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Datasheet for the decision of 14 February 2022

Case Number: T 3012/19 - 3.3.07

Application Number: 11794725.9

Publication Number: 2648767

IPC: A61K51/08, C07B63/00

Language of the proceedings: EN

Title of invention:
RADIOTRACER COMPOSITIONS

Applicant:
GE Healthcare Limited

Headword:
Radiotracer compositions / GE HEALTHCARE

Relevant legal provisions:
RPBA 2020 Art. 13(1), 13(2)
EPC Art. 56

Keyword:
Late-filed evidence - admitted (yes)
Main request - admitted (yes)
Inventive step - (yes)

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Case Number: T 3012/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 February 2022

Appellant: (Applicant)	GE Healthcare Limited Pollards Wood Nightingales Lane Chalfont St. Giles, Buckinghamshire HP8 4SP (GB)
Representative:	Coles, Andrea Birgit Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 17 June 2019 refusing European patent application No. 11794725.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	A. Jimenez

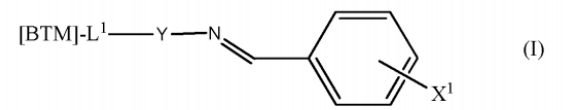
Summary of Facts and Submissions

I. The appeal was filed by the applicant (appellant) against the decision of the examining division to refuse European patent application No. 11 794 725.9 (hereinafter "the application").

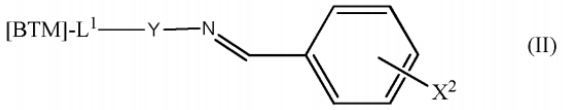
II. The decision was based on a main request filed on 18 April 2019 and an auxiliary request filed during oral proceedings on 22 May 2019.

The independent claims 1 and 9 of the main request read as follows:

"1. A radiopharmaceutical composition which comprises an imaging agent of Formula (I) together with multiple non-radioactive aryl derivatives of Formula (II) together with a biocompatible carrier, in a form suitable for mammalian administration:



(I)



(II)

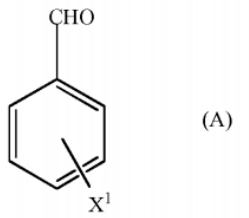
wherein:

BTM is a biological targeting moiety;

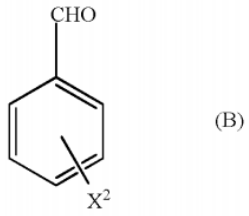
L^1 is a synthetic linker group of formula $-(A)_m-$ wherein each A is independently $-CR_2-$, -CR=CR-, -CC-, $-CR_2CO_2-$. $-CO_2CR_2-$,-NRCO-, -CONR-, -CR=N-O-, -NR(C=O)NR-, -NR(C=S)NR-, SO_2NR-,

$-NRSO_2-$, $-CR_2OCR_2-$, $-CR_2SCR_2-$, $-CR_2NRCR_2-$, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, -Ar-, -NR-Ar-,-O-Ar-, -Ar-(CO)-, an amino acid, a sugar or a monodisperse polyethyleneglycol (PEG) building block, wherein each Ar is independently a C_{5-12} arylene group, or a C_{3-12} heteroarylene group;
each R is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;
m is an integer of value 1 to 20;
Y is -O-;
X^1 is ^{18}F, $-O(CH_2)_q{}^{18}F$ or
$-OCH_2-CH(OH)-CH_2{}^{18}F$,
wherein q is 2, 3 or 4;
X^2 is $-N^+(CH_3)_3$, $-N(CH_3)_2$, $-OCH_3$, H, $-CH_3$, -OH, $-SCH_3$, $-OC_6H_4CHO$ or ^{19}F;
wherein BTM, L^1 and Y are the same in Formula (I) and (II);
and wherein the total concentration of derivatives of Formula (II) present in the composition is less than 150 µg/mL."

"9. A method of radiolabelling a biological targeting moiety which comprises:
(i) provision of a biological targeting moiety functionalized with an aminooxy group of Formula (IV):
[BTM-L'-Y-NH2] (IV)
(ii) provision of a composition which comprises a solution of a radioactive aldehyde of Formula (A) together with multiple non-radioactive aldehydes of Formula (B):

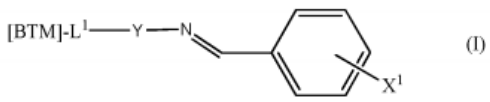


(A)



(B)

wherein the total concentration of derivatives of Formula (B) present in the composition is less than 150 µg/mL;
and wherein the composition is obtained in a method comprising dilution of a crude labelling mixture with ammonium hydroxide solution and purification on an MCX mixed mode solid phase extraction (SPE) cartridge;
(iii) reaction of the functionalized- biological targeting moiety from step (i) with the radioactive aldehyde composition of claim 7 or claim 8, such that the radioactive aldehyde of Formula (A) condenses with said aminooxy group, to give the radiolabelled biological targeting moiety of Formula (I):



(I)

wherein:
BTM, L^1, Y and X^1 are as defined in any one of claims 1 to 6.

Independent claim 1 of the auxiliary request read as follows:

"1. A method of radiolabelling a biological targeting moiety which comprises:

(i) provision of a biological targeting moiety functionalized with an aminooxy group of Formula (IV):

[BTM-L'-Y-NH2] (IV)

wherein:

BTM is a biological targeting moiety;

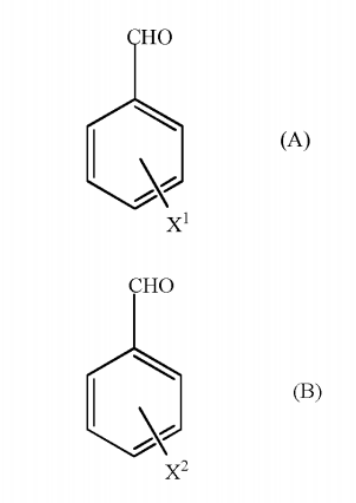
L^1 is a synthetic linker group of formula $-(A)_m-$ wherein each A is independently $-CR_2-$, -CR=CR-, -CC-, $-CR_2CO_2-$. $-CO_2CR_2-$,-NRCO-, -CONR-, -CR=N-O-, -NR(C=O)NR-, -NR(C=S)NR-, SO_2NR-, $-NRSO_2-$, $-CR_2OCR_2-$, $-CR_2SCR_2-$, $-CR_2NRCR_2-$, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, -Ar-, -NR-Ar-,-O-Ar-, -Ar-(CO)-, an amino acid, a sugar or a monodisperse polyethyleneglycol (PEG) building block, wherein each Ar is independently a C_{5-12} arylene group, or a C_{3-12} heteroarylene group;

each R is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl;

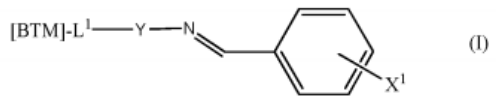
m is an integer of value 1 to 20;

Y is -O-;

(ii) making a composition which comprises a solution of a radioactive aldehyde of Formula (A) together with multiple non-radioactive aldehydes of Formula (B):



wherein:
X^1 is ^{18}F, $-O(CH_2)_q{}^{18}F$ or $-OCH_2-CH(OH)-CH_2{}^{18}F$, wherein q is 2, 3 or4;
X^2 is $-N^+(CH_3)_3$, $-N(CH_3)_2$, $-OCH_3$, H, $-CH_3$, $-OH$, $-SCH_3$, $-OC_6H_4CHO$ or ^{19}F;
wherein the total concentration of derivatives of Formula (B) present in the composition is less than 150 µg/mL;
using a method comprising dilution of a crude labelling mixture with ammonium hydroxide solution and purification on an MCX mixed mode solid phase extraction (SPE) cartridge;
(iii) reaction of the functionalized- biological targeting moiety from step (i) with the radioactive aldehyde composition of step (ii), such that the radioactive aldehyde of Formula (A) condenses with said aminooxy group, to give the radiolabelled biological targeting moiety of Formula (I):



wherein:
BTM, L^1, Y and X^1 are as defined for Formula (IV)."

III. The decision of the examining division, posted on 17 June 2019, cited *inter alia* the following documents:

D2: Poethko T. et al., The Journal of Nuclear Medicine, vol. 45, no. 5, May 2004, pages 892-902
D3: WO 2010/079079 A2

IV. The examining division decided in particular as follows:

(a) The subject-matter of the main request fulfilled the requirements of Article 123(2) EPC but it was not novel over D2.

(b) The auxiliary request fulfilled the requirements of Article 123(2) EPC. The process claimed differed from the one described in D2 in the nature of the column used for the purification, namely a MCX solid phase extraction (SPE) cartridge. However D2 as well as D3 already suggested the use of a cation exchange and reverse phase cartridge to separate the same impurities from the same radiolabelled compounds. Furthermore, the addition of ammonium hydroxide before the purification was, in the absence of any particular effect, considered as part of routine experimentation for the skilled person. Accordingly the subject-matter of the auxiliary request did not involve an inventive step.

V. On 17 October 2019, with its statement setting out the grounds of appeal the appellant filed a main request, which corresponded to the auxiliary request on which the decision of the examining division was based, and a new auxiliary request.

VI. On 29 June 2021, the Board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) 2020, which included the Board's preliminary opinion that the requests on file did not meet the requirements of Article 56 EPC.

VII. With letter dated 14 January 2022, the appellant submitted further arguments and experimental data as Annex 1 and Annex 2.

VIII. On 20 January 2022, the Board issued a communication including a preliminary opinion regarding the issue of inventive step in light of Annex 1 and Annex 2.

IX. Oral proceedings were held by videoconference on 14 February 2022. At the beginning of the oral proceedings, the appellant submitted three further auxiliary requests (auxiliary requests 2-4). In the course of the oral proceedings, the appellant withdrew all requests but auxiliary request 4, which became the new main and sole request.

X. The content of the claims upon which the present decision is based can be illustrated as follows:

Independent claim 1 of the main request corresponded to claim 1 of the auxiliary request filed during first instance oral proceedings, wherein the definitions of X^1 and X^2 were amended and read as follow:

"X^1 is ^{18}F;
X^2 is a combination of $-N^+(CH_3)_3$, $-N(CH_3)_2$, and $-OH$;"

Dependent claim 6 of the main request was also amended and read as follows:

"6. The method of any one of claims 1 to 5, where X^1 is ^{18}F and X^2 is OH."

XI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request filed during oral proceedings (filed as auxiliary request 4).

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) Annex 1, Annex 2 and the main request were filed in response to communications of the Board in order to resolve the issue on file and should thus be admitted into the appeal proceedings.

(b) The dilution of the crude [^{18}F]-fluorobenzaldehyde ([^{18}F]-FBA) composition with ammonium hydroxide prior to the column chromatography, which constituted the distinguishing feature versus the closest prior art D2, was shown to allow the separation of *inter alia* the newly identified hydroxybenzaldehyde (HBA) side product from the crude [^{18}F]-FBA composition. The increased chemical purity of the crude [^{18}F]-FBA composition reduced the risk of competition of benzaldehyde side products with [^{18}F]-FBA for the reaction with the functionalized biological target moiety. The application as filed as well as Annex 1 and Annex 2 provided details of the specific impurities removed from the crude [^{18}F]-FBA mixture using the claimed purification method, thus substantiating the achievement of said effect. Neither D2 nor D3 recognised the presence of chemical impurities. None of these documents thus suggested to dilute

the crude composition with ammonium hydroxide instead of water to solve the problem of providing a method of radiolabelling a biological target moiety with a radioactive aldehyde wherein the purity of the radioactive aldehyde is improved.

Reasons for the Decision

1. Admittance of items of evidence

1.1 With letter dated 14 January 2022, the appellant submitted further items of evidence, namely Annex 1 and Annex 2. Their admittance is to be decided on the basis of Article 13(1) and (2) RPBA 2020.

1.2 The appellant explained in its letter dated 14 January 2022 that these data resolve an issue particularly raised by the Board in its preliminary opinion (namely the absence of comparative data *versus* D2) and do not raise any new issue.

1.3 The Board observes that these data aim at substantiating the effect of the distinguishing feature relating to the addition of ammonium hydroxide. In the decision of the examining division, this addition was not explicitly identified as distinguishing feature in the problem solution approach. One sentence at the end of the reasoning mentioned this aspect: "As regards the addition of ammonium hydroxide to the crude labelling mixture, in the absence of any evidence of a specific effect attributed to it, it is considered to represent a mere disclosure of the pH condition suitable for the process, which is considered to belong to routine experimentation for the skilled person". The preliminary opinion of the Board of 29 June 2021 followed the appellant's approach and explicitly

identified the addition of ammonium hydroxide as distinguishing feature versus D2. The preliminary opinion addressed then in more details the effect of this difference as alleged by the appellant and concluded that this effect had not been experimentally substantiated. The Board's preliminary opinion focused therefore more specifically on this feature compared to the decision of the opposition division (which focused on the nature of the column for the chromatography), even if the same conclusion regarding the absence of substantiation of a particular effect was reached. Hence, Annex 1 and Annex 2 were filed in direct response to the new particular aspect raised by the Board in its preliminary opinion. Hence, the Board considers that the filing of these items of evidence was an appropriate reaction to the preliminary opinion of the Board. Furthermore these items of evidence are suitable to resolve the issue raised in the preliminary opinion of the Board. Accordingly, the Board considers that there are exceptional circumstances justified by cogent reasons to admit Annex 1 and Annex 2 into the appeal proceedings.

Main request

2. Admittance

2.1 The main request was filed during oral proceedings (as auxiliary request 4). Its admittance must be decided on the basis Article 13(1) and (2) RPBA 2020.

2.2 This request was submitted in response to the communication of the Board dated 20 January 2022, wherein the Board indicated that the requests on file did not appear to meet the requirements of Article 56 EPC but that a new independent claim, wherein the

composition defined in step (ii) would mandatorily comprise hydroxy-benzaldehyde (HBA), would preliminarily appear to involve an inventive step. Hence, the Board considers that the filing of the present main request was a proper reaction to the communication of the Board. Furthermore, this request is suitable to resolve the issue of non-compliance with the requirements of Article 56 EPC of the requests previously on file. Accordingly, the Board considers that there are exceptional circumstances justified by cogent reasons to admit the main request into the appeal proceedings.

3. Amendments

3.1 The subject-matter of independent claim 1 is disclosed in original claim 13 together with original claims 1 and 9, as well as:
- original page 10 line 8 (limitation of Y to O),
- original page 19 lines 14-15 (limitation of X^1 to ^{18}F and X^2 to a combination of $-N^+(CH_3)_3$, $-N(CH_3)_2$ and OH; one fold selection for the definition of X^2), and
- original page 20 line 27 to page 21 line 1 (dilution with ammonium hydroxide solution and purification on an MCX mixed mode solid phase extraction (SPE) cartridge).

3.2 Dependent claims 2-5, 6 and 7 correspond to original claims 3-6, 10 and 14. In claim 6, the definition of X^2 was limited to OH, which constitutes an allowable one fold selection.

3.3 Accordingly, the main request meets the requirements of Article 123(2) EPC.

4. Sufficiency of disclosure and novelty

The examining division did not raise any objection of lack of sufficiency of disclosure or novelty for the subject-matter presently claimed. The Board agrees that the subject-matter of the main request fulfills the requirements of Article 83 and 54 EPC.

5. Inventive step

5.1 Closest prior art

5.1.1 The main request relates to a method of radiolabelling a biological targeting moiety with a radioactive benzaldehyde. According to the application as filed, the core of the invention lies in the method of purification of the radioactive benzaldehyde composition. The main purpose is to reduce the number of chemical impurities, in particular those derived from benzaldehyde, to avoid competition reactions with the radioactive benzaldehyde in the next reaction step. The main impurities to be separated are the unreacted starting benzaldehyde, trimethylammonium-benzaldehyde (TMAB), and the side products, dimethylamino-benzaldehyde (DMAB) and hydroxy-benzaldehyde (HBA), see pages 19-21 of the application as published.

5.1.2 In agreement with the examining division and the appellant, the Board considers D2 to represent the closest prior art.

D2 generally discloses a method for the preparation of radiolabelled peptides. The method is based on the same chemical reactions as the method described in the present application, namely:
- the preparation of a [^{18}F]-fluorobenzaldehyde ([^{18}F]-FBA) by fluorination of the corresponding trimethylammoniumbenzaldehyde triflate, and

- the coupling of the obtained [^{18}F]-fluorobenzaldehyde with an aminooxy-functionalised peptide.

In one embodiment of D2, the crude [^{18}F]-FBA is purified using successively a cation-exchange cartridge and a reverse phase cartridge (see Abstract, page 896 1st column 1st paragraph and page 897 1st column 1st full paragraph). D2 mentions that this purification scheme allows the removal of the unreacted [^{18}F]-FBA precursor (*i.e.* TMAB). No further impurity is identified in D2. D2 reports a good radiochemical yield and a high radiochemical purity.

5.2 *Distinguishing feature and related technical effect*

5.2.1 The method of the main request differs from the one of D2 mainly in the method used for the purification of the [^{18}F]-FBA. The present method comprises the addition of ammonium hydroxide and the subsequent purification on a MCX mixed mode solid phase extraction (SPE) cartridge, while in D2, a simple dilution in water is done before a two step SPE (cation-exchange cartridge first and reverse phase cartridge afterwards).

5.2.2 According to the application as filed, the alkaline conditions induced by dilution with ammonium hydroxide ensure that HBA is in ionized form and does not bind to the cartridge allowing its separation from the crude radioactive benzaldehyde composition (see page 21 lines 3-7). The Board further observes that the chromatograms provided in Annex 1 and Annex 2 substantiate that the dilution with ammonium hydroxide prior to MCX-SPE column chromatography allows to separate HBA from a crude [^{18}F]—FBA mixture, while this does not occur when merely diluting with water as in D2. These data thus substantiate that the addition of ammonium hydroxide

prior to the MCX-SPE column chromatography allows to remove not only unreacted TMBA but also HBA from a crude [^{18}F]-FBA mixture. Furthermore, during oral proceedings, the appellant stated that the crude [^{18}F]-FBA mixture analysed by chromatography in Annex 2 had been prepared according to original example 2. Hence, Annex 2 experimentally substantiate the presence of HBA as impurity when following a preparation method according to the invention and D2. Annex 1 and Annex 2 thus experimentally confirm the effect already described in detail in the application as filed.

As explained by the appellant, the fact that HBA is removed avoids competition in the next conjugation step and thus credibly leads to a higher yield of radiolabelled conjugate.

5.3 *Objective technical problem*

5.3.1 It follows that, starting from D2, the objective technical problem to be solved resides in the provision of an improved method for radiolabelling of a biological targeting moiety based on the formation of oximes.

5.3.2 As the claims of the main request define the compulsory presence of HBA in the crude [18F]-FBA composition, the Board is satisfied that this problem has been solved by the present method (see 5.2.2).

5.4 *Obviousness of the solution*

None of the prior art identifies the presence of HBA as impurity nor suggests the presence of any chemical impurity potentially competing with the radiolabelled benzaldehyde for the conjugation step. The skilled

person may consider it obvious to use ammonium hydroxide to ionise HBA and thus allow its separation through MCX-SPE cartridge. However this presupposes that the skilled practitioner has knowledge of the nature of the impurity. There is no indication in any of the cited prior art that this was the case. Therefore, the skilled person would not have found any indication in the prior art that the dilution with ammonium hydroxide prior to the chromatographic purification would lead to an improved labelling method.

5.5 As a result the main request fulfills the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with claims 1-7 of the main request filed as auxiliary request 4 during oral proceedings of 14 February 2022 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated