Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXI, No. 6

Synthesis of Carbon-14 Labeled Gadoteridol, [1,4,7-Tris(carboxymethyl)-10-(2-hydroxy-1-[^{14}C]propyl)-1,4,7,10-tetraazacyclododecanato]gadolinium.

D.D. Dischino and J.E. Swigor

Central Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492
and
Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Company, P.O. Box 4755, Syracuse, N.Y. 13221

Summary

Carbon-14 labeled Gadoteridol, [1,4,7-tris(carboxymethyl)-10-(2-hydroxy-1-[^{14}C]propyl)-1,4,7,10-tetraazacyclododecanto] gadolinium, was prepared from 1-[^{14}C] propylene oxide in a total yield of 30.4% and a radiochemical purity of 99.2%.

Keywords: MRI Contrast Agent, Gd(HP-DO3A), [^{14}C] Gadoteridol, [^{14}C]Prohance, Gadolinium Chelate.

Introduction

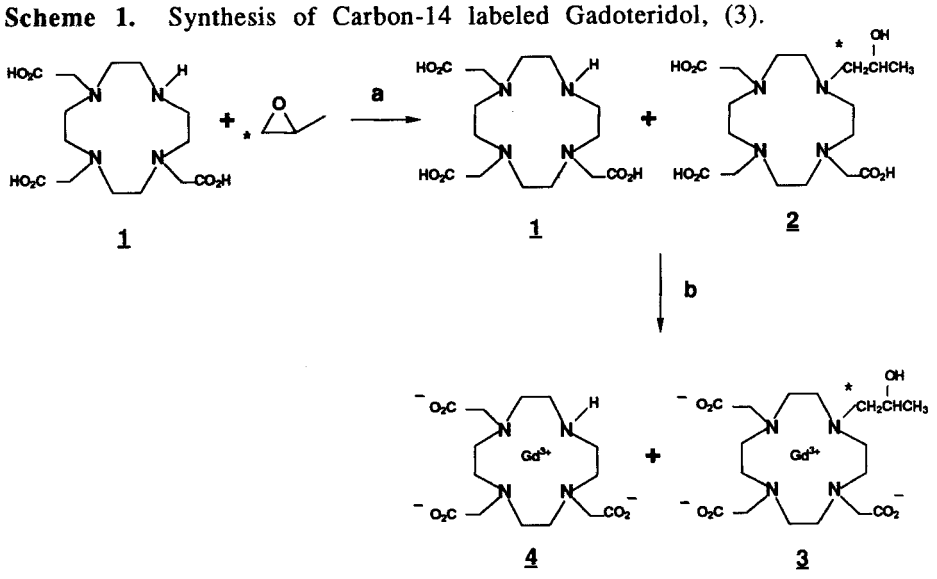
Gadoteridol, Prohance, Gd(HP-DO3A), [1,4,7-tris(carboxymethyl)-10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecanto] gadolinium, (3), is a nonionic gadolinium chelate currently under development as a contrast agent in magnetic resonance imaging.[1,2] Carbon-14 labeled gadoteridol was prepared for use in an environmental impact study to support the NDA filing of this agent.

The synthesis of Gadoteridol involved a one-pot two step reaction wherein Carbon-14 labeled 1-[^{14}C]propylene oxide was reacted with excess 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane, (1), in a mixture of aqueous sodium hydroxide and 1,4-dioxane (**Scheme 1**). The crude reaction mixture was then treated with excess gadolinium acetate and the product purified via column chromatography on CHP-20P. The product was crystallized from methanol and acetone.

0362–4803/92/060455–04$05.00

Received 13 February, 1992
Revised 24 February, 1992

Scheme 1. Synthesis of Carbon-14 labeled Gadoteridol, (3).



Reagents: (a) NaOH, H_2O, 1,4-dioxane; (b) $Gd(OAc)_3 \cdot 4H_2O$, CH_3CO_2H.

Discussion

Gadoteridol is routinely prepared by reacting an excess of propylene oxide with (1) followed by chelation of the resulting ligand, 1,4,7-tris(carboxymethyl)-10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane, (2), with either gadolinium acetate or gadolinium oxide. However, in this synthesis the radiolabeled propylene oxide was the limiting reagent resulting in an incomplete conversion of (1) to (2). Therefore the critical step in the synthesis of (3) was the purification of the desired gadolinium chelate from gadolinium acetate, [1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecanato]gadolinium, (4), and both organic and inorganic salts. This purification was accomplished by column chromatography of the crude chelate reaction mixture on Dianion CHP-20P resin. This divinylstyrene based polymer resin offers both high loading capacity and resolving capabilities comparable to or superior to that of C-18 reverse-phase HPLC columns. The retention of various compounds on this resin is a function of the hydrophobic interactions of these compounds with the porous nature of the polymer support. Very hydrophilic compounds can be eluted from the column with H_2O whereas other compounds which are more tightly held may require varying amounts of an organic modifier in the aqueous eluent.

During the purification of carbon-14 labeled gadoteridol, the inorganic and organic salts, gadolinium acetate, and (4) eluted from the column using H_2O as the eluent. The desired chelate (3) was eluted from the column by changing the eluent to 2% aqueous methanol.

Experimental

Materials

[1-14C] Propylene oxide was purchased from Moravek BioChemicals Inc., Brea, CA. (91 mCi, 28 mCi/mmol). MCI gel high porous polymer Dianion CHP-20P resin (75-150 micron) was obtained from Mitsubshi Kasei Corporation, Tokyo, Japan. Gadolinium acetate hydrate was obtained from Aldrich Chemical Company. All other reagents were ACS grade or the highest quality material commercially available. Distilled deionized water was obtained from a Millipore Super Q Purification System and used to minimize trace metal contamination of the ligands and chelates.

All experimental conditions were optimized using non-radiolabeled materials. The identity of the final product (3), was established by co-elution via HPLC of the radiolabeled substance with authentic unlabeled compound obtained from Bristol-Myers Squibb Company (New Brunswick, N.J.).

Analytical Methods

HPLC was used to evaluate the purity of both the ligand and chelate preparations.[2,3] The ligand assay (Method 1) involves adding an excess of Cu^{2+} as 10 mmol of copper (II) acetate to a solution of the ligand (<10 mmol) and then analyzing the resulting copper complexes on a 250 X 4.1 mm Hamilton PRP-X100 Anion-Exchange HPLC column. The mobile phase consisted of 92.5% (1.25 mmol Tris Acetate, 2.5 mmol Na_2EDTA, pH 7.3) and 7.5% CH_3OH. The flow rate of the column was 2 ml/min. The copper complexes were detected by UV (280nm). The copper complexes of (1) and (2) had retention times of approximately 2.9 and 5.2 minutes respectively. The gadolinium assay (Method 2) involves analyzing the gadolinium chelates on a 250 X 4.1 mm Nucleosil 5 C18 reverse-phase HPLC column. The mobile phase consisted of 98% (50 mmol Tris Acetate, 10 mmol Na_2EDTA, pH 7.3), and 2% CH_3CN. The flow rate of the column was 1.0 ml/min. The gadolinium chelates were detected by fluorescence using a Hitachi F-1050 Fluorescence Spectrophotometer (excitation 274 nm, emission 314 nm). The gadolinium chelates (3) and (4) had retention times of approximately 10.7 and 6.0 minutes respectively.

Radioactivity was measured by a Beckmann LS9000 liquid scintillator. Radiochemical purity was determined by HPLC.

Synthesis

1,4,7-Tris(carboxymethyl)-10-(2-hydroxy-1-[14C]propyl)-1,4,7,10-tetraazacyclododecane (2)

Into a 50 mL RB flask containing (1), (1.35 g, 0.0039 mole), and NaOH (0.624 g, 0.0039 mole) in H_2O (5 mL) at 0°C was added [1-^{14}C]propylene oxide (91 mCi, 28 mCi/mmol) dissolved in 1,4-dioxane (2 mL). The shipping vessel originally containing the radioactive propylene oxide was rinsed with cold H_2O (1 mL) and this was also added to the reaction flask. The reaction flask was then sealed with a rubber septum. After 30 min., the flask was removed from the ice-water bath and allowed to warm to ambient temperature. After 24 h, the crude reaction mixture was used as is in the next step.

[1,4,7-Tris(carboxymethyl)-10-(2-hydroxy-1-[14C]propyl)-1,4,7,10-tetraazacyclododecanatolgadolinium (3)

To the crude reaction mixture containing (2) was added $Gd(OAc)_3 \cdot 4H_2O$ (1.74 g ,0.00429 mole) and CH_3CO_2H (0.2 mL). The solution was allowed to stir for 48 h. After 48 h, the solvent was removed on a rotary evaporator. The residue dissolved in H_2O (15 mL) and applied to a 5 X 50 cm column of Dianion CHP-20P resin. The column was eluted with H_2O at a flow rate of 10 mL/min. Fractions were collected and analyzed via HPLC (Method 2). After all of the Gd(DO3A), (4), had eluted from the column, the eluent was changed to 2% CH_3OH. Fractions containing the desired product were then combined and concentrated on a rotary evaporator. The residue was then dissolved in anhydrous CH_3OH (20 mL) and concentrated to dryness (2X). The residue was dissolved in anhydrous CH_3OH (10 mL), filtered through a 0.22 micron filter and crystallized by the addition of acetone. The crystals were collected by filtration to yield 0.752 g (27.7 mCi, 30.4% yield) of (3) as a white fluffy solid. The radiochemical purity as determined by HPLC was 99.2%, and the specific activity was 36.8 uCi/mg.

Acknowledgements

The authors would like to thank Drs. R. Pillai, and R. Standridge for useful discussions during this project, and Dr. D. Walker for his assistance during the purification of (3). The radiochemical purity and specific activity determinations of (3) were conducted by Ms. Elizabeth Noga.

References

1. Tweedle, M.F., Gaughan, G.T., Hagan, J.J.- U.S. Patent No. 4,885,363, 1989. Eur. Pat. Appl. EP 232-751-A, 1986.

2. Dischino, D.D., Delaney, E.J., Emswiler, J.E., Gaughan, G.T., Prasad, J.S., Srivastava, J.K., Tweedle, M.F.- Inorg. Chem. 30:1265 (1991).

3. Hagan, J.J., Taylor, S.C., Tweedle, M.F.- Anal. Chem. 60:514 (1988).