SYNTHESIS OF NON - CARRIER ADDED [N - METHYL - ^{11}C] ROXITHROMYCINE

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SUMMARY

Roxithromycine, a new macrolide, was labelled with [^{11}C]CH_3I in a good radiochemical yield (40-45%)and high specific activities (500-550mCi/µmol). This antibiotic may be useful for detecting pulmonar or cerebral infection foci using positron emission tomography.
Key Words: carbon-11, antibiotic, positron emission tomography.

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INTRODUCTION

Roxithromycine is a novel macrolide which possesses the usual anti-bacterial spectrum associated with this family of antibiotics. The feature of this molecule is its pharmacokinetic characteristics (1) (half life 12 hours and a good tissue entry). The first antibiotic described in positron emission tomography (PET) was [^{11}C] erythromycin A (2), labelled by a reductive methylation of N-demethyl erythromycin A with [^{11}C] formaldehyde. The intravenous injection of the labelled antibiotic, [^{11}C] roxithromycine, a positron emitting radionuclide, would make possible the measurement of the local concentration in vascular compartments, extravascular fluids and parenchyma. This non invasive technique, coupled with other investigations (such as bronchoalveolar lavage for bronchopulmonary infections) and the knowledge of the concentration of this antibiotic in infection foci would allow the estimation of its efficacy. We here report the radiosynthesis and purification of [^{11}C] roxithromycine.

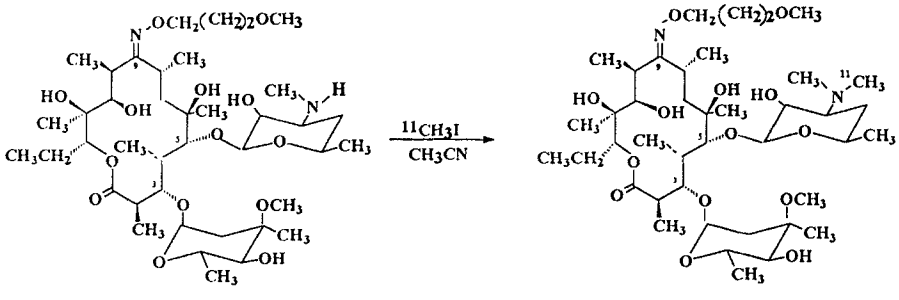
CCC 0362–4803/95/080801–03

Received 22 February 1995
Revised 10 March 1995

RESULTS

Roxithromycine **2** is a lactone with a 14 membered rings substituted at C_3 and C_5 respectively by sugars: cladinose and desosamine and possesses an oxime function at C_9. This macrolide was labelled by alkylation with $[^{11}C]CH_3I$ of secondary amine of desosamine **1**. The reaction was attempted under a range of conditions: solvent (ethanol, chloroform, dimethylsulfoxide, acetone, water); temperature (20°C,70°C,80°C,100°C) and reaction time (5min, 10min). The best radiochemical yield was obtained when the mixture was heated for 10min at 100°C using acetone/water (10/1,v/v) as solvent.

A rapid purification of the [^{11}C]roxithromycine was achieved by a semi-preparative HPLC. The average time of the synthesis was 55-60min from the end of bombardment to formulated product ready for biological studies. The radiochemical yield based on [^{11}C] iodomethane was 40-45% with a specific activity of 500-550mCi/μmol at the end of the synthesis. The radiochemical purity was greater than 99%



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EXPERIMENTAL

Roxithromycine and a sample of authentic N-demethylroxithromycine were obtained from Roussel Uclaf Laboratories. Purification and analysis mixture were performed with a Waters system. Isolated radiochemical yield was determined with a

dose calibrator (capintec CRC-12). All solvents were "HPLC" grade and purchased from Merck (Darmstadt, Germany).

[^{11}C]Roxithromycine: [^{11}C]iodomethane produced as previously described (3) was carried by a stream of nitrogen into a fresly prepared solution of N-demethylroxithromycine (8.2mg) in acetone/water (500µl), containing 5mg of potassium carbonate. The reaction mixture was heated at 70°C for 10min in a sealed reactor. Before the injection onto a HPLC column (µ Bondapak C_{18} Waters), the solvents were removed and the residue taken up with the HPLC solvent [500µl; CH_3CN / MeOH / H_2O / Phosphate buffer (0.2M) PH=7 , 40/20/35/5; v/v/v/v] and filtrated through a Millipore Millex HV_{13} .The column was heated at 65°C, the eluate was monitored continuously for absorbance at 205nm, the flow rate was 5ml/min and the radioactivity was measured with an ionisation chamber. Under these conditions the retention time for [^{11}C]Roxithromycine was found to be 12min. To check the purity of [^{11}C]Roxithromycine, a sample of the radioactive fraction eluted from the semi-preparative HPLC was analyzed by thin layer chromatography using silica gel plates ($60F_{254}$, 0.2mm layer) eluted with a mixture of: CH_3CN / EtOH / NH_4OH; 85/15/0.02, v/v/v and developed in iodine (Rf :0.4).The collected radioactive fraction was evaporated to dryness and redissolved in 2ml of physiological saline and sterilized through 0.22µm filter for i.v. injection.

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