JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2002; **45**: 213–216.
DOI: 10.1002/jlcr.545

Research Article

Preparation of N_4'-[^{11}C]methyl-ciprofloxacin for positron emission tomography studies

Patrick Goethals[1] and Anneke Volkaert[2]*
[1] *Institute for Nuclear Sciences, Ghent University, Proeftuinstraat, 86 B-9000 Gent, Flanders, Belgium*
[2] *Department Pathology, Bacteriology and Poultry diseases, Faculty of Veterinary Medicine, Salisburylaan, 133, B-9820 Merelbeke, Flanders, Belgium*

Summary

The synthesis of N_4'-[^{11}C]methyl-ciprofloxacin for pharmacological studies using positron emission tomography is described. The starting material was treated with [^{11}C]methyl iodide at 120°C in DMF for 5 min. After HPLC separation on a C_{18}-column with water/ethanol as mobile phase, the [^{11}C]methyl labelled compound was produced with a radiochemical yield of at least 25% (end of synthesis from [^{11}C]CO_2). Activities from 1.48 to 2.22 GBq (40 to 60 mCi) were obtained 1 h after the irradiation, ready for intravenous injection. The carrier ranged between 0.05 and 0.08 μmol (0.010–0.016 μmol/ml). Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: N_4'-[^{11}C]methyl-ciprofloxacin; PET; Infection

1. Introduction

The fluoroquinolines show pronounced activity against mycobacteria. Among the most interesting compounds in clinical use currently are oflaxacin and ciprofloxacin. The labelling procedure of trovafloxacin[(1)] and lomefloxacin[2] with ^{18}F by ^{19}F exchange is already described. Bio-

*Correspondence to: A. Volkaert, Department Pathology, Faculty of Veterinary Medicine, Salisburylaan, 133, B-9820 Merelbeke, Flanders, Belgium.

Received 16 May 2001
Revised 8 October 2001
Accepted 27 October 2001

distribution studies in rats demonstrated that significant concentrations accumulated in most tissues.[1] Tewson *et al.* performed PET studies in humans and showed the distribution of ^{18}F-lomefloxacin in the liver and lungs.[2]

Ciprofloxacin has a broad antibacterial spectrum against gram-positive and gram-negative bacteria. It seems that the N_4'-alkylated ciprofloxacins are mostly two or four times more active against Mycobacterium tuberculosis than ciprofloxacin is.[3] The aim of this project was to develop the synthesis of N_4'-[^{11}C]methyl-ciprofloxacin for use in research concerning the pharmacokinetics and metabolism of the drug. PET studies are expected to give additional information about the fate of the drug upon administration to infections.

1.1. Experimental

1.1.1. Materials and apparatus

Ciprofloxacin was purchased from Bayer Leverkusen (Germany). N_4'-methyl-ciprofloxacin, commercially not available, was synthesized in bulk (5 g) and the identity and purity were controlled by ^{1}H-NMR and MS.

HPLC was performed using columns and conditions noted below with a UV detector in series with a Canberra (Type 2007F) 2×2 in NaI-detector or GM tube for monitoring the effluent. Traces of organic solvents were detected with a Philips PU 4500 GC-FID on a Porapac-Q column (Altech) eluted with helium (column: 140°C; injector: 250°C; detector: 220°C).

1.2. Preparation of N_4'-[^{11}C]methyl-ciprofloxacin

The production of [^{11}C]methyl iodide has already been reported in detail.[4,5] In a conical 5 ml reaction vial, 2.5 mg (7.5 μmol) of ciprofloxacin was dissolved in 200 μl DMF. Four millilitres of TBA (6.0 μmol) was added as base. [^{11}C]Methyl iodide, purified over P_2O_5, was trapped by bubbling the carrier helium gas through the solution cooled at about −40°C for 5 min. The vial was heated for 5 min at 120°C resulting in the formation of N_4'-[^{11}C]methyl-ciprofloxacin (Figure 1).

The reaction mixture was injected into the HPLC semi-preparative column (Bio-Rad C_{18} column, 25×1 cm, 10 μm). Elution with a 70/30 solvent mixture (water/ethanol) at a flow rate of 3 ml/min separated

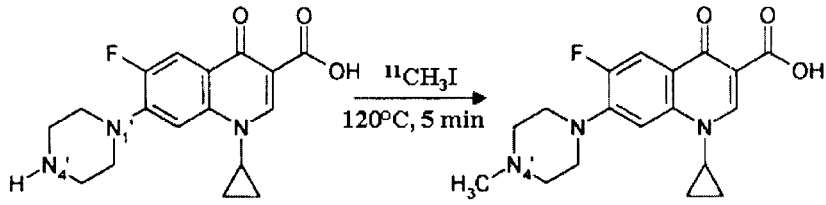

Figure 1. Reaction scheme for the synthesis of N_4'-[^{11}C]methyl-ciprofloxacin

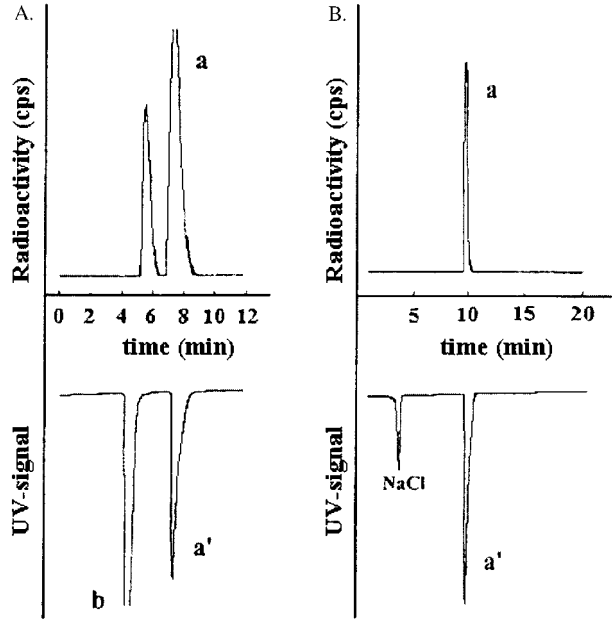

Figure 2. HPLC chromatograms of purified N_4'-[^{11}C]methyl-ciprofloxacin. (A) preparative purification, (B) analytical separation. (a)N_4'-[^{11}C]methyl-ciprofloxacin, (a′) N_4'–methyl-ciprofloxacin and (b) ciprofloxacin

the different components. The effluent was monitored by a GM tube and by a UV detector (254 nm.) The N_4'-[^{11}C]methyl-ciprofloxacin, with a retention time of 8 min (Figure 2A), was collected in a conical-shaped flask, preheated to 85°C and flushed with a nitrogen flow of 25 ml/min. After 5 min, most of the ethanol was evaporated and the solution was made isotonic with a concentrated sterile sodium chloride solution (0.9%). The solution was finally passed over a 0.22 μm Millipore® filter and collected in a capped vial, properly sterilized beforehand.

2. Results and discussion

The accent was placed on the non-carrier added synthesis of N_4'-[^{11}C]methyl-ciprofloxacin on a routine basis. The preparation, semi-preparative HPLC purification included, was completed within 60 min. Activities from 1.48 to 2.22 GBq (40–60 mCi) were obtained. The carrier amount ranged between 0.05 and 0.08 μmol (0.010–0.016 μmol/ml). The product was obtained in a sterile, isotonic solution ready for medical use. As shown in the HPLC semi-preparative chromatogram (Figure 2A), the N_4'-[^{11}C]methyl-ciprofloxacin was the baseline separated from the labelled and unlabelled components, giving a first indication of the radiochemical and chemical purity of the product of interest. The purified labelled product was again analysed by HPLC, using an analytical Bio-Rad C_{18}-column (25×0.46 cm, 5 μm) eluted with a mixture of 75/25 water/ethanol. The effluent was monitored for both radioactivity (NaI detector) and UV absorption at 254 nm. A single radioactive peak with a retention time of 10 min was obtained. No radiochemical or chemical impurities could be detected (Figure 2B).

The carrier amount ranged between 0.05 and 0.08 μmol (0.010–0.016 μmol/ml). Additional GC demonstrated that no traces of organic solvents (THF, DMF) could be found in the final product except ethanol. The overall radiochemical yield was at least 25% compared to the initial [^{11}C]CO_2 (decay corrected). Tests proved the sterility and apyrogenicity of the solution. This enables the investigation of the pharmacokinetics and metabolism of the drug in small animals (Wistar rats) using PET.

References

1. Babich JW, Rubin RH, Graham WA, Wilkinson RA, Vincent J, Fischman AJ. *Nucl Med Biol* 1996; **23**: 995–998.
2. Tewson TJ, Yang D, Wong G, *et al. Nucl Med Biol* 1996; **23**: 767–772.
3. Haemers A, Leysen D, Bollaert W, Zhang M, Pattyn S. 1990. *Antimicrob Agents Chemotherapy* **34**: 496–497.
4. Goethals P, Sambre J, Coene M, Castelyn K, Poupeye E. *Int J Appl Radiat Isotopes* 1992; **43**: 952–954.
5. Goethals P, Volders F, Van der Eycken J, van Eijkeren M, Lemahieu I, Dams R. *Nucl Med Biol* 1997; **24**: 713–718.

