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Synthesis of ^{14}C-Labelled Sodium Pariprazole (E3810)

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SUMMARY

Sodium pariprazole (E3810), an inhibitor of H^+,K^+-ATPase, was synthesized labelled with carbon-14, starting from 2-mercapto[2-^{14}C]-benzimidazole **1** with a specific activity of 888 MBq/mmol. It was obtained in 49.3% radiochemical yield with a radiochemical purity of more than 98 %.

Key Words: ^{14}C-labelled sodium pariprazole(E3810), benzimidazole derivative,H^+,K^+-ATPase inhibitor

INTRODUCTION

Sodium pariprazole, an anti-ulcer agent, has a potent inhibitory activity against gastric acid secretion which is based on an inhibition of H^+,K^+-ATPase [1 - 4]. This paper describes the synthesis of ^{14}C-labelled sodium pariprazole for pharmacokinetic profile studies in 3 stepes from 2-mercapto[2-^{14}C]benzimidazole according to Scheme 1.

RESULTS AND DISCUSSION

Sodium [^{14}C]pariprazole was synthesized from 2-mercapto-[2-^{14}C]benzimidazole **1** in 52.2% chemical and 49.3% radiochemical yield. The radiochemical purity was over 98%, which was satisfactory for pharmacokinetic study.

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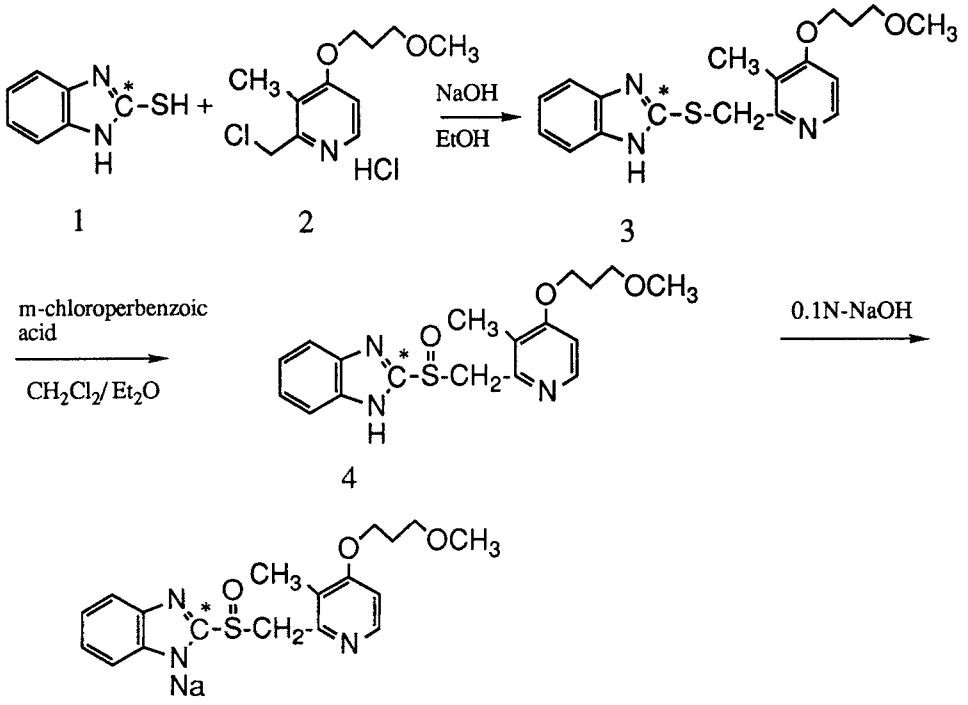


1 2 3 4

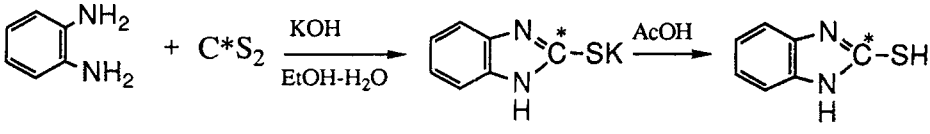
5 Sodium[^{14}C] pariprazole

Scheme 1 Synthetic process for Sodium [^{14}C] pariprazole

EXPERIMENTAL

2-Mercapto[2-^{14}C]benzimidazole with a specific activity of 2.02 GBq/mmol was purchased from Amersham Japan. 2-Mercapto[2-^{14}C]-benzimidazole **1**, the starting material, was synthesized, as illustrated in Scheme 2, by Amersham International plc.

Treatment of [^{14}C]carbon disulfide with phenylenediamine in potassium hydroxide solution, followed by desalination with acetic acid gave compound **1** (total radioactivity 3.59 GBq, specific activity 2.02 GBq/mmol). The product was diluted to 1.01 GBq/mmol with the same amount of non labeled 2-mercaptobenzimidazole.



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Scheme 2 Synthesis of 2-mercapto [2-^{14}C]benzimidazole

All chemicals used in the synthesis were purchased, and used without further purification. All solvents were either distilled or of analytical reagent grade.
Thin layer chromatographic analysis of sodium [^{14}C]pariprazole produced was carried out on silica gel plates (Merck 60F-254, 20 x 20 cm) using two developing solvents: A. chloroform:methanol (6:1,v/v), B. ethyl acetate:acetone:28% ammonia solution (5:6:0.1,v/v/v). Radioactivity on the TLC plate was measured with a thin-layer chromatogram scanner from Aloka. Radioactivity in silica gel of the TLC plate was measured with an Aloka Model LSC-900 liquid scintillation spectrometer.
After developing and drying TLC plate, silica gel powder was scraped off from the zone contained the ^{14}C, and placed in a vial (Wheaton,U.S.A.), 0.5 ml of methanol was added to the vial, the mixture was sonicated, liquid scintillation added and mixed and the radioactivity measured.

2-[[4-(3-Methoxypropoxy)-3-methylpyridine-2yl]methylthio][2-^{14}C]-1H-benzimidazole 3

0.27 g of 2-mercapto[2-^{14}C]benzimidazole (3.59 GBq, 1.8 mmol) was added to the ethanolic solution (20 ml) containing 0.27 g of 2-mercapto-benzimidazole, 1.08 g of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine hydrochloride **2** and 0.6 g of sodium hydroxide, and the mixture refluxed with stirring for 1 hour. After **1** disappeared and was no longer detected by TLC (Rf= 0.92 by TLC in silica gel with a solvent system of ethyl acetate only), the reaction mixture was cooled to room temperature and filtered to remove inorganic compounds.
The solvent was removed in vacuo. 30 ml of dichloromethane and 20 ml of water were added to the residue to extract **3**. In addition, 3 x 10 ml dichloromethane was added to the aqueous phase. The separated organic layers were collected and washed with 30 ml of saturated saline, and the solvent was removed in vacuo.
The residue was subjected to column chromatography on silica (40 g) first eluting with 66.7% n-hexane/ethyl acetate (300 ml), and then with 50% n-hexane/ethyl acetate (300 ml), and finally with 33.3% n-hexane/ethyl acetate (300 ml). **3** was isolated as white crystals (1.17 g, 3.41 GBq, 94.7%), Rf= 0.39 by TLC in silica gel with a solvent system of ethyl acetate only.

2-[[4-(3-methoxyproxy)-3-methylpyridine-2-yl]methylsulfinyl][2-^{14}C]-1H-benzimidazole 4

3 was dissolved in 20 ml dichloromethane (M.S.4A, containing dipotassium carbonate). Ethyl ether 2.5 ml and 0.34g of m-chloroperbenzoic acid (purity 80%) were added to 10 ml of this solution (1.7 mmol, 1.70GBq) after cooling to -68°C and the mixture was stirred for 1 hour (the solvent temperature increased up -40 °C).
Triethylamine 0.20g was added to the mixture and stirred for 10 minutes, and then 1N sodium hydroxide aqueous solution 10 ml was added. The solution was stirred for 30 minutes at room temperature.
The aqueous layer was washed with dichloromethane (3 x 10 ml) to remove unreacted thioether **3** (Rf= 0.51 by TLC in silica gel with a solvent system of 5%methanol/chloroform). The aqueous layer was treated with 2M ammonium acetate solution (4.5 ml) and dichloromethane (20 ml, 3 x 10 ml). The combined organic layers were dried over magnesium sulfate and then the solution filtered. The filtrate was concentrated under reduced pressure to a volume of 1 ml. Ethyl ether 20 ml was added to the resulting solution and the solid produced was filtered off and air-dried at room temperature to give compound **4** (0.35 g, 57.0%) (Rf= 0.41 by TLC in silica gel with a solvent system of 5%methanol/chloroform).

2-[[4-(3-methoxypropoxy)-3-methylpyridine-2-yl]methylsulfinyl] [2-^{14}C]-1H-benzimidazole sodium salt 5

4 was dissolved in a mixture of 0.1N sodium hydroxide solution (9.7 ml) and ethanol (10 ml). The solution was filtered through a glass filter and the filter washed with ethanol:dichloromethane (1:1) (10 ml x 5). The combined organic solvent was removed under reduced pressure. Ethanol was added to the residue and the solvent was again removed. The residue was dried in vacuo and then treated with ethyl ether to afford compound **5** (0.36 g) as a pale yellowish solid, 838 MBq, 49.3 % radiochemical yield based on thioether **3**. Identification of **5** was confirmed by comparison of its Rf-values with an unlabelled authentic standard by TLC (Rf=0.84 by solvent system A, Rf=0.32 by solvent system B). The specific activity was 888 MBq/mmol. The radiochemical purity was 98.2 % by TLC using solvent A and 98.7 % using solvent B as the developing solvent .

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