(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 September 2012 (13.09.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/120025 A1

(51) International Patent Classification:
C07C 229/48 (2006.01) *C07C 227/16* (2006.01)

(21) International Application Number:
PCT/EP2012/053867

(22) International Filing Date:
7 March 2012 (07.03.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/450,177 8 March 2011 (08.03.2011) US

(71) Applicant *(for all designated States except US)*: **GE HEALTHCARE LIMITED** [GB/GB]; Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FAIRWAY, Steven, Michael** [GB/NO]; GE Healthcare AS, Nycoveien 1-2, Postboks 4220, Nydalen, N-0401 Oslo (NO). **ROLAN-DSGARD, Marit** [NO/NO]; GE Healthcare AS, Nycoveien 1-2, Postboks 4220, Nydalen, N-0401 Oslo (NO).

(74) Agents: **BANNAN, Sally** et al.; GE Healthcare Limited, Pollards Wood, Nightingales Lane, Chalfont St Giles, Buckinghamshire HP8 4SP (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2012/120025 A1

(54) Title: PREPARATION OF A 1-AMINO-3-HYDROXY-CYCLOBUTANE-1-CARBOXYLIC ACID DERIVATIVE

(57) Abstract: The invention relates to a process for preparation of radiopharmaceutical precursors, and in particular protected amino acid derivatives which are used as precursors for production of radiolabelled amino acids for use in *in vivo* imaging procedures such as positron emission tomography (PET). Particularly, the invention relates to a process for preparation of a precursor of the [^{18}F]-1-amino-3-fluorocyclobutanecarboxylic acid ([^{18}F] FACBC) PET agent, ensuring that the reaction efficiently goes to completion.

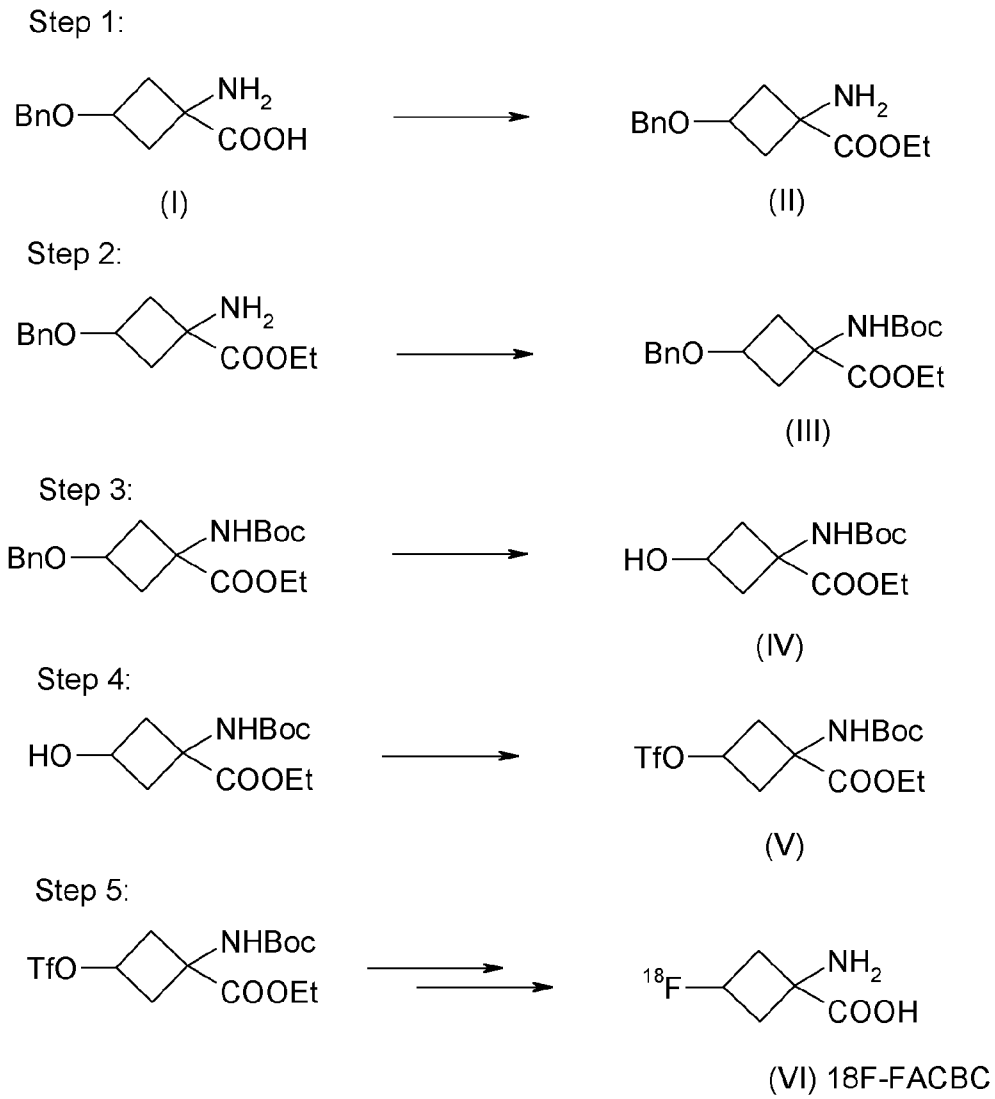
PREPARATION OF A 1 -AMINO - 3 - HYDROXY - CYCLOBUTANE - 1 - CARBOXYLIC ACID DERIVATIVE

The invention relates to a process for preparation of radiopharmaceutical precursors, and in particular protected amino acid derivatives which are used as precursors for production of radiolabelled amino acids for use in *in vivo* imaging procedures such as positron emission tomography (PET). Particularly, the invention relates to a process for preparation of a precursor of the [^{18}F]-1-amino-3-fluorocyclobutanecarboxylic acid ([^{18}F] FACBC) PET agent.

Nuclear medicine examination represented by positron emission tomography (PET) is effective in diagnosing a variety of diseases including heart diseases and cancer. These techniques involve administering an agent labeled with a specific radioisotope (hereinafter referred to as radiopharmaceutical) to a patient, followed by detecting γ-rays emitted directly or indirectly from the agent. Nuclear medicine examination is characteristic in that it has not only high specificity and sensitivity to diseases, but also an advantage of providing information on the functionality of lesions, compared to other examination techniques. For example, [^{18}F]2-fluoro-2-deoxy-D-glucose ("[^{18}F]FDG"), one radiopharmaceutical used for PET examination, tends to be concentrated in area where glucose metabolism is enhanced, thereby making it possible to specifically detect tumors in which glucose metabolism is enhanced. Nuclear medicine examination is performed by tracing a distribution of an administered radiopharmaceutical, and data obtained there from vary depending on nature of the radiopharmaceutical. Thus, different radiopharmaceuticals have been developed for different diseases, and some of them are put into clinical use. There have been developed, for example, various tumor diagnostic agents, bloodstream diagnostic agents and receptor mapping agents.

In recent years, a series of radioactive halogen-labeled amino acid compounds including [^{18}F]-1-amino-3-fluorocyclobutanecarboxylic acid ([^{18}F]FACBC) have been designed as novel radiopharmaceuticals. [^{18}F]FACBC is considered to be effective as a diagnostic agent for highly proliferative tumors, because it has a property of being taken up specifically by amino acid transporters. Improved processes for preparation of [^{18}F]FACBC and its precursors are sought.

EP1978015 (A1) provides processes for producing [^{18}F] FACBC on a small scale. One of the intermediates in this process is 1-(N-(*t*-butoxycarbonyl) amino)-3-hydroxy-cyclobutane-1-carboxylic acid ethyl ester (Formula IV in Scheme 1 below). In the process step of EP1978015 (A1) for preparing this intermediate, dry palladium at neutral pH is used. Scheme 1 shows the multi-step synthesis, as outlined in EP1978015 (A1), for preparation of [^{18}F] FACBC.

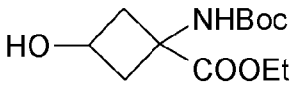


Scheme 1

In Scheme 1 above, BnO denotes Benzyl ether, Boc denotes *tert*-butyl carbamate (tert-butoxycarbonyl) and OTf denotes Trifluoromethanesulfonate.

The last steps of the synthesis of [^{18}F]FACBC, performed on an automated synthesiser unit, are based on nucleophilic displacement of a triflate group by [^{18}F]fluoride from the precursor of Formula (V). The [^{18}F]fluoride may be introduced with a solution of kryptofix (K222), potassium carbonate, water and acetonitrile into the reaction vessel. The ^{18}F-labelled intermediate compound then undergoes two deprotecting steps, where the ethyl and the Boc protecting groups are removed by basic and acidic hydrolysis, respectively.

The compound of Formula (IV):



(IV)

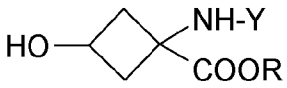
is named 1-(N-(*t*-butoxycarbonyl) amino)-3-hydroxy-cyclobutane-1-carboxylic acid ethyl ester. This intermediate is prepared by hydrogenolysis of 1-(N-(*t*-butoxycarbonyl) amino)-3-benzyloxy-cyclobutane-1-carboxylic acid ethyl ester (Formula III), as shown in step 3 of Scheme 1. Such hydrogenolysis, or debenzylation, may be performed by the use of a palladium catalyst and hydrogen gas. In small scale a dry palladium catalyst is acceptable to use, but in a larger scale it would be better to use a wet palladium catalyst from safety perspectives, as palladium is pyrophoric under certain conditions and can hence ignite. However, when performing this hydrogenolysis in larger scale and exchanging the dry palladium with wet palladium, it was experienced that the removal of the benzyl group was incomplete, even after several days. On a smaller scale, and using dry palladium, the hydrogenolysis reaction went to completion after 2-4 days.

Therefore, there is a need for a process for preparing the compound of Formula (IV) which is safe and which efficiently goes to completion.

It has now surprisingly been found that using particular conditions that the process can be successfully carried out using wet palladium. The method of the invention therefore avoids the risks of ignition associated with dry palladium, and the

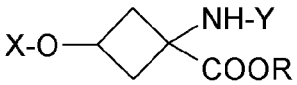
hydrogenolysis reaction goes to completion in an acceptable time period. The solution found is to reduce the pH of the starting material comprising the compound to be hydrogenolysed, and using wet palladium.

Therefore, in a first aspect the invention provides a process for preparation of a compound of Formula IVa:



(IVa)

from a compound of Formula IIIa:



(IIIa)

wherein:

R denotes an alkyl group with 1 to 5 carbon atoms;

Y denotes a protecting group for an amine;

X denotes a protecting group for an alcohol;

wherein the process includes adjusting the pH of a reaction medium comprising the compound of Formula IIIa to 2.0-5.0, and performing a hydrogenolysis of X using a wet catalyst selected from the platinum group metals.

The moiety R is a linear or branched alkyl chain, and is preferably an alkyl group selected from methyl, ethyl, 1-propyl or isopropyl, and is most preferably ethyl.

The term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical having the general formula C_nH_{2n+1}. Examples of such radicals include methyl, ethyl, and isopropyl.

The term "alcohol" herein refers to a substituent comprising the group –OH.

The term "amine" herein refers to the group –NR'R" wherein R' and R" are independently hydrogen or an alkyl, and are preferably both hydrogen.

By the term "protecting group" is meant a group which inhibits or suppresses undesirable chemical reactions, but which is designed to be sufficiently reactive that it may be cleaved from the functional group in question to obtain the desired product under mild enough conditions that do not modify the rest of the molecule. Protecting groups are well known to those skilled in the art and are described in 'Protective Groups in Organic Synthesis', Theorodora W. Greene and Peter G. M. Wuts, (Fourth Edition, John Wiley & Sons, 2007).

A preferred amino protecting group for use in the present invention is selected from the group consisting of a t-butoxycarbonyl group, an allyloxycarbonyl group, a phthalimide group and N-benzylideneamine substituent. The Y moiety is hence a protecting group for an amine, such as for a carbamate.

The X moiety is a protecting group for alcohol, the protecting group is chosen so that the protecting group forms its related ether, such as; benzyl (Bn), benzyl carbonates, methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), methylthiomethyl (MTM), tetrahydropyranyl (THP), benzyloxymethyl (BOM), *p*-Methoxyphenyl, *p*-methoxybenzyl (MPM), *p*-methoxybenzyloxymethyl (PMBM), triisopropylsilyl (TIPS), *tert*-butyldimethylsilyl (TBDMS), 2-(trimethylsilyl)ethoxymethyl (SEM) and (phenyldimethylsilyl)methoxymethyl (SMOM). A group that can be removed by hydrogenation is preferred and in a preferred embodiment X is benzyl.

In a particularly preferred embodiment R is an ethyl group, Y is BOC and X is benzyl such that the compound of Formula IVa is a compound of Formula IV and the compound of Formual IIIa is a compound of Formula III, according to Scheme 1.

The catalyst used in the process of the invention is selected from the group of platinum metal group, and is accordingly selected from the group of ruthenium, rhodium, palladium, osmium, iridium, and platinum. More preferably, the catalyst is palladium.

The catalyst used in the process of the invention should be wet to avoid any risk of ignition. The catalyst used is preferably in the form of a thick slurry, and such slurry includes water. In one embodiment the wet catalyst includes 30-70 % weight%

water, more preferably 40-60 weight% water, and most preferably 45-55 weight% water. In a particularly preferable embodiment the wet catalyst includes about 50 weight% water. Further, the catalyst used is preferably a heterogeneous catalyst, meaning that it includes solid particles of the metal which is suspended in the reaction medium. The catalyst used in the invention, such as palladium, is preferably distributed over finely divided carbon, referred to as palladium on carbon (Pd/C). Such catalysts are commercially available with a metal loading of 1 – 30 %, and these can be used in the method of the invention. The metal loading, such as the palladium loading, is more preferably 1-10% and most preferably 5-10 %. The amount of catalyst to be used in the process depends on which catalyst is chosen, and on the percentage of loading. With e.g. a 10 % loaded palladium on carbon catalyst, the amount of catalyst to be used in the method of the invention is 1-30 weight%/compound, more preferably 5-20 weight%/compound and most preferably around 10 weight%/compound. The "compound" in this context is the start material, i.e. a compound of Formula IIIa, such as the compound of Formula III.

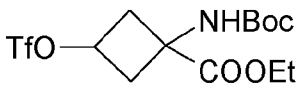
The hydrogenolysis reaction of the process of the invention is conducted catalytically using a hydrogen source. The preferred hydrogen source is hydrogen gas.

When performing the process of the invention it has surprisingly been found that by combining the use of wet catalyst and adjusting pH, the debenzylation was successfully driven to completion. The pH of a reaction medium comprising a compound of Formula IIIa, such as a compound of Formula III, and a solvent, is adjusted to 2.0-5.0 by the addition of an acid. More preferably, the pH is adjusted to 2.5-3.5 and most preferably to 3.0. It has surprisingly been found that the debenzylation reaction went to completion at these conditions in an acceptable short time, at the same time as the protecting group of the amine function (group Y) was not affected. This protecting group is later to be removed by acidic hydrolysis, and it is crucial that it is not removed during the dehydrogenolysis step of the process of the invention. The acid used in the process is a mineral acid or an organic acid and is preferably selected from the group of hydrochloric acid, acetic acid, formic acid and sulphuric acid. Most preferably the acid is acetic acid. In the process of the invention the compound of Formula IIIa is hence dissolved in a solvent and the pH is measured

and adjusted to the desired level by the addition of an acid to the reaction medium. The solvent used to dissolve the compound of Formula IIIa, such as the compound of Formula III, is a polar solvent, either protic or aprotic, and is preferably selected from the group of alcohols, esters, ethers and chlorinated solvents. The solvent is more preferably an alcohol and most preferably ethanol. The amount of solvent should be sufficient to completely solve the compound of Formula IIIa. The mol/ml ratio between the compound of Formula IIIa and the solvent is e.g. between 1:4 to 1:8.

The process of the invention can be used in all scales and is particularly useful when preparing in large scale, such as when preparing 100 grams or more, such as 300 grams, or up to 500 grams or more, of the compound of Formula IVa. In smaller scales, a dry platinum group metal catalyst may be used, but when scaling up, for safety reasons it is advantageous to use such catalyst in wet form. The process of the invention including wet palladium and adjusting the pH of the reaction medium to 2.0-5.0 has been found much safer, more efficient, and also more cost efficient as the hydrogenolysis reaction goes to completion in short time. Without the addition of the acid the reaction was incomplete, while when performing the process of the invention the dehydrogenolysis goes to completion, such as in five days or less, preferably in four days or less and most preferably in 3 days of less.

In a further aspect, the invention provides a process for preparing the precursor compound of ^{18}F-FACBC, according to Formula V:



(V)

including a step of preparing the compound of Formula IV according to the process of the first aspect. OTf denotes trifluorormethanesulfonate. Y in Formula IVa is then Boc and R is ethyl.

The invention is illustrated by way of the example below.

Examples:

Example 1:

1-(N-(*t*-butoxycarbonyl) amino)-3-benzyloxy-cyclobutane-1-carboxylic acid ethyl ester (Compound of Formula III) in various amounts was added ethanol (18.4-20.0 ml/g). Several tests were performed to optimize the debenzylation reaction to prepare 1-(N-(*t*-butoxycarbonyl)amino)-3-hydroxy-cyclobutane-1-carboxylic acid ethyl ester (Compound of Formula IV). Various amounts of acetic acid was added to the reaction media comprising the compound of Formula III and ethanol, to adjust the pH to around 3. Various amounts of palladium on carbon (10% loading), were used for the dehydogenolysis, testing both wet and dry catalysts. The reactions were traced by TLC. The results are found in table 1.

Table 1:

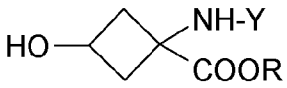
Test no.	Com-pound III (g)	Acetic acid (ml/g compou nd III)	Pd-C (g/g compoun d III)	Weight% Pd-C/comp-ound III (%)	Pd quality	Reaction time (days)	Reactio n comple tion by TLC
1	1		0,25	25	dry	4	Yes
2	20		0,12	12	dry	2	Yes
3	14		0,12	12	dry	3	Almost
4	270		0,12	12	dry	2	Yes
5	30		0,12	12	dry	8	No
6	3		0,17	17	wet	8	No
7	3		1,316	131.6	wet	10	Yes
8	3		0,379	37.9	dry	5	Almost
9	1	0,21	0,33	16.5	wet	2	Yes
10	1	0,20	0,30	15	wet	2	Yes
11	1	0,20	0,10	5	wet	4	Yes
12	1	1,99	0,20	10	wet	2	Yes
13	6	0,20	0,20	10	wet	3	Yes
14	32	0,25	0,20	10	wet	2	Yes

It was found that when using the palladium catalyst in the wet form, and adjusting the pH to around 3, the reaction went to completion in only 2-4 days. Without the pH adjustment, performing the reaction at neutral pH, and using wet palladium, the

debenzylation did either not go to completion, or it took as much as 10 days to complete.

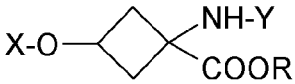
Claims:

1. A process for preparation of a compound of Formula IVa:



(IVa)

from a compound of Formula IIIa:



(IIIa)

wherein:

R denotes an alkyl group with 1 to 5 carbon atoms;

Y denotes a protecting group for an amine; and,

X denotes a protecting group for an alcohol;

wherein the process includes adjusting the pH of a reaction medium comprising compound of Formula IIIa to 2.0-5.0, and performing a hydrogenolysis of X using a wet catalyst selected from the platinum group metals.

2. A process as defined in Claim 1 wherein R is an ethyl group, Y is BOC and X is benzyl.

3. A process as defined in either Claim 1 or Claim 2 wherein the catalyst is selected from the group of ruthenium, rhodium, palladium, osmium, iridium, and platinum.

4. A process as defined in any one of Claims 1 to 3 wherein the catalyst is palladium.

5. A process as defined in any one of Claims 1 to 4 wherein the catalyst is palladium on carbon with a palladium loading of 1-10 %.

6. A process as defined in any one of Claims 1 to 5 wherein the reaction medium further comprises a solvent.

7. A process as defined in Claim 6 wherein the solvent is ethanol.

8. A process as defined in any one of Claims 1 to 7 wherein the adjustment of pH is performed by adding an acid to the reaction medium.

9. A process as defined in Claim 8 wherein the acid is acetic acid.

10. A process as defined in any one of Claims 1 to 9 wherein the pH is adjusted to 2.5-3.5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/053867

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C229/48 C07C227/16
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHOUP T M ET AL: "Synthesis of ÄF-18Ü-1-amino-3-fluorocyclobutane-1-carboxylic acid (FACBC): a PET tracer for tumor delineation", JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, JOHN WILEY, CHICHESTER, GB, vol. 42, no. 3, 1 January 1999 (1999-01-01), pages 215-225, XP003003890, ISSN: 0362-4803, DOI: 10.1002/(SICI)1099-1344(199903)42:3<215::AID-JLCR180>3.0.CO;2-0 page 217, Figure 1, compound 7 to compound 8; page 222, lines 3-12 ----- -/--	1-10

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2012	17/07/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YU W ET AL: "Stereoselective synthesis and biological evaluation of syn-1-amino-3-[<18>F]fluorocyclobutyl-1-carboxylic acid as a potential positron emission tomography brain tumor imaging agent", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 17, no. 5, 1 March 2009 (2009-03-01), pages 1982-1990, XP025992071, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2009.01.032 [retrieved on 2009-01-21] page 1983, Scheme 1, compound 7 to compound 8, step d; page 1988, 4.7. with 4.7.1., 4.7.2. and 4.7.3.	1-10
Y	EP 1 978 015 A1 (NIHON MEDIPHYSICS CO LTD [JP]) 8 October 2008 (2008-10-08) [0038]; Figure 2	1-10
Y	AVRAM, M ET AL: "Untersuchungen in der Cyclobutane reihe, I - 1,3-Disubstituierte Cyclobutanderivate", CHEMISCHE BERICHTE, vol. 90, 1957, pages 1424-1431, XP002679070, page 1425, second equation, compound IV to compound V; page 1427, line 2 from the bottom to page1428, line 5	1-10
Y	US 2009/233903 A1 (RODGERS JAMES D [US] ET AL) 17 September 2009 (2009-09-17) pages 41-42, [0330]-[0332]	1-10
Y	ALIBES, RAMON ET AL: "Highly Efficient and Diastereoselective Synthesis of (+)-Lineatin", ORGANIC LETTERS, vol. 6, no. 9, 2004, pages 1449-1452, XP002679071, DOI: 10.1021/ol0497032 page 1451, Scheme 4: compound 14 to compound 15	1-10
Y	WO 2007/062333 A2 (GLAXO GROUP LTD [GB]; IGO DAVID H [US]; NORTON BETH A [US]) 31 May 2007 (2007-05-31) page 13, lines 19-32, compound 4f to compound 4g	1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/053867

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1978015 A1	08-10-2008	AU 2006319987 A1	07-06-2007
		BR PI0619213 A2	20-09-2011
		CA 2629227 A1	07-06-2007
		CN 101316812 A	03-12-2008
		EP 1978015 A1	08-10-2008
		KR 20080071146 A	01-08-2008
		NZ 568179 A	25-06-2010
		TW 200800869 A	01-01-2008
		US 2008281121 A1	13-11-2008
		WO 2007063824 A1	07-06-2007
US 2009233903 A1	17-09-2009	AU 2009223640 A1	17-09-2009
		CA 2718271 A1	17-09-2009
		CN 102026999 A	20-04-2011
		CO 6290658 A2	20-06-2011
		DO P2010000270 A	15-10-2010
		EA 201071057 A1	28-02-2011
		EC SP10010475 A	30-10-2010
		EP 2288610 A1	02-03-2011
		JP 2011514909 A	12-05-2011
		KR 20100121657 A	18-11-2010
		PA 8819201 A1	27-07-2010
		PE 17122009 A1	21-11-2009
		SV 2010003662 A	17-03-2011
		TW 200942545 A	16-10-2009
		US 2009233903 A1	17-09-2009
		US 2012077798 A1	29-03-2012
		WO 2009114512 A1	17-09-2009
WO 2007062333 A2	31-05-2007	AR 058197 A1	23-01-2008
		AU 2006318238 A1	31-05-2007
		BR PI0618775 A2	13-09-2011
		CA 2630254 A1	31-05-2007
		CN 101360712 A	04-02-2009
		EA 200801364 A1	27-02-2009
		EP 1951671 A2	06-08-2008
		JP 2009516704 A	23-04-2009
		KR 20080080125 A	02-09-2008
		MA 29950 B1	03-11-2008
		US 2008269342 A1	30-10-2008
		WO 2007062333 A2	31-05-2007