A SYNTHESIS OF [^{14}C]ALFUZOSINE HYDROCHLORIDE

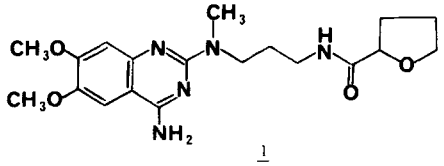
J. ALLEN
Synthélabo - L.E.R.S.
Department of Chemistry
Labelled Compounds and Metabolism Group
31, avenue Paul Vaillant Couturier
92220 BAGNEUX - FRANCE

SUMMARY

Alfuzosine hydrochloride, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)-methylamino]propyl] tetrahydro-2-furancarboxamide hydrochloride, labelled with carbon-14 was synthesised in high overall yield from potassium [^{14}C]cyanate for pharmacokinetic and metabolism studies.

Key words : Alfuzosine, Carbon-14, Synthesis.

Alfuzosine hydrochloride, N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)-methylamino]propyl] tetrahydro-2-furancarboxamide hydrochloride, hereinafter referred to as SL 77.499 hydrochloride 1[1] is a drug undergoing development which possesses blood pressure lowering properties (antihypertensive agent).

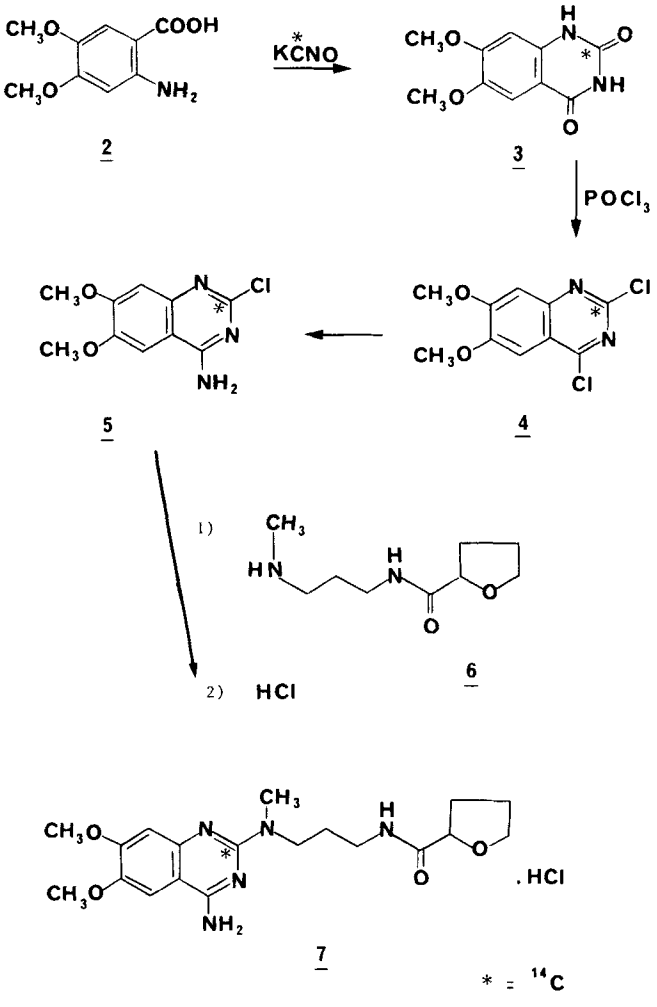


1

A structurally related 4-amino-6,7-dimethoxyquinazoline, Prazosin is a clinically useful antihypertensive drug[2]. SL 77.499 has an α-adrenergic antagonist activity of peripheral origin having certain distinct advantages over existing compounds. This compound was desired labelled with carbon-14

0362-4803/83/111283-04$1.00

Received December 20, 1982
Revised August 15, 1983



SCHEME 1

for pharmacokinetic and drug metabolism studies as part of our development program with this drug. The synthesis of [^{14}C]Prazosin has been outlined[3] but not described in detail and so it was considered useful to describe the radiolabelled synthesis of this compound here.

The synthetic route used has been outlined in Scheme 1. 2-Amino-4,5-dimethoxybenzoic acid 2 with potassium [^{14}C]cyanate in water yielded the [2-^{14}C]quinazolinedione 3 which on treatment with phosphorus oxychloride and recrystallisation of the product from methanol gave the

2,4-dichloro[2-^{14}C]quinazoline 4 in a 69 % radiochemical yield from potassium [^{14}C]cyanate. This with liquid ammonia in THF in a glass pressure vessel gave the 4-amino-2-chloro[2-^{14}C]quinazoline 5 which with tetrahydro-N-[3-(methylamino]propyl]-2-furancarboxamide 6[1] in isoamyl alcohol and purification of the product formed by hplc gave [^{14}C]SL 77.499 base in an overall yield of 47.3 % from potassium [^{14}C]cyanate. This was converted into the [^{14}C]SL 77.499 hydrochloride 7 on treatment with an etheral solution of hydrogen chloride.

EXPERIMENTAL

Potassium [^{14}C]cyanate was purchased from Amersham France. Samples were counted on a Searle Mark III counter using Instagel (Packard) as counting medium. The photographic film used for autoradiography was Kodak "Kodirex" X-ray film. Tlc plates were scanned using a Chromelec scanner coupled to an Interzoom computer. All solvents were redistilled before use.

6,7-Dimethoxy-2,4(1H,3H)-[2-^{14}C]quinazolinedione 3

A suspension of 2-amino-4,5-dimethoxybenzoic acid 2 (380.2 mg, 1.93 mmol) in water (12.5 ml) and glacial acetic acid (0.21 ml) was treated portionwise with potassium [^{14}C]cyanate (100 mCi, 1.75 mmol) in water (2 ml) over 15 minutes. The reaction mixture was then rapidly stirred for 2-5 hours. Sodium hydroxide pellets (3.7 g) were added portionwise with stirring and the reaction mixture then heated at 90°C for 30 minutes. The solution was then cooled and concentrated hydrochloric acid (9 ml) added slowly with stirring. On further cooling the product was filtered, washed with water, hot ethanol and then dried under vacuum and used directly for the next stage.

2,4-Dichloro-6,7-dimethoxy[2-^{14}C]quinazoline 4

To the [2-^{14}C]quinazolinedione 3 (273 mg, 1.22 mmol) was added phosphorus oxychloride (0.68 ml) and N,N'dimethylaniline (71 µl) and heated to 120°C for 3 hours. This was carefully added to water and extracted with chloroform, washed with water, then with 10 % sodium bicarbonate, water, dried (Na_2SO_4) and evaporated to yield the 2,4-dichloro-6,7-dimethoxy[2-^{14}C]-quinazoline 4 (69 mCi).

4-Amino-2-chloro-6,7-dimethoxy[2-^{14}C]quinazoline 5

2,4-Dichloro-6,7-dimethoxy[2-^{14}C]quinazoline 4 (69 mCi) in THF (20 ml) was transferred to a glass pressure vessel and a large excess of liquid ammonia

distilled in. The vessel was closed and the reaction stirred at room temperature for 40 hours.

The THF and excess ammonia were evaporated off under a stream of nitrogen and the product crystallised from methanol to afford the 4-amino-2-chloro-6,7-dimethoxy[2-^{14}C]quinazoline 5 (337 mg, 1.40 mmol).

N-[3-[(4-Amino-6,7-dimethoxy-2-[2-^{14}C]quinazolinyl)methylamino]propyl]-tetrahydro-2-furancarboxamide hydrochloride 7

A suspension of 4-amino-2-chloro-6,7-dimethoxy[2-^{14}C]quinazoline 5 (337 mg, 1.40 mmol) and tetrahydro-N-[3-(methylamino]propyl]-2-furancarboxamide 6 (518 mg, 2.78 mmol) in isoamyl alcohol (5 ml) under nitrogen were stirred for 7 hours under reflux. The isoamyl alcohol was evaporated off under nitrogen, ethanol followed by a few drops of ammonium hydroxide were added and the solvent again evaporated under nitrogen. The product was dissolved in chloroform, washed with water, dried and evaporated. The crude product was purified by hplc on silica lichroprep Si 60 (25-40 μm, column 25 x 2.5 cm) eluting with chloroform : methanol (9 : 1) to afford the [^{14}C]SL 77.499 base (47.3 mCi, 0.94 mmol, 50.5 mCi/mmol) in a radiochemical yield of 47.3 % from potassium [^{14}C]cyanate. A portion of the base (27.6 mCi) was used to prepare the hydrochloride. Treatment of this in ethanol (8 ml) with an etheral solution of hydrogen chloride (2 ml) gave the [^{14}C]SL 77.499 hydrochloride 7 (22.74 mCi, 192.4 mg, 50.5 mCi/mmol) which had a radiochemical purity of 99 % as determined by t.l.c. on Merck Silica GF-254 in the following systems :

(i) Ethyl acetate : methanol (2 : 1), Rf : 0.17.
(ii) Ethyl acetate : methanol : dimethylamine (75 : 20 : 5), Rf : 0.71.
(iii) Chloroform : methanol (8 : 2), Rf : 0.32.

The hydrochloride 7 on storage in aqueous solution at 1 mCi/ml at -80°C for three years showed a radiochemical degradation of only 4 %.

REFERENCES

1. Manoury P., French Patent, 79.24373, October 1979.

2. Hess H.J. - In Prazosin, Clinical Symposium Proceedings, Postgraduate Medicine Special Issue, November 1975.

3. Taylor J.A., Twomey T.M. and Schach von Wittenau M. - Xenobiotica, 17 (6), 357, (1977).