



US009409926B2

(12) **United States Patent**
Takenaka et al.

(10) **Patent No.:** **US 9,409,926 B2**

(45) **Date of Patent:** **Aug. 9, 2016**

(54) **CHIRAL 4-BORONOPHENYLALANINE (BPA) DERIVATIVE AND METHOD FOR PRODUCING SAME, AND METHOD FOR PRODUCING ¹⁸F-LABELED BPA USING SAID DERIVATIVE**

(58) **Field of Classification Search**
CPC C07F 5/025; C07F 5/027
See application file for complete search history.

(56) **References Cited**

(71) Applicants: **Osaka Prefecture University Public Corporation**, Sakai-Shi, Osaka (JP); **Stella Pharma Corporation**, Chuo-ku, Osaka-Shi, Osaka (JP)

FOREIGN PATENT DOCUMENTS

JP 2000 212185 A 8/2000
JP 2008-214319 A 9/2008

(72) Inventors: **Hiroshi Takenaka**, Osaka (JP); **Yoichiro Ohta**, Osaka (JP); **Yusuke Taguchi**, Osaka (JP); **Sayuri Ueda**, Osaka (JP); **Yuko Ishino**, Osaka (JP); **Hideki Nakashima**, Osaka (JP); **Kohki Uehara**, Osaka (JP); **Mitsunori Kirihata**, Sakai (JP)

OTHER PUBLICATIONS

Suominen, 2001, *Frontiers in Neutron Capture Therapy*, p. 839-841.*
Endo, Yasuyuki, et al., Role of the hydrophobic moiety of tumor promoters. *Synthesis and Activity of 9-Alkylated Benzolactams*, *Chem. Pharm. Bull.*, 44(5), p. 1138-1140, 1996.
Ishiwata, Kiichi, et al., *Synthesis and Radiation Dosimetry of 4-Borono-2-[¹⁸F] Fluoro-D, L-phenylalanine; a Target Compound for PET and Boron Neutron Capture Therapy*. *Appl. Radiat. Isot.*, vol. 42, No. 4, 325-328, 1991.
McAllister, Laura A., et al., A General Strategy for the Synthesis of Cyclic N-Aryl Hydroxamic Acids via Partial Nitro Group Reduction, *Journal of Organic Chemistry*, 76(9), p. 3484-3497, 2011.
Meyer, Falco-Magnus, et al., Functionalization of Aromatic Amino Acids via Direct C—H Activation: Generation of Versatile Building Blocks for Accessing Novel Peptide Space, *Organic Letters*, 12(17), p. 3870-3873, 2010.
Porcari, P. et al., In vivo ¹⁹F MR imaging and spectroscopy for the BNCT optimization, *Applied Radiation and Isotopes*, 67, S365-368, 2009.
Tuttle, Jamison B., et al., Synthesis of ortho-substituted nitroaromatics via improved Negishi coupling conditions, *Tetrahedron Letters*, 52(41), p. 5211-5213, 2011.
Vahatalo, Jyrki K., et al., Synthesis of 4-dihydroxyboryl-2-[¹⁸F] fluorophenylalanine with relatively high-specific activity. *J. Labelled Compounds and Radiopharmaceuticals*, 45, p. 697-704, 2002.

(73) Assignee: **STELLA PHARMA CORPORATION; OSAKA PREFECTURE UNIVERSITY PUBLIC CORPORATION**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/435,678**

(22) PCT Filed: **Oct. 8, 2013**

(86) PCT No.: **PCT/JP2013/077366**

§ 371 (c)(1),

(2) Date: **Apr. 14, 2015**

(87) PCT Pub. No.: **WO2014/061508**

PCT Pub. Date: **Apr. 24, 2014**

(65) **Prior Publication Data**

US 2015/0329564 A1 Nov. 19, 2015

(30) **Foreign Application Priority Data**

Oct. 15, 2012 (JP) 2012-228053

(51) **Int. Cl.**

C07F 5/02 (2006.01)

C07C 229/08 (2006.01)

C07F 5/04 (2006.01)

C07C 229/36 (2006.01)

C07B 59/00 (2006.01)

C07C 271/22 (2006.01)

C07C 251/24 (2006.01)

(52) **U.S. Cl.**

CPC **C07F 5/025** (2013.01); **C07B 59/001** (2013.01); **C07C 229/08** (2013.01); **C07C 229/36** (2013.01); **C07C 251/24** (2013.01); **C07C 271/22** (2013.01); **C07F 5/027** (2013.01); **C07F 5/04** (2013.01); **Y02P 20/55** (2015.11)

(Continued)

Primary Examiner — Michael Barker

Assistant Examiner — Karen Cheng

(74) *Attorney, Agent, or Firm* — Knobbe Martens Olson & Bear LLP

(57) **ABSTRACT**

Provided are: a novel chiral 4-boronophenylalanine (BPA) derivative; a method for producing the derivative; and a method for producing ¹⁸F-2-fluoro-4-borono-L-phenylalanine (¹⁸F-labeled BPA; 18F-BPA) using the derivative. A compound represented by formula (1) is prepared. In the formula, R represents BR³R⁴, BX₃⁻ or BX₃⁻M⁺ (wherein X represents a halogen atom, and M⁺ represents a monovalent monoatomic cation, a polyatomic cation or a complex cation); R₁ represents a hydrogen atom or a protecting group PG1; R₂ represents a hydrogen atom or a protecting group PG2; R₃ and R₄ independently represent OH, or R³, R⁴ and B together form a ring that serves as a protecting group; and Y represents a halogen atom, NO₂, NH₂, Sn(R⁶)₃, N=N—NR⁷R⁸, OSO₂R⁹, NR¹⁰R¹¹, a substituted or unsubstituted phenylido group or a substituted or unsubstituted heterocyclic iodo group. The compound is reacted with a fluorination reagent to prepare ¹⁸F-labeled BPA.

7 Claims, No Drawings