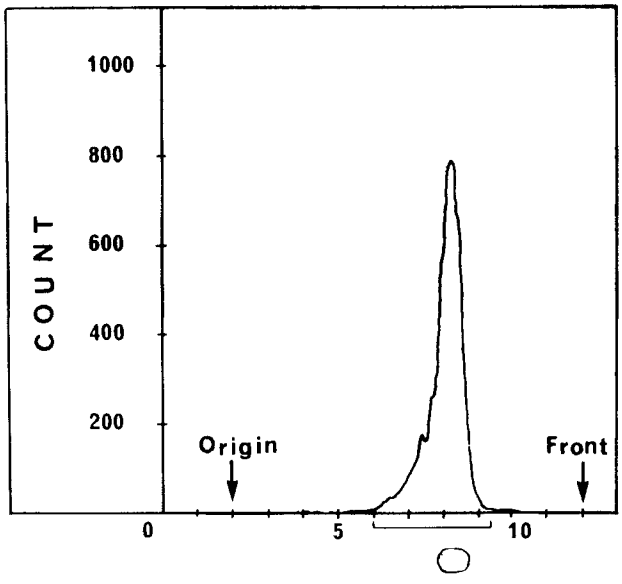

Fig. 3. Radioscans of (4) on TLC developed with chloroform/methanol (10:1)

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