NOVEL SYNTHESIS OF GADOLINIUM BASED (MRI) CONTRAST AGENT

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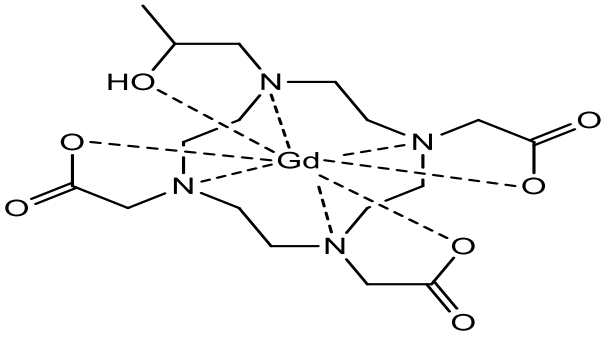
Abstract: *The present invention relates to Gadoteridol of formula I. Specifically, the present invention relates to improved process for the preparation of Gadoteridol by forming novel intermediate. The present invention relates to the improvement in yield with better purity of Gadoteridol by forming novel intermediate in process.*

Introduction

Gadolinium(III) complexes are widely utilized as contrast agents(CAs) for magnetic resonance imaging (MRI) in clinical diagnosis.1Among the multiple diagnostic imaging techniques, MRI isespecially advantageous as a noninvasive modality: it can image deep into tissues, there is no ionizing radiation, it provides 3D images with submillimeter spatial resolution, excellent soft tissue contrast, there are multiple types of contrast available, the imaging is not operator dependent, and it can provide whole body images with excellent spatial and anatomical resolution.1,2 Ever since the introduction of MRI as a diagnostic tool, the interest in the development of efficient, responsive, and tissue-specific CAs hasgrown tremendously.3 Despite the high spatial resolution and tissuepenetration of MRI, this technique suffers from a low sensitivity.Further, the efficiency of commercial MRI contrast agents is too lowfor the application of MRI to molecular imaging.

Gadoteridol is a gadolinium-based MRI contrast agent, used particularly in the imaging of the central nervous system. It is sold under the brand name ProHance.Gadoteridol available as a 0.5M sterile clear colourless to slightly yellow aqueous solution in vials and syringes for intravenous injection. Gadoteridol is the gadolinium complex of 10-(2-hydroxy-propyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid with a molecular weight of 558.7, an empirical formula of C17H29N4O7Gd and has the following structural formula:



Formula I

Gadoteridol is marked by Bracco Diagnostics INC under trade name ProHance ®.Each mL of ProHance contains 279.3 mg gadoteridol, 0.23 mg calteridol calcium, 1.21 mg tromethamine and water for injection. ProHance contains no antimicrobial preservative. ProHance has a pH of 6.5 to 8.0.

The preparation of compound (I) at high purity level in easily reproducible conditions is an essential requirement for the preparation of these important diagnostic agents an industrial scale.

US 4885363 appear to claim Gadoteridol compound. The same patent also discloses the process for the preparation of Gadoteridol.

A PATENT US5925752, US6042810, US6046324 has claimed the process for the preparation Gadoteridol. US6066259 which uses the method for the deionization of substances that are not stable at acidic pH. Moreover Chinese patent CN 102399199 also claims the process for the preparation of Gadoteridol.

Journal article ACS Nano, 8(10), 10168-10177; 2014 has also disclose the process for preparation of Gadoteridol by using tri-fluroacetic acid as for hydrolysing and the coupling with propylene oxide followed by treatment with Galladium acetate to give Gadoteridol. Process is having drawback of overall low yield (25%) and long hours for process.

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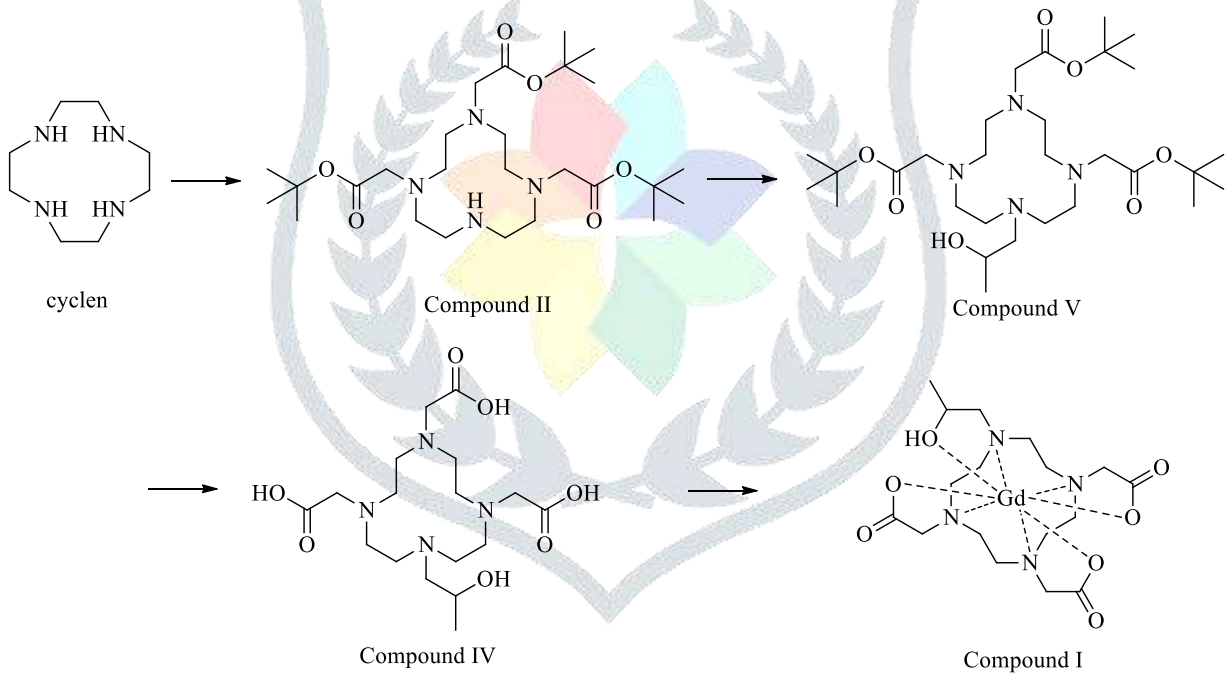
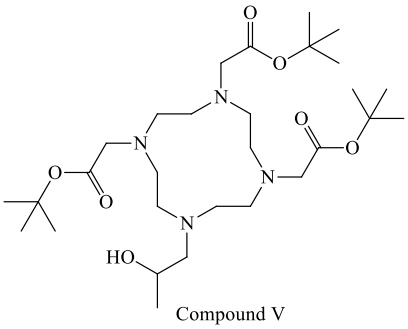


Description of the invention

Very important aspects in the preparation of Gadoteridol are quality and production costs of the end product. Owing to regulatory requirements, high quality standards have to be met. Of interest in this context are purity and content of the active compound. Coupled to purity, it is in particular the spectrum of by-products which needs to be monitored. Minor components have to be toxicologically qualified and assessed. Accordingly, they are listed in specifications and the maximum occurrence in the product is defined. For reasons of product safety and for the good of the patient, the by-product spectrum and the presence of individual contaminants are kept as low as possible to achieve the desire result.

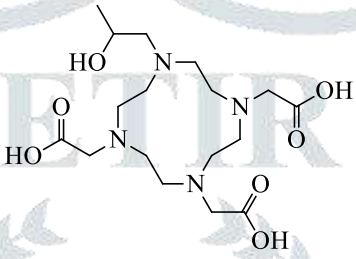
In the first embodiment, the present invention step 1 is performed in a same manner as performed in "Graphene Oxide Enhances Cellular Delivery of Hydrophilic Small Molecules by Co-Incubation" from ACS Nano, 8(10), 10168-10177; 2014 to get the compound II.

In step 2 of the present invention compound II is treated with propylene oxide in suitable solvent to get novelcompound of formula V.



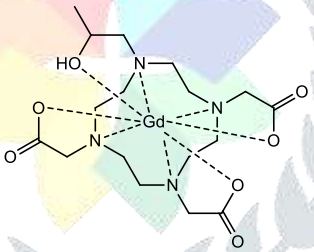
Compound V

In another embodiment of present invention compound V is further treated with hydrolysing agent in suitable solvent to get the Compound IV.



Compound IV

Compound IV on further treatment with Gadolinium chloride in suitable solvent gives compound I.



In the second embodiments of the present application provides detailed process for preparing a Gadoteridol comprising steps of:

a) Protecting the cyclen with tert-butyl 2-haloacetatein solvent to get tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (Compound II);

b) coupling the tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (Compound II) with propylene oxide to get tri-tert-butyl 2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate(Compound III).

c) hydrolysing the tri-tert-butyl 2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate(Compound III)to get 2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid(Compound IV).

d) gadolinium complex formation by treating 2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid(Compound IV) with gadolinium chloride to get Gadoteridol(Compound I).

Protecting the cyclen in step a includes; reactinga cyclen with tert-butyl 2-haloacetate to get compound II; wherein halo can either be fluro, chloro, bromo or iodo.

Suitable base is required for the step a to proceed, base is not limited to sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, potassium hydroxide etc.

Suitable solvents which can be used in step a for the preparation of compound II includes nitriles such as acetonitrile, propionitrile and the like; cyclic ether such as tetrahydrofuran, furan, ethylene oxide, solvents like DMSO, DMF, DMA and the like; any mixtures of two or more thereof. Preferably nitrile solvent, more preferably acetonitrile.

A suitable temperature for the reaction of step a, may be about -20° to about 50°C, preferably less than about 40°C, or less than about 30°C, or any other suitable temperatures. The reaction may be carried out for any desired time period ranging from about 30 minutes to about 24 hours or longer.

Step b involves coupling of compound II with propylene oxide by using base in suitable solvent to get compound V.

Suitable base which is used for the coupling can be selected from organic or in-organic base, base is not limited to sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, potassium hydroxide etc. Preferably potassium carbonate is selected for reaction.

Suitable solvents which can be used in step b for the preparation of compound V includes nitriles such as acetonitrile, propionitrile and the like; cyclic ether such as tetrahydrofuran, furan, ethylene oxide, solvents like dichloromethane, DMSO, DMF, DMA and the like; and any mixtures of one or more thereof. Preferably nitrile solvent is selected, more preferably acetonitrile.

A suitable temperature for the reaction of step b, may be about 0° to about 80°C, preferably less than about 70°C, or less than about 60°C, more preferably at about 55-60°C. The reaction may be carried out for any desired time period ranging from about 30 minutes to about 24 hours or longer, preferably about 12-15 hours.

Step C involves the hydrolysis of compound V in the presence of reagent and solvent to get compound IV.

Suitable reagent required for hydrolysis includes acetic acid, trifluroacetic acid, sulfuric acid, hydrochloric acid or trichloroacetic acid. Preferably sulfuric acid and trifluroacetic acid, more preferably trifluroacetic acid.

Suitable solvent required for step C includes halogenated solvents like dichloromethane, carbon tetra chloride, chloroform and ethylene dichloride. Preferably dichloromethane and ethylene dichloride, more preferably dichloromethane.

A suitable temperature for the reaction of step c, may be about 0° to about 80°C, preferably less than about 70°C, or less than about 60°C, more preferably at about 55-60°C. The reaction may be carried out for any desired time period ranging from about 30 minutes to about 24 hours or longer, preferably about 12-15 hours.

The isolation of crystalline Gadoteridol may be induced by using conventional techniques known in the art. For example, useful techniques include but are not limited to, concentrating, cooling, separation, stirring, shaking, combining with an anti-solvent, adding seed crystals, evaporation, flash evaporation, simple evaporation, rotational drying, or the like. The solid that is obtained may carry a small proportion of occluded mother liquor containing a higher percentage of impurities and, if desired, the solid may be washed with a solvent to wash out the mother liquor. Evaporation as used herein refers to distilling of solvent almost completely at atmospheric pressure or under reduced pressure. Flash evaporation as used herein refers to distilling of solvent by using a technique includes but is not limited to tray drying, fluidized bed drying. The recovery of crystalline Gadoteridol can be done by decantation, centrifugation, gravity filtration, suction filtration and like.

The resulting compound Gadoteridol may be optionally further dried. Drying can be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying can be carried out at temperatures of less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperatures; at atmospheric pressure or under a reduced pressure; as long as the crystalline Gadoteridol is not degraded in its quality. The drying can be carried out for any desired times until the required product quality is achieved. Suitable time for drying can vary from few minutes to several hours for example from about 30 minutes to about 24 or more hours.

Once obtained, crystals of Gadoteridol may be used as the nucleating agent or "seed" crystals for subsequent crystallizations of Gadoteridol from solutions.

A suitable temperature for the reaction of step a, step b and step c may be less than about 0° to about 80°C,preferably less than about 60°C, or less than about 45°C, or less than about 30°C, or any other suitable temperatures. The reaction may be carried out for any desired time period ranging from about 30minutes to about 24 hours or longer.

The Gadoteridol synthesize by this route have advantageous properties selected from at least one of: chemical purity, stability - such as storage stability, stability to dehydration, stability to polymorphic conversion, flow ability, solubility, morphology or crystal habit, low hygroscopicity and low content of residual solvents.

Certain specific aspects and embodiments of the present application will be explained in more detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the present application in any manner.

Experimental Section

Preparation of Gadoteridol

Example-1: Preparation of tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate

Charged Cyclen (100 gm) and Acetonitrile (5 L) into clean RB flask at 25-35°C. The sodium bicarbonate (146.28 gm) was added in reaction mass at 25-30 °C. Reaction mass stirred at 25-35°C for 15 minutes. Cooled the reaction mass at -15°C to -10°C. Meanwhile dissolved tertiary butyl bromo acetate (339.67 gm) into Acetonitrile (1 L) at 25-30°C. Started addition of above tertiary butyl bromo acetate solution in Acetonitrile into reaction mass at -15°C to -10°C. Reaction mass stirred at -15°C to -10°C for 7-10 hrs. Slowly raised the temperature upto 25-30°C and stirred the reaction mass at 25-30°C for 72 hours. After the completion of reaction, mass was filtered and washed with acetonitrile (1L). Filtrate was distilled off till 3 Vol. of Acetonitrile remain. Slowly charged Diisopropyl ether (1.2 L) into reaction mass. Stirred the reaction mass at 25-30°C for 5-6 hours. Reaction mass was filtered and washed with Diisopropyl ether (200ml) to get tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate.

Yield=50%

HPLC purity> 99.00%

Example-2:Preparation of tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate

Tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (100g) was dissolved in acetonitrile (1000 ml). Reaction mixture was further charged with potassium carbonate (116g) and propylene oxide (100 mL). Reaction was further heated to 40-45°C and stirred for 12-15 hrs.at40-45°C. Cooled the reaction mass at 25-30°C and charged propylene oxide (25 mL) into reaction mass. Reaction was further heated to 40-45°C and stirred for 5-6 hrs. at 40-45°C. Cooled the reaction mass at 25-30°C and charged propylene oxide (25 mL) into reaction mass. Reaction was further heated to 40-45°C and stirred for 5-6 hrs. at 40-45°C. After completion of reaction filtered the reaction mass through celite bed and washed bed with Acetonitrile (100 mL X 3). Filtrate distilled out under vacuum. Charged Diisopropylether (1000 mL) into reaction mass. Heated reaction mass at 40-45°C for 2 hours. After cooling to 25-30°C, mass was filtered and washed with Diisopropylether (100 mL) to get tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate as white solid.

Yield=80-90%

HPLC Purity > 95%

Example-3: Preparation of tri-tert-butyl 2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid

Charged tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (100 gm) and Process water (400 mL) into reaction mass at 25-30°C. Slowly charged Con. Sulphuric acid (20 mL) into reaction mass at 25-30°C. Heated reaction mass at 60-65°C. A reaction was performed for 4 hours at the same temperature and cooled to room temperature (20 to 25 °C) upon confirming termination of the reaction. When the cooling was completed, the same was treated with resin (5 v/w) and concentrated. 90 ml of methanol and 300 ml of acetone / Ethyl acetate were added to the concentrated residue and resulting crystal was washed with acetone.

Yield:-70-80%

HPLC Purity > 90.00%

Or

Example-3: Preparation of tri-tert-butyl 2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid

Charged tri-tert-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (100 gm) and Dichloromethane (1000 mL) into reaction mass at 25-30°C. Slowly charged Trifluroacetic acid (500 mL) into reaction mass at 25-30°C. Stirred reaction mass at 25-30°C for 12-15 hrs..Distilled out reaction mass completely and cooled to 25-30°C. When the cooling was completed, the same was treated with resin (5 v/w) and concentrated. 90 ml of methanol and 300 ml of acetone/ Ethyl acetate were added to the concentrated residue and resulting crystal was washed with acetone.

Yield:-70-80%

HPLC Purity > 90.00%

Example-4: Preparation of Gadoteridol

2,2',2''-(10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (100g) was dissolved in methanol (1000ml). Potassium hydroxide (55.48 g) and gadolinium chloride (65.17 g) were added in the reaction mass and mixture was stirred at 55-60°C for 10-12 hrs. After completion of reaction, mixture was acidified to pH 5.5-6.5 with dilute HCl. Reaction mass was distilled off and after cooling solid were dissolved in water. When the cooling was completed, the same was treated with resin (5 v/w) and concentrated. After distillation under vacuum, residue were taken in isopropyl alcohol (500 ml) and then stirred at 25-30°C for 1-2 hours. Solid was filtered & washed with isopropyl alcohol (50 ml X2) to get pure Gadoteridol.

Yield=75-85%

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