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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	04/20/2021	10980901	173545 (304773-00005)	9416

23363 7590 03/31/2021

Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Alfred MORGENSTERN, Karlsruhe, GERMANY;
THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION, Brussels, BELGIUM;
Frank BRUCHERTSEIFER, Stutensee, GERMANY;
UNIVERSITÄT HEIDELBERG, Heidelberg, GERMANY;
Christos APOSTOLIDIS, Heidelberg, GERMANY;
Uwe HABERKORN, Schwetzingen, GERMANY;
Frederik GIESEL, Heidelberg, GERMANY;
Clemens KRATOCHWIL, Hirschberg a.d.B., GERMANY;

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Fusion Pharmaceuticals, Inc.
Exhibit 1004.001

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23363 7590 01/11/2021
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Stacey Dawson	(Typed or printed name)
/Stacey Dawson/	(Signature)
March 15, 2021 (E-FILED)	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

TITLE OF INVENTION: TREATMENT OF PMSA EXPRESSING CANCERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	04/12/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
SAMALA, JAGADISHWAR RAO	1618	424-001650

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Lewis Roca Rothgerber
2 Christie LLP
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
The European Atomic Energy Community (EURATOM), Represented by The European Commission and	Brussels, Belgium
Universität Heidelberg	Heidelberg, Germany

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 03-1728

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Art Hasan/ Date March 15, 2021

Typed or printed name Art Hasan Registration No. 41,057

Fusion Pharmaceuticals, Inc.
Exhibit 1004.002

PATENT

Date of Notice
of Allowance : January 11, 2021

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on March 15, 2021 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor(s)	:	Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	:	16/470,104	
Filed	:	June 14, 2019	
Title	:	TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	:	1618	
Examiner	:	Jagadishwar Rao Samala	
Docket No.	:	173545 (304773-00005)	

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

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March 15, 2021

Commissioner:

Reasons for allowance are only warranted in instances in which "the record of the prosecution as a whole does not make clear his or her reasons for allowing a claim or claims." (37 CFR § 1.104(e))

Applicant believes the Examiner's stated reasons for allowance are unnecessary. The applicant does not necessarily agree with each statement in the reasons for allowance. While applicant agrees that the claims are allowable, applicant does not acquiesce with each statement in the reasons for allowance, that patentability requires each stated feature exactly as expressed by the Examiner, nor that each stated feature is required for patentability.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

113855835.1

Electronic Patent Application Fee Transmittal

Application Number:	16470104
Filing Date:	14-Jun-2019
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Filer:	Syed A. Hasan/Stacey Dawson
Attorney Docket Number:	173545/304773-00005

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1200**

Electronic Acknowledgement Receipt

EFS ID:	42186519
Application Number:	16470104
International Application Number:	
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Syed A. Hasan/Stacey Dawson
Filer Authorized By:	Syed A. Hasan
Attorney Docket Number:	173545/304773-00005
Receipt Date:	15-MAR-2021
Filing Date:	14-JUN-2019
Time Stamp:	19:38:00
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	E20213EJ38572064
Deposit Account	031728
Authorized User	Stacey Dawson
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.17 (Patent application and reexamination processing fees) 37 CFR 1.19 (Document supply fees)	

37 CFR 1.20 (Post Issuance fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	173545_Issue_Fee.pdf	1187658 2a3664fa2590c55d84f2c74b792396f89e9f3f20	no	1
Warnings:					
Information:					
2	Post Allowance Communication - Incoming	173545_RFA_Comments.pdf	99863 a140100d8c9972de248a5ca033a3f3cbd525cbcc	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30415 56000f938c051ae66cc88f30ad1ea1322f017292	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1317936		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

23363 7590 03/11/2021

Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

EXAMINER	
SAMALA, JAGADISHWAR RAO	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
03/11/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PLPrivatePair@lrrc.com
pair_cph@firsttofile.com
pto@lrrc.com

Fusion Pharmaceuticals, Inc.
Exhibit 1004.008

Response to Rule 312 Communication	Application No.	Applicant(s)	
	16/470,104	MORGENSTERN et al.	
	Examiner	Art Unit	AIA (FITF) Status
	JAGADISHWAR R SAMALA	1618	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 23 February 2021 under 37 CFR 1.312 has been considered, and has been:
   a) ☑ entered.
   b) ☐ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.

/J.R.S/ Examiner, Art Unit 1618	/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618

Fusion Pharmaceuticals, Inc.
Exhibit 1004.009

OK TO ENTER: /J.R.S/ 03/04/2021

PATENT

Date of Notice
of Allowance : January 11, 2021

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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/Stacey Dawson/
Stacey Dawson

Inventor	:	Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	:	16/470,104	
Filed	:	June 14, 2019	
Title	:	TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	:	1618	
Examiner	:	Jagadishwar Rao Samala	
Docket No.	:	173545 (304773-00005)	

AMENDMENT UNDER 37 CFR § 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
February 23, 2021

Commissioner:

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 12 of this paper.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.010

PATENT

Date of Notice
of Allowance : January 11, 2021

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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/Stacey Dawson/
Stacey Dawson

Inventor	:	Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	:	16/470,104	
Filed	:	June 14, 2019	
Title	:	TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	:	1618	
Examiner	:	Jagadishwar Rao Samala	
Docket No.	:	173545 (304773-00005)	

AMENDMENT UNDER 37 CFR § 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
February 23, 2021

Commissioner:

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 12 of this paper.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.011

Electronic Acknowledgement Receipt

EFS ID:	42000615
Application Number:	16470104
International Application Number:	
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Syed A. Hasan/Stacey Dawson
Filer Authorized By:	Syed A. Hasan
Attorney Docket Number:	173545 (304773-00005)
Receipt Date:	23-FEB-2021
Filing Date:	14-JUN-2019
Time Stamp:	16:50:49
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		173545_312Amendment.pdf	1380812 40449ca20d54e10b29932cc7acd9b316d9debedf	yes	12

Fusion Pharmaceuticals, Inc.
Exhibit 1004.012

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	12	12
	Claims	2	11
	Amendment after Notice of Allowance (Rule 312)	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	1380812	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS/ARGUMENTS

Claims 13-24 and 36 have been allowed and are presented above according to the amendments set forth in the Examiner's Amendment in the January 11, 2021 Notice of Allowance. Claim 15 has been amended herein to include the chelated Ac-225 radionuclide. Specifically, Applicant has amended claim 15 to clarify that the "*1,4,7,10-tetraazacyclododecane-N,N',N'', N'''-tetraacetic acid moiety*" is acting as the chelator moiety in the specifically depicted formula of claim 15. No new matter has been added and the amendment does not alter the scope of the claim or the structure of the radiopharmaceutical.

Applicant respectfully requests entry of the above amendment pursuant to 37 C.F.R. § 1.312. If there are any remaining issues that can be addressed over the telephone, the Examiner is cordially invited to call the Applicant's attorney at the number listed below

Payment of any fee required to enter and process this amendment is provided. The Director is authorized to charge any underpayment of fees or credit any overpayment of fees to Deposit Account No. 03-1728.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.014

Amendments to the Claims:

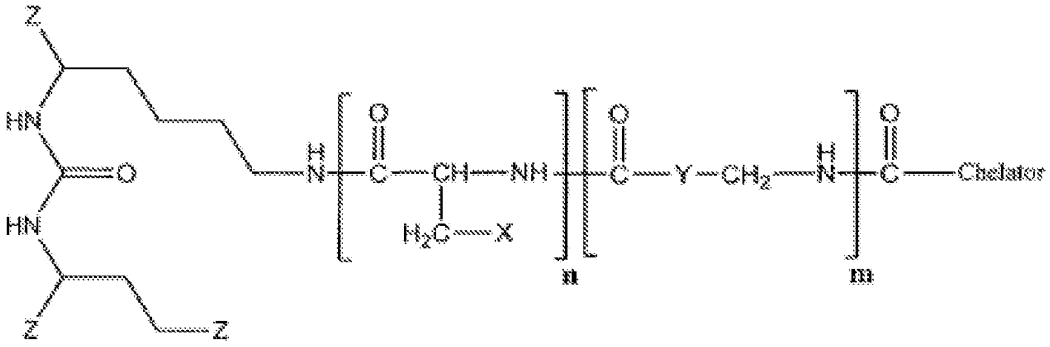
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-12. (Canceled)

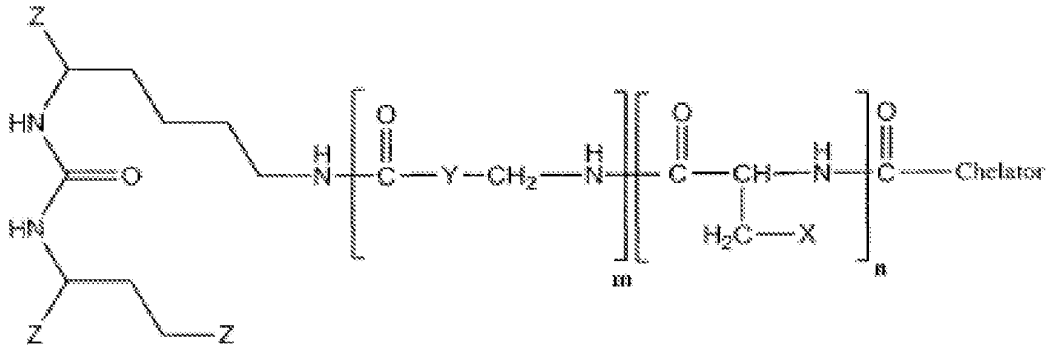
13. (Previously Presented) A method for treating PSMA expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

Formula (A)



or

Formula (B)



with:

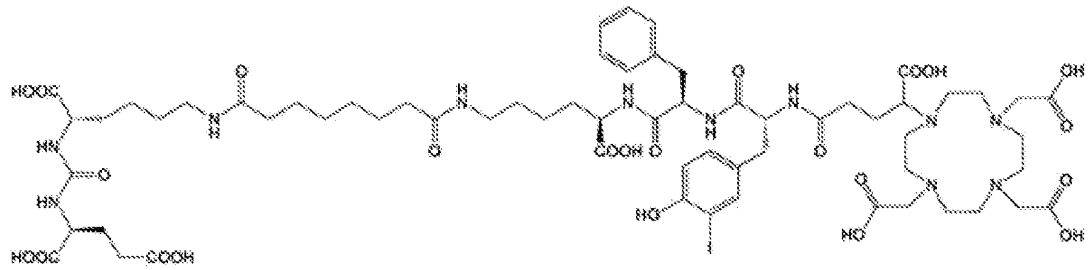
n:	0,1
m:	1,2,3,4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N''-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA), 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA), 1,4,7-triazacyclononane phosphinic acid (TRAP), 1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),

Fusion Pharmaceuticals, Inc.
Exhibit 1004.016

3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),
N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),
diethylenetriaminepentaacetic acid (DTPA),
Trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A)
p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA)

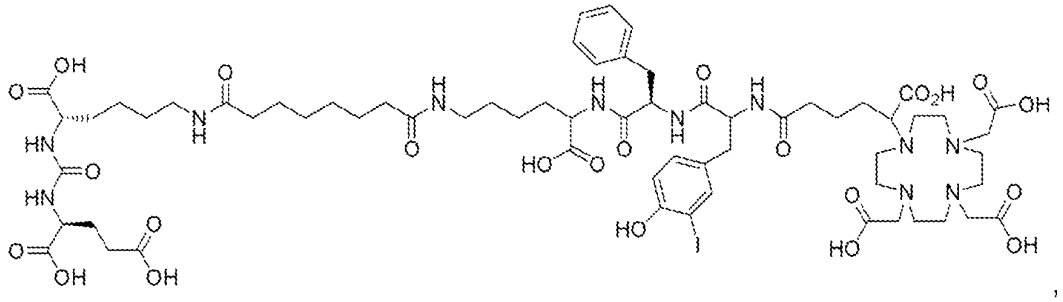
or

Formula (C)



or

Formula (D)



,

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Exhibit 1004.017

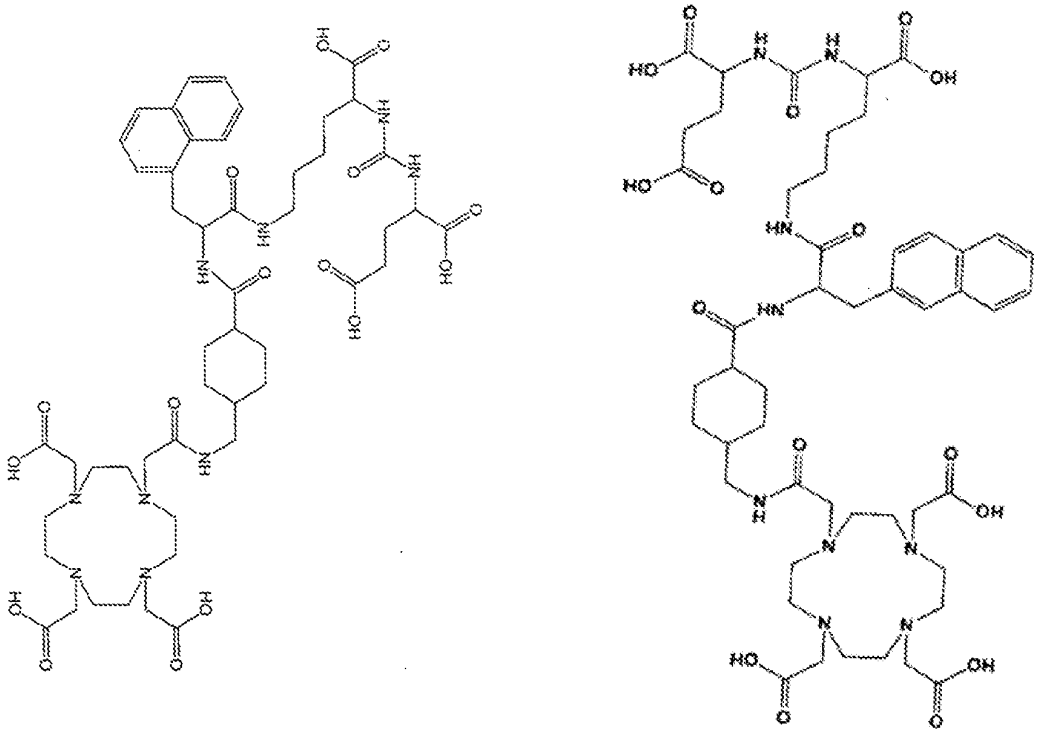
or

Formula (E)

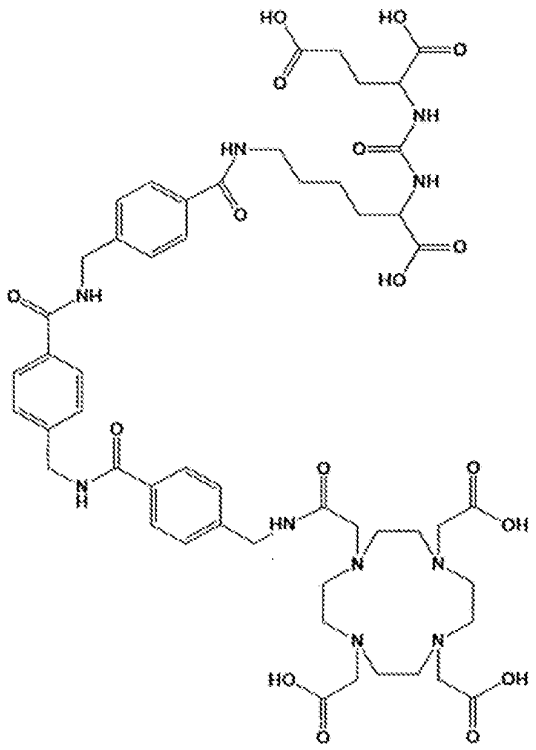
(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

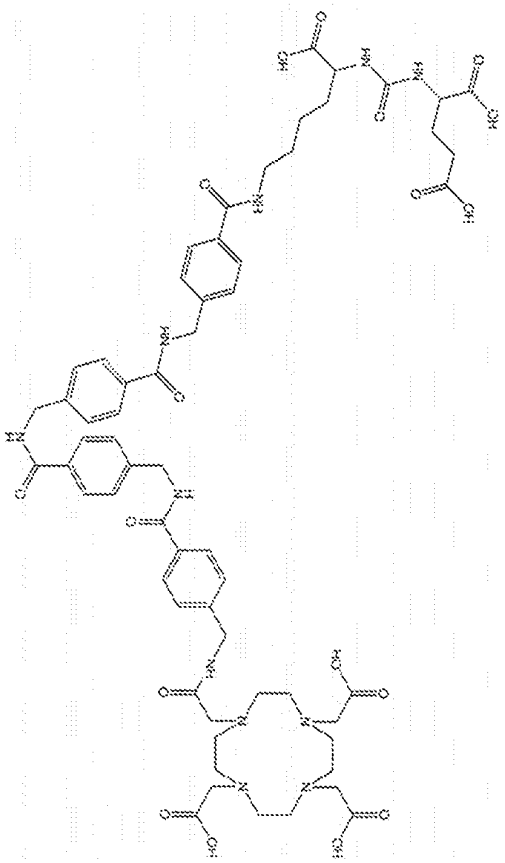
wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

14. (Previously Presented) The method of claim 13, wherein the one or more Ac-225-radiopharmaceuticals are selected from:

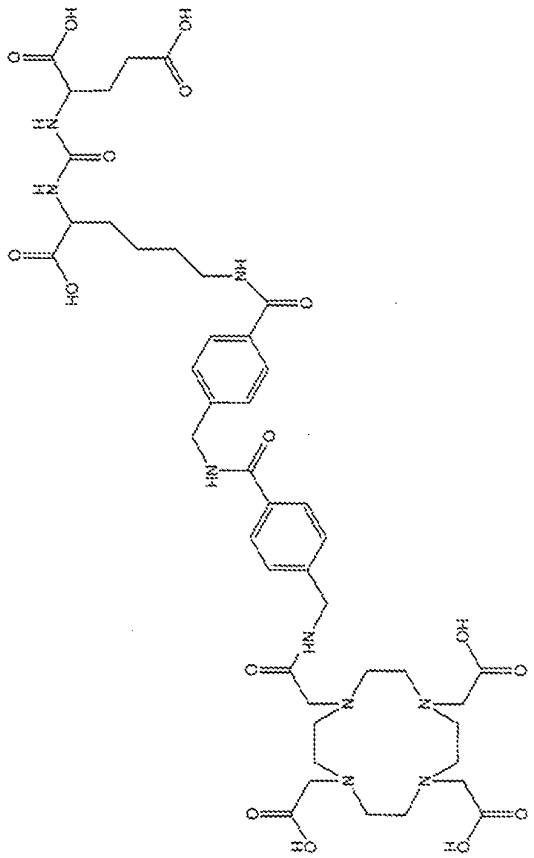


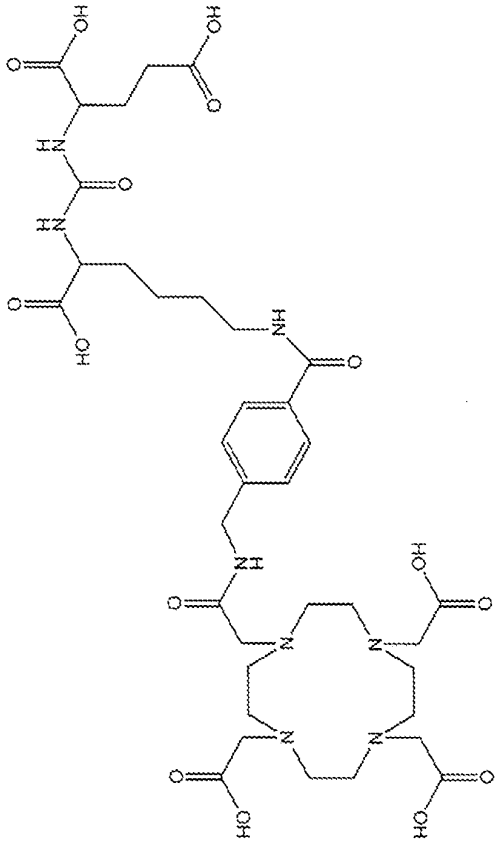
Fusion Pharmaceuticals, Inc.
Exhibit 1004.018



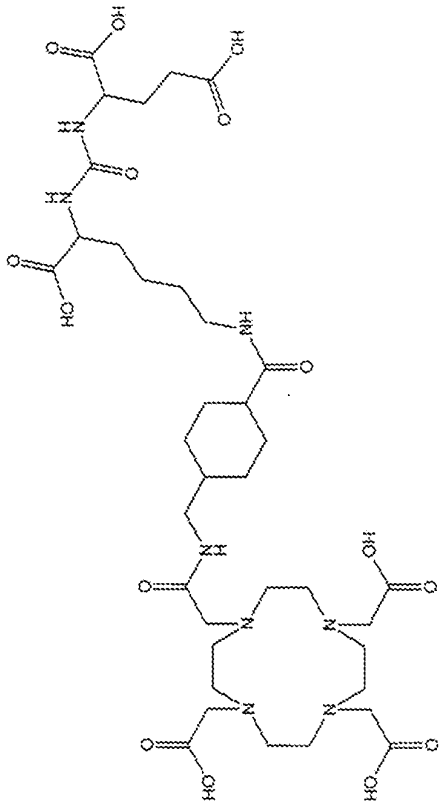


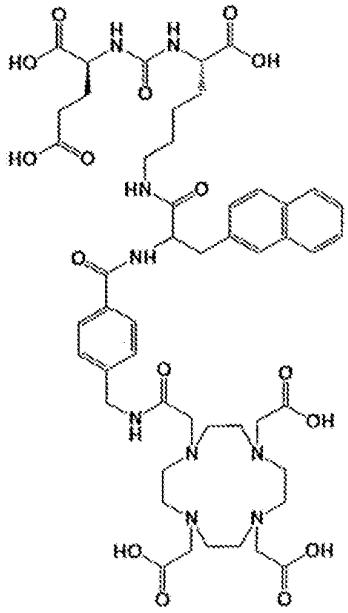
Fusion Pharmaceuticals, Inc.
Exhibit 1004.019

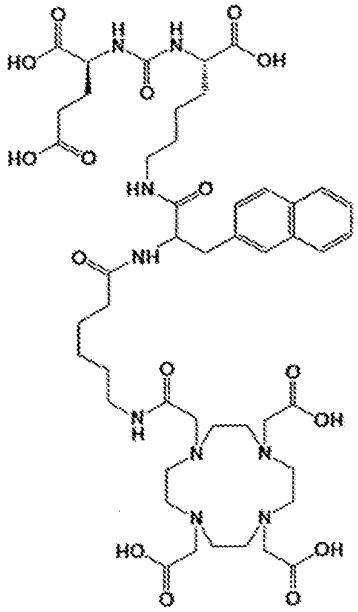


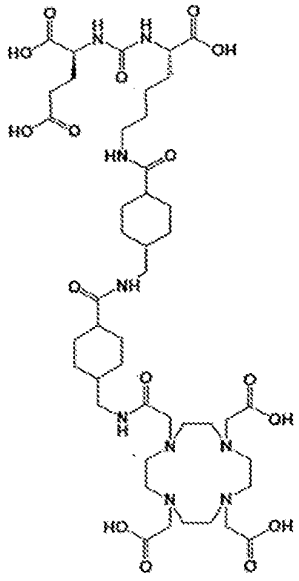


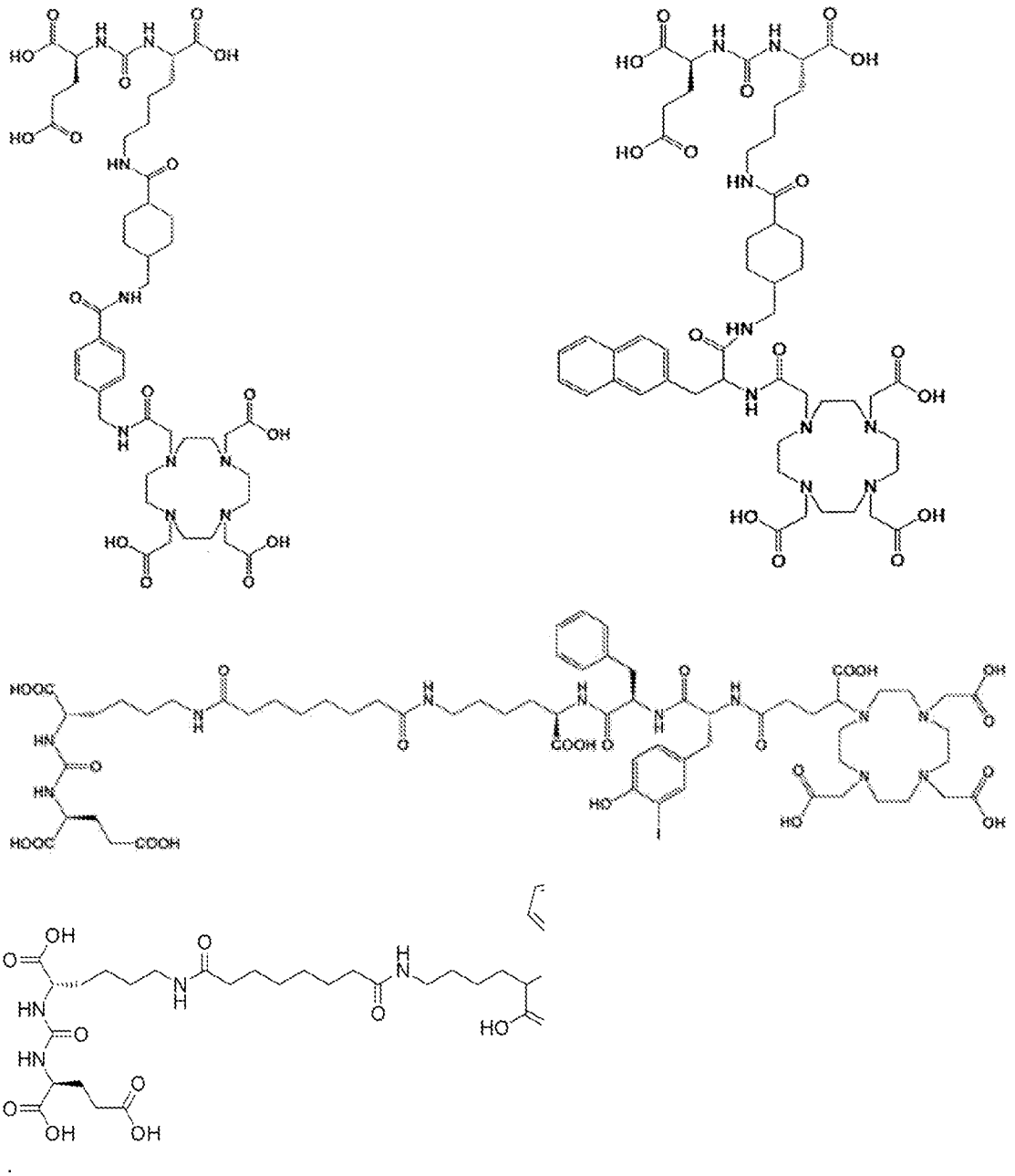
Fusion Pharmaceuticals, Inc.
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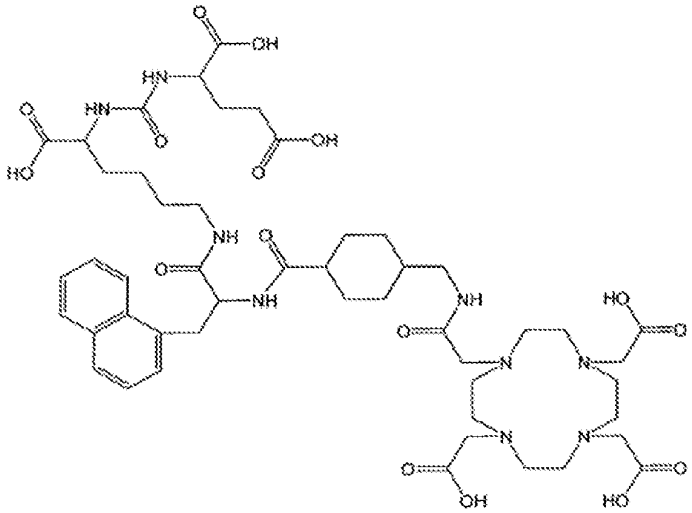








15. (Currently Amended) The method of claim 13, wherein at least one Ac-225-radiopharmaceutical is Ac-225-PSMA-617, wherein Ac-225-PSMA-617 is a compound according to a formula



chelating a Ac-225 radionuclide with its 1,4,7,10-tetraazacyclododecane-N,N',N'', N'''-tetraacetic acid moiety.

16. (Previously Presented) The method of claim 13, wherein said PSMA expressing cancers are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers.

17. (Previously Presented) The method of claim 13, wherein the cancer is a disseminated cancer.

18. (Previously Presented) The method of claim 16, wherein said PSMA expressing cancer is prostate cancer.

19. (Previously Presented) The method of claim 16, wherein said PSMA expressing cancer is breast cancer.

20. (Previously Presented) The method of claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

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Exhibit 1004.023

21. (Previously Presented) The method of claim 20, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

22. (Previously Presented) The method of claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

23. (Previously Presented) The method of claim 22, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

24. (Previously Presented) The method of claim 20, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

25-35. (Canceled).

36. (Previously Presented) The method of claim 22, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

23363 7590 01/25/2021

Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

EXAMINER	
SAMALA, JAGADISHWAR RAO	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
01/25/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pair_cph@firsttofile.com
pto@lrrc.com

Fusion Pharmaceuticals, Inc.
Exhibit 1004.025

Examiner-Initiated Interview Summary	Application No. 16/470,104	Applicant(s) MORGENSTERN et al.	
	Examiner JAGADISHWAR R SAMALA	Art Unit 1618	AIA (FITF) Status Yes

All participants (applicant, applicant's representative, PTO personnel):

(1) JAGADISHWAR RAO. SAMALA. (3) _____.

(2) Lauren Schneider. (4) _____.

Date of Interview: 10 December 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: Pending.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant Atty. Lauren Schneider has authorized for the Examiner's Amendments. This interview summary form is a substitute to correct an inadvertent error in the Interview issued on 01/11/2021. The previous communication indicated Art Hasan has authorized for the examiner's amendments. The correct Atty. Is Lauren Schneider..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J.R.S/ Examiner, Art Unit 1618	/JAKE M VU/ Primary Examiner, Art Unit 1618

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Exhibit 1004.026

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NOTICE OF ALLOWANCE AND FEE(S) DUE

23363 7590 01/11/2021
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 01/11/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

TITLE OF INVENTION: TREATMENT OF PMSA EXPRESSING CANCERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	04/12/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.027

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23363 7590 01/11/2021
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

TITLE OF INVENTION: TREATMENT OF PMSA EXPRESSING CANCERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	04/12/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
SAMALA, JAGADISHWAR RAO	1618	424-001650

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Fusion Pharmaceuticals, Inc.
Exhibit 1004.028

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

23363 7590 01/11/2021

Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 01/11/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.029

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.030

Notice of Allowability	Application No. 16/470,104	Applicant(s) MORGENSTERN et al.	
	Examiner JAGADISHWAR R SAMALA	Art Unit 1618	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 01/28/2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 13-24 and 36 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 12/10/2020.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.R.S/ Examiner, Art Unit 1618	/JAKE M VU/ Primary Examiner, Art Unit 1618

Fusion Pharmaceuticals, Inc.
Exhibit 1004.031

Notice of Pre-AIA or AIA Status

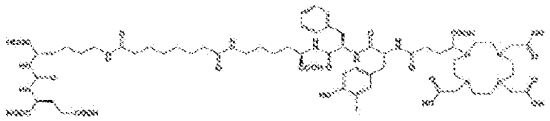
The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

EXAMINER'S AMENDMENT

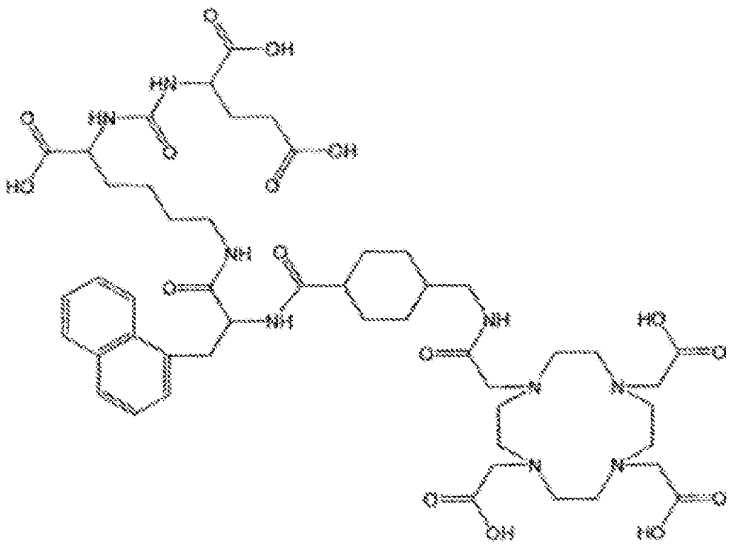
An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Art Hasan on 06/16/2020.

The application has been amended as follows:

In claim 13, line 44, after "  " insert --- or ---

In claim 15, line 2, after "Ac-225-PSMA-617" insert --- , wherein Ac-225-PSMA-617 is a compound according to a formula



Reasons for Allowance

The following is an examiner's statement of reasons for allowance: The compounds of the instant claims, pharmaceutical compositions thereof and methods of suing the compounds are novel and non-obvious over the prior art because of the structural limitations. The closet prior art is US 8,926,944 ('944) which discloses compounds of general formula I and II (abstract) and complexes with radionuclides to obtain radiographic images of one or more regions of a patient. However, compounds of general formula I and II of '944 differs from instantly claimed one or more Ac-225-radiopharmaceutical compounds of formula (A) – (E) in chemical structure of the variable linker, the proposed changes in chemical structure of the linker results in change of lipophilic interactions in the linker regions, as well as binding affinity to prostate-specific membrane antigen (PSMA) protein..

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR RAO SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on Monday-Friday 9am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Hartley G Michael can be reached on 571 272 0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.R.S/
Examiner, Art Unit 1618

/JAKE M VU/
Primary Examiner, Art Unit 1618

Examiner-Initiated Interview Summary	Application No. 16/470,104	Applicant(s) MORGENSTERN et al.	
	Examiner JAGADISHWAR R SAMALA	Art Unit 1618	AIA (FITF) Status Yes

All participants (applicant, applicant's representative, PTO personnel):

(1) JAGADISHWAR RAO. SAMALA. (3) _____.

(2) Art Hasan. (4) _____.

Date of Interview: 10 December 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: Pending.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant Atty. Art Hasan has authorized for the Examiner's Amendments.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J.R.S/ Examiner, Art Unit 1618	/JAKE M VU/ Primary Examiner, Art Unit 1618

Fusion Pharmaceuticals, Inc.
Exhibit 1004.036

Notice of References Cited	Application/Control No. 16/470,104	Applicant(s)/Patent Under Reexamination MORGENSTERN et al.	
	Examiner JAGADISHWAR R SAMALA	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-8926944-B2	01-2015	Babich; John W.	C07F5/003	424/1.65
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.037

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/470,104	MORGENSTERN et al.
	Examiner	**Art Unit**
	JAGADISHWAR R SAMALA	1618

CPC							
Symbol						**Type**	**Version**
A61K	/	51	/	0482		F	2013-01-01
A61P	/	35	/	04		I	2018-01-01
A61K	/	51	/	0497		I	2013-01-01

CPC Combination Sets								
Symbol						**Type**	**Set**	**Ranking**	**Version**
	/		/						

/JAGADISHWAR R SAMALA/ Examiner, Art Unit 1618	16 June 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/JAKE M VU/ Primary Examiner, Art Unit 1618	28 December 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200612

Fusion Pharmaceuticals, Inc.
Exhibit 1004.038

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/470,104	MORGENSTERN et al.
	Examiner	**Art Unit**
	JAGADISHWAR R SAMALA	1618

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	51	/	04	
A61K	/	49	/	00	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JAGADISHWAR R SAMALA/ Examiner, Art Unit 1618	16 June 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/JAKE M VU/ Primary Examiner, Art Unit 1618	28 December 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Fusion Pharmaceuticals, Inc.
Exhibit 1004.039

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/470,104	MORGENSTERN et al.
	Examiner	**Art Unit**
	JAGADISHWAR R SAMALA	1618

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JAGADISHWAR R SAMALA/ Examiner, Art Unit 1618	16 June 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/JAKE M VU/ Primary Examiner, Art Unit 1618	28 December 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200612

Fusion Pharmaceuticals, Inc.
Exhibit 1004.040

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/470,104	MORGENSTERN et al.
	Examiner	Art Unit
	JAGADISHWAR R SAMALA	1618

CPC - Searched*		
Symbol	Date	Examiner
A61K49/00; A61K51/04	07/28/2017	SJR

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST SEARCH (USPGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	06/21/2017	SJR
EAST INVENTOR NAME SEARCH	06/21/2017	SJR
PALM INVENTOR NAME SEARCH	06/21/2017	SJR
STN-SEARCH	06/23/2017	SJR
PAT CONF MICHAEL HARTLEY	12/21/2020	SJR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	49/00; 51/04	06/12/2020	SJR

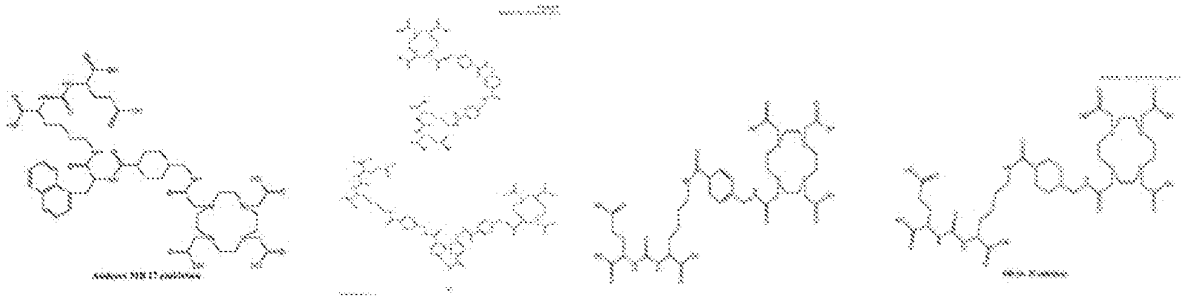
Fusion Pharmaceuticals, Inc.
Exhibit 1004.041

Appl. 15/131,118

Message 15131118_Claims_2016-04-18.pdf

Good Afternoon

Kindly search for compound of formula:



Claims 1-3.

Thanks
Jagadishwar Samala

Fusion Pharmaceuticals, Inc.
Exhibit 1004.042

INVENTOR SEARCH

```
=> fil capl; d que nos l132
FILE 'CAPLUS' ENTERED AT 15:31:43 ON 22 JUN 2017
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FILE COVERS 1907 - 22 Jun 2017 VOL 167 ISS 1
FILE LAST UPDATED: 21 Jun 2017 (20170621/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015

CAplus includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2017.

CAplus now includes the comprehensive Cooperative Patent Classification
(CPC).  See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


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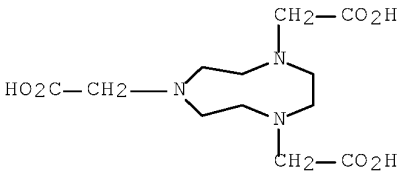

Fusion Pharmaceuticals, Inc.
Exhibit 1004.044

L132 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1938084 CAPLUS Full-text
TITLE: Design of internalizing PSMA-specific Glu-ureido-based radiotherapeutics
AUTHOR(S): Wuestemann, Till; Bauder-Wust, Ulrike; Schaefer, Martin; Eder, Matthias; Benesova, Martina; Leotta, Karin; Kratochwil, Clemens; Haberkorn, Uwe; Kopka, Klaus; Mier, Walter
CORPORATE SOURCE: AffiliationDepartment for Nuclear Medicine, Heidelberg University Hospital, Heidelberg, 69120, Germany
SOURCE: Theranostics (2016), 6(8), 1085-1095
CODEN: THERDS; ISSN: 1838-7640
DIGITAL OBJECT ID: 10.7150/thno.13448
PUBLISHER: Ivyspring International Publisher
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

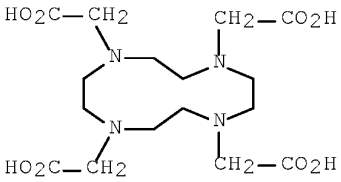
AB Despite the progress in diagnosis and treatment, prostate cancer (PCa) is one of the main causes for cancer-associated deaths among men. Recently, prostate-specific membrane antigen (PSMA) binding tracers have revolutionized the mol. imaging of this disease. The translation of these tracers into therapeutic applications is challenging because of high PSMA-associated kidney uptake. While both the tumor uptake and the uptake in the kidneys are PSMA-specific, the kidneys show a more rapid clearance than tumor lesions. Consequently, the potential of endoradiotherapeutic drugs targeting PSMA is highly dependent on a sustained retention in the tumor - ideally achieved by predominant internalization of the resp. tracer. Previously, we were able to show that the pharmacokinetics of the tracers containing the Glu-urea-based binding motif can be further enhanced with a specifically designed linker. Here, we evaluate an eventual influence of the chelator moiety on the pharmacokinetics, including the tumor internalization. A series of tracers modified by different chelators were synthesized using solid phase chemical The conjugates were radiolabeled to evaluate the influence on the receptor binding affinity, the ligand-induced internalization and the biodistribution behavior. Competitive binding and internalization assays were performed on PSMA pos. LNCaP cells and the biodistribution of the most promising compound was evaluated by positron emission tomog. (PET) in LNCaP-tumor-bearing mice. Interestingly, conjugation of the different chelators did not cause significant differences: all compds. showed nanomolar binding affinities with only minor differences. PET imaging of the 68Ga-labeled CHX-A''-DTPA conjugate revealed that the chelator moiety does not impair the specificity of tumor uptake when compared to the gold standard PSMA-617. However, strong differences of the internalization ratios caused by the chelator moiety were observed: differences in internalization between 15% and 65% were observed, with the CHX-A''-DTPA conjugate displaying the highest internalization ratio. A first-in-man PET/CT study proved the high tumor uptake of this 68Ga-labeled PSMA-targeting compound These data indicate that hydrophobic entities at the chelator mediate the internalization efficacy. Based on its specific tumor uptake in combination with its very high internalization ratio, the clin. performance of the chelator-conjugated Glu-urea-based PSMA inhibitors will be further elucidated.

IT INDEXING IN PROGRESS
IT 56491-86-2, NOTA 60239-18-1 949575-22-8, MIP-1095
RL: BSU (Biological study, unclassified); BIOL (Biological study) (design of internalizing PSMA-specific Glu-ureido-based radiotherapeutics)
RN 56491-86-2 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, hexahydro- (CA INDEX NAME)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.045

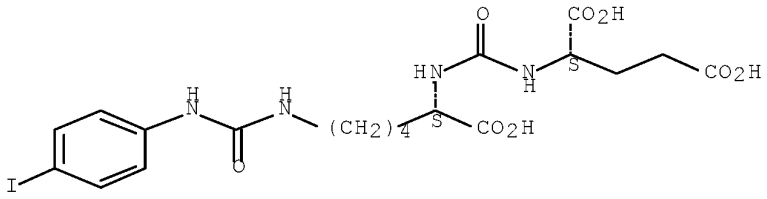


RN 60239-18-1 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (CA INDEX NAME)



RN 949575-22-8 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-1-carboxy-5-[[[(4-iodophenyl)amino]carbonyl]amino]pentyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L132 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1315963 CAPLUS Full-text
DOCUMENT NUMBER: 165:284529
TITLE: Labeled inhibitors of prostate specific membrane antigen (PSMA), their use as imaging agents and pharmaceutical agents for the treatment of prostate cancer
INVENTOR(S): Eder, Matthias; Kopka, Klaus; Schaefer, Martin; Bauder-Wuest, Ulrike; Haberkorn, Uwe; Eisenhut, Michael; Miex, Walter; Benesova, Martina
PATENT ASSIGNEE(S): Ruprecht-Karls-Universitaet Heidelberg, Germany; Deutsches Krebsforschungszentrum
SOURCE: U.S. Pat. Appl. Publ., 45pp., Cont.-in-part of Appl. No. PCT/EP2014/002808.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.046

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160228587	A1	20160811	US 2016-15131118	20160418
EP 2862857	A1	20150422	EP 2013-4991	20131018
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WO 2015055318	A1	20150423	WO 2014-EP2808	20141017
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				

PRIORITY APPLN. INFO.:

EP 2013-4991	A	20131018
EP 2014-175612	A	20140703
WO 2014-EP2808	A2	20141017

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 165:284529; MARPAT 165:284529

AB The present invention generally relates to the field of radiopharmaceuticals and their use in nuclear medicine as tracers, imaging agents and for the treatment of various disease states of prostate cancer.

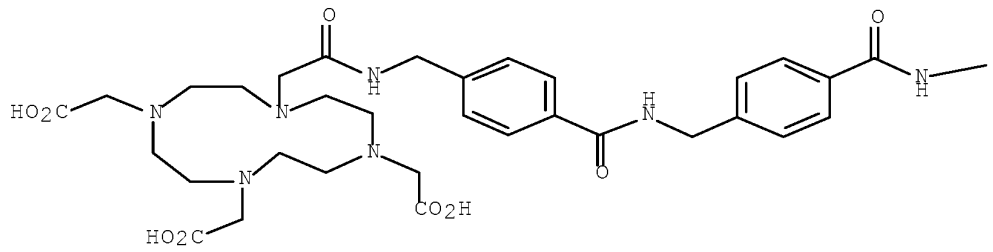
IT 1702720-91-9P 1702967-37-0P 1983157-53-4P
RL: DGN (Diagnostic use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(labeled inhibitors of prostate specific membrane antigen and their use as imaging agents and for treatment of prostate cancer)

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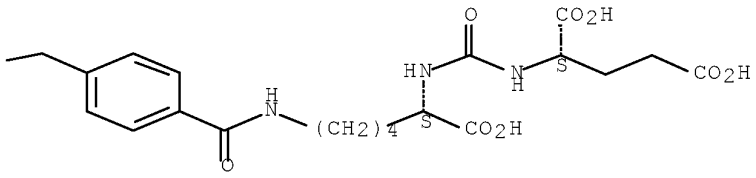
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.047

PAGE 1-A



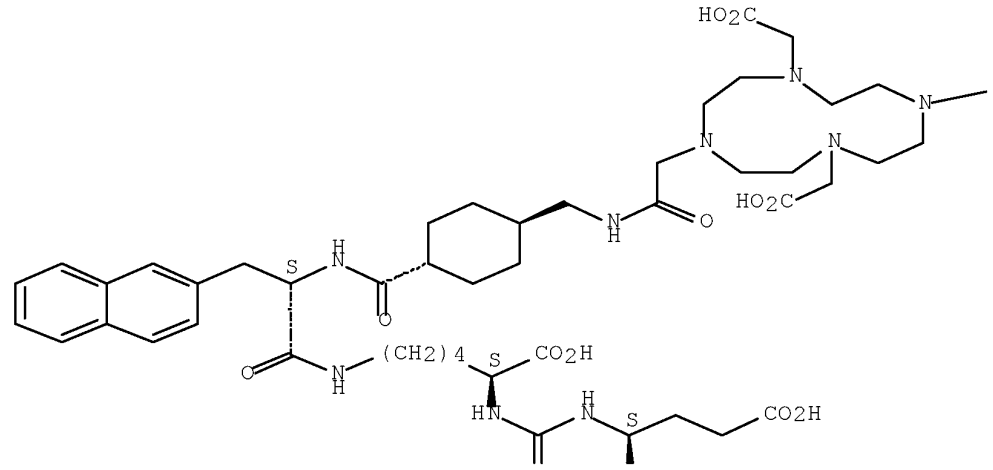
PAGE 1-B



RN 1702967-37-0 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

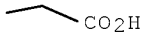
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.048

PAGE 1-B



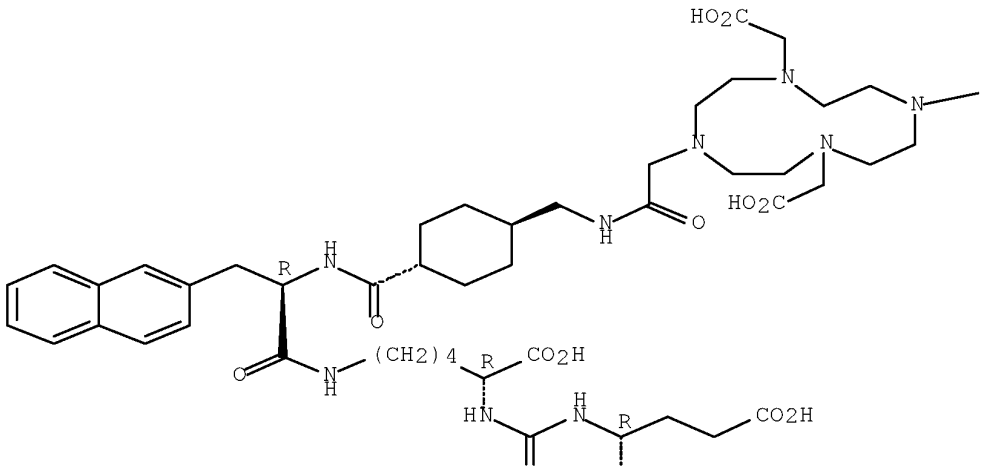
PAGE 2-A



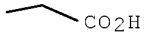
RN 1983157-53-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A

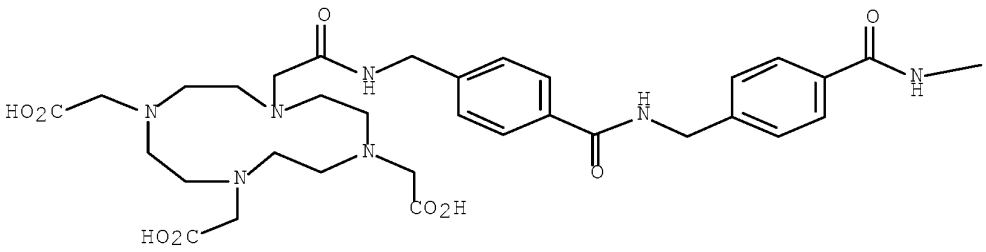


Fusion Pharmaceuticals, Inc.
Exhibit 1004.049

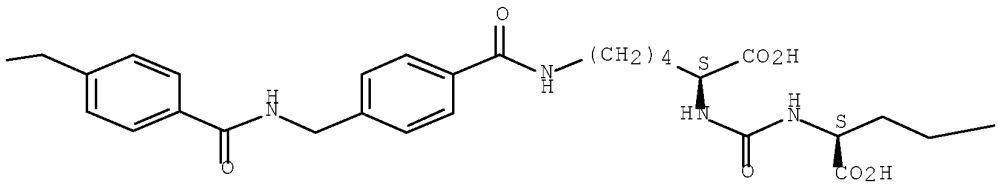
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1702721-02-5 1702967-48-3 1702967-50-7
1702967-52-9 1702967-62-1 1983157-54-5
RL: DGN (Diagnostic use); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(labeled inhibitors of prostate specific membrane antigen and their use as imaging agents and for treatment of prostate cancer)
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Absolute stereochemistry.

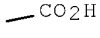
PAGE 1-A



PAGE 1-B



PAGE 1-C

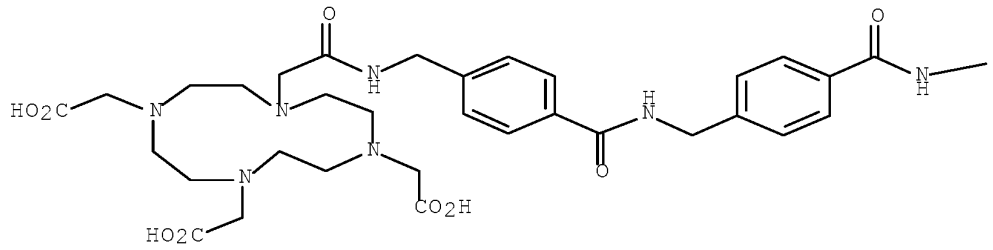


Fusion Pharmaceuticals, Inc.
Exhibit 1004.050

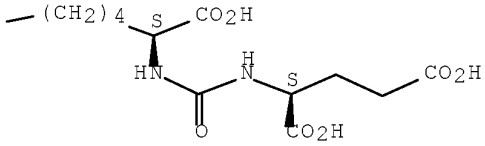
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Absolute stereochemistry.

PAGE 1-A



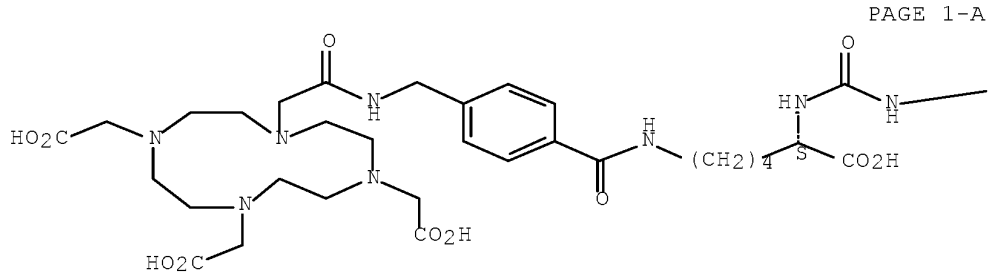
PAGE 1-B



RN 1702721-00-3 CAPLUS
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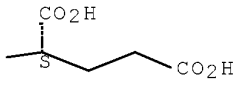
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.051

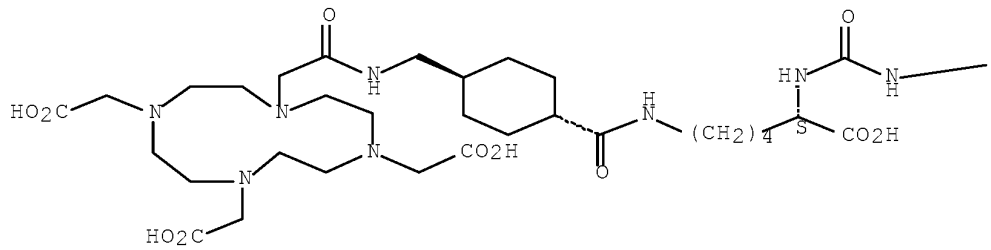
PAGE 1-B



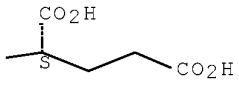
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

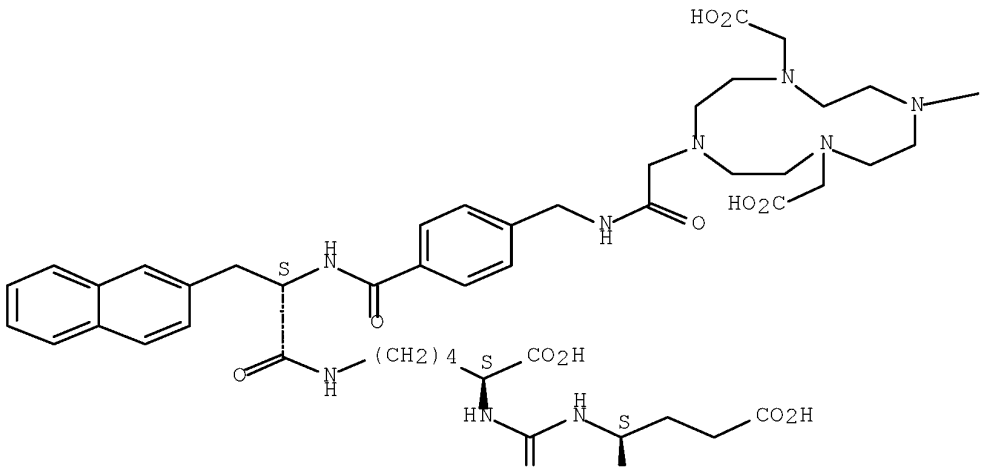


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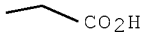
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.052

PAGE 1-A



PAGE 1-B



PAGE 2-A

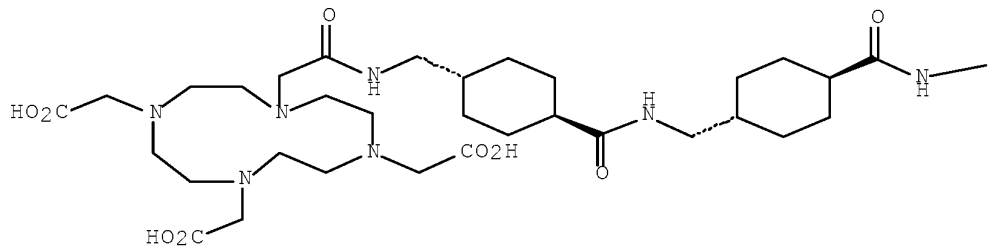


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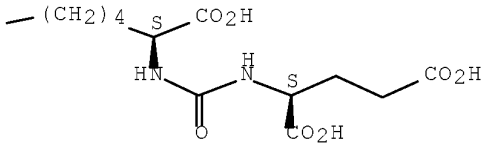
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.053

PAGE 1-A



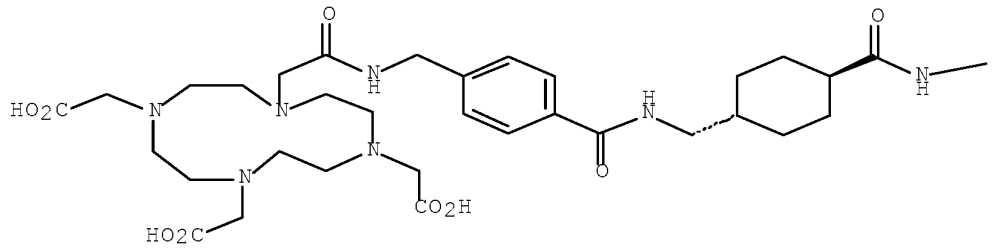
PAGE 1-B



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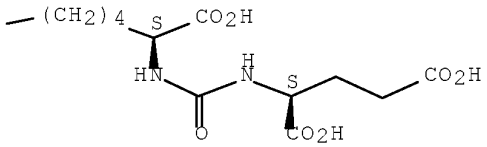
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.054

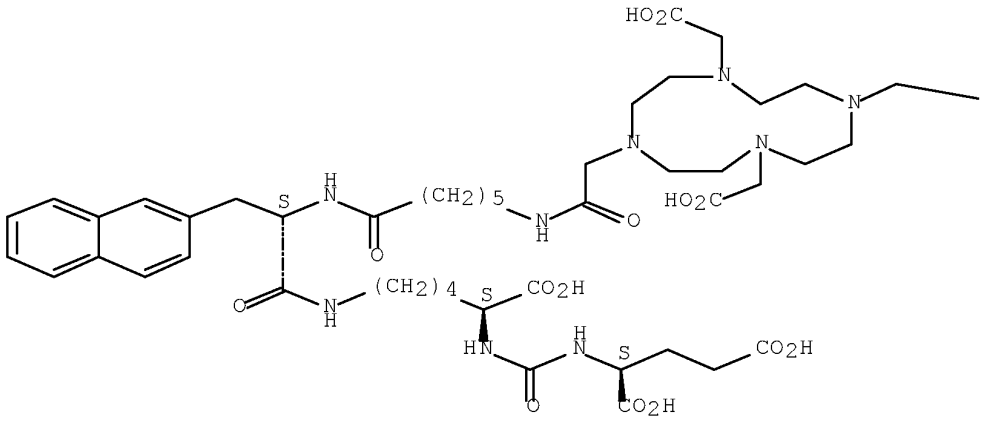
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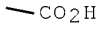
RN 1702967-62-1 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[1-oxo-6-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]hexyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



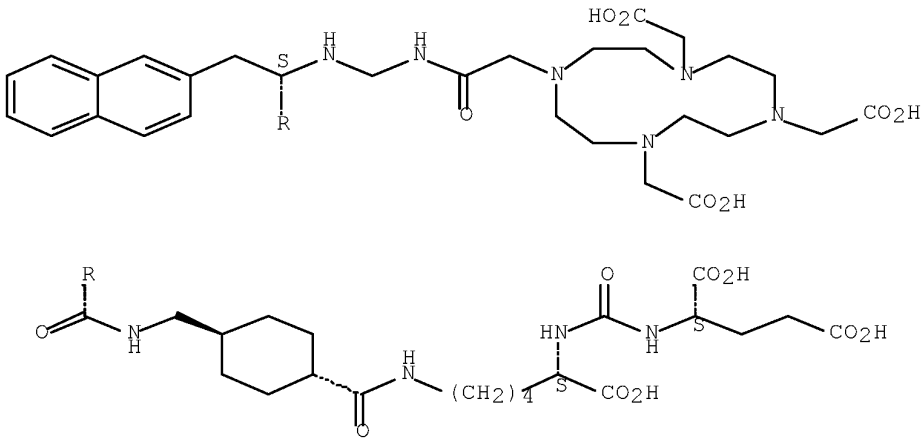
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RN 1983157-54-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

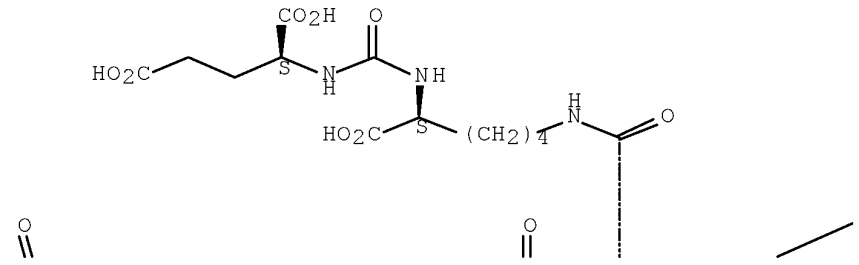
Fusion Pharmaceuticals, Inc.
Exhibit 1004.055



IT 1983157-55-6P
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(labeled inhibitors of prostate specific membrane antigen and their use as imaging agents and for treatment of prostate cancer)
RN 1983157-55-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

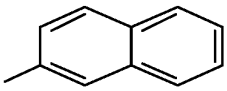
Absolute stereochemistry.

PAGE 1-A

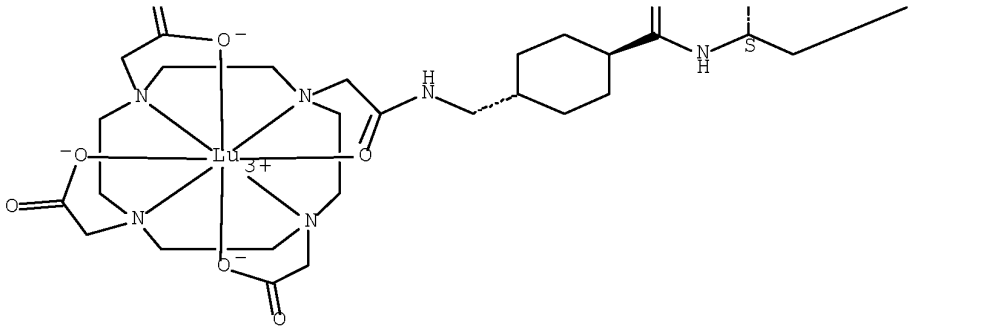


Fusion Pharmaceuticals, Inc.
Exhibit 1004.056

PAGE 1-B



PAGE 2-A

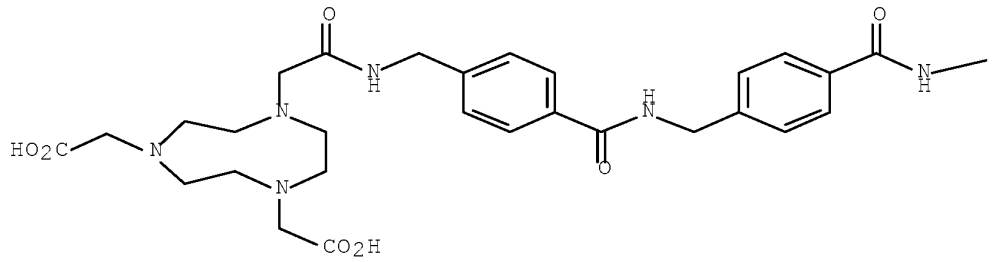


IT 1983142-60-4P 1983142-61-5P 1983142-62-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(labeled inhibitors of prostate specific membrane antigen and their use as imaging agents and for treatment of prostate cancer)
RN 1983142-60-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

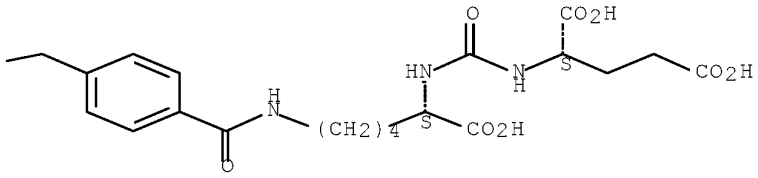
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.057

PAGE 1-A



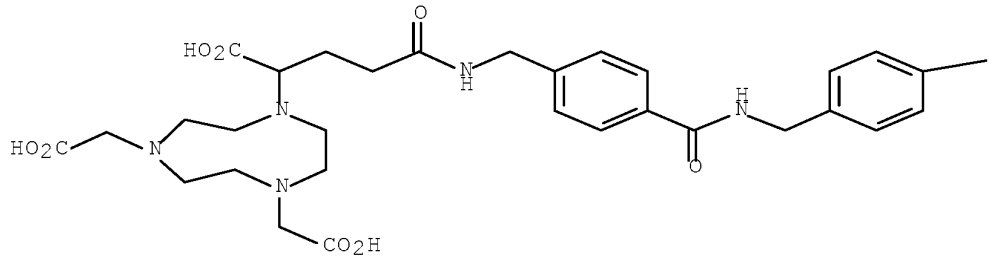
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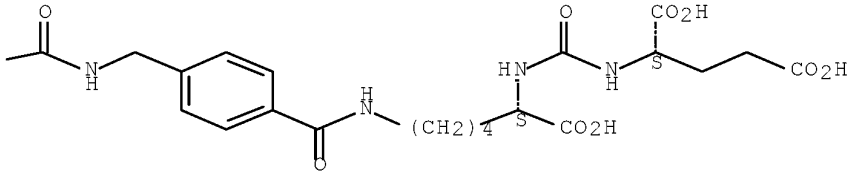
RN 1983142-61-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

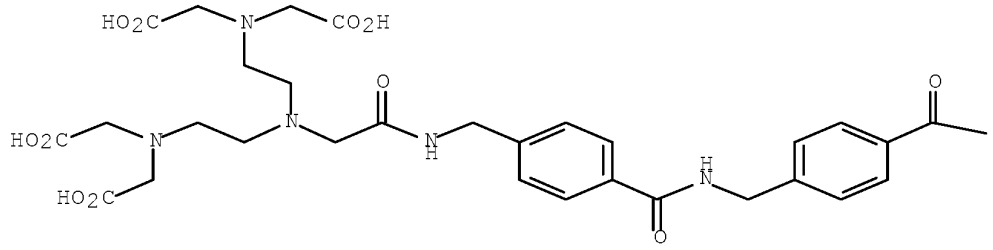


Fusion Pharmaceuticals, Inc.
Exhibit 1004.058

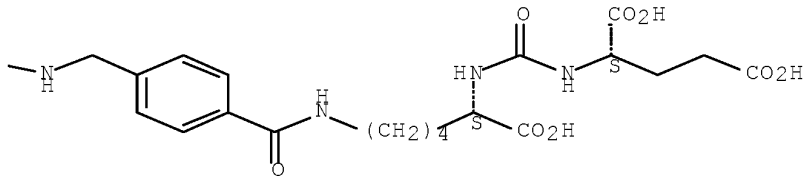
RN 1983142-62-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

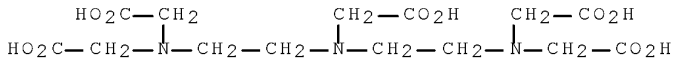
PAGE 1-A



PAGE 1-B

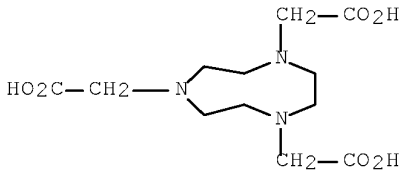


IT 67-43-6, Diethylenetriaminepentaacetic acid 56491-86-2
, 1,4,7-Triazacyclononane-1,4,7-triacetic acid 129162-88-5
1092370-12-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(labeled inhibitors of prostate specific membrane antigen and their use as imaging agents and for treatment of prostate cancer)
RN 67-43-6 CAPLUS
CN Glycine, N,N-bis[2-[bis(carboxymethyl)amino]ethyl]- (CA INDEX NAME)

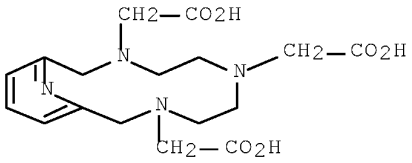


RN 56491-86-2 CAPLUS
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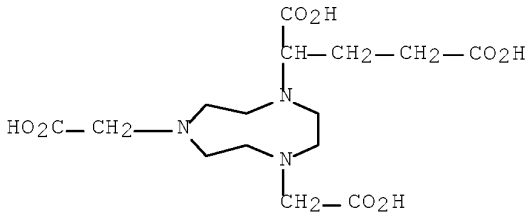
Fusion Pharmaceuticals, Inc.
Exhibit 1004.059



RN 129162-88-5 CAPLUS
CN 3,6,9,15-Tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (CA INDEX NAME)



RN 1092370-12-1 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, α1-(2-carboxyethyl)hexahydro- (CA INDEX NAME)



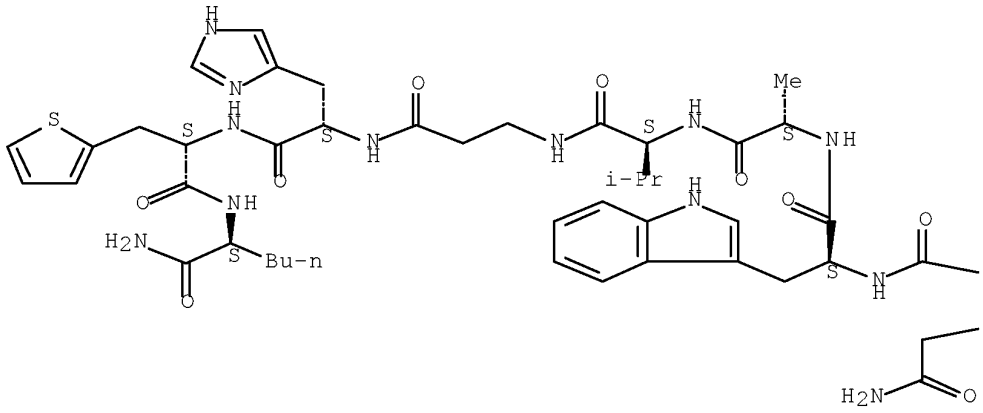
L132 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1088801 CAPLUS Full-text
DOCUMENT NUMBER: 165:436565
TITLE: Correction to Novel Bispecific PSMA/GRPr Targeting Radioligands with Optimized Pharmacokinetics for Improved PET Imaging of Prostate Cancer [Erratum to document cited in CA164:322413]
AUTHOR(S): Liolios, Christos; Schafer, Martin; Haberkorn, Uwe; Eder, Matthias; Kopka, Klaus
CORPORATE SOURCE: Division of Radiopharmaceutical Chemistry, German Cancer Research Center (DKFZ), Heidelberg, 69120, Germany
SOURCE: Bioconjugate Chemistry (2016), 27(7), 1770
CODEN: BCCHES; ISSN: 1043-1802
DIGITAL OBJECT ID: 10.1021/acs.bioconjchem.6b00311
PUBLISHER: American Chemical Society

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Exhibit 1004.060

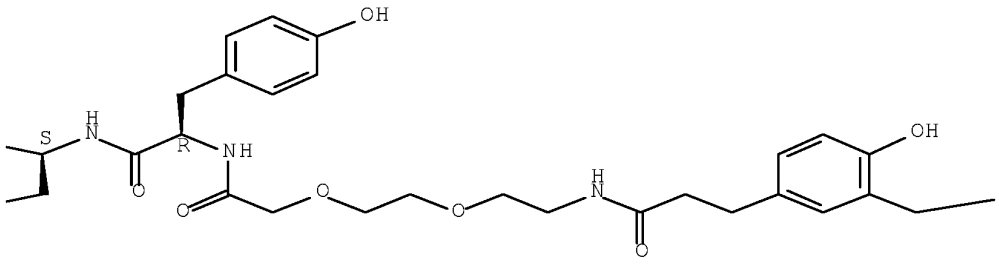
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The corrected Figure 5a is included here. In the Results section, page 738, first paragraph, 12th line, the abbreviation number for GRPm is 12 rather than 16.
IT 1853278-34-8DP, 68Ga-labeled 1853278-35-9DP, 68Ga-labeled 1853278-36-0DP, 68Ga-labeled 1853278-37-1DP, 68Ga-labeled
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(novel bispecific PSMA/GRPR-targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer (erratum))
RN 1853278-34-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A

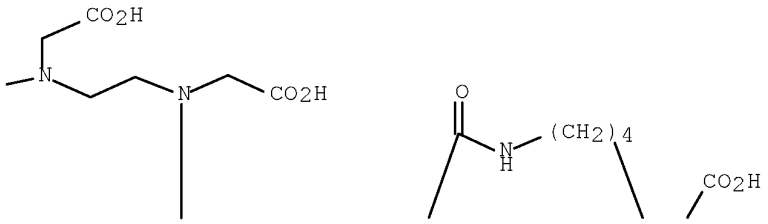


PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.061

PAGE 1-C



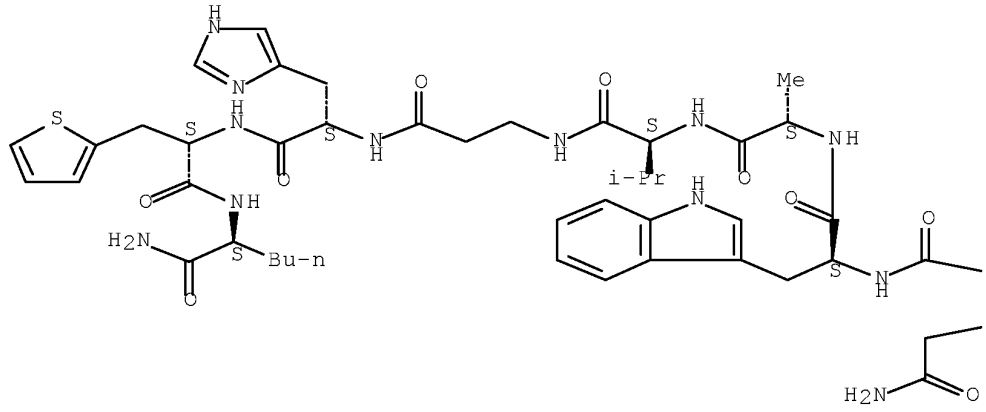
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RN 1853278-35-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

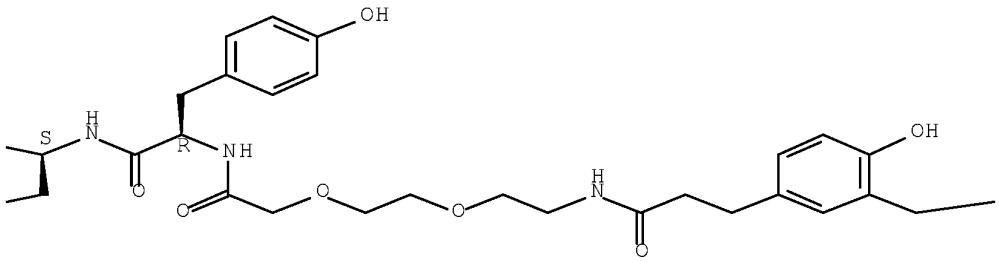
Absolute stereochemistry.

PAGE 1-A

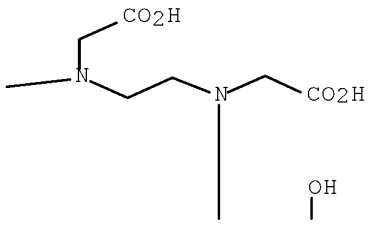


Fusion Pharmaceuticals, Inc.
Exhibit 1004.062

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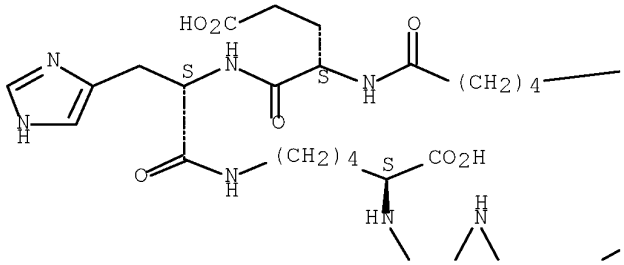


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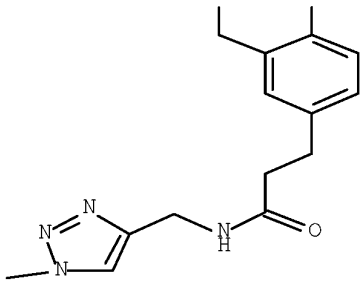


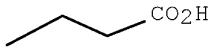
Fusion Pharmaceuticals, Inc.
Exhibit 1004.063

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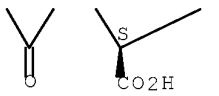


PAGE 2-C





PAGE 3-B

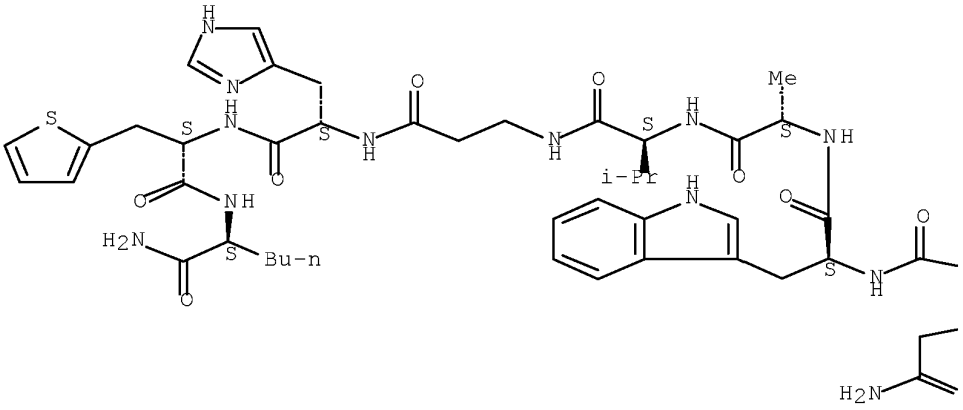


RN 1853278-36-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

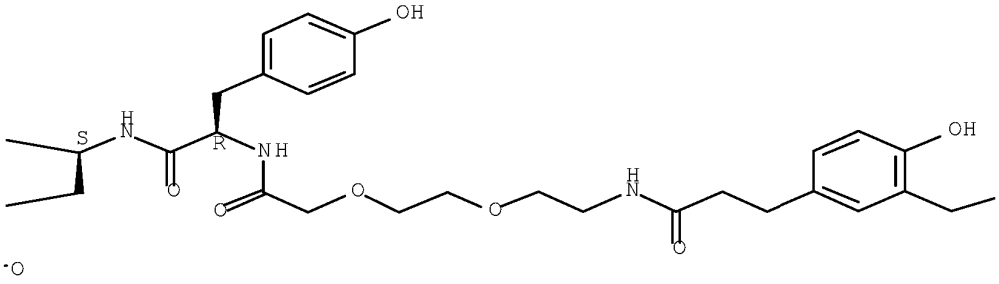
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.064

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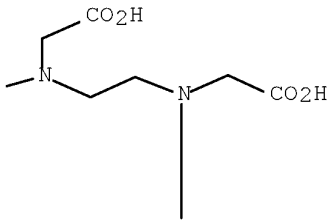


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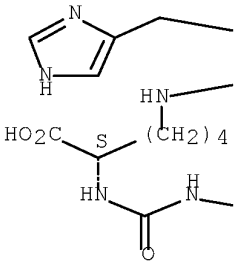


Fusion Pharmaceuticals, Inc.
Exhibit 1004.065

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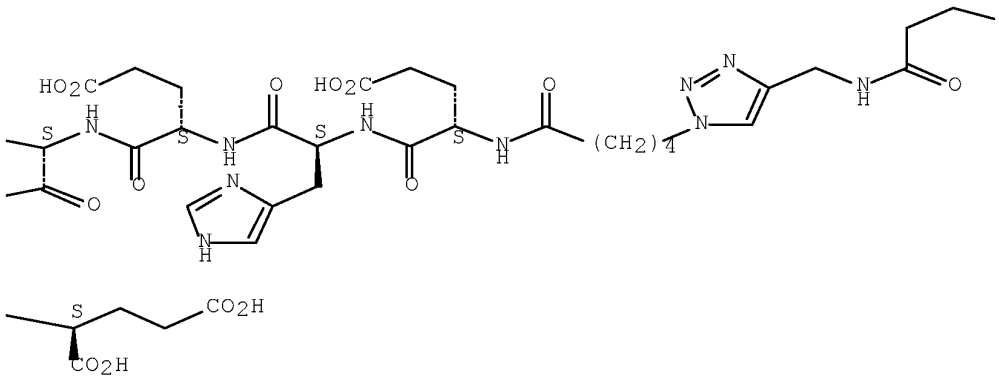


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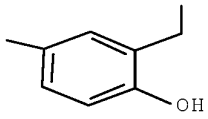


Fusion Pharmaceuticals, Inc.
Exhibit 1004.066

PAGE 2-B



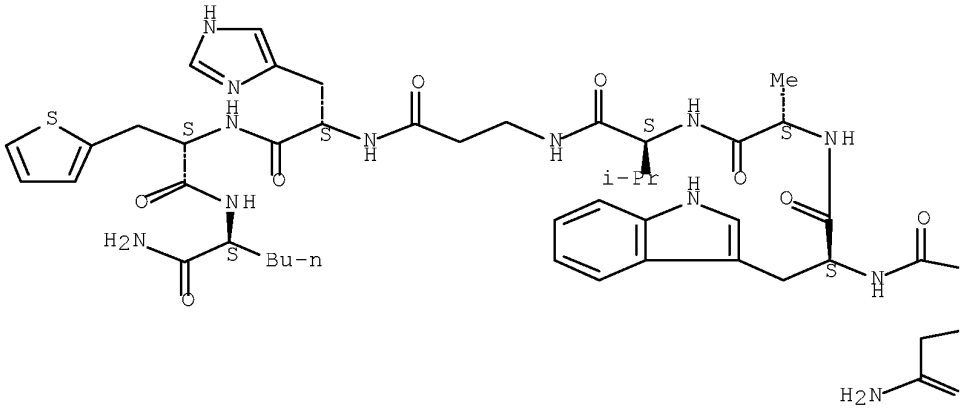
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RN 1853278-37-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

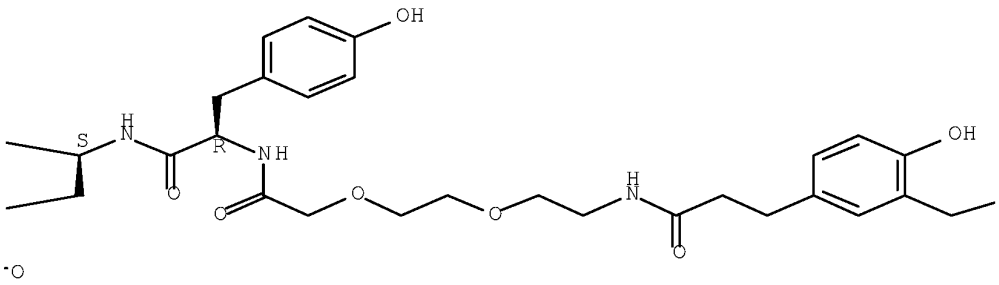
Absolute stereochemistry.

PAGE 1-A

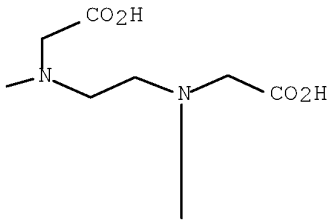


Fusion Pharmaceuticals, Inc.
Exhibit 1004.067

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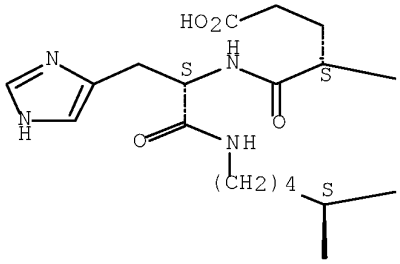


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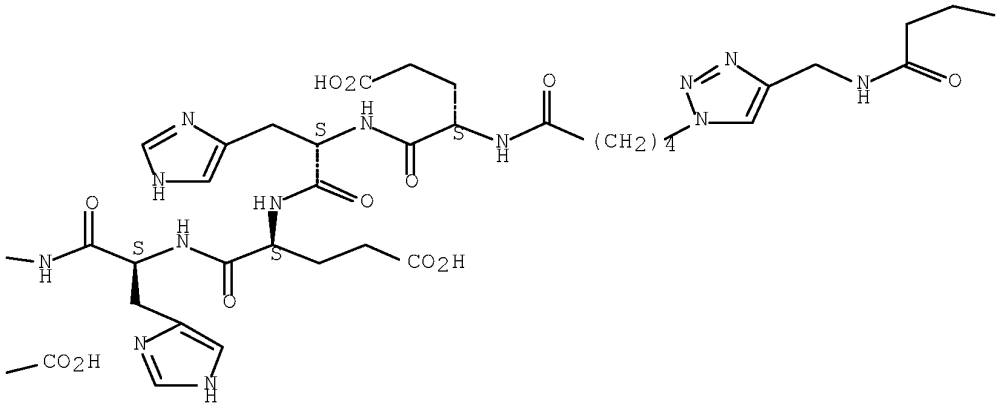


Fusion Pharmaceuticals, Inc.
Exhibit 1004.068

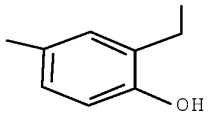
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PAGE 2-B

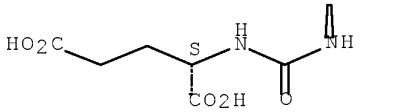


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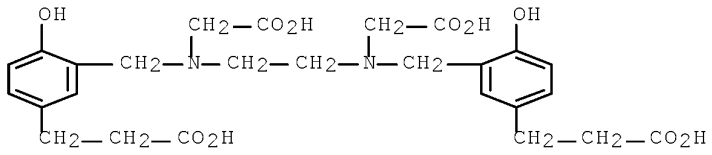


Fusion Pharmaceuticals, Inc.
Exhibit 1004.069

PAGE 3-A

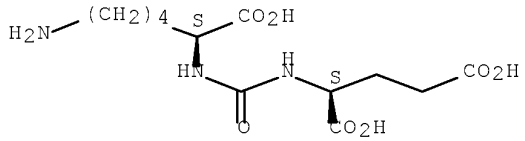


IT 143557-99-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(novel bispecific PSMA/GRPR-targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer (erratum))
RN 143557-99-7 CAPLUS
CN Benzenepropanoic acid, 3,3'-[1,2-ethanediylbis[[(carboxymethyl)imino]methylene]]bis[4-hydroxy- (CA INDEX NAME)



IT 1025796-32-0P 1853278-29-1P 1853278-30-4P
1853278-31-5P 1853278-34-8P 1853278-35-9P
1853278-36-0P 1853278-37-1P 1853291-10-7P
1853291-11-8P 1853291-12-9P 1853291-34-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(novel bispecific PSMA/GRPR-targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer (erratum))
RN 1025796-32-0 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-5-amino-1-carboxypentyl]amino]carbonyl]- (CA INDEX NAME)

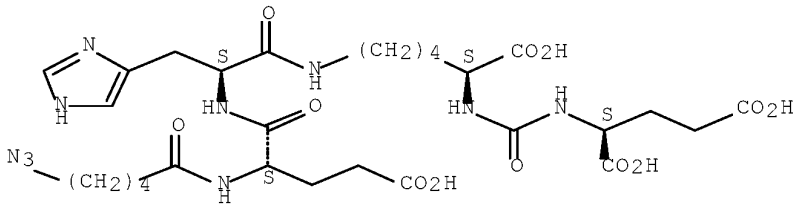
Absolute stereochemistry.



RN 1853278-29-1 CAPLUS
CN L-Lysine, N6-[N-(5-azido-1-oxopentyl)-L-α-glutamyl-L-histidyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]- (CA INDEX NAME)

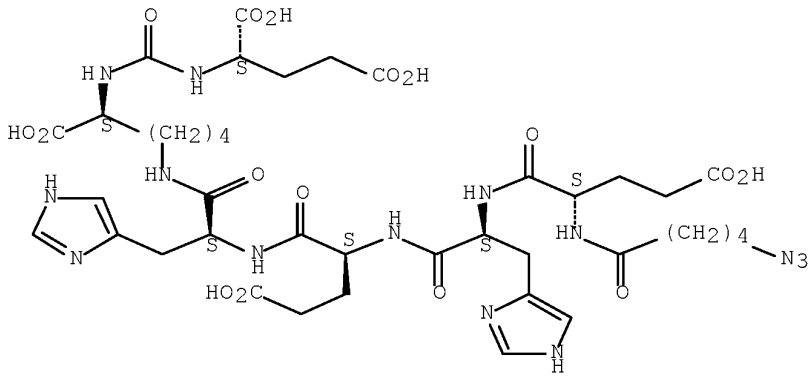
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.070



RN 1853278-30-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

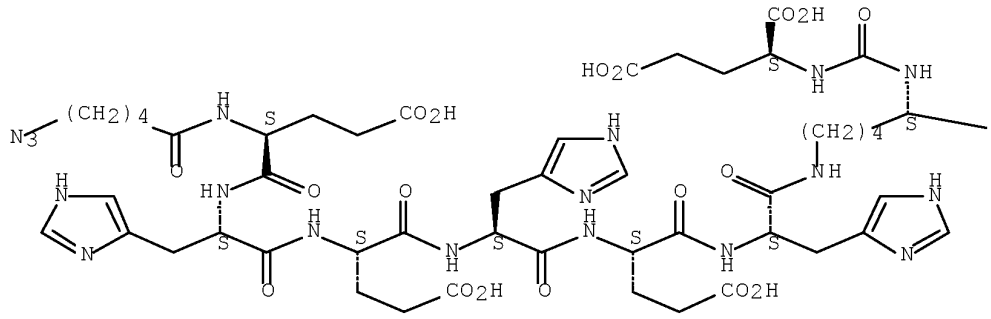
Absolute stereochemistry.



RN 1853278-31-5 CAPLUS
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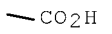
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.071

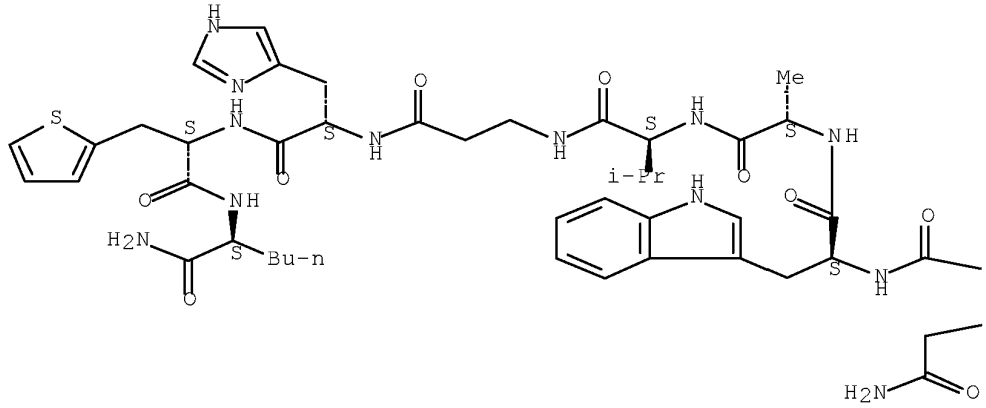
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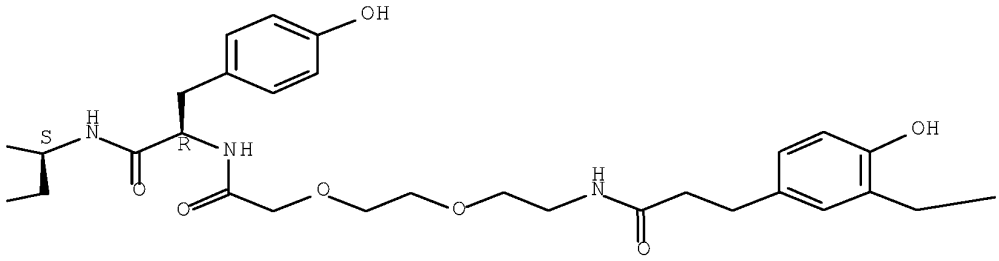
RN 1853278-34-8 CAPLUS
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Absolute stereochemistry.

PAGE 1-A

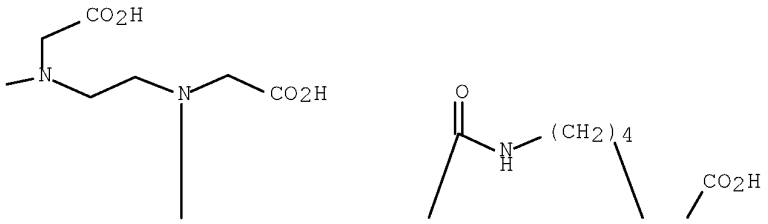


PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.072

PAGE 1-C



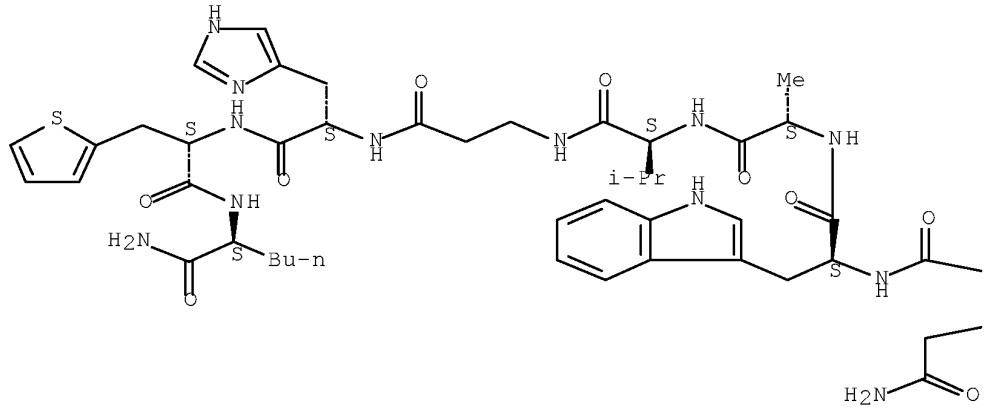
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RN 1853278-35-9 CAPLUS
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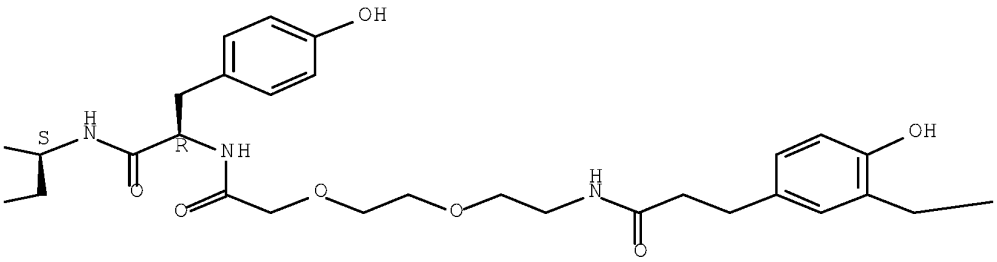
Absolute stereochemistry.

PAGE 1-A

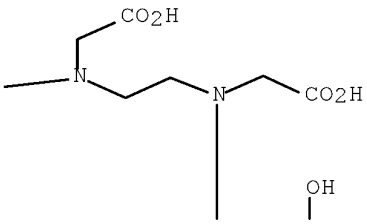


Fusion Pharmaceuticals, Inc.
Exhibit 1004.073

PAGE 1-B

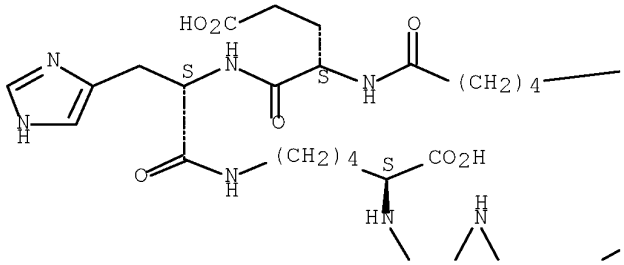


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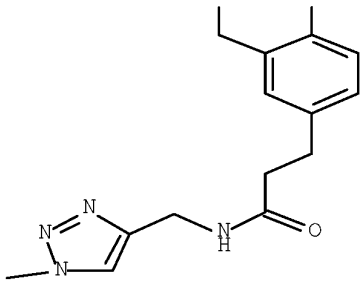


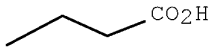
Fusion Pharmaceuticals, Inc.
Exhibit 1004.074

PAGE 2-B

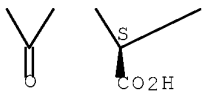


PAGE 2-C





PAGE 3-B

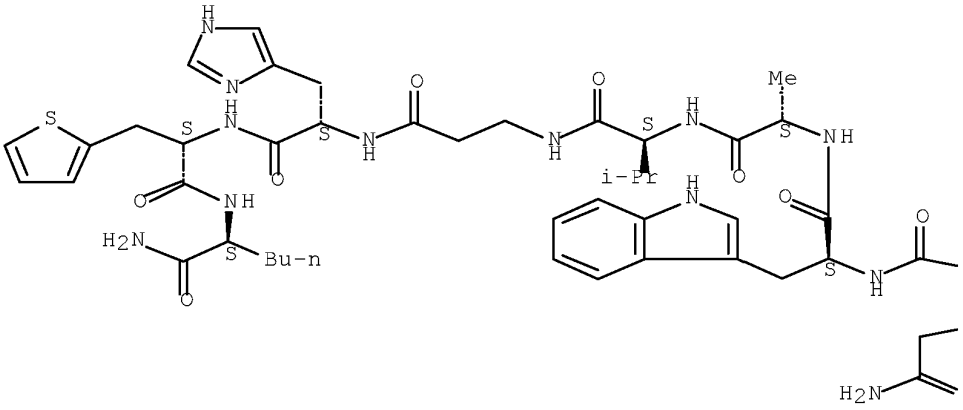


RN 1853278-36-0 CAPLUS
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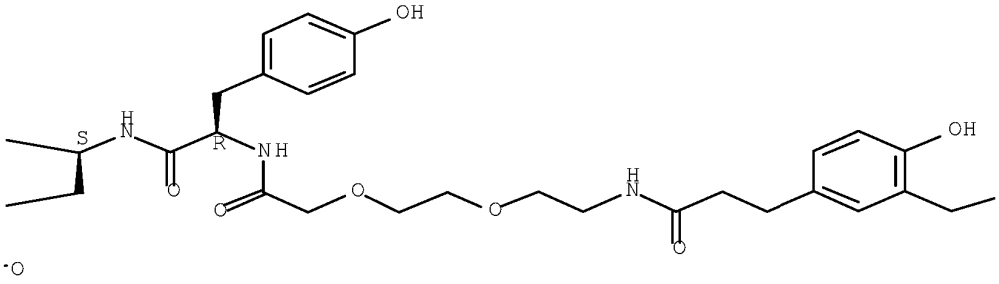
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.075

PAGE 1-A

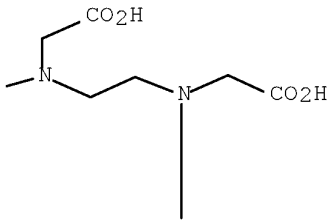


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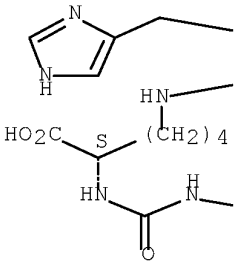


Fusion Pharmaceuticals, Inc.
Exhibit 1004.076

PAGE 1-C

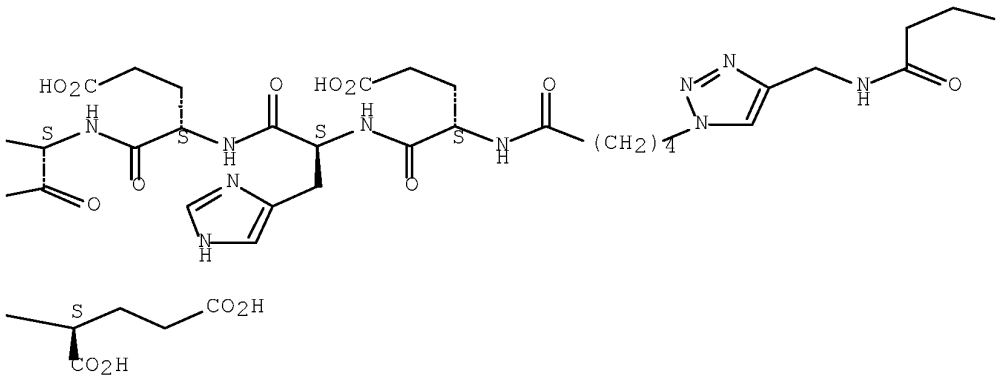


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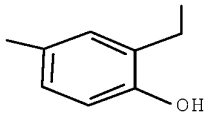


Fusion Pharmaceuticals, Inc.
Exhibit 1004.077

PAGE 2-B



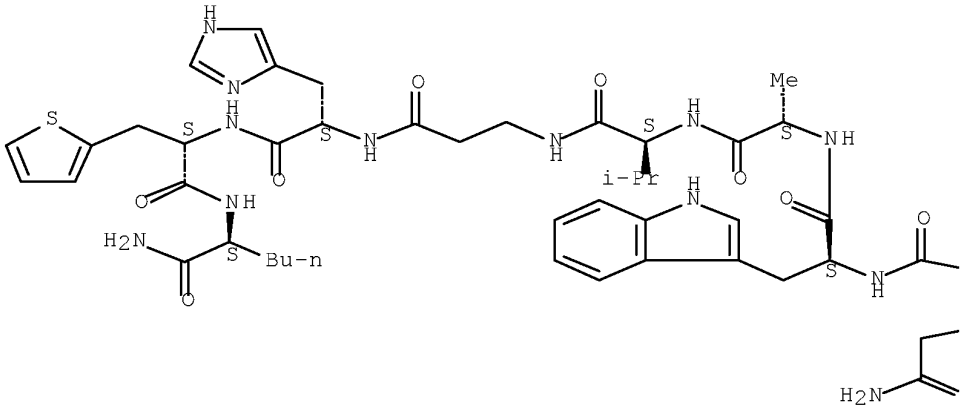
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RN 1853278-37-1 CAPLUS
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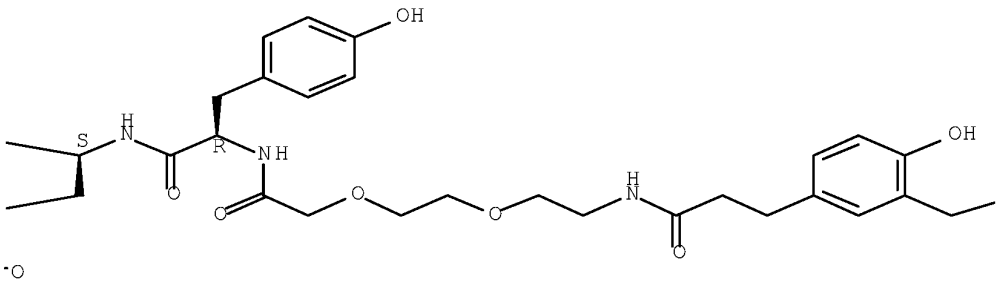
Absolute stereochemistry.

PAGE 1-A

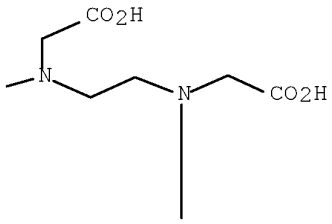


Fusion Pharmaceuticals, Inc.
Exhibit 1004.078

PAGE 1-B

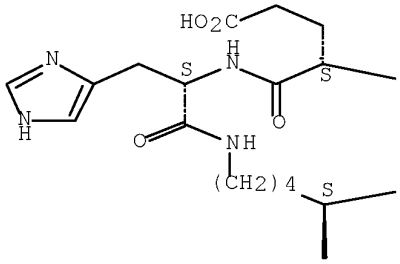


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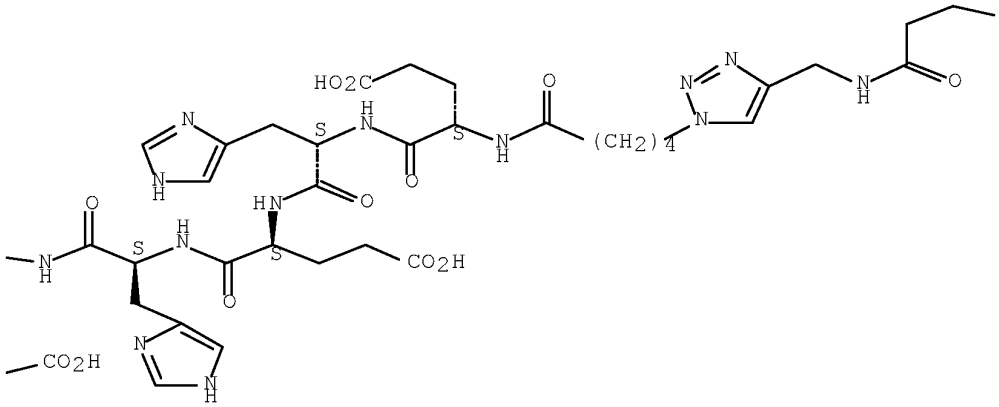


Fusion Pharmaceuticals, Inc.
Exhibit 1004.079

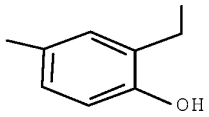
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PAGE 2-B

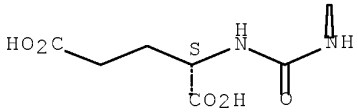


PAGE 2-C



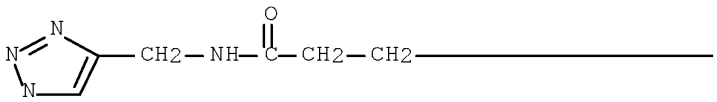
Fusion Pharmaceuticals, Inc.
Exhibit 1004.080

PAGE 3-A

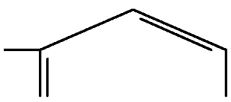


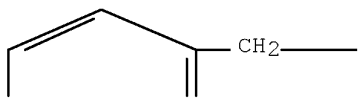
RN 1853291-10-7 CAPLUS
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PAGE 1-A



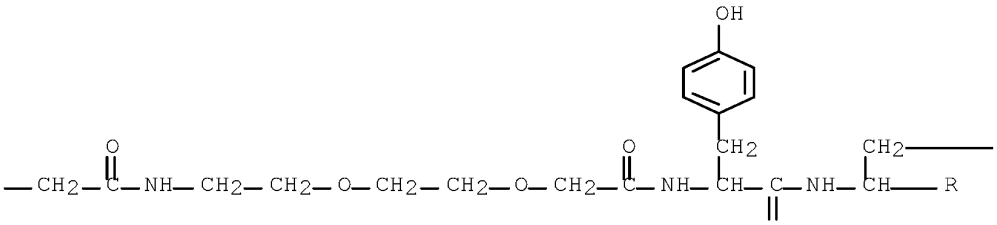
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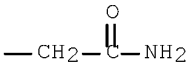


Fusion Pharmaceuticals, Inc.
Exhibit 1004.081

PAGE 1-C

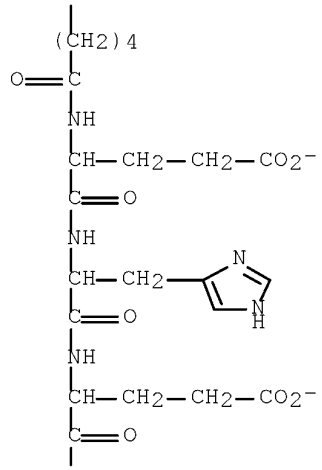


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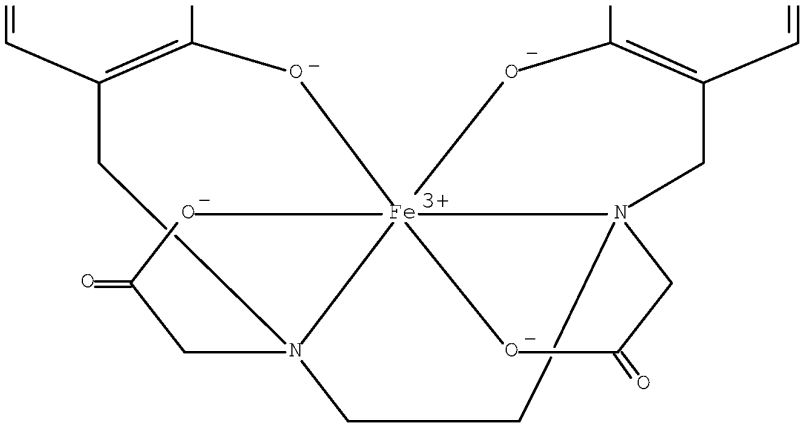


Fusion Pharmaceuticals, Inc.
Exhibit 1004.082

PAGE 2-A



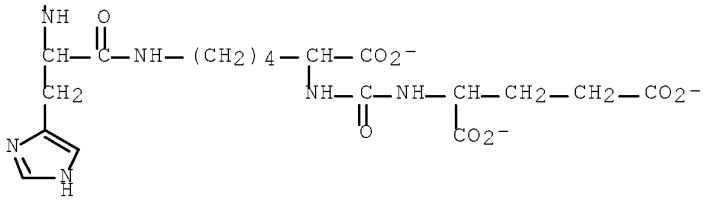
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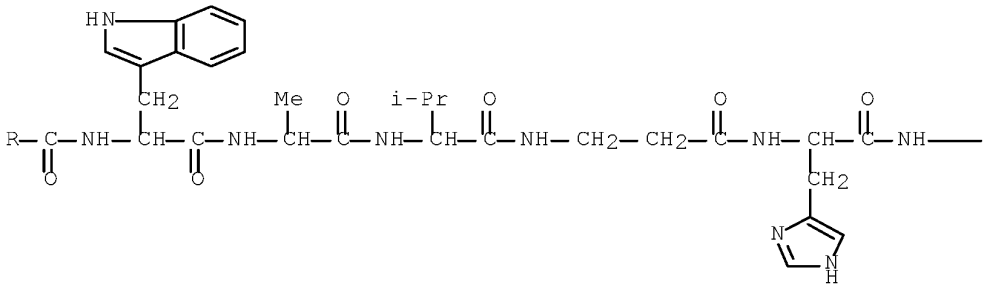
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.083

PAGE 3-A

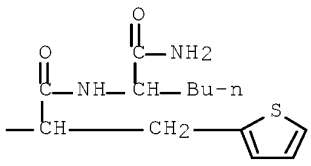


PAGE 4-A



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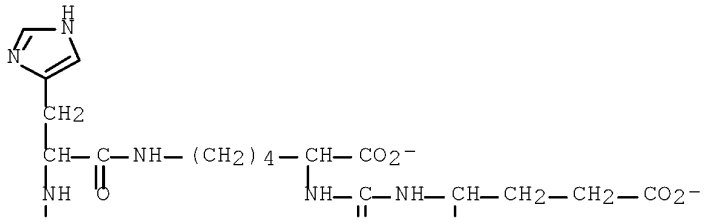
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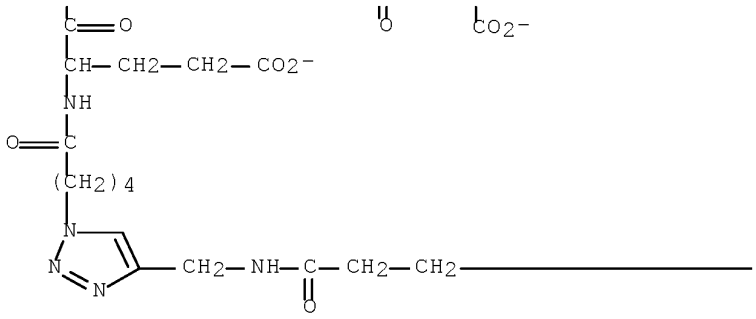
RN 1853291-11-8 CAPLUS
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.084

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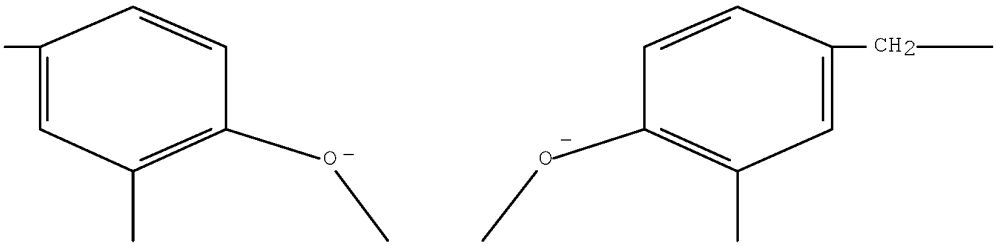


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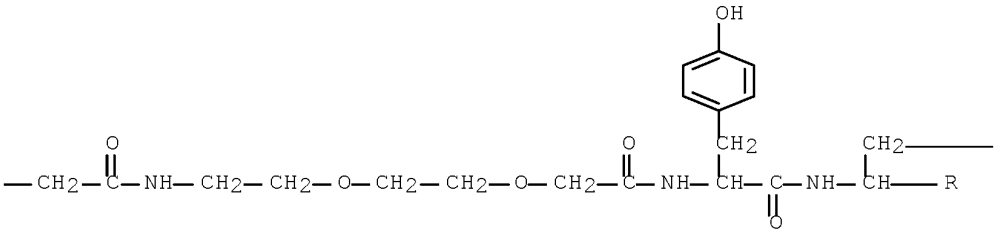


Fusion Pharmaceuticals, Inc.
Exhibit 1004.085

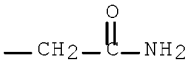
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PAGE 2-C

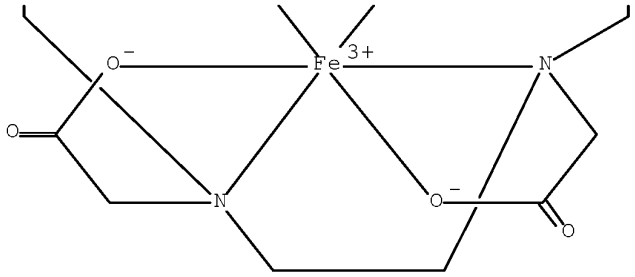


PAGE 2-D

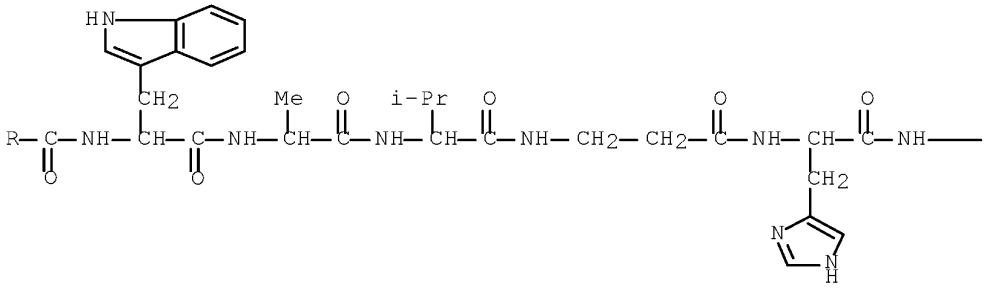


Fusion Pharmaceuticals, Inc.
Exhibit 1004.086

PAGE 3-B

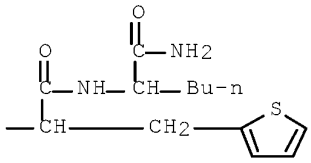


PAGE 4-A



●4 H+

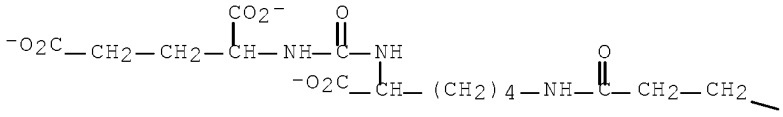
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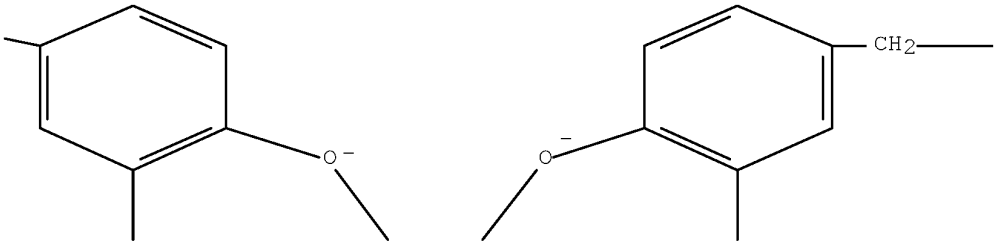
RN 1853291-12-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Fusion Pharmaceuticals, Inc.
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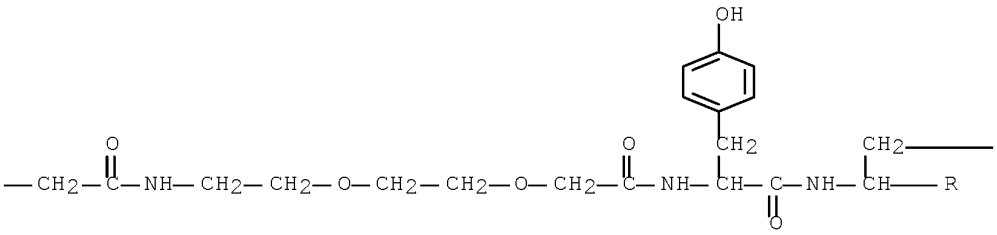
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PAGE 1-B

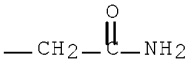


PAGE 1-C

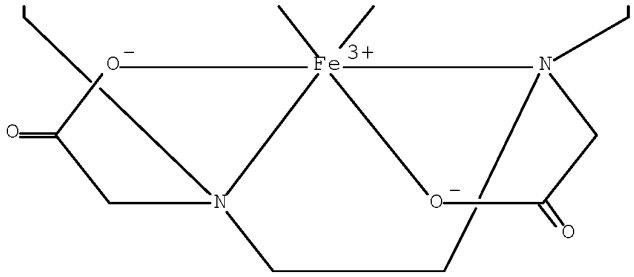


Fusion Pharmaceuticals, Inc.
Exhibit 1004.088

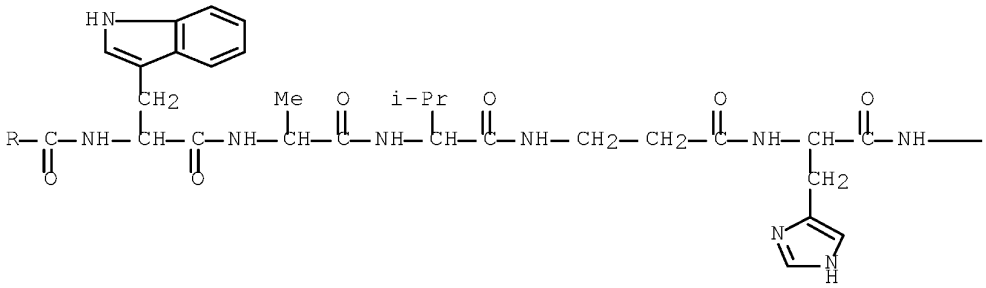
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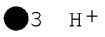


PAGE 2-B



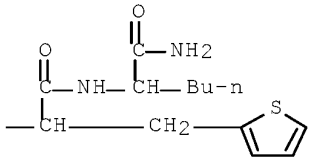
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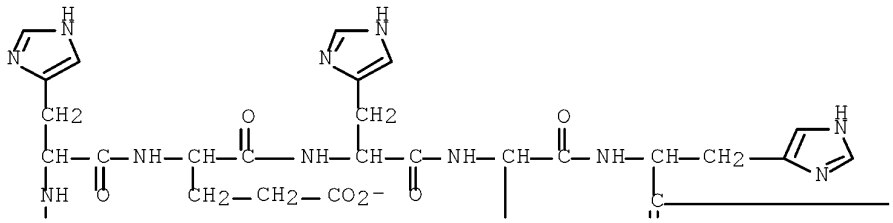
Fusion Pharmaceuticals, Inc.
Exhibit 1004.089

PAGE 3-B

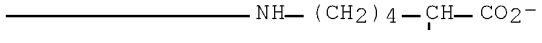


RN 1853291-34-5 CAPLUS
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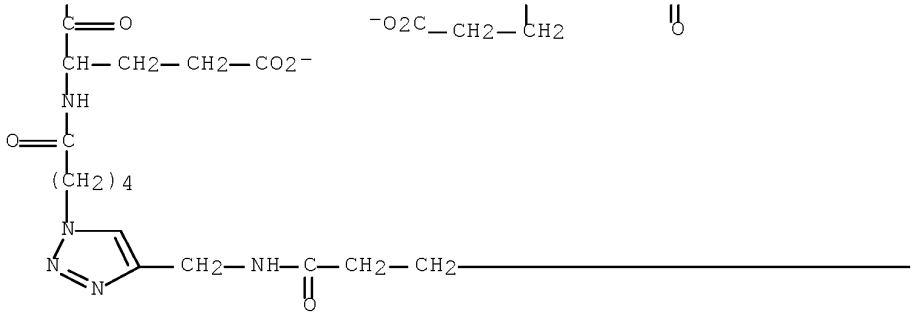


PAGE 1-B

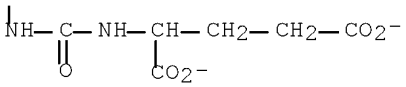


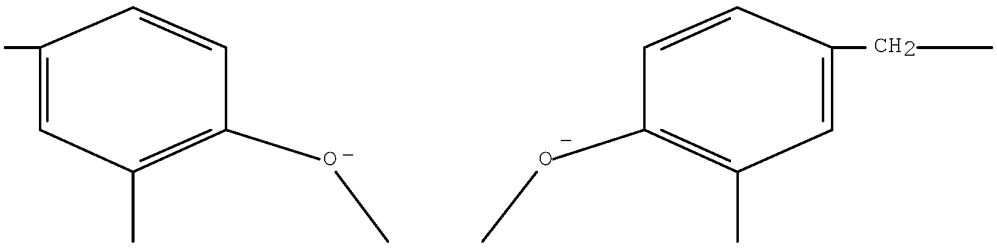
Fusion Pharmaceuticals, Inc.
Exhibit 1004.090

PAGE 2-A



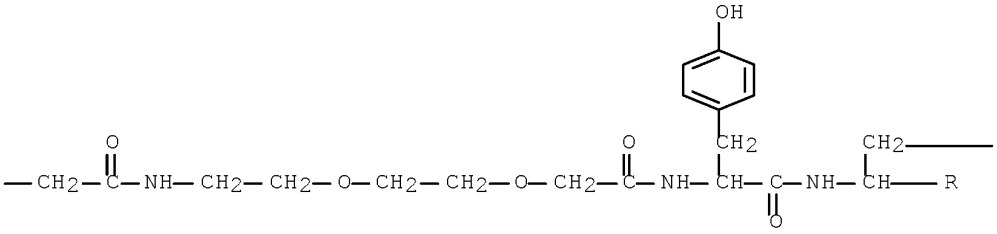
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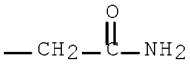


Fusion Pharmaceuticals, Inc.
Exhibit 1004.091

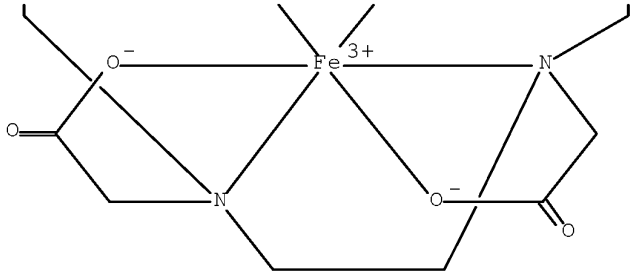
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PAGE 2-D

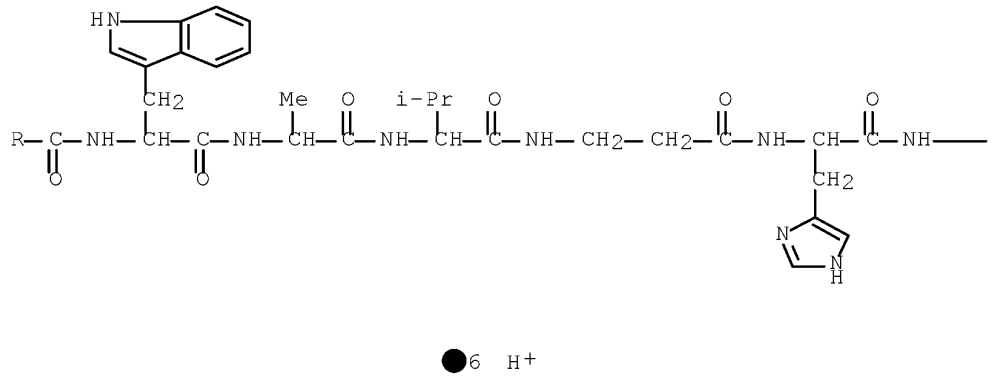


PAGE 3-B



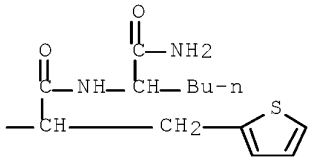
Fusion Pharmaceuticals, Inc.
Exhibit 1004.092

PAGE 4-A



●6 H+

PAGE 4-B



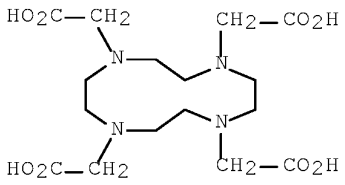
L132 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:255581 CAPLUS Full-text
DOCUMENT NUMBER: 164:332143
TITLE: Linker Modification Strategies To Control the Prostate-Specific Membrane Antigen (PSMA)-Targeting and Pharmacokinetic Properties of DOTA-Conjugated PSMA Inhibitors
AUTHOR(S): Benesova, Martina; Bauder-Wuest, Ulrike; Schaefer, Martin; Klika, Karel D.; Mier, Walter; Haberkorn, Uwe; Kopka, Klaus; Eder, Matthias
CORPORATE SOURCE: Division of Radiopharmaceutical Chemistry, German Cancer Research Center, Heidelberg, 69120, Germany
SOURCE: Journal of Medicinal Chemistry (2016), 59(5), 1761-1775
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/acs.jmedchem.5b01210
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 164:332143

AB Since prostate-specific membrane antigen (PSMA) is up-regulated in nearly all stages of prostate cancer (PCa), PSMA can be considered as a viable diagnostic biomarker and treatment target in PCa. This project is focused on the development and evaluation of a series of compds. directed against PSMA. The modifications to the linker are designed to improve the binding potential and pharmacokinetics for theranostic application. In addition, the results help to further elucidate

Fusion Pharmaceuticals, Inc.
Exhibit 1004.093

the structure-activity relationships (SAR) of the resulting PSMA inhibitors. Both in vitro and in vivo expts. of 18 synthesized PSMA inhibitor variants showed that systematic chemical modification of the linker has a significant impact on the tumor-targeting and pharmacokinetic properties. This approach can lead to an improved management of patients suffering from recurrent prostate cancer by the use of one radiolabeling precursor, which can be radiolabeled either with 68Ga for diagnosis or with 177Lu or 225Ac for therapy.

IT 60239-18-1, DOTA
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(linker modification strategies to control the prostate-specific membrane antigen-targeting and pharmacokinetic properties of DOTA-conjugated prostate-specific membrane antigen inhibitors)
RN 60239-18-1 CAPLUS
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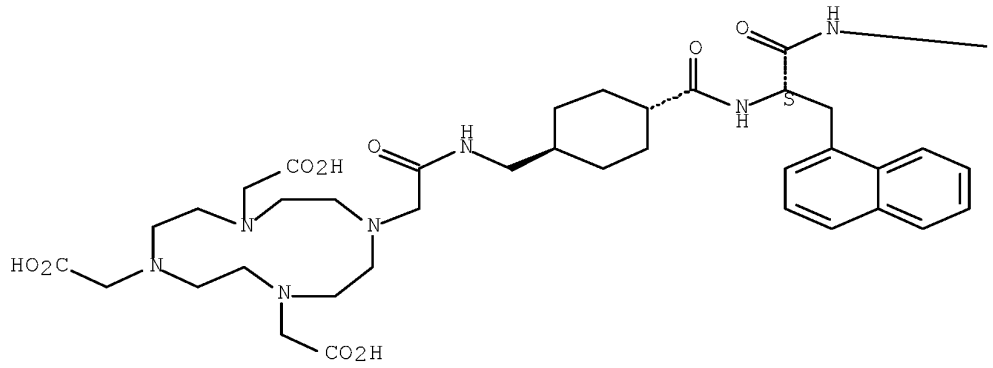


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1802854-21-8P 1802854-22-9P 1802854-23-0P
1802854-24-1P 1802854-25-2P 1802854-26-3P
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(linker modification strategies to control the prostate-specific membrane antigen-targeting and pharmacokinetic properties of DOTA-conjugated prostate-specific membrane antigen inhibitors)
RN 1702720-89-5 CAPLUS
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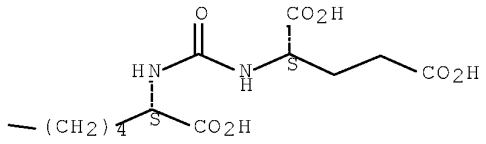
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.094

PAGE 1-A



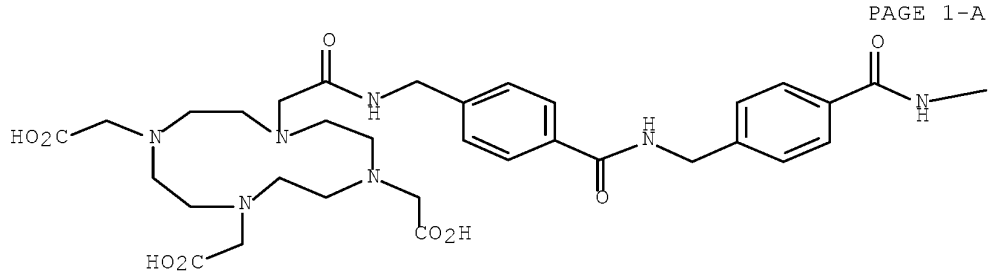
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RN 1702720-91-9 CAPLUS
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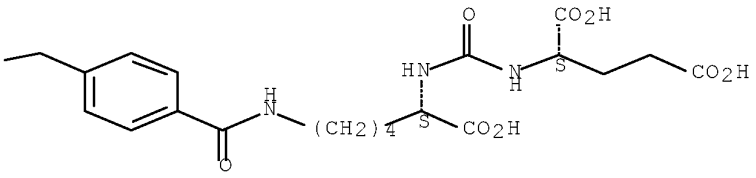
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PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.095

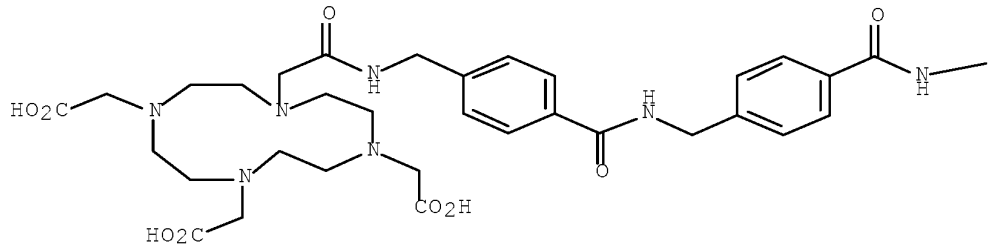
PAGE 1-B



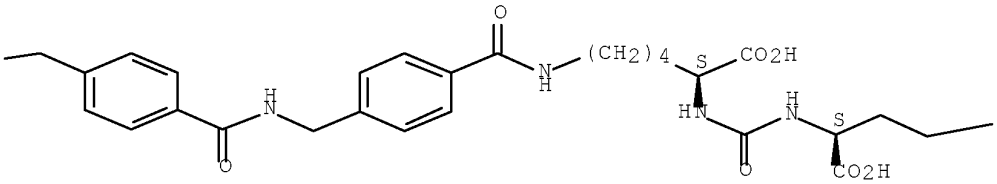
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mino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]ph
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 1-C

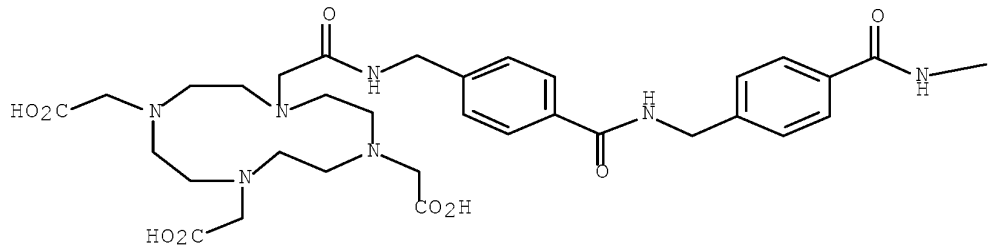


Fusion Pharmaceuticals, Inc.
Exhibit 1004.096

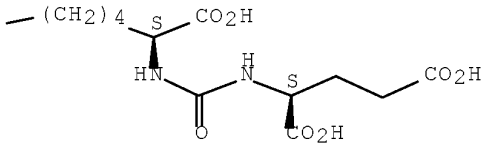
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Absolute stereochemistry.

PAGE 1-A



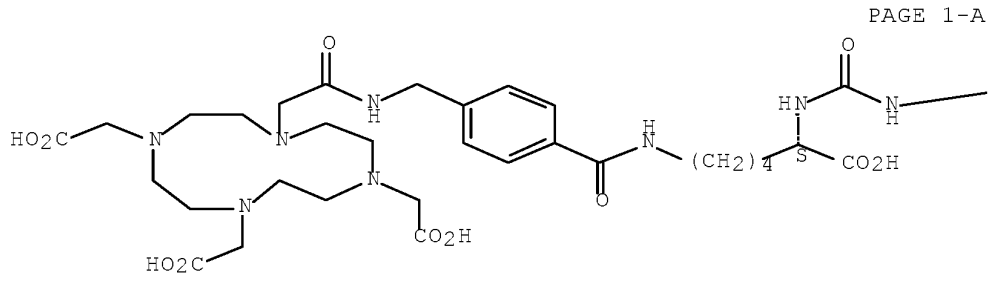
PAGE 1-B



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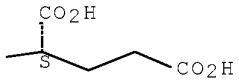
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.097

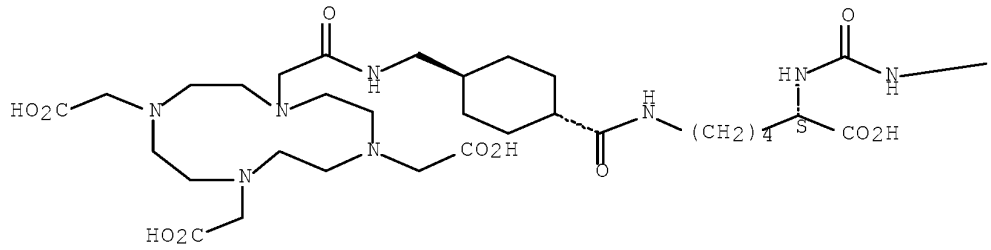
PAGE 1-B



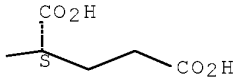
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

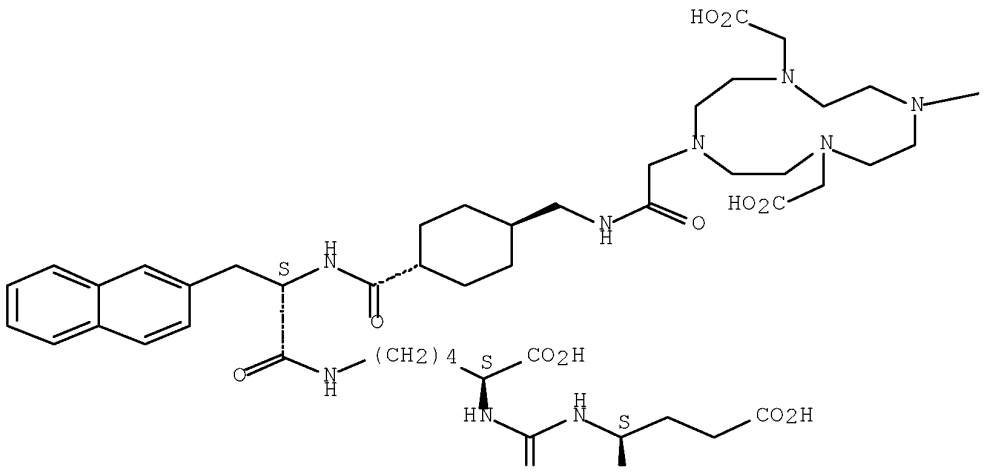


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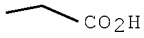
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.098

PAGE 1-A



PAGE 1-B



PAGE 2-A

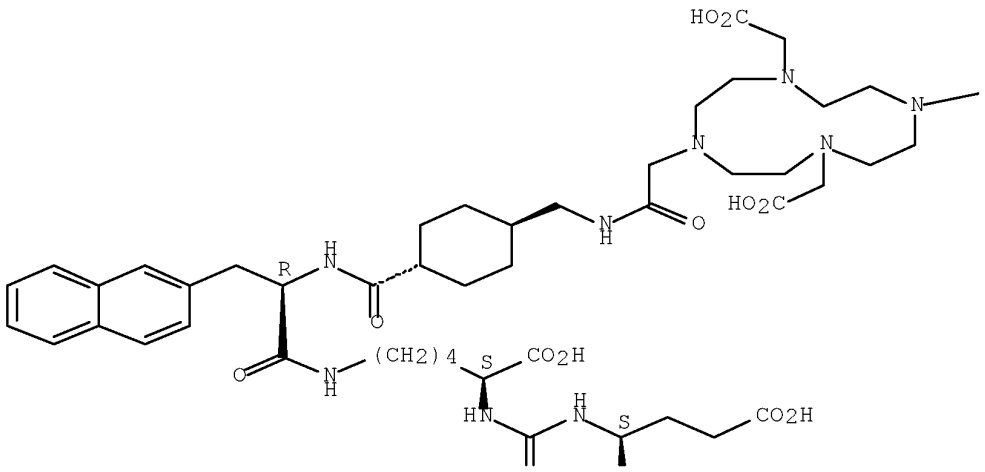


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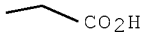
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.099

PAGE 1-A



PAGE 1-B



PAGE 2-A

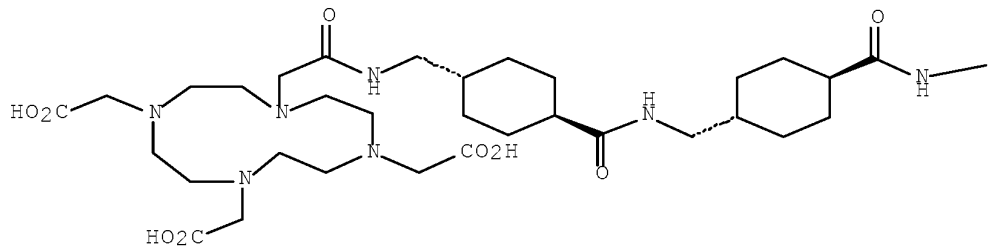


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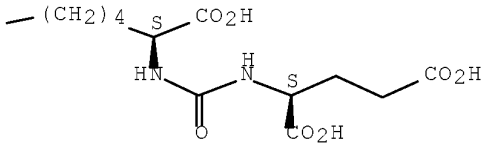
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.100

PAGE 1-A



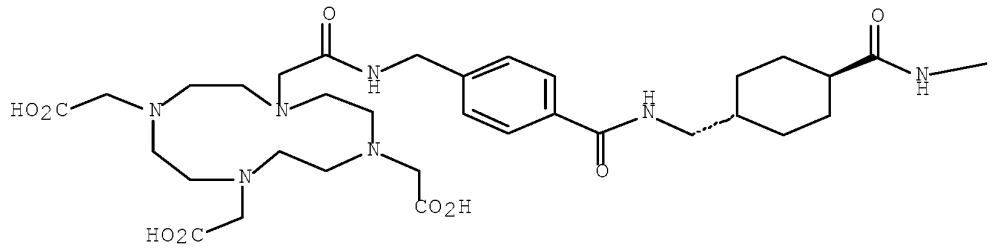
PAGE 1-B



RN 1702967-52-9 CAPLUS
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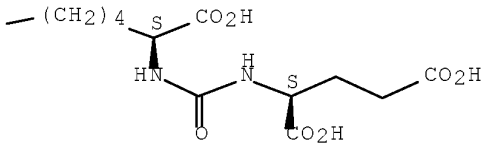
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.101

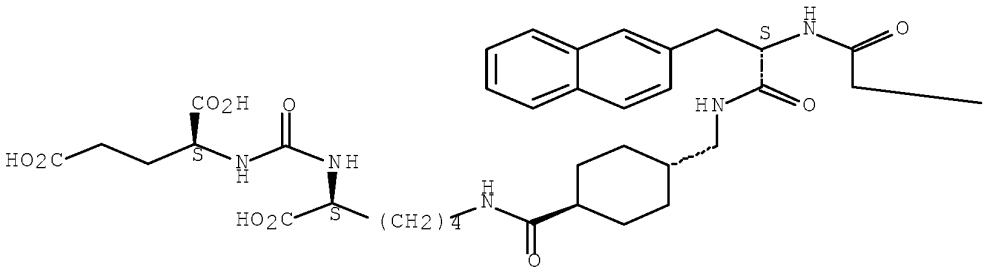
PAGE 1-B



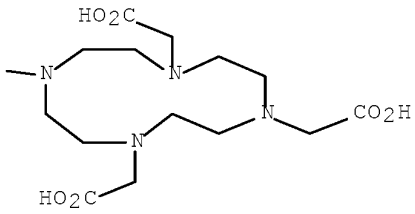
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

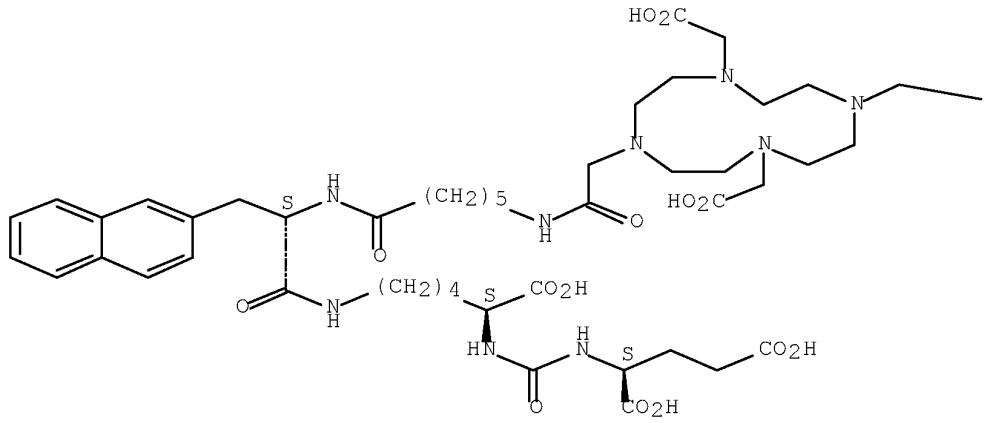


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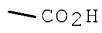
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.102

PAGE 1-A



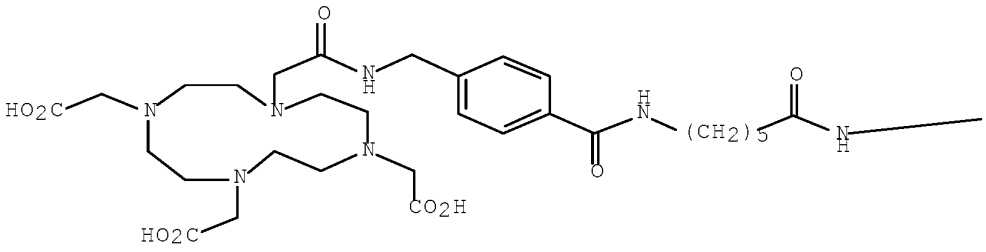
PAGE 1-B



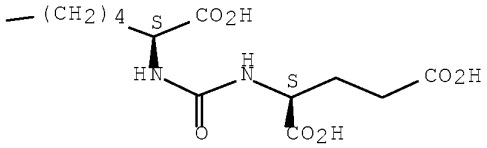
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CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A

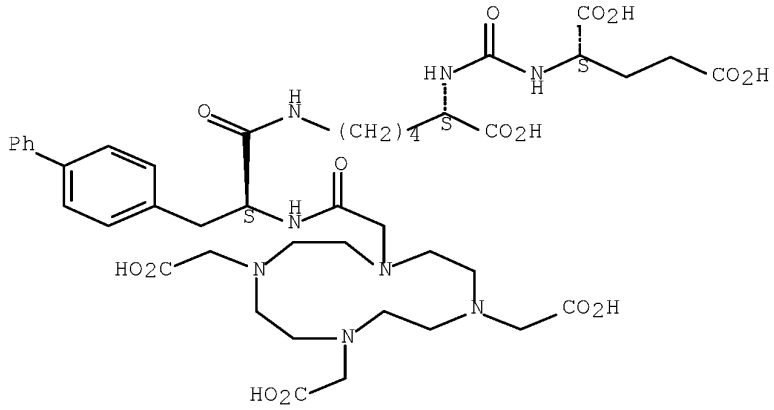


Fusion Pharmaceuticals, Inc.
Exhibit 1004.103



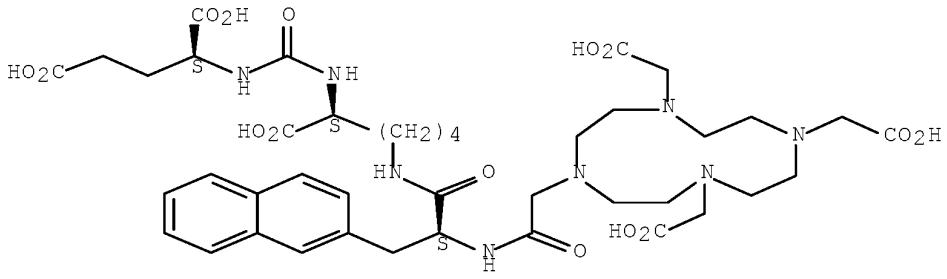
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CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 1882854-23-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

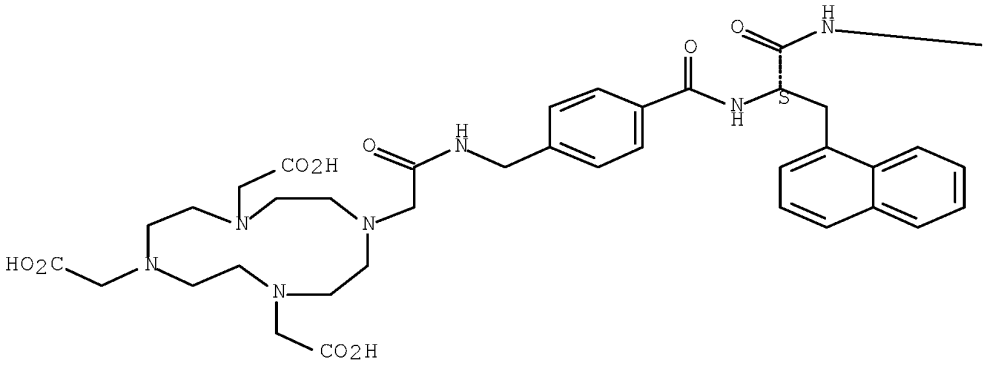


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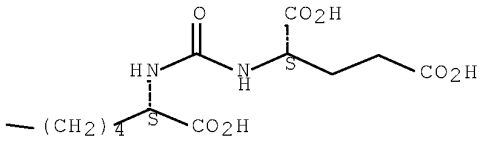
Fusion Pharmaceuticals, Inc.
Exhibit 1004.104

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

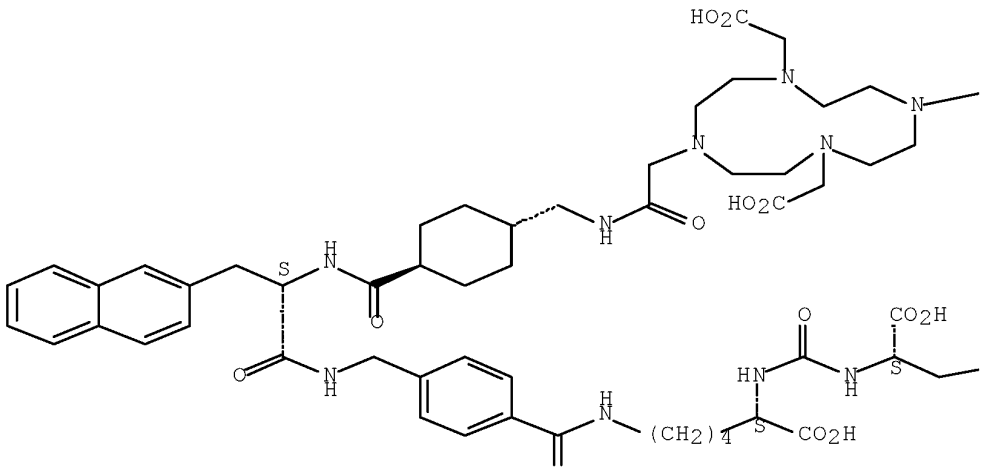


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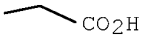
Absolute stereochemistry.

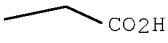
Fusion Pharmaceuticals, Inc.
Exhibit 1004.105

PAGE 1-A



PAGE 1-B





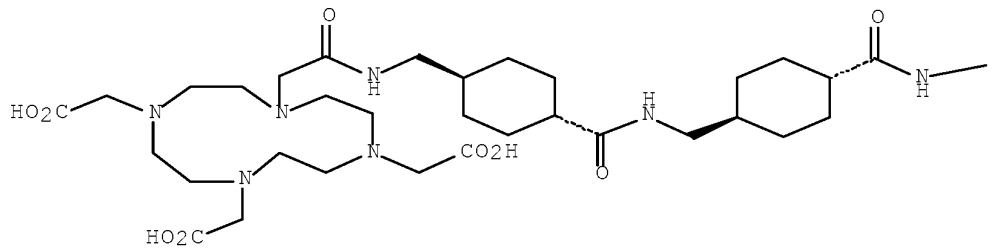
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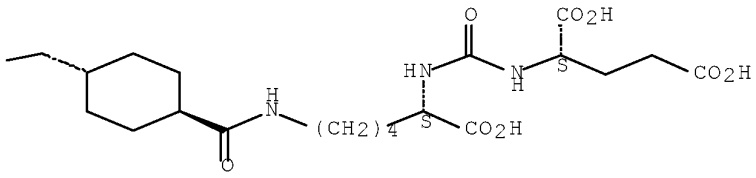
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.106

PAGE 1-A



PAGE 1-B



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REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:14309 CAPLUS Full-text
DOCUMENT NUMBER: 164:322413
TITLE: Novel Bispecific PSMA/GRPr Targeting Radioligands with Optimized Pharmacokinetics for Improved PET Imaging of Prostate Cancer
AUTHOR(S): Liolios, C.; Schaefer, M.; Haberkorn, U.; Eder, M.; Kopka, K.
CORPORATE SOURCE: Division of Radiopharmaceutical Chemistry, German Cancer Research Center (DKFZ), Heidelberg, 69120, Germany
SOURCE: Bioconjugate Chemistry (2016), 27(3), 737-751
CODEN: BCCHES; ISSN: 1043-1802
DIGITAL OBJECT ID: 10.1021/acs.bioconjchem.5b00687
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 164:322413

AB A new series of bispecific radioligands (BRLs) targeting prostate-specific membrane antigen (PSMA) and gastrin releasing peptide receptor (GRPr), both expressed on prostate cancer cells, was developed. Their design was based on the bombesin (BN) analog, H2N-PEG2-[D-Tyr6,β-Ala11,Thi13,Nle14]BN(6-14), which binds to GRPr with high affinity and specificity, and the peptidomimetic urea-based pseudoirreversible inhibitor of PSMA, Glu-ureido-Lys. The two pharmacophores were coupled through copper(I)-catalyzed azide-alkyne cycloaddn. to the bis(tetrafluorophenyl) ester of the chelating agent HBED-CC via amino acid linkers made of pos. charged His (H)

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Exhibit 1004.107

and neg. charged Glu (E): -(HE)n- (n = 0-3). The BRLs were labeled with 68Ga, and their preliminary pharmacol. properties were evaluated in vitro (competitive and time kinetic binding assays) on prostate cancer (PC-3, LNCaP) and rat pancreatic (AR42J) cell lines and in vivo by biodistribution and small animal PET imaging studies in both normal and tumor-bearing mice. The IC50/Ki values determined for all BRLs essentially matched those of the resp. monomers. The maximal cellular uptake of the BLRs was observed between 20 and 30 min. The BRLs showed a synergistic ability in vivo by targeting both PSMA (LNCaP) and GRPr (PC-3) pos. tumors, whereas the charged -(HE)n- (n = 1-3) linkers significantly reduced the kidney and spleen uptake. The bispecific (PSMA and GRPr) targeting ability and optimized pharmacokinetics of the compds. developed in this study could lead to their future application in clin. practice as more sensitive radiotracers for noninvasive imaging of prostate cancer (PCa) by PET/CT and PET/MRI.

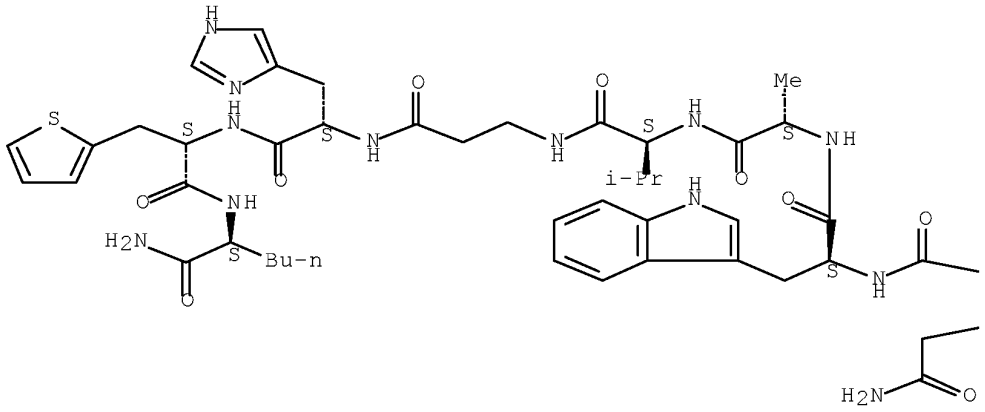
IT 1853278-34-8DP, 68Ga-labeled 1853278-35-9DP, 68Ga-labeled 1853278-36-0DP, 68Ga-labeled 1853278-37-1DP, 68Ga-labeled
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(novel bispecific PSMA/GRPR-targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer)

RN 1853278-34-8 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

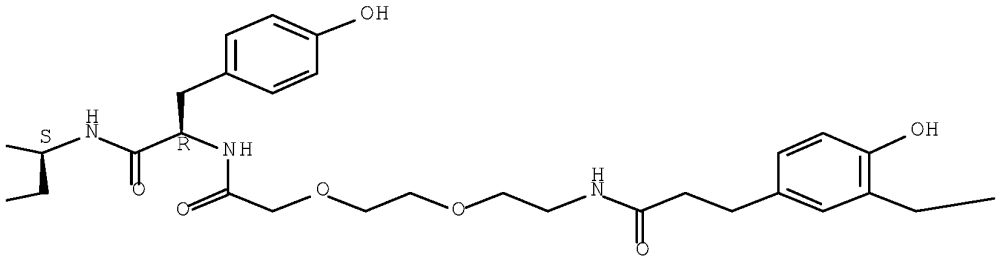
Absolute stereochemistry.

PAGE 1-A

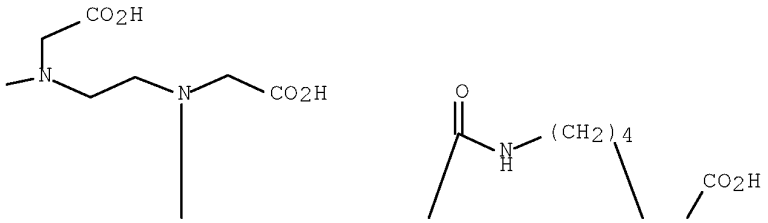


Fusion Pharmaceuticals, Inc.
Exhibit 1004.108

PAGE 1-B



PAGE 1-C



PAGE 2-C

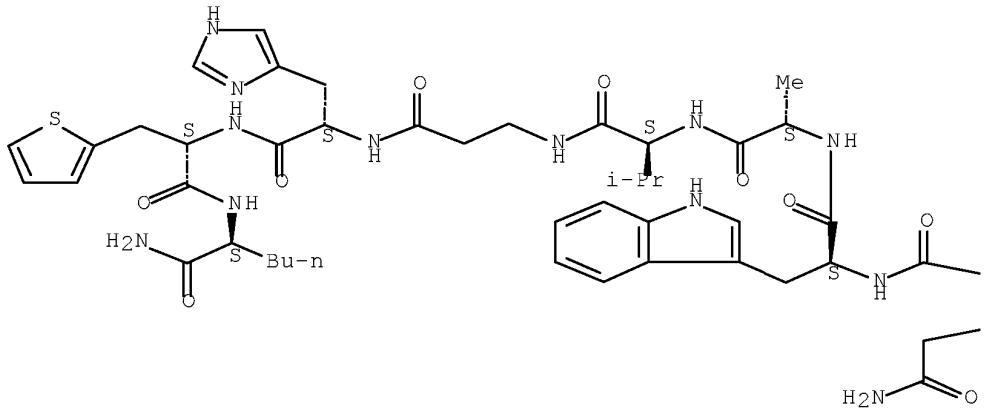


RN 1853278-35-9 CAPLUS
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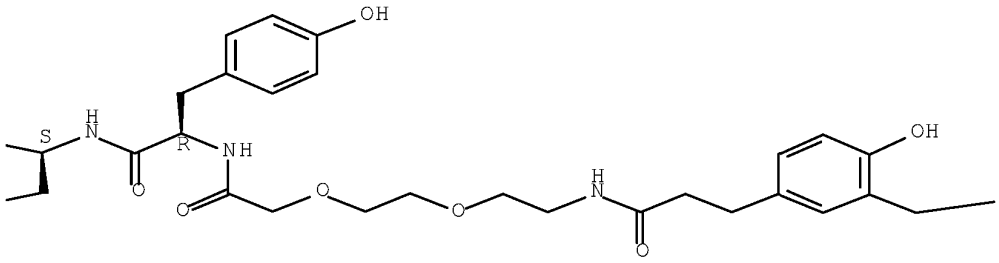
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.109

PAGE 1-A

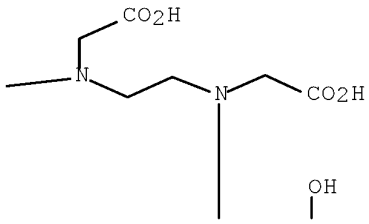


PAGE 1-B

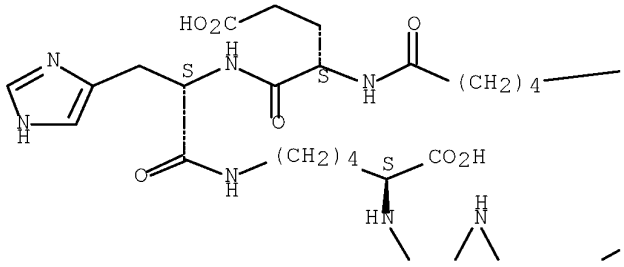


Fusion Pharmaceuticals, Inc.
Exhibit 1004.110

PAGE 1-C

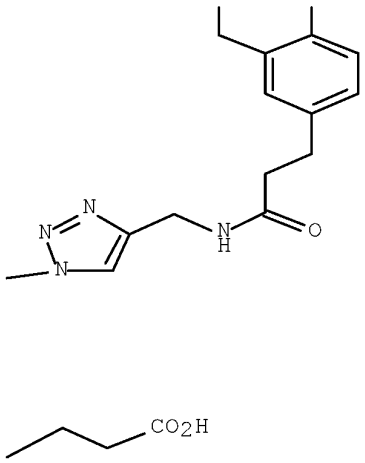


PAGE 2-B

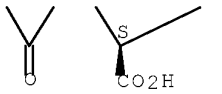


Fusion Pharmaceuticals, Inc.
Exhibit 1004.111

PAGE 2-C



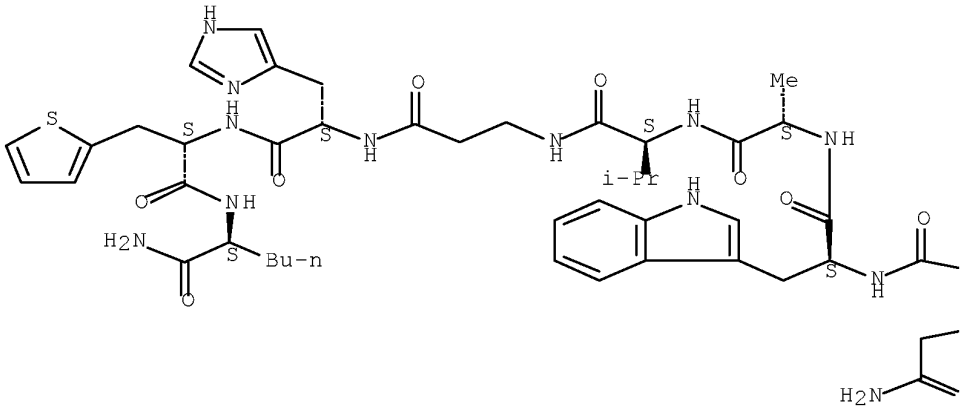
PAGE 3-B



RN 1853278-36-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

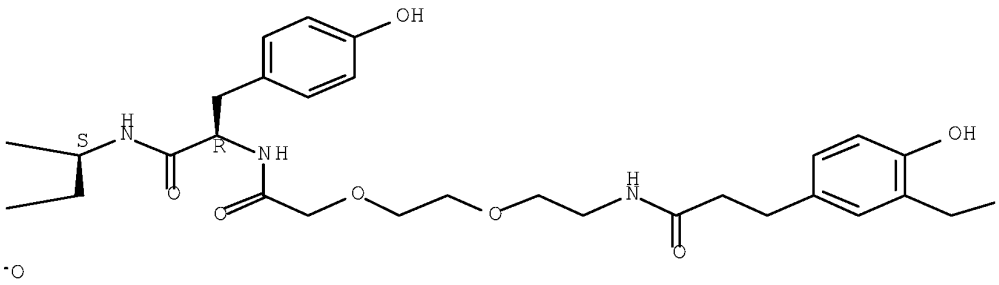
Absolute stereochemistry.

PAGE 1-A

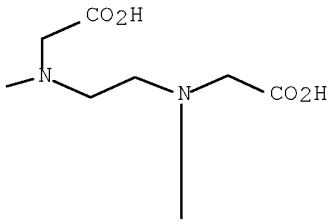


Fusion Pharmaceuticals, Inc.
Exhibit 1004.112

PAGE 1-B

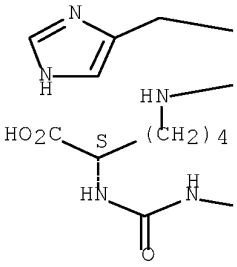


PAGE 1-C

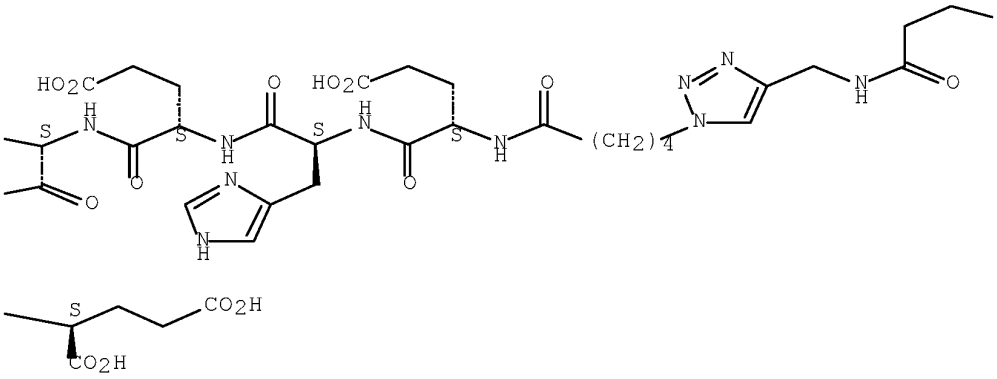


Fusion Pharmaceuticals, Inc.
Exhibit 1004.113

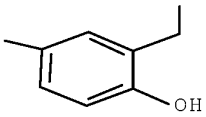
PAGE 2-A



PAGE 2-B



PAGE 2-C

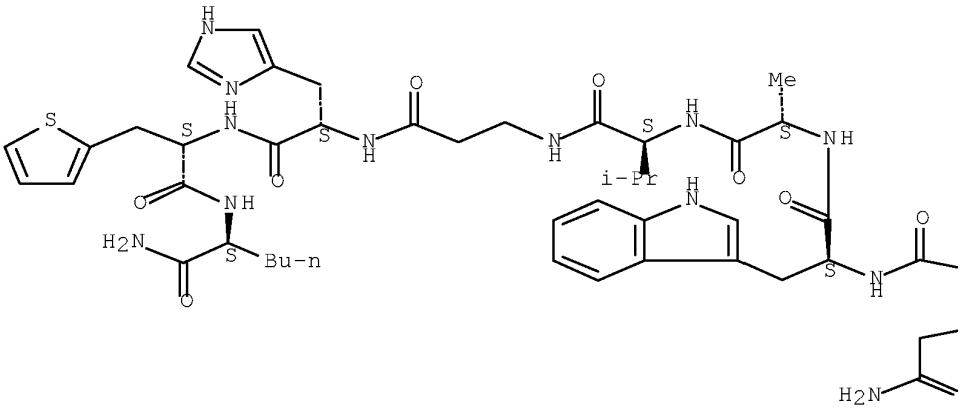


RN 1853278-37-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

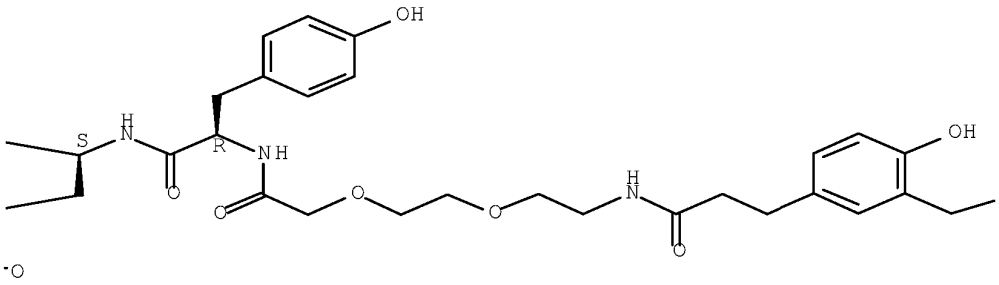
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.114

PAGE 1-A

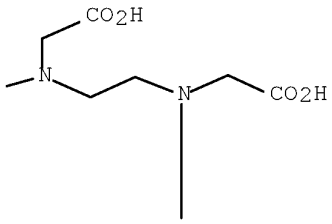


PAGE 1-B

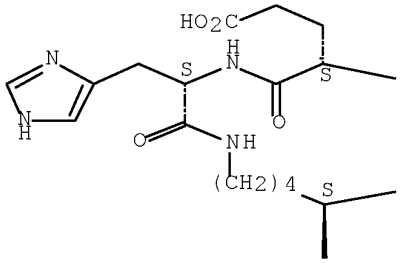


Fusion Pharmaceuticals, Inc.
Exhibit 1004.115

PAGE 1-C

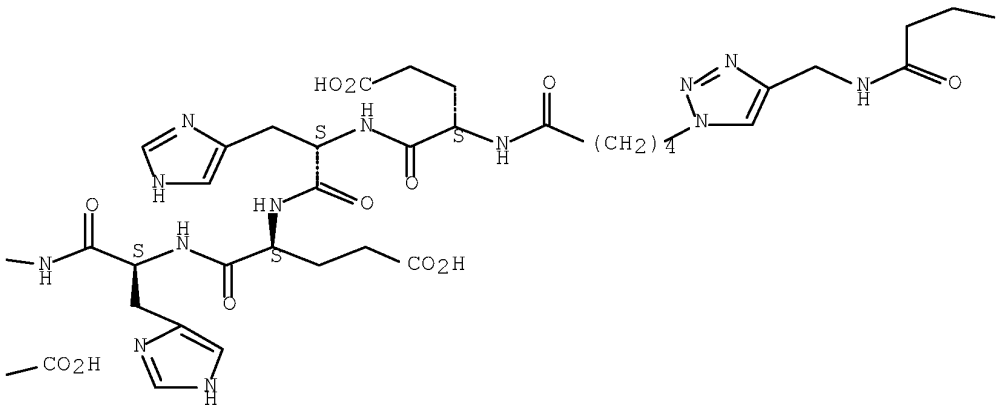


PAGE 2-A

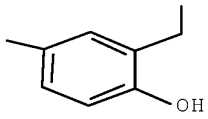


Fusion Pharmaceuticals, Inc.
Exhibit 1004.116

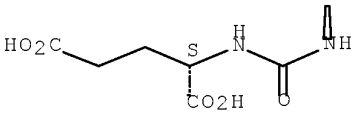
PAGE 2-B



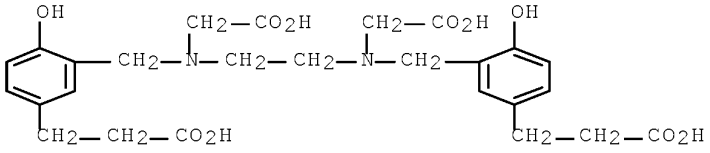
PAGE 2-C



PAGE 3-A



IT 143557-99-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(novel bispecific PSMA/GRPR-targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer)
RN 143557-99-7 CAPLUS
CN Benzenepropanoic acid, 3,3'-[1,2-ethanediylbis[[(carboxymethyl)imino]methylene]]bis[4-hydroxy- (CA INDEX NAME)

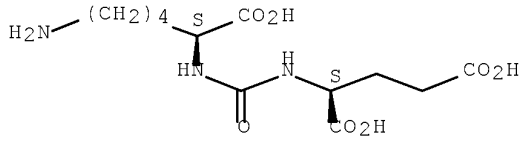


Fusion Pharmaceuticals, Inc.
Exhibit 1004.117

IT 1025796-32-0P 1853278-29-1P 1853278-30-4P
1853278-31-5P 1853278-34-8P 1853278-35-9P
1853278-36-0P 1853278-37-1P 1853291-10-7P
1853291-11-8P 1853291-12-9P 1853291-34-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(novel bispecific PSMA/GRPR-targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer)

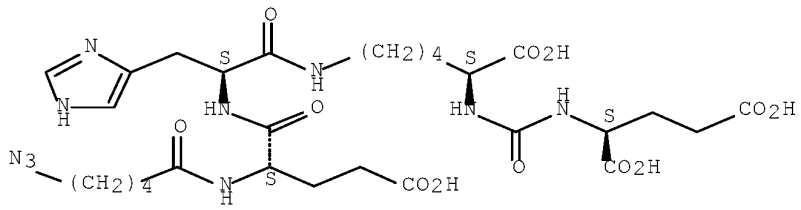
RN 1025796-32-0 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-5-amino-1-carboxypentyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 1853278-29-1 CAPLUS
CN L-Lysine, N6-[N-(5-azido-1-oxopentyl)-L-α-glutamyl-L-histidyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]- (CA INDEX NAME)

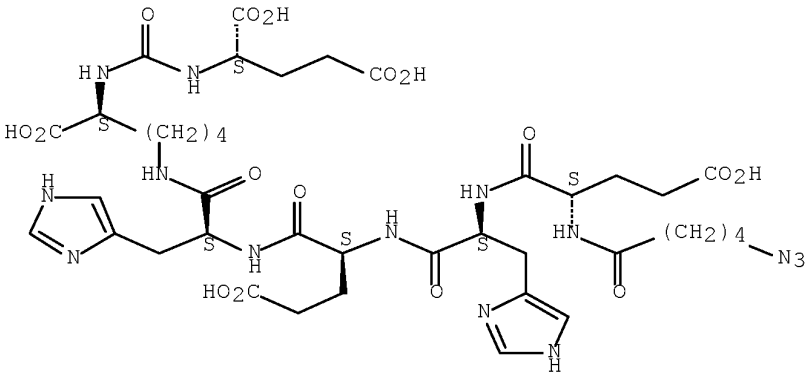
Absolute stereochemistry.



RN 1853278-30-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

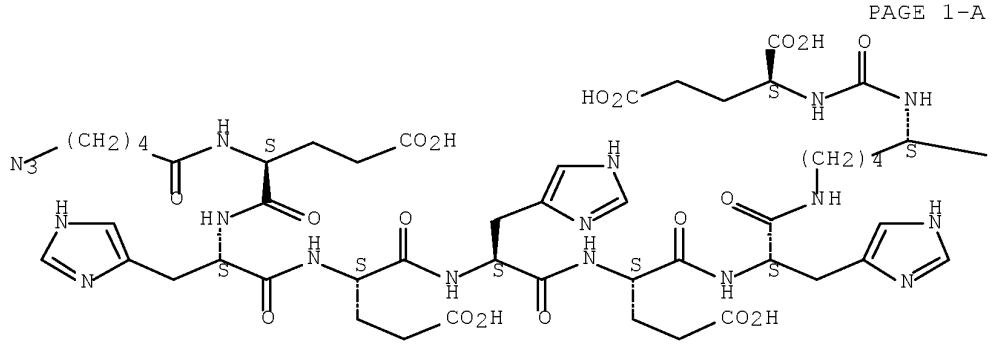
Fusion Pharmaceuticals, Inc.
Exhibit 1004.118



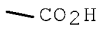
RN 1853278-31-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

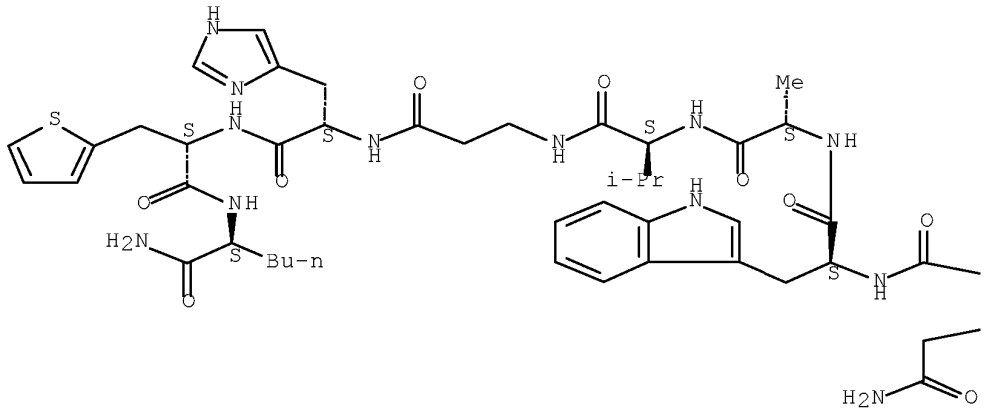


RN 1853278-34-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

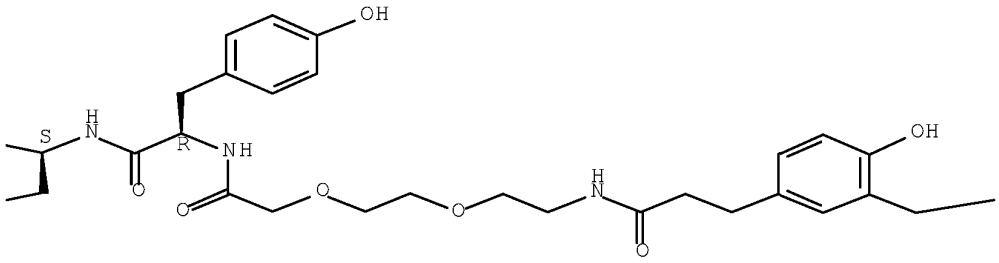
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.119

PAGE 1-A

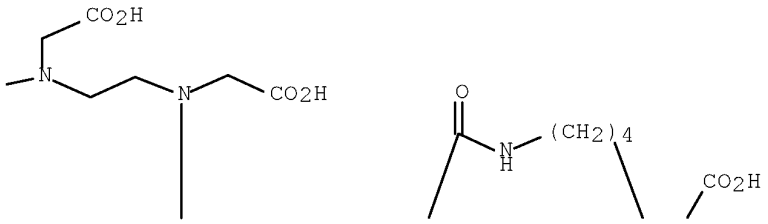


PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.120

PAGE 1-C



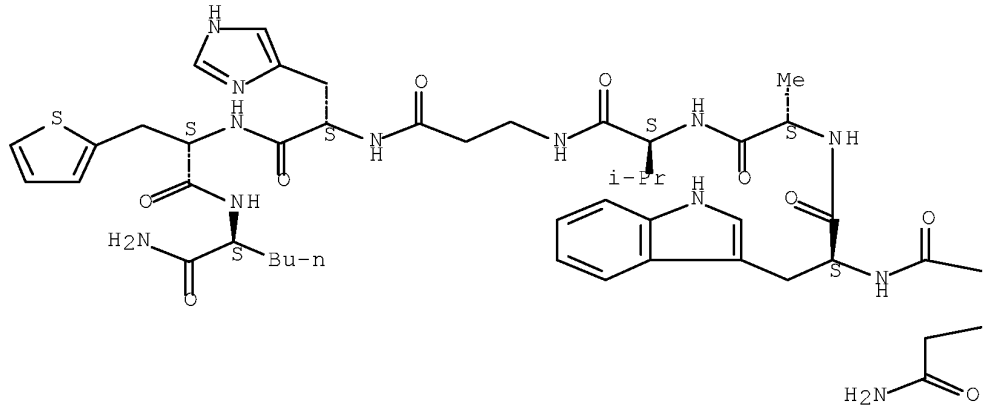
PAGE 2-C



RN 1853278-35-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

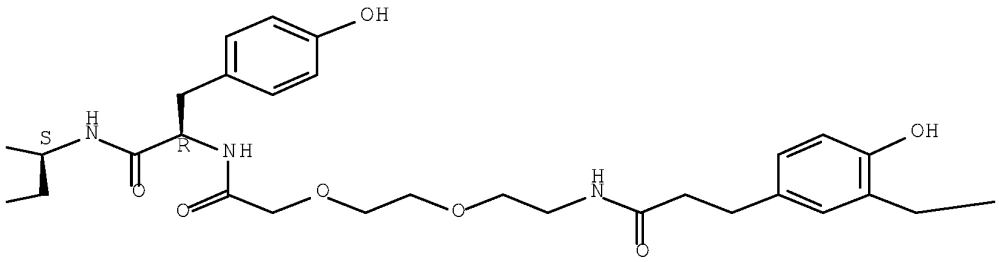
Absolute stereochemistry.

PAGE 1-A

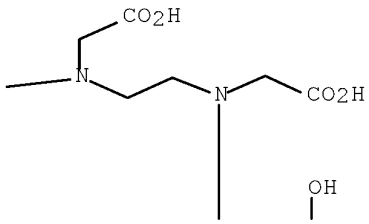


Fusion Pharmaceuticals, Inc.
Exhibit 1004.121

PAGE 1-B

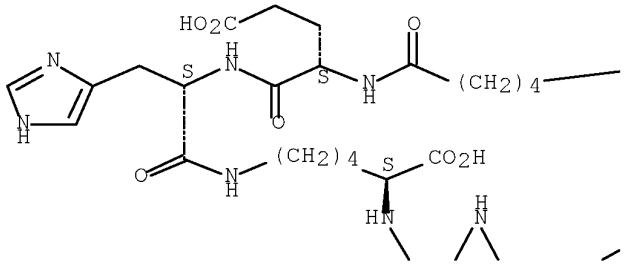


PAGE 1-C

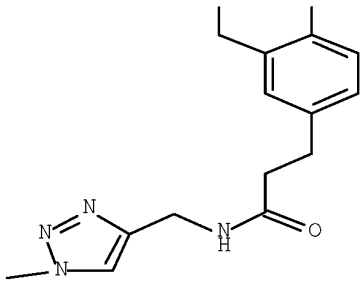


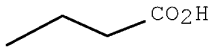
Fusion Pharmaceuticals, Inc.
Exhibit 1004.122

PAGE 2-B

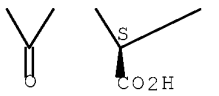


PAGE 2-C





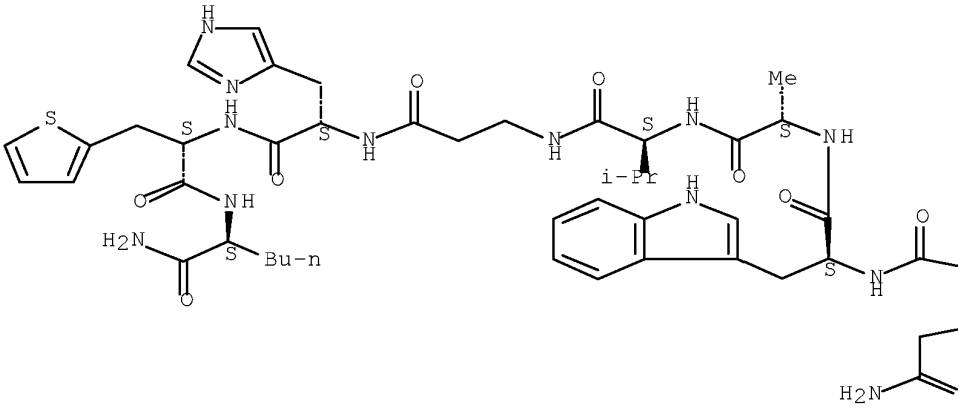
PAGE 3-B



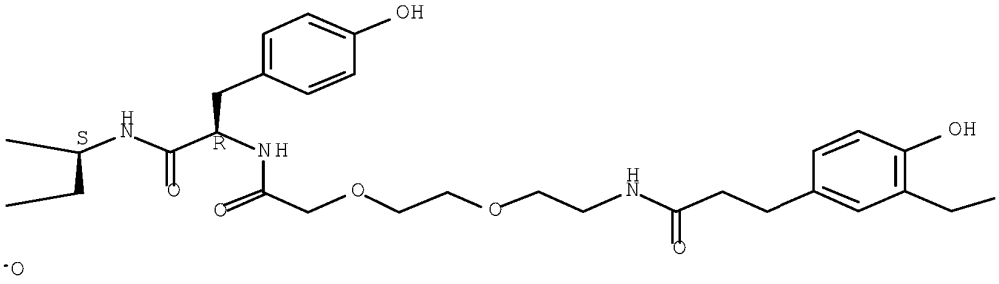
RN 1853278-36-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A

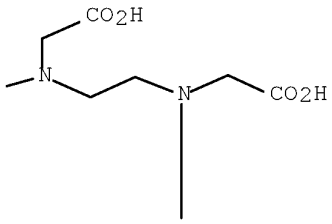


PAGE 1-B

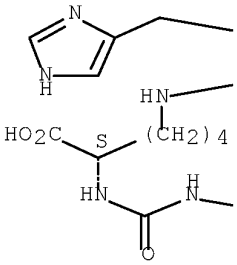


Fusion Pharmaceuticals, Inc.
Exhibit 1004.124

PAGE 1-C

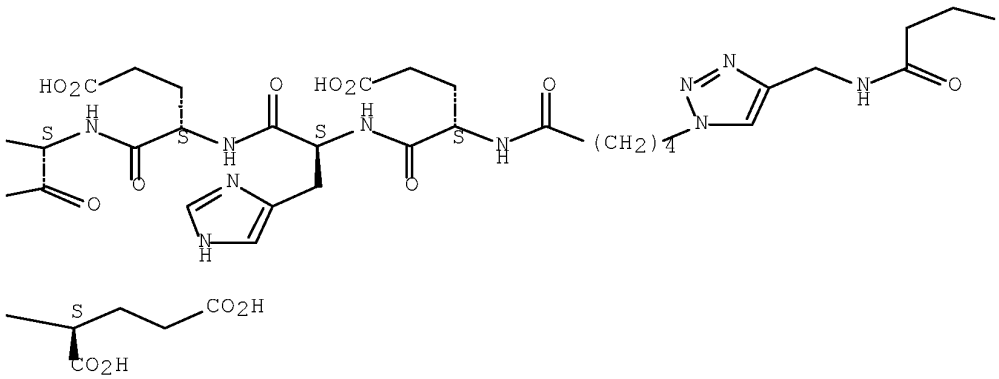


PAGE 2-A

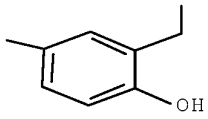


Fusion Pharmaceuticals, Inc.
Exhibit 1004.125

PAGE 2-B



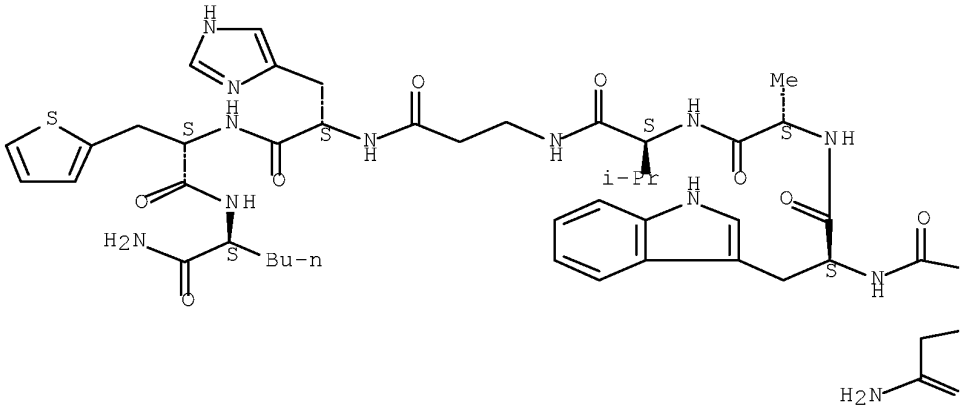
PAGE 2-C



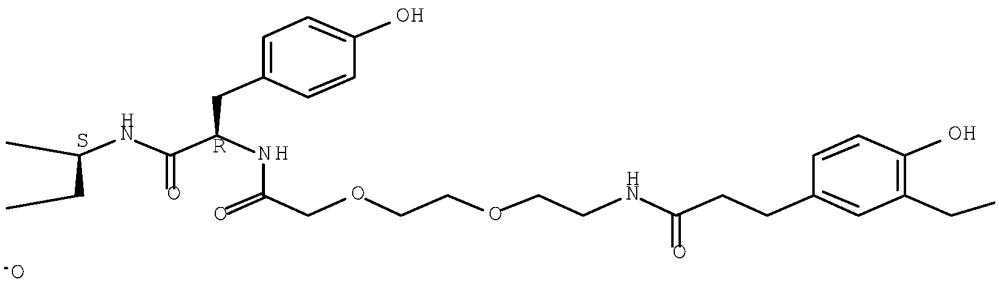
RN 1853278-37-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

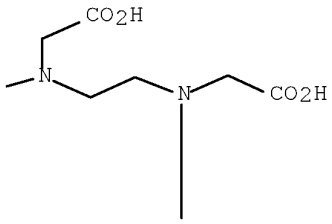
PAGE 1-A



PAGE 1-B

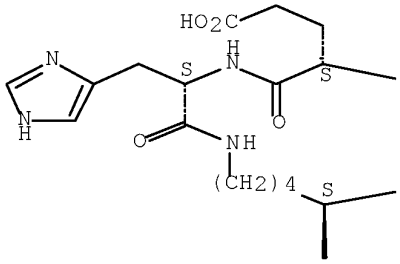


PAGE 1-C

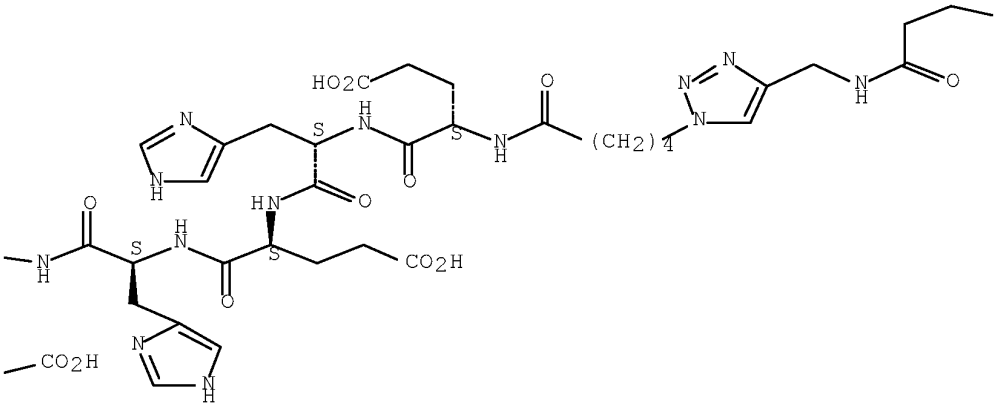


Fusion Pharmaceuticals, Inc.
Exhibit 1004.127

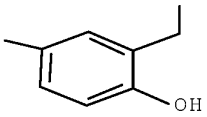
PAGE 2-A



PAGE 2-B

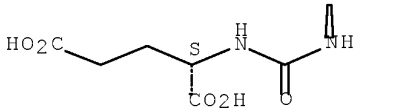


PAGE 2-C



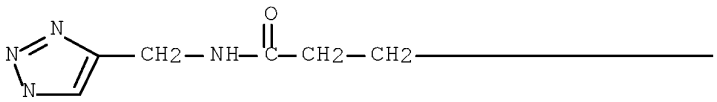
Fusion Pharmaceuticals, Inc.
Exhibit 1004.128

PAGE 3-A

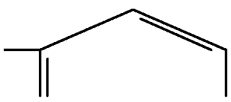


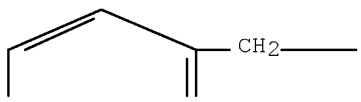
RN 1853291-10-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

PAGE 1-A



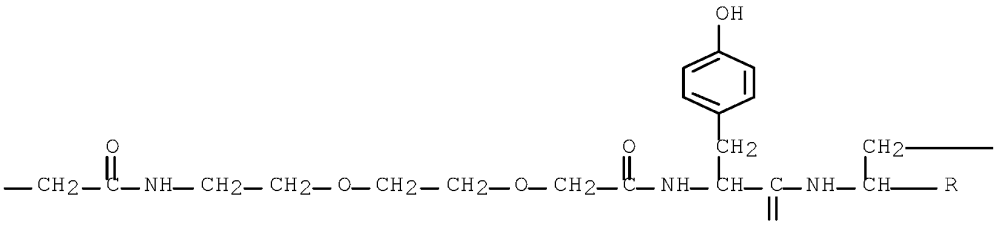
PAGE 1-B



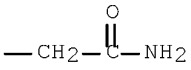


Fusion Pharmaceuticals, Inc.
Exhibit 1004.129

PAGE 1-C

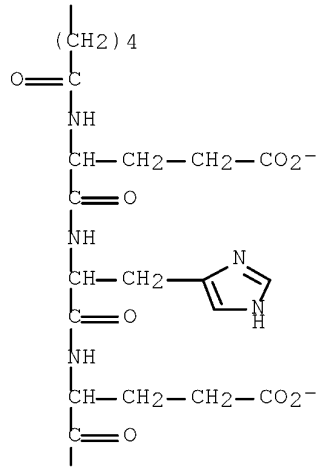


PAGE 1-D

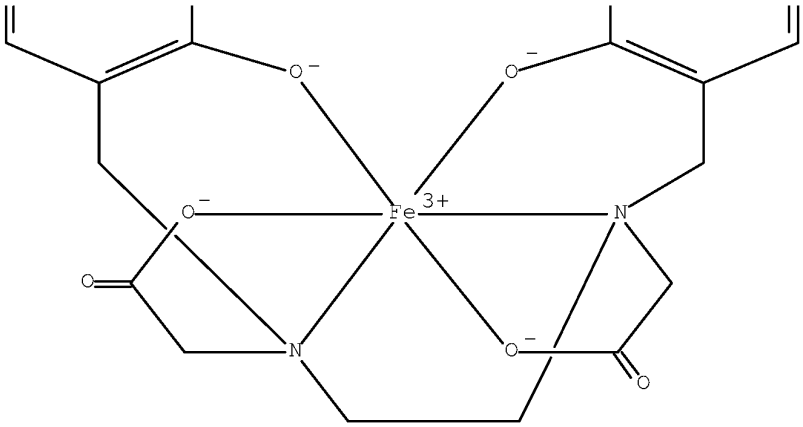


Fusion Pharmaceuticals, Inc.
Exhibit 1004.130

PAGE 2-A



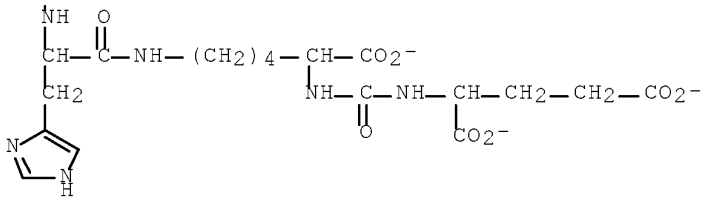
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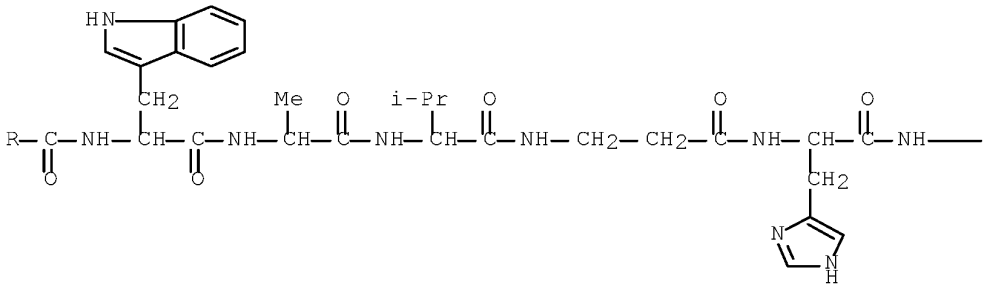
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.131

PAGE 3-A

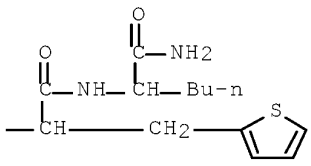


PAGE 4-A



● 5 H^+

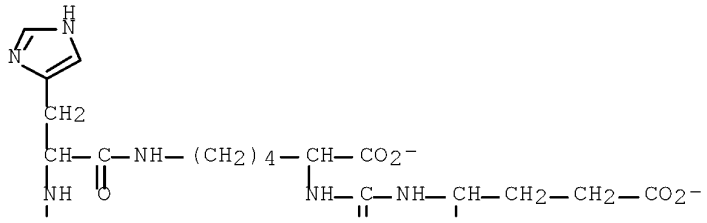
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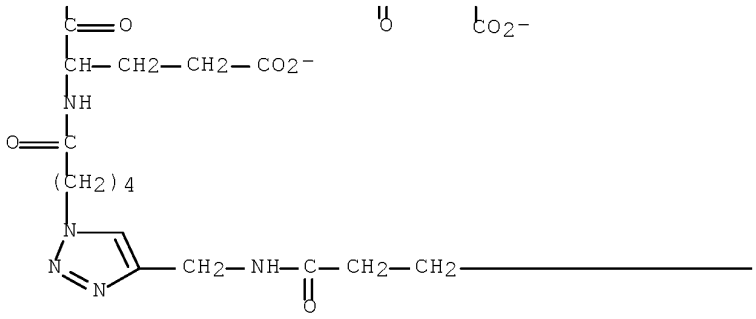
RN 1853291-11-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Fusion Pharmaceuticals, Inc.
Exhibit 1004.132

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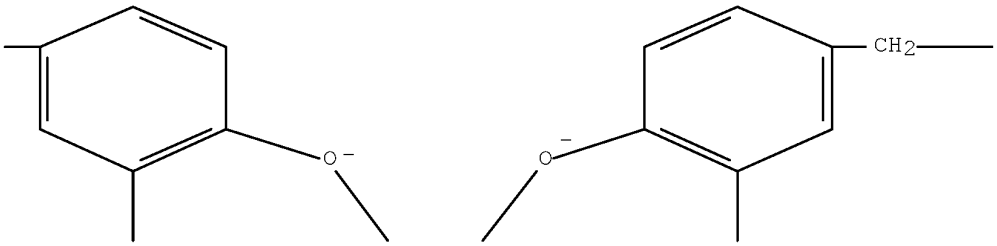


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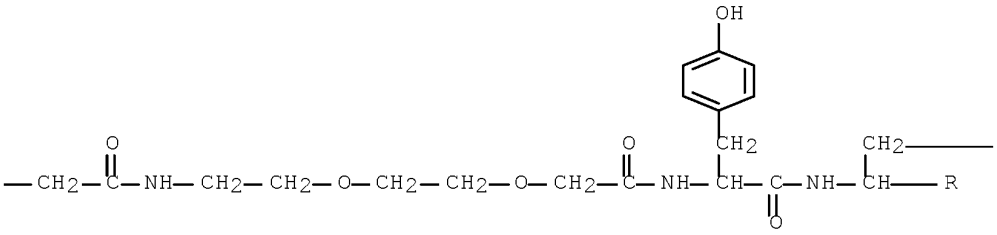


Fusion Pharmaceuticals, Inc.
Exhibit 1004.133

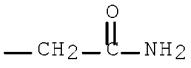
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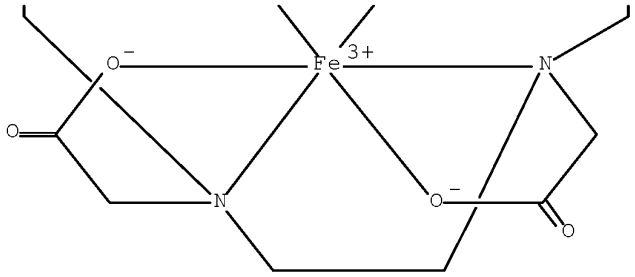


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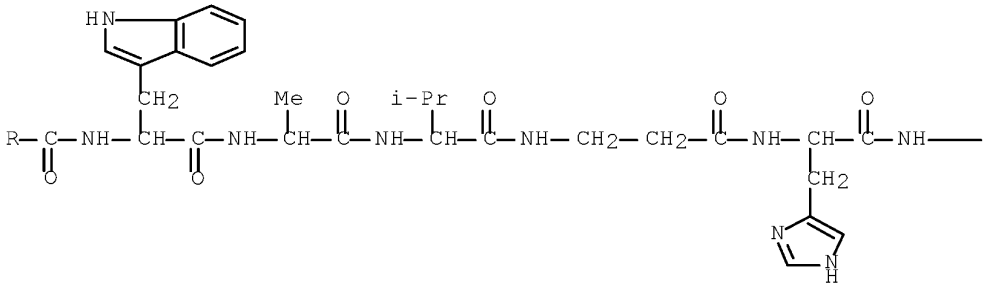


Fusion Pharmaceuticals, Inc.
Exhibit 1004.134

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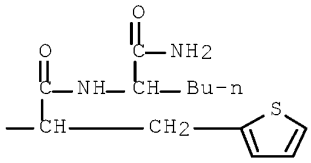


PAGE 4-A



●4 H+

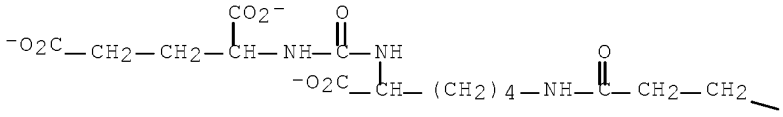
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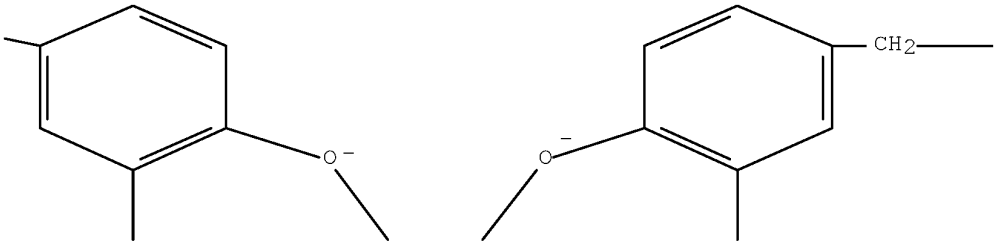
RN 1853291-12-9 CAPLUS
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Fusion Pharmaceuticals, Inc.
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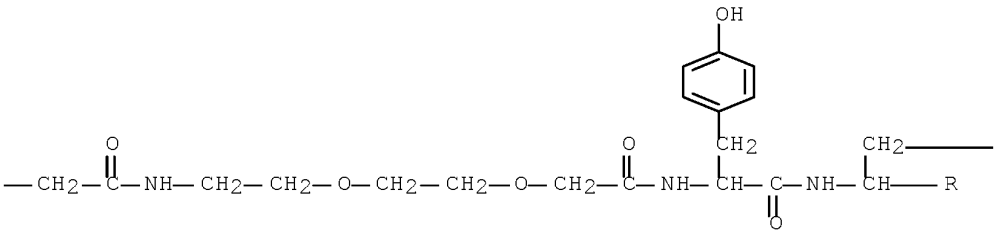
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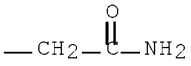


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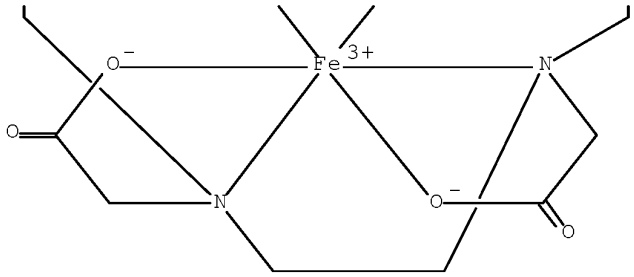


Fusion Pharmaceuticals, Inc.
Exhibit 1004.136

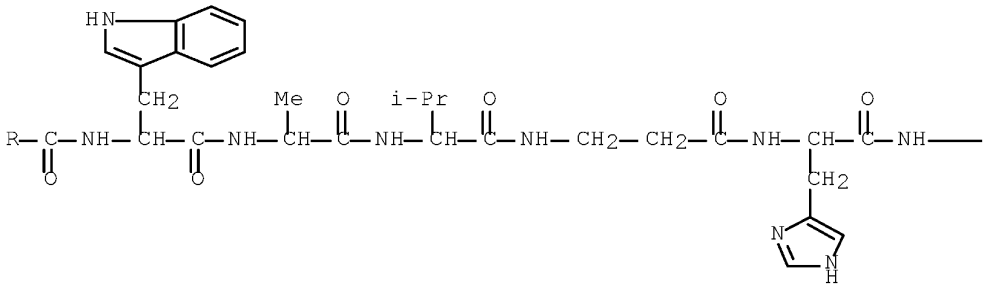
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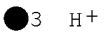


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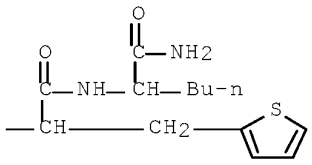
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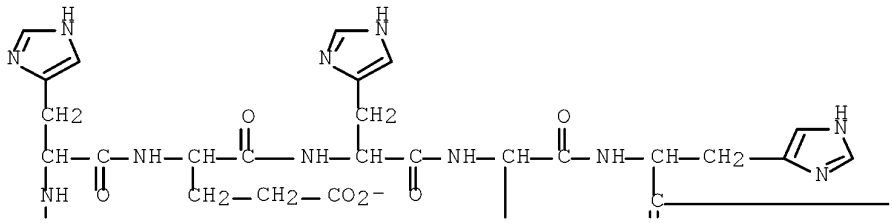
Fusion Pharmaceuticals, Inc.
Exhibit 1004.137

PAGE 3-B

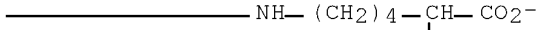


RN 1853291-34-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

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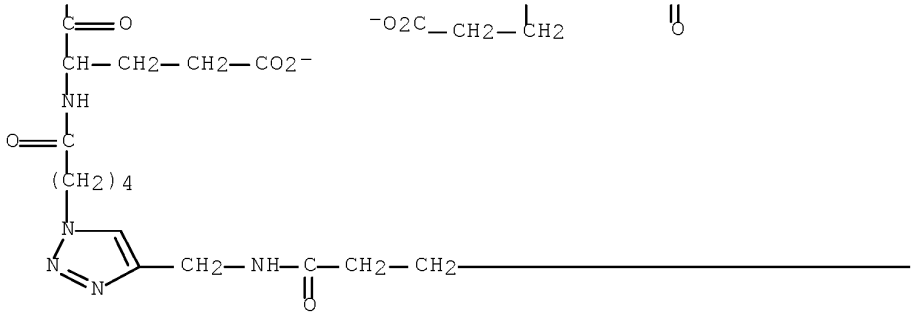


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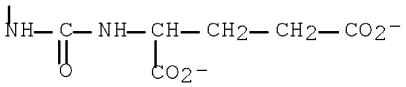


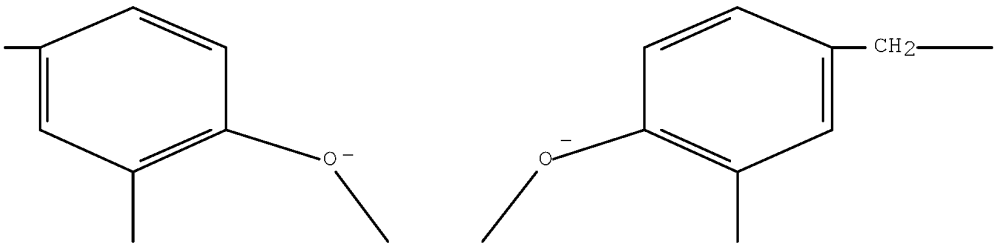
Fusion Pharmaceuticals, Inc.
Exhibit 1004.138

PAGE 2-A



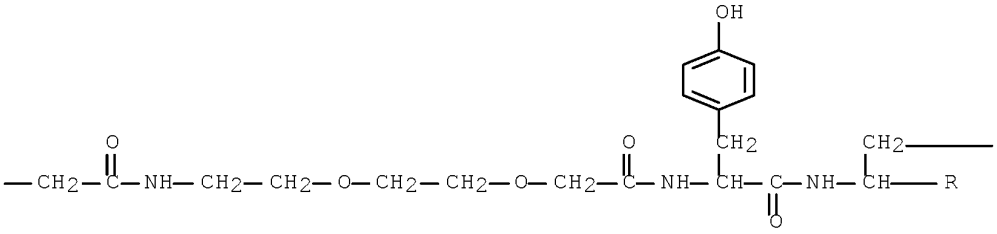
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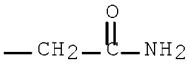


Fusion Pharmaceuticals, Inc.
Exhibit 1004.139

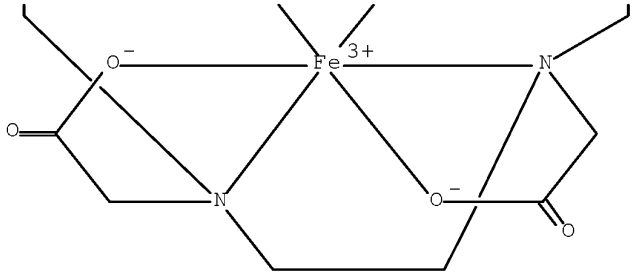
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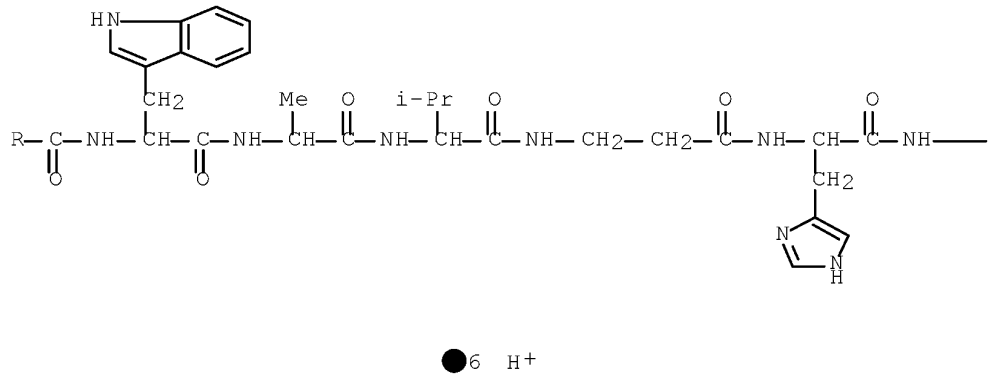


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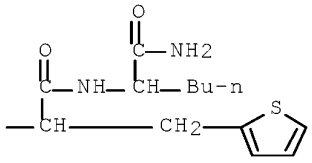
Fusion Pharmaceuticals, Inc.
Exhibit 1004.140

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●6 H+

PAGE 4-B



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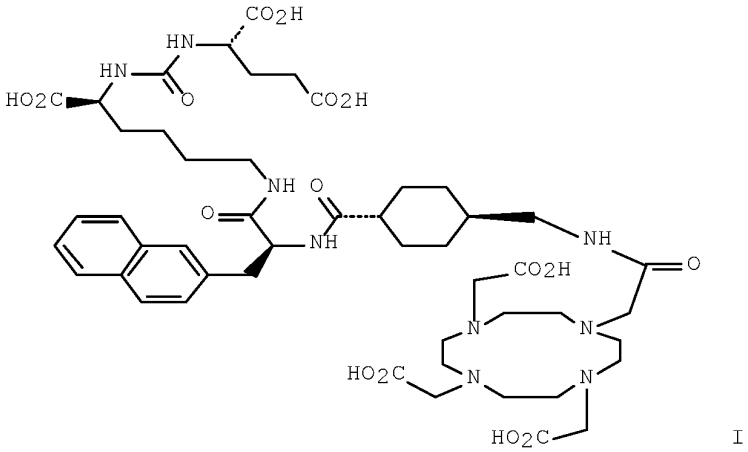
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DOCUMENT NUMBER: 162:577349
TITLE: Preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-lysines, their DOTA complexes and their radionuclides conjugates, their use as imaging agents and pharmaceutical agents for the treatment of prostate cancer
INVENTOR(S): Eder, Matthias; Kopka, Klaus; Schaefer, Martin; Bauder-Wust, Ulrike; Haberkorn, Uwe
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum, Germany; Ruprecht-Karls-Universitaet Heidelberg
SOURCE: PCT Int. Appl., 70pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015055318	A1	20150423	WO 2014-EP2808	20141017

Fusion Pharmaceuticals, Inc.
Exhibit 1004.141

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                                          WO 2014-EP2808       W  20141017
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S):         MARPAT 162:577349
GI
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.142



I

AB The invention is related to the preparation of glutamate-urea-lysines (GUL) in which a chelator group is conjugated to the GUL moiety via a linker, e.g., I, that are potent inhibitors of PSMA activity and to their radionuclides conjugates useful in nuclear medicine as tracers, imaging agents and for the treatment of various disease states of prostate cancer. Thus, the DOTA conjugated-PSMA inhibitor I was prepared via solid phase peptide synthesis using bis(tert-butyl)-L-glutamate hydrochloride, N-(9-fluorenylmethoxycarbonyl)-3-(2-naphthyl)-L-alanine, trans-4-(Fmoc-aminomethyl)cyclohexanecarboxylic acid tris(t-bu)-DOTA. I was evaluated in in vitro assays (affinity, internalization) and in vivo expts. (microPET screening and organ distribution). In the PET diagrams the compds. of the present invention, in particular I, showed a rapid background clearance as well as a substantial reduction of the enrichment in the kidney after 2 h while it is further accumulated and retained in the PSMA-expressing tumor.

IT 1702720-89-5P 1702720-95-3P 1702720-97-5P
1702721-00-3P 1702721-02-5P 1702967-37-0P
1702967-48-3P 1702967-50-7P 1702967-52-9P
1702967-55-2P 1702967-62-1P
RL: DGN (Diagnostic use); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of radiolabeled prostate specific membrane antigen inhibitors as tracers, imaging agents and for treating prostate cancer)

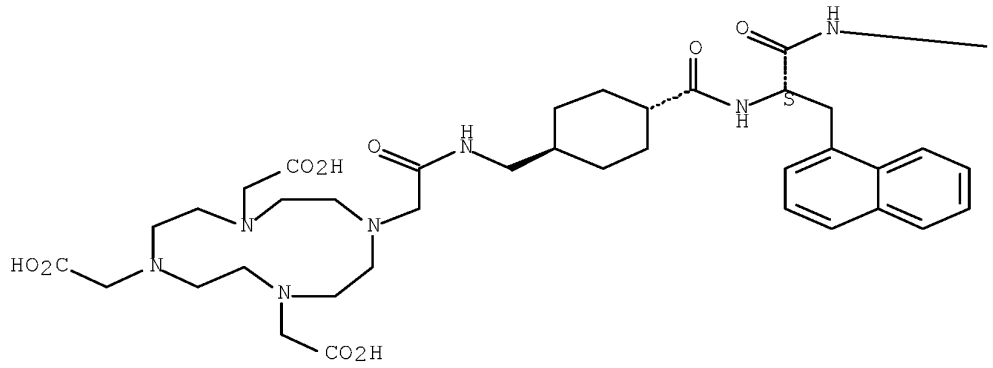
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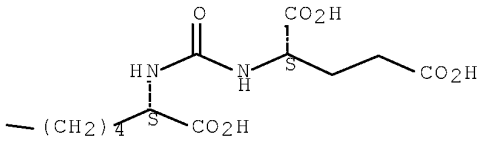
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.143

PAGE 1-A



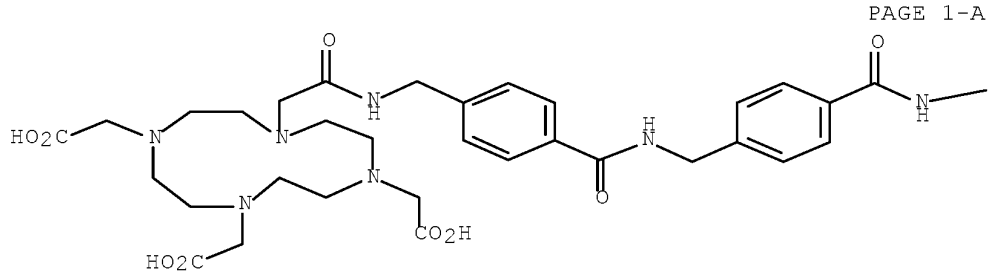
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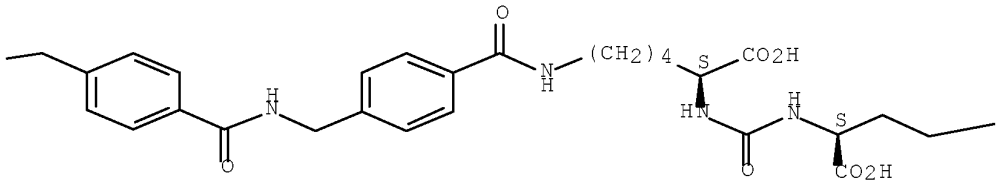
Absolute stereochemistry.

PAGE 1-A

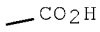


Fusion Pharmaceuticals, Inc.
Exhibit 1004.144

PAGE 1-B



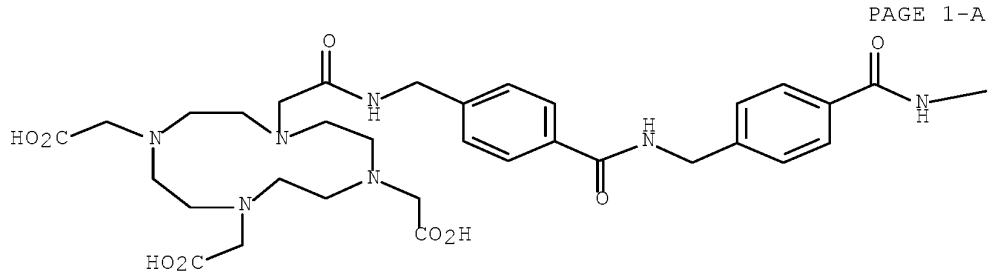
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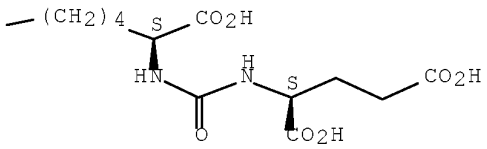
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

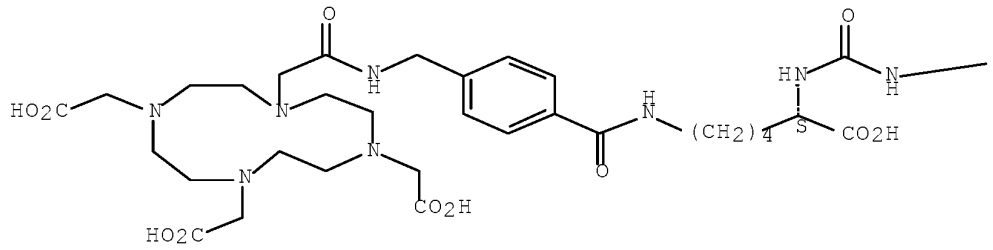


Fusion Pharmaceuticals, Inc.
Exhibit 1004.145

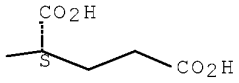
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Absolute stereochemistry.

PAGE 1-A



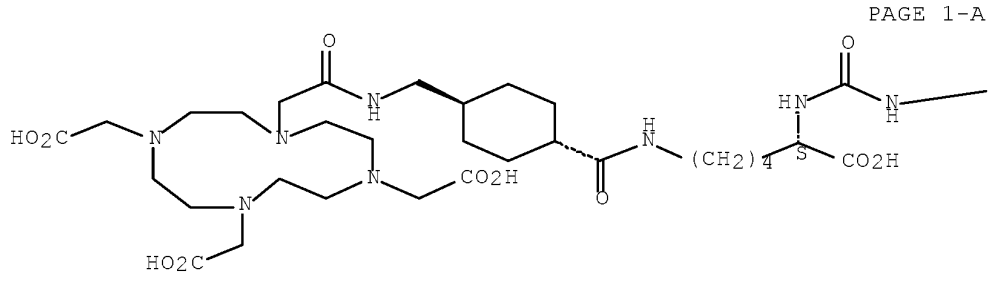
PAGE 1-B



RN 1702721-02-5 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]cyclohexyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

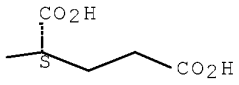
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.146

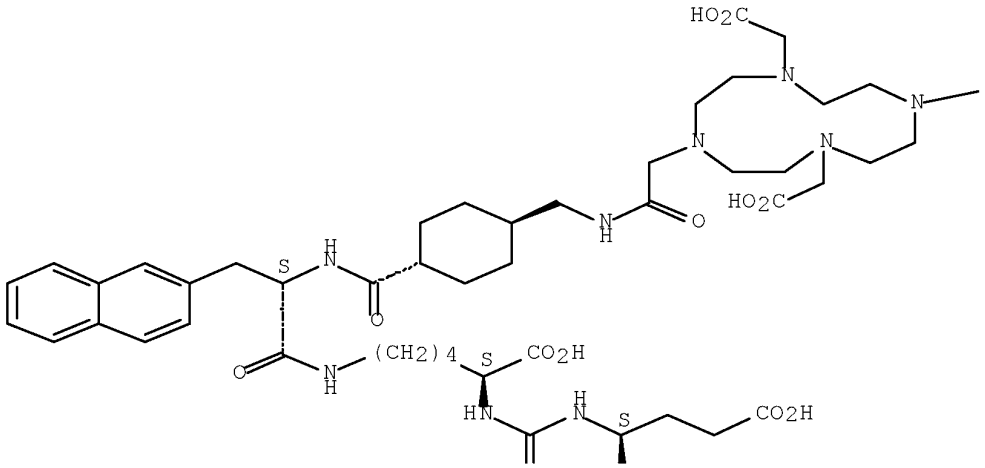
PAGE 1-B



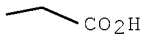
RN 1702967-37-0 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A



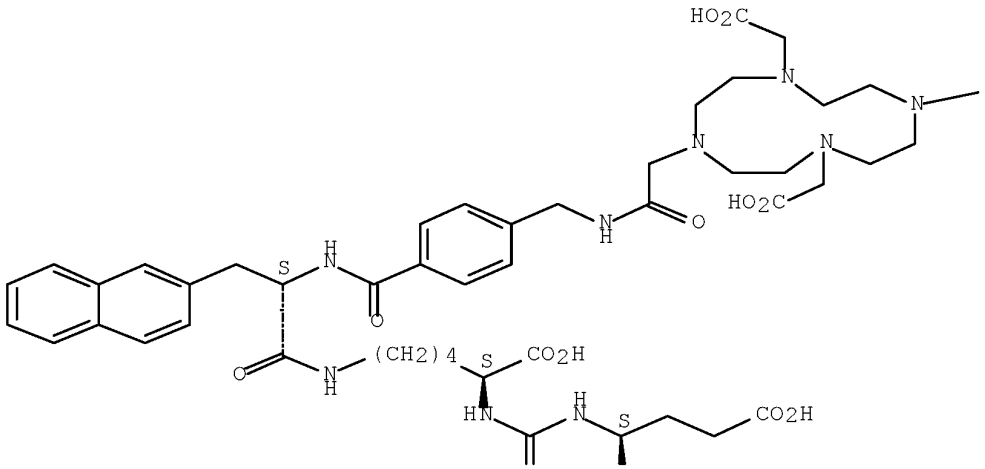
RN 1702967-48-3 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-

Fusion Pharmaceuticals, Inc.
Exhibit 1004.147

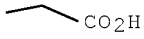
tetraazacyclododec-1-yl]acetyl]amino]methyl]benzoyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A

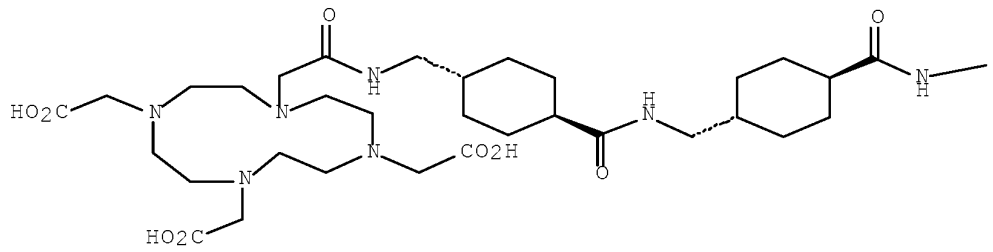


RN 1702967-50-7 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[trans-4-[[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]cyclohexyl]methyl]amino]carbonyl]cyclohexyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

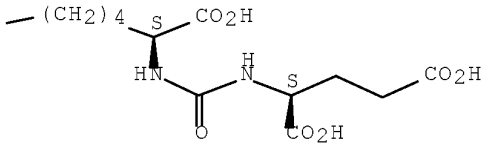
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.148

PAGE 1-A



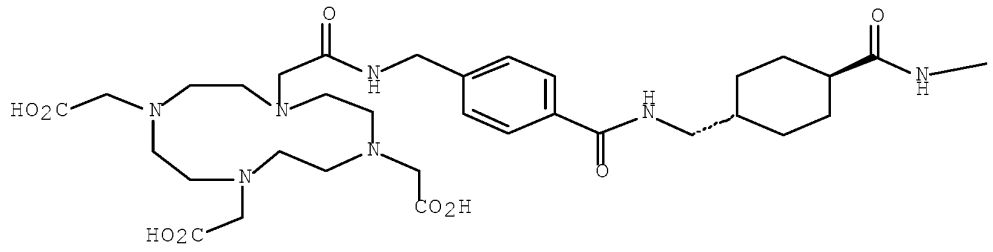
PAGE 1-B



RN 1702967-52-9 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid,
10-[2-[[[4-[[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-
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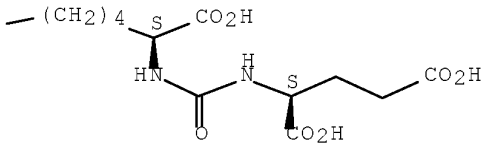
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.149

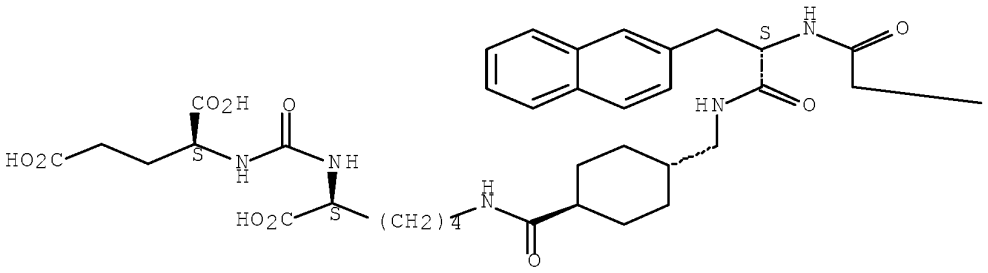
PAGE 1-B



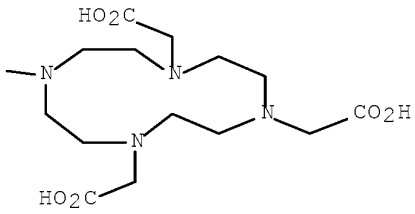
RN 1702967-55-2 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-alanyl-trans-4-(aminomethyl)cyclohexanecarbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

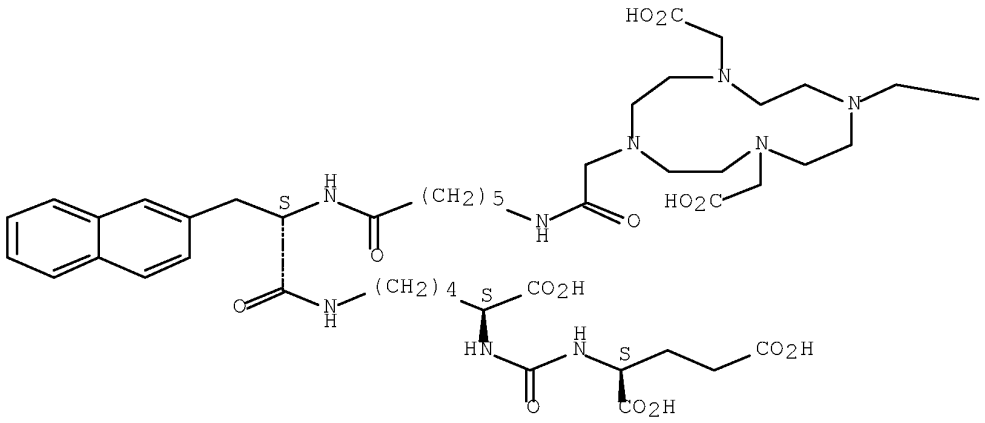


RN 1702967-62-1 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[1-oxo-6-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]hexyl]-L-alanyl]- (CA INDEX NAME)

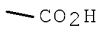
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.150

PAGE 1-A



PAGE 1-B



IT 1702720-91-9DP, gallium-68 complexes 1702720-95-3DP, gallium-68 complexes 1702720-97-5DP, gallium-68 complexes 1702721-00-3DP, gallium-68 complexes 1702721-02-5DP, gallium-68 complexes 1702967-37-0DP, gallium-68 complexes 1702967-44-9DP, gallium-68 complexes 1702967-48-3DP, gallium-68 complexes 1702967-50-7DP, gallium-68 complexes 1702967-52-9DP, gallium-68 complexes 1702967-55-2DP, gallium-68 complexes 1702967-62-1DP, gallium-68 complexes 1703749-62-5P 1703760-73-3P 1703760-75-5P 1703760-76-6DP, gallium-68 complexes 1703760-77-7P 1703760-78-8P 1703760-79-9P
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of radiolabeled prostate specific membrane antigen inhibitors as tracers, imaging agents and for treating prostate cancer)

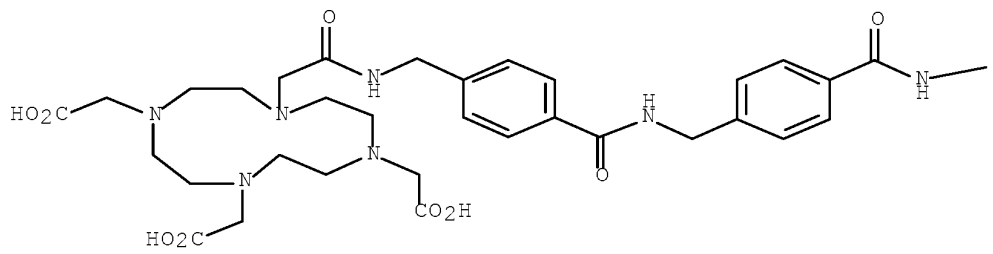
RN 1702720-91-9 CAPLUS

CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[4-[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

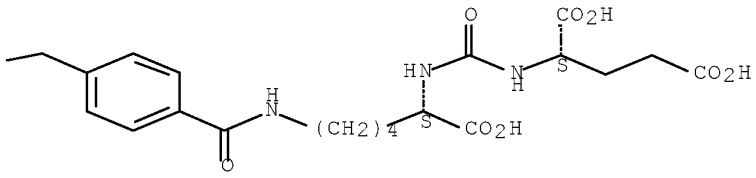
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.151

PAGE 1-A



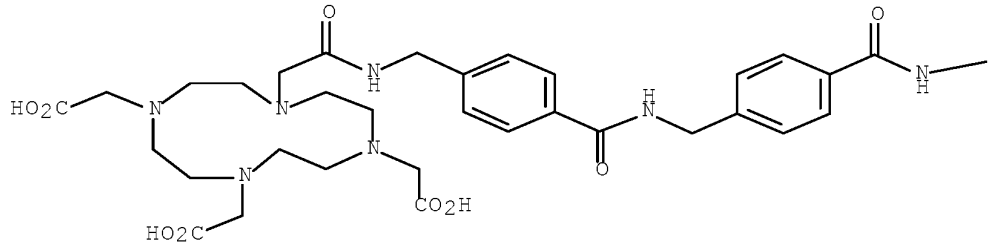
PAGE 1-B



RN 1702720-95-3 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[[4-[[[[4-[[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

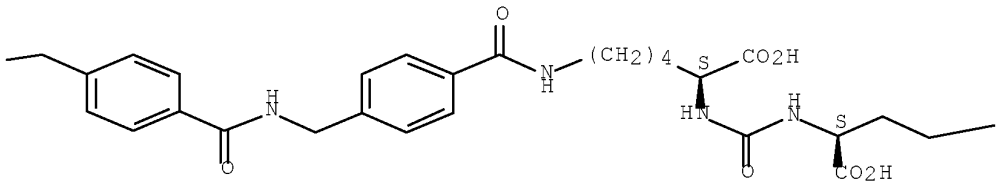
Absolute stereochemistry.

PAGE 1-A

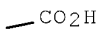


Fusion Pharmaceuticals, Inc.
Exhibit 1004.152

PAGE 1-B



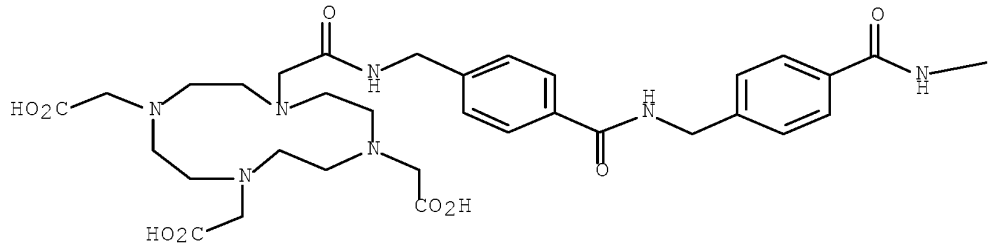
PAGE 1-C



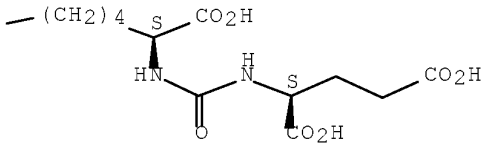
RN 1702720-97-5 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid,
10-[2-[[[4-[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-
dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]a
mino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



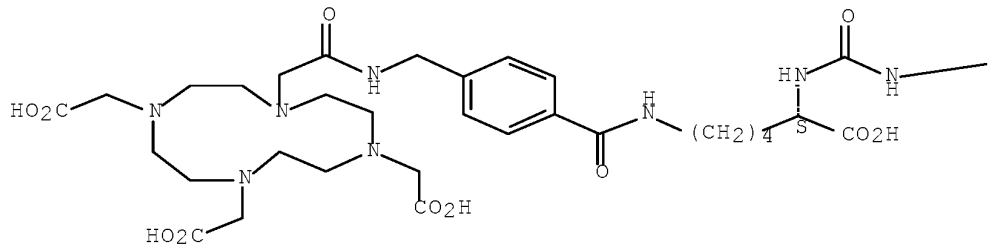
RN 1702721-00-3 CAPLUS

Fusion Pharmaceuticals, Inc.
Exhibit 1004.153

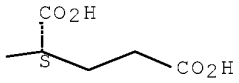
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

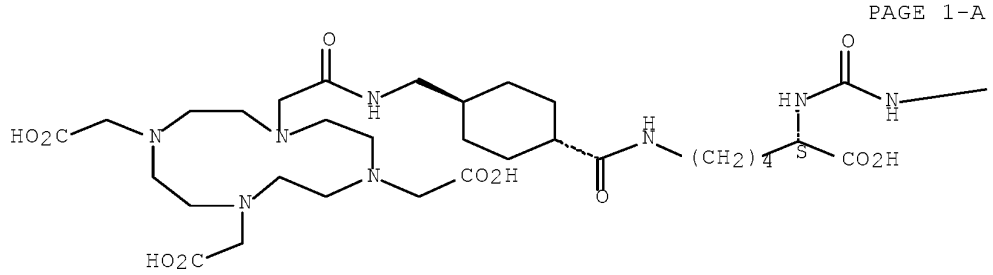


RN 1702721-02-5 CAPLUS

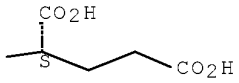
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]cyclohexyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

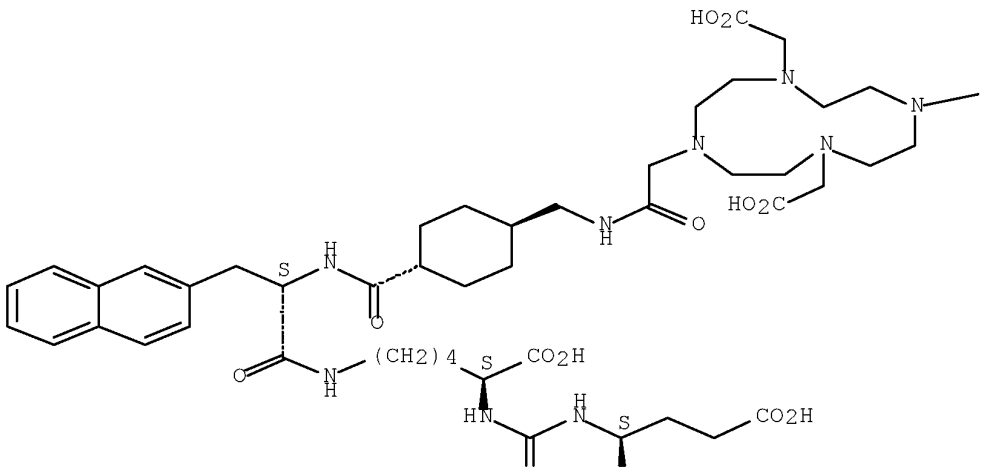


Fusion Pharmaceuticals, Inc.
Exhibit 1004.154

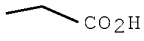
RN 1702967-37-0 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A

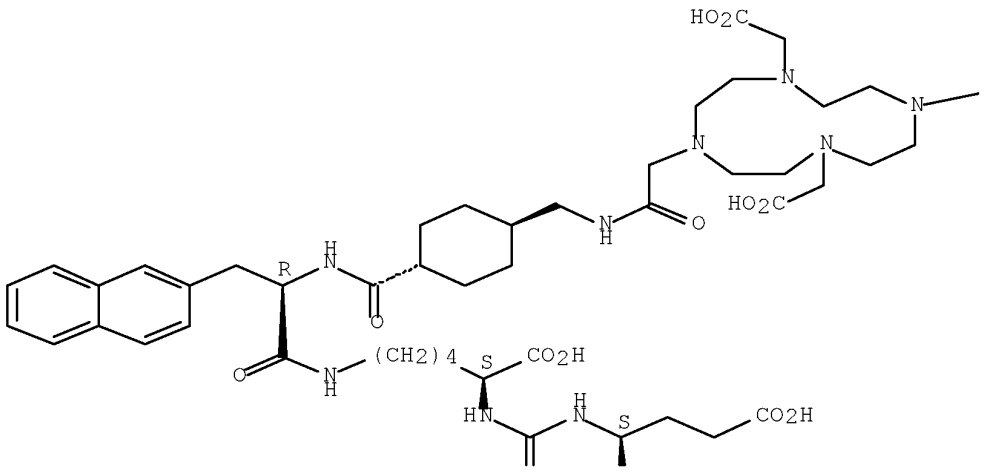


RN 1702967-44-9 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-D-alanyl]- (CA INDEX NAME)

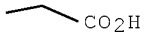
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.155

PAGE 1-A



PAGE 1-B



PAGE 2-A

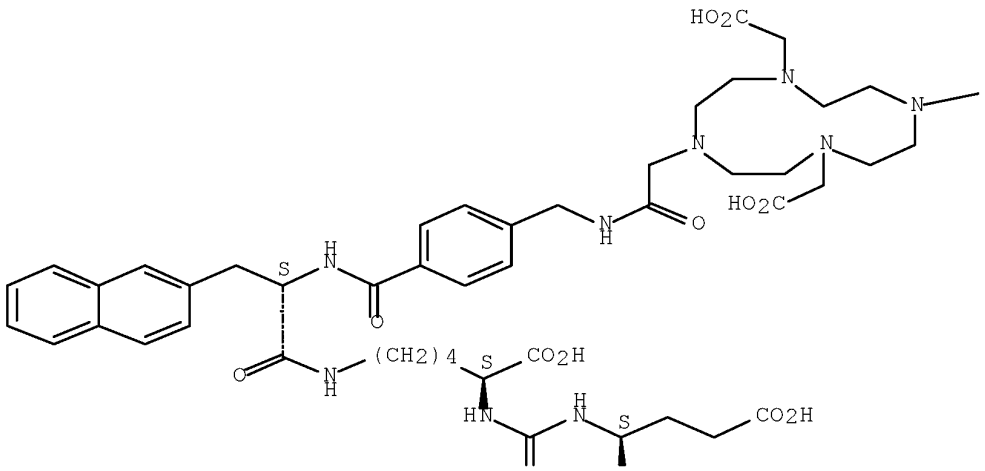


RN 1702967-48-3 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]benzoyl]-L-alanyl]- (CA INDEX NAME)

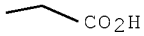
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.156

PAGE 1-A



PAGE 1-B



PAGE 2-A

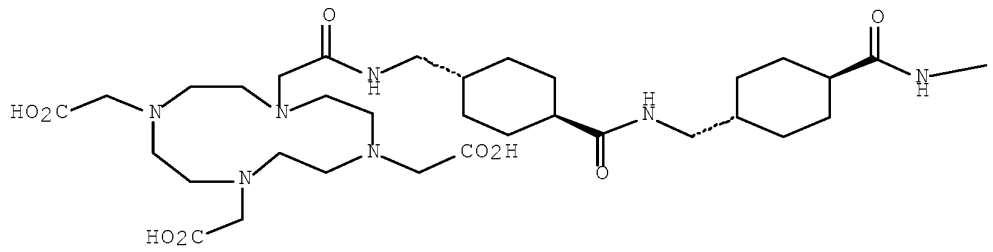


RN 1702967-50-7 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[trans-4-[[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]cyclohexyl]methyl]amino]carbonyl]cyclohexyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

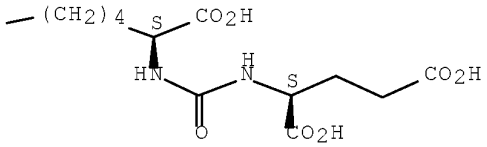
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.157

PAGE 1-A



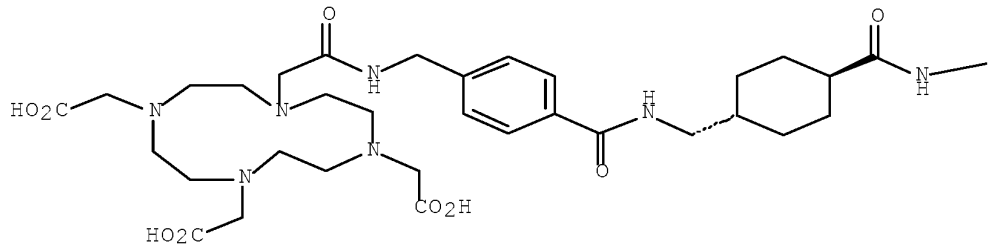
PAGE 1-B



RN 1702967-52-9 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid,
10-[2-[[[4-[[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-
dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]cyclohexyl]meth
yl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

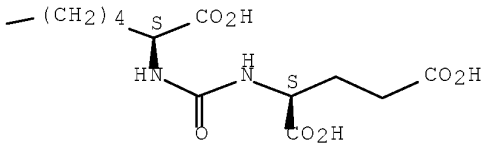
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.158

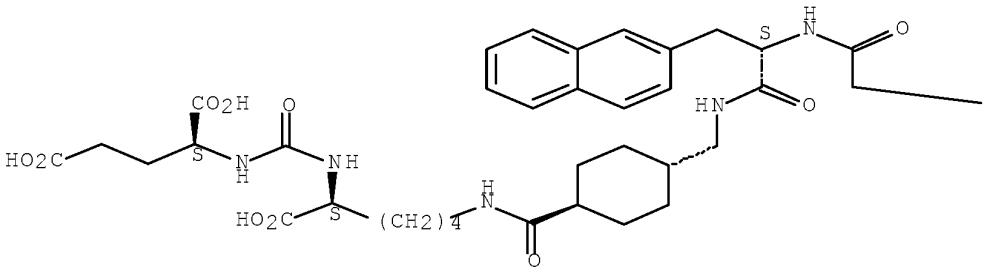
PAGE 1-B



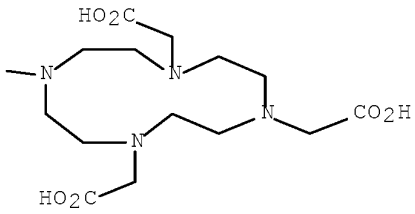
RN 1702967-55-2 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-alanyl-trans-4-(aminomethyl)cyclohexanecarbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

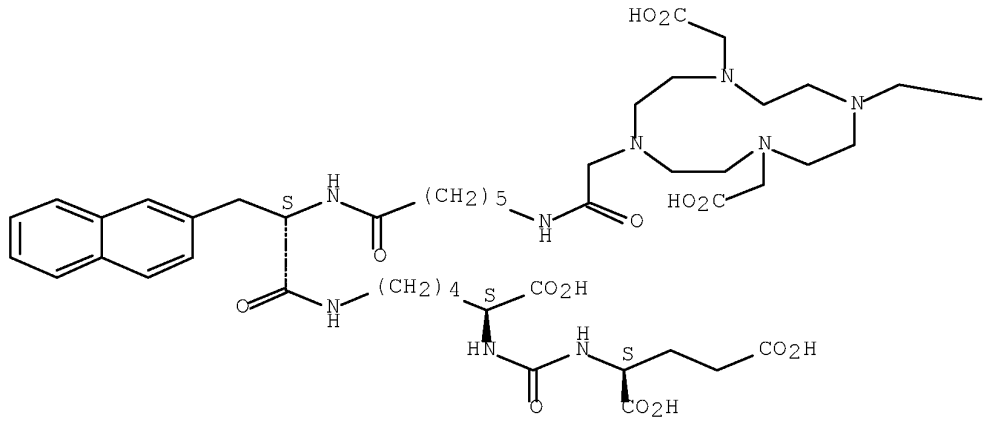


RN 1702967-62-1 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[1-oxo-6-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]hexyl]-L-alanyl]- (CA INDEX NAME)

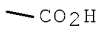
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.159

PAGE 1-A



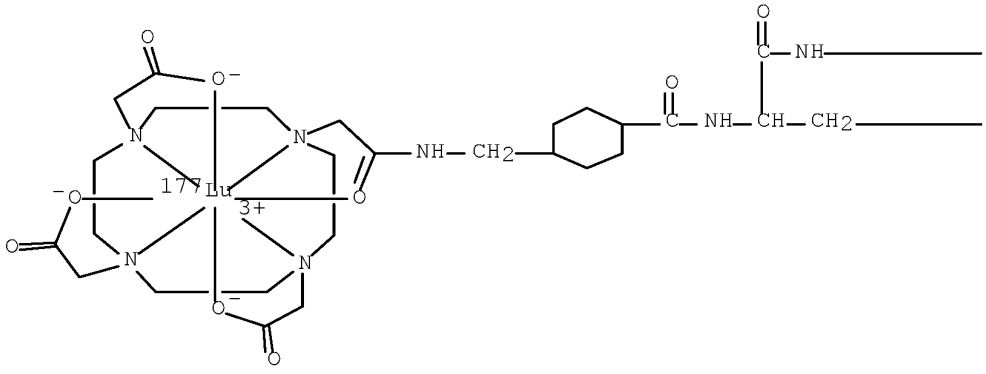
PAGE 1-B



RN 1703749-62-5 CAPLUS

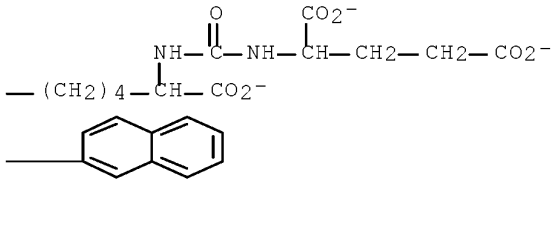
CN Lutetate(3-)-177Lu, [N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris[(carboxy-κO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κN1,κN4,κN7,κN10]acetyl-κO]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]-L-lysinato(6-)]-, hydrogen (1:3) (CA INDEX NAME)

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.160

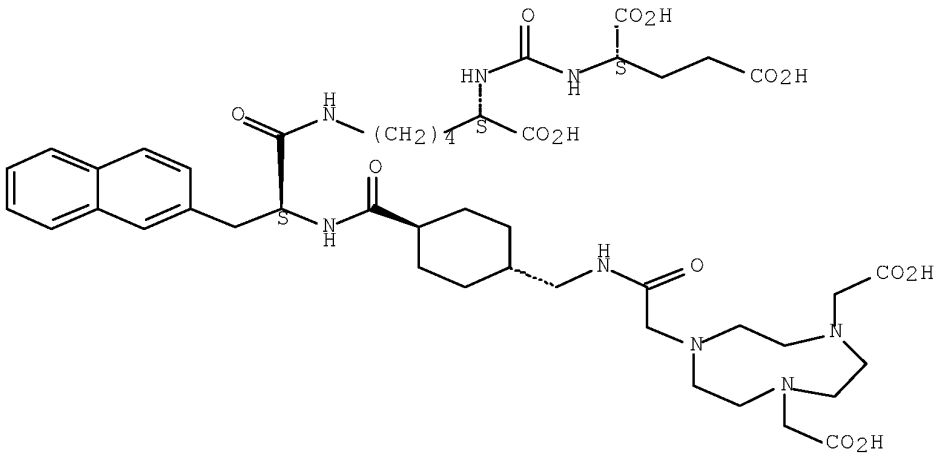
PAGE 1-B



●3 H+

RN 1703768-73-3 CAPLUS
CN L-Lysine, N6-[N-[[trans-4-[[[2-[4,7-bis(carboxymethyl)octahydro-1H-1,4,7-triazonin-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-3-(2-naphthalenyl)-L-alanyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry.



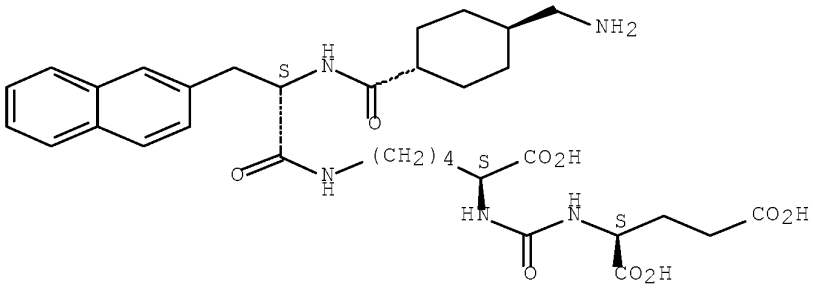
RN 1703768-75-5 CAPLUS
CN L-Lysine, N6-[N-[[trans-4-(aminomethyl)cyclohexyl]carbonyl]-3-(2-naphthalenyl)-L-alanyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-, amide with N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycine (CA INDEX NAME)

CM 1

CRN 1703768-74-4
CMF C33 H45 N5 O9

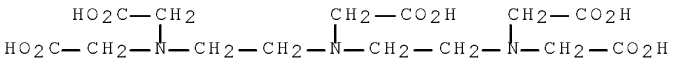
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.161



CM 2

CRN 67-43-6
CMF C14 H23 N3 O10

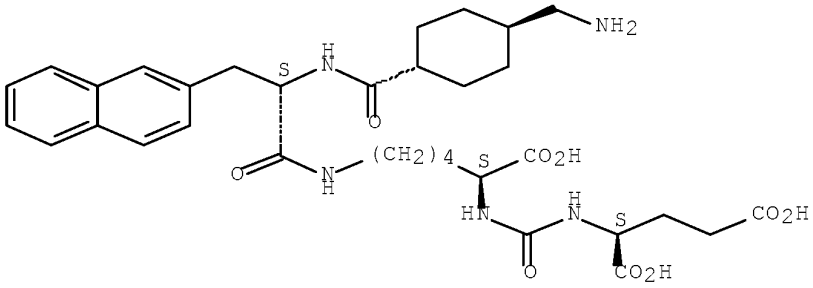


RN 1703768-76-6 CAPLUS
CN L-Lysine, N6-[N-[[trans-4-(aminomethyl)cyclohexyl]carbonyl]-3-(2-naphthalenyl)-L-alanyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-, amide with rel-N-[(1R,2R)-2-[bis(carboxymethyl)amino]cyclohexyl]-N-[2-[bis(carboxymethyl)amino]ethyl]glycine (CA INDEX NAME)

CM 1

CRN 1703768-74-4
CMF C33 H45 N5 O9

Absolute stereochemistry.

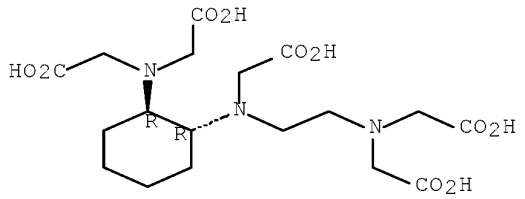


CM 2

CRN 137731-38-5
CMF C18 H29 N3 O10

Fusion Pharmaceuticals, Inc.
Exhibit 1004.162

Relative stereochemistry.

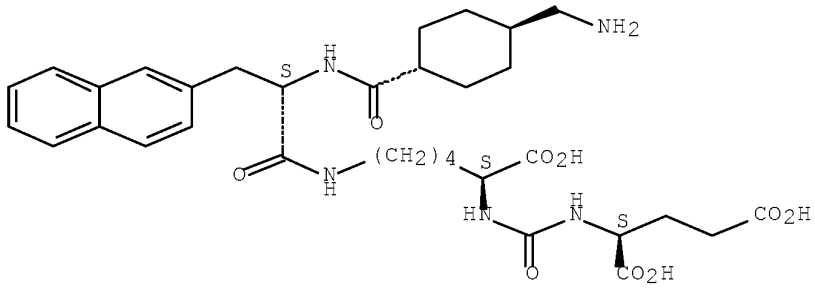


RN 1703768-77-7 CAPLUS
CN L-Lysine, N6-[N-[[trans-4-(aminomethyl)cyclohexyl]carbonyl]-3-(2-naphthalenyl)-L-alanyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-, amide with 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (CA INDEX NAME)

CM 1

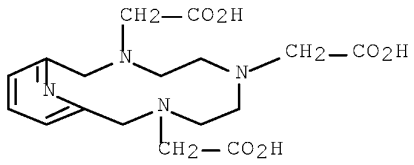
CRN 1703768-74-4
CMF C33 H45 N5 O9

Absolute stereochemistry.



CM 2

CRN 129162-88-5
CMF C17 H24 N4 O6



RN 1703768-78-8 CAPLUS

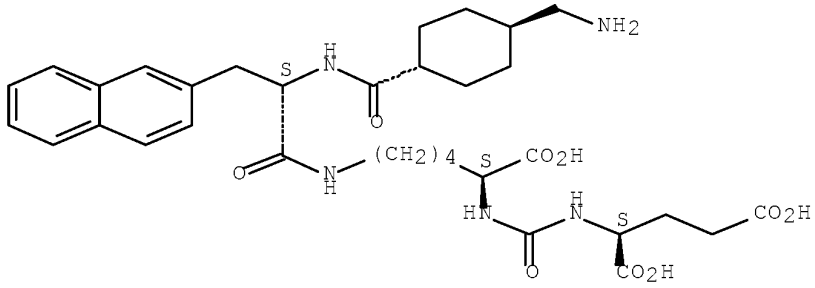
Fusion Pharmaceuticals, Inc.
Exhibit 1004.163

CN L-Lysine, N6-[N-[[trans-4-(aminomethyl)cyclohexyl]carbonyl]-3-(2-naphthalenyl)-L-alanyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-, amide with 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (CA INDEX NAME)

CM 1

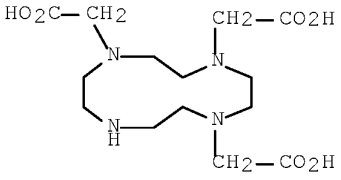
CRN 1703768-74-4
CMF C33 H45 N5 O9

Absolute stereochemistry.



CM 2

CRN 114873-37-9
CMF C14 H26 N4 O6



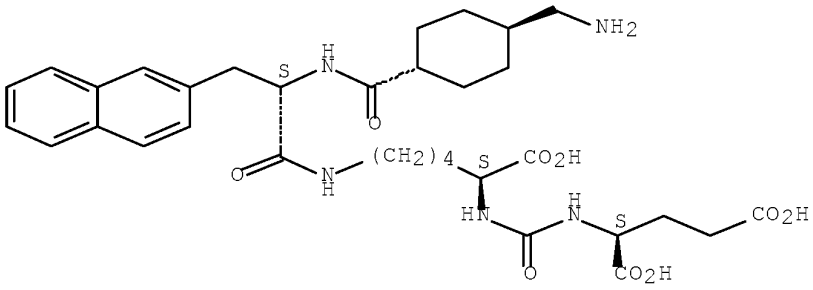
RN 1703768-79-9 CAPLUS
CN L-Lysine, N6-[N-[[trans-4-(aminomethyl)cyclohexyl]carbonyl]-3-(2-naphthalenyl)-L-alanyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-, amide with α1-(2-carboxyethyl)hexahydro-1H-1,4,7-triazonine-1,4,7-triacetic acid (CA INDEX NAME)

CM 1

CRN 1703768-74-4
CMF C33 H45 N5 O9

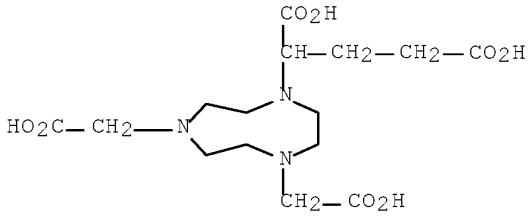
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.164

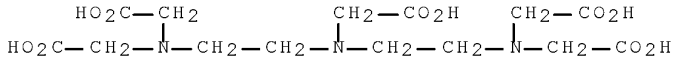


CM 2

CRN 1092370-12-1
CMF C15 H25 N3 O8

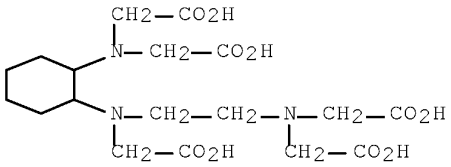


IT 67-43-6, Dtpa, protected derivative 3565-84-2D, CHX-DTPA, protected derivative 56491-86-2D, Nota, protected derivative 129162-88-5D, PCTA, protected derivative 1092370-12-1D, Nodaga, protected derivative
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of radiolabeled prostate specific membrane antigen inhibitors as tracers, imaging agents and for treating prostate cancer)
RN 67-43-6 CAPLUS
CN Glycine, N,N-bis[2-[bis(carboxymethyl)amino]ethyl]- (CA INDEX NAME)

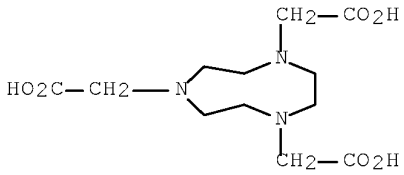


RN 3565-84-2 CAPLUS
CN Glycine, N-[2-[bis(carboxymethyl)amino]cyclohexyl]-N-[2-[bis(carboxymethyl)amino]ethyl]- (CA INDEX NAME)

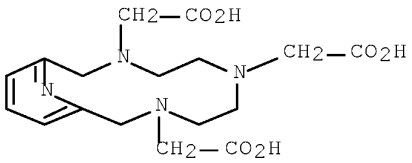
Fusion Pharmaceuticals, Inc.
Exhibit 1004.165



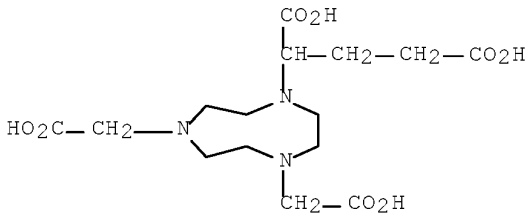
RN 56491-86-2 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, hexahydro- (CA INDEX NAME)



RN 129162-88-5 CAPLUS
CN 3,6,9,15-Tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (CA INDEX NAME)



RN 1092370-12-1 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, α1-(2-carboxyethyl)hexahydro- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Fusion Pharmaceuticals, Inc.
Exhibit 1004.166

L132 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:694893 CAPLUS Full-text
DOCUMENT NUMBER: 162:572152
TITLE: Double-labeled probe for molecular imaging and use thereof
INVENTOR(S): Eder, Matthias; Kopka, Klaus; Schaefer, Martin; Bauder-Wuest, Ulrike; Haberkorn, Uwe
PATENT ASSIGNEE(S): Ruprecht-Karls-Universitat Heidelberg, Germany; Deutsches Krebsforschungszentrum
SOURCE: U.S. Pat. Appl. Publ., 48pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

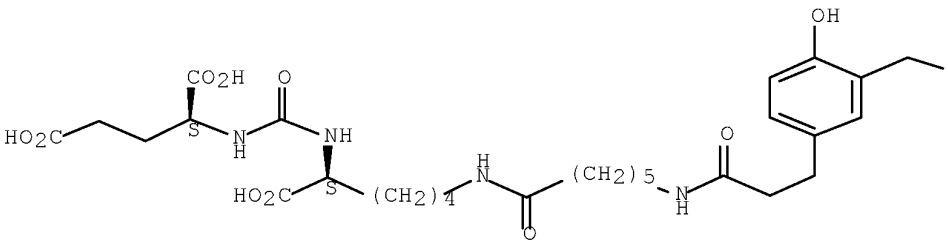
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20150110715	A1	20150423	US 2014-14335055		20140718
DE 202014008232	U1	20150430	DE 2014-202014008232		20141016
PRIORITY APPLN. INFO.:			US 2013-61892022	P	20131017
			US 2014-14335055	A	20140718

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 162:572152; MARPAT 162:572152
AB The present invention relates to a compound or a pharmaceutically acceptable salt thereof having a chemical structure comprising: (A) at least one motif specifically binding to cell membranes of neoplastic cells; (B) at least one chelator moiety of radiometals; and (C) at least one dye moiety; wherein said compound has a mol. weight of not more than 5 kDa. Further, the invention refers to a method for producing such compound and to the in vivo and in vitro uses thereof.
IT 1704198-91-3 1704198-94-6 1704198-97-9
1704198-98-0 1704199-01-8 1704199-04-1
1704199-05-2
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(double-labeled probes for tumor imaging)
RN 1704198-91-3 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-1-carboxy-5-[[6-[[3-[3-[[(carboxymethyl)[2-[(carboxymethyl)[[5-[14-[(3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-5-yl)amino]-3-oxo-14-thioxo-7,10-dioxa-4,13-diazatetradec-1-yl]-2-hydroxyphenyl]methyl]amino]ethyl]amino]methyl]-4-hydroxyphenyl]-1-oxopropyl]amino]-1-oxohexyl]amino]pentyl]amino]carbonyl]-
(CA INDEX NAME)

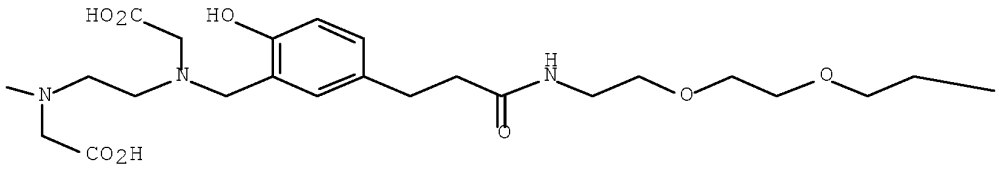
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.167

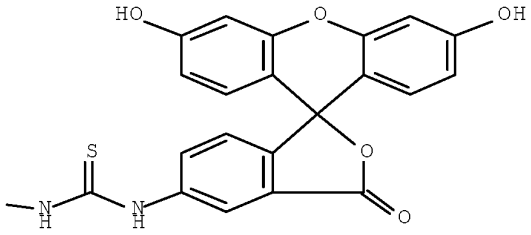
PAGE 1-A



PAGE 1-B



PAGE 1-C



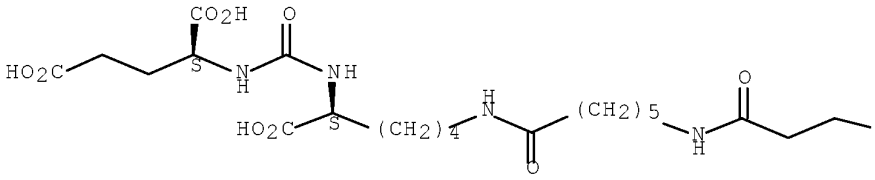
RN 1704198-94-6 CAPLUS
CN Xanthylium, 3,6-diamino-9-[2-carboxy-5-[14-[3-[[(carboxymethyl)[2-[(carboxymethyl)[[2-hydroxy-5-[(16S,20S)-16,20,22-tricarboxy-3,10,18-trioxo-4,11,17,19-tetraazadocos-1-yl]phenyl]methyl]amino]ethyl]amino]methyl]-4-hydroxyphenyl]-1,12-dioxo-5,8-dioxa-2,11-diazatetradec-1-yl]phenyl]-4,5-disulfo-, inner salt (CA INDEX

Fusion Pharmaceuticals, Inc.
Exhibit 1004.168

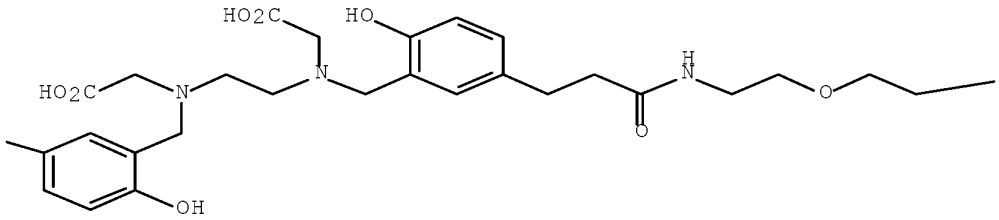
NAME)

Absolute stereochemistry.

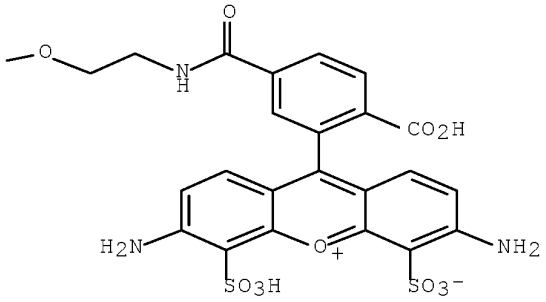
PAGE 1-A



PAGE 1-B



PAGE 1-C



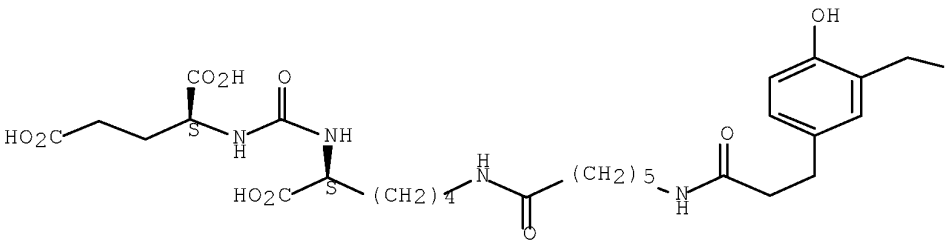
RN 1704198-97-9 CAPLUS
CN 1H-Benz[e]indolium, 2-[5-[3-[19-[3-[[(carboxymethyl)[2-[(carboxymethyl)[[2-hydroxy-5-[(16S,20S)-16,20,22-tricarboxy-3,10,18-trioxo-4,11,17,19-tetraazadocos-1-yl]phenyl]methyl]amino]ethyl]amino]methyl]-4-hydroxyphenyl]-6,17-dioxo-10,13-dioxa-7,16-diazanonadec-1-yl]-1,3-dihydro-1,1-dimethyl-2H-benz[e]indol-2-ylidene]-1,3-pentadien-1-yl]-3-ethyl-1,1-dimethyl-, inner salt (CA INDEX NAME)

Absolute stereochemistry.

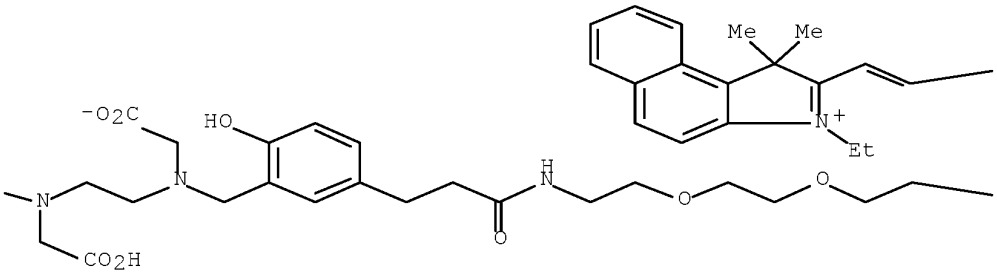
Fusion Pharmaceuticals, Inc.
Exhibit 1004.169

Double bond geometry unknown.

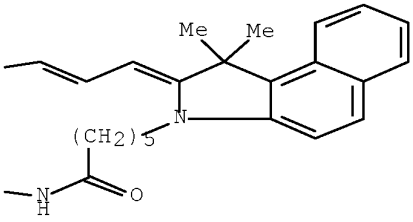
PAGE 1-A



PAGE 1-B



PAGE 1-C



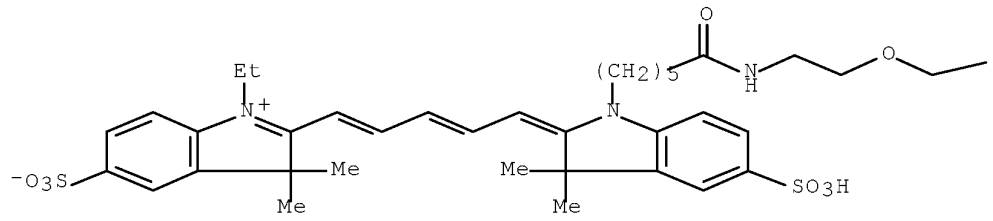
RN 1704198-98-0 CAPLUS
CN 3H-Indolium, 2-[5-[1-[19-[3-[[(carboxymethyl)[2-[(carboxymethyl)[[2-hydroxy-5-[(16S,20S)-16,20,22-tricarboxy-3,10,18-trioxo-4,11,17,19-tetraazadocos-1-yl]phenyl]methyl]amino]ethyl]amino]methyl]-4-

Fusion Pharmaceuticals, Inc.
Exhibit 1004.170

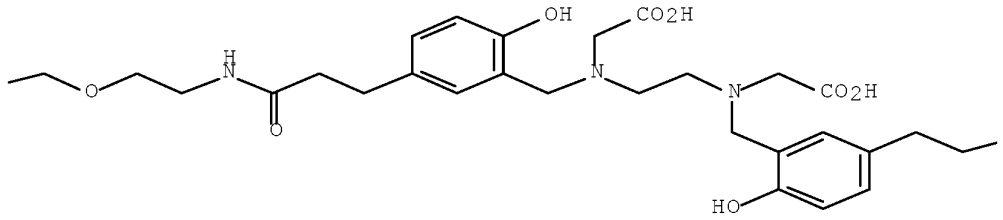
hydroxyphenyl]-6,17-dioxo-10,13-dioxa-7,16-diazanonadec-1-yl]-1,3-dihydro-3,3-dimethyl-5-sulfo-2H-indol-2-ylidene]-1,3-pentadien-1-yl]-1-ethyl-3,3-dimethyl-5-sulfo-, inner salt (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

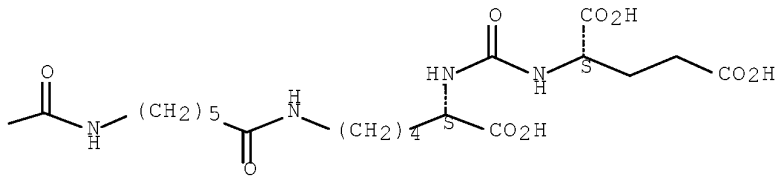
PAGE 1-A



PAGE 1-B



PAGE 1-C

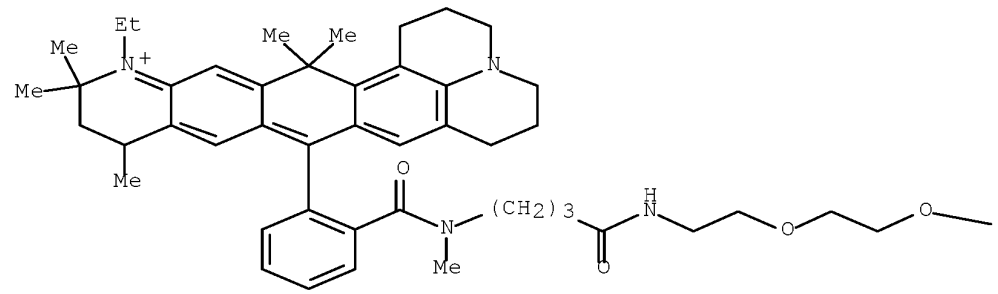


RN 1704199-01-8 CAPLUS
CN 1H,5H-Pyrido[3',2':6,7]anthra[1,2,3-ij]quinolizinium, 9-[2-[19-[3-[[(carboxymethyl)[2-[(carboxymethyl)[[2-hydroxy-5-[(16S,20S)-16,20,22-tricarboxy-3,10,18-trioxo-4,11,17,19-tetraazadocos-1-yl]phenyl]methyl]amino]ethyl]amino]methyl]-4-hydroxyphenyl]-2-methyl-1,6,17-trioxo-10,13-dioxa-2,7,16-triazanonadec-1-yl]phenyl]-14-ethyl-2,3,6,7,11,12,13,16-octahydro-11,13,13,16,16-pentamethyl-, inner salt (CA INDEX NAME)

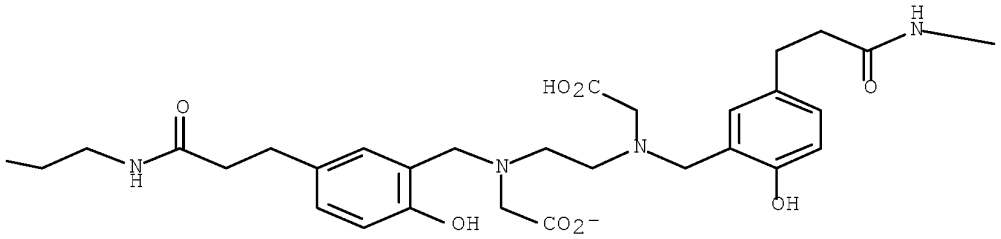
Fusion Pharmaceuticals, Inc.
Exhibit 1004.171

Absolute stereochemistry.

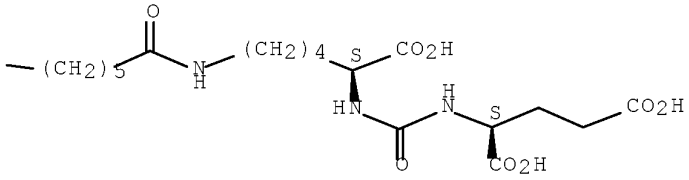
PAGE 1-A



PAGE 1-B



PAGE 1-C



RN 1704199-04-1 CAPLUS

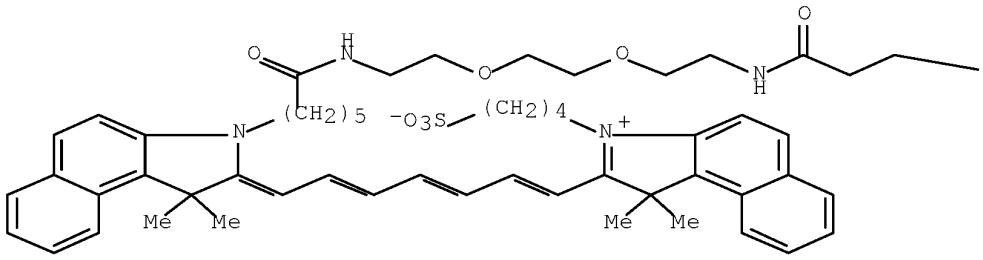
CN 1H-Benz[e]indolium, 2-[7-[3-[19-[3-[[(carboxymethyl)[2-[(carboxymethyl)[[2-hydroxy-5-[(16S,20S)-16,20,22-tricarboxy-3,10,18-trioxo-4,11,17,19-tetraazadocos-1-yl]phenyl]methyl]amino]ethyl]amino]methyl]-4-hydroxyphenyl]-6,17-dioxo-10,13-dioxa-7,16-diazanonadec-1-yl]-1,3-dihydro-1,1-dimethyl-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrien-1-yl]-1,1-

Fusion Pharmaceuticals, Inc.
Exhibit 1004.172

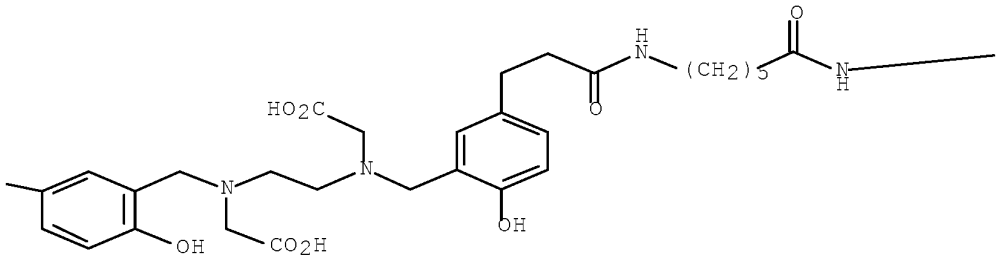
dimethyl-3-(4-sulfobutyl)-, inner salt (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

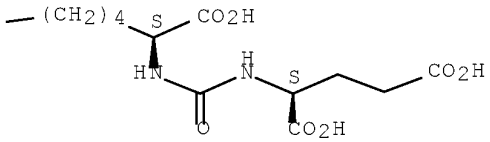
PAGE 1-A



PAGE 1-B



PAGE 1-C

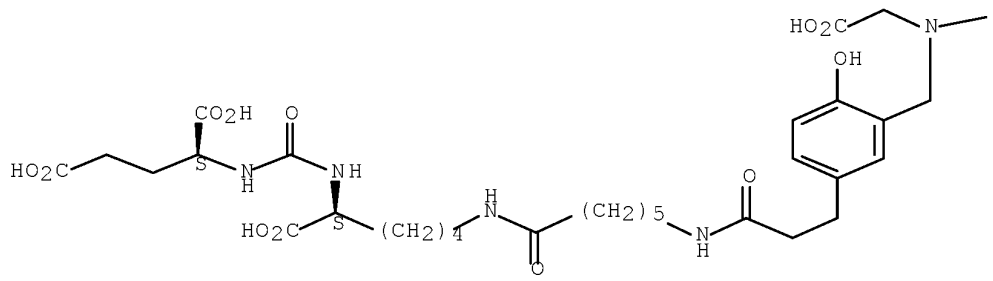


RN 1704199-05-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

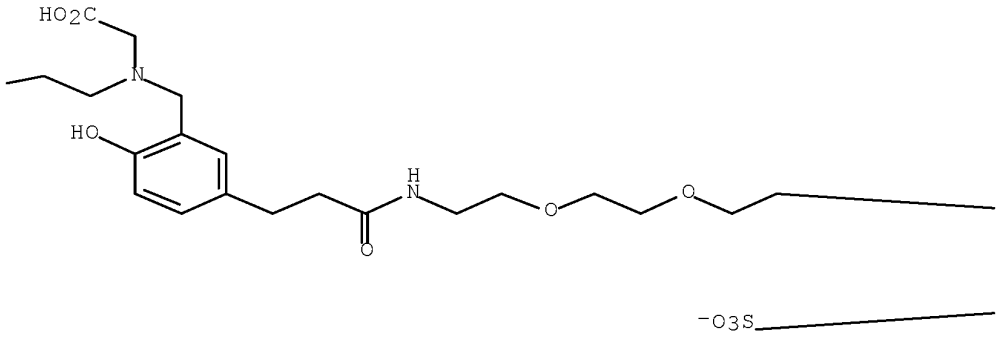
Absolute stereochemistry.
Double bond geometry unknown.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.173

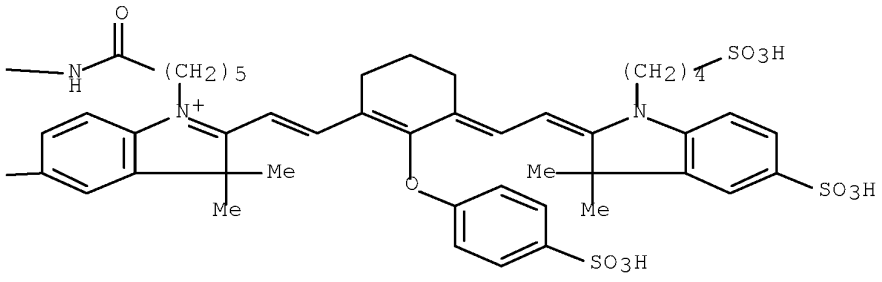
PAGE 1-A



PAGE 1-B



PAGE 1-C



Fusion Pharmaceuticals, Inc.
Exhibit 1004.174

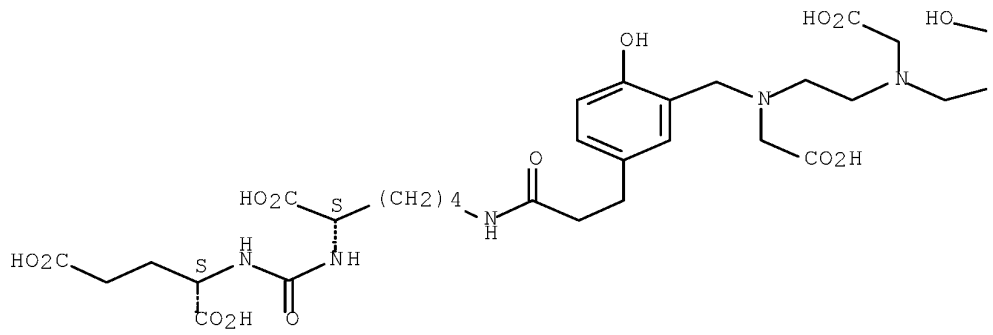
PAGE 2-A

●3 Na

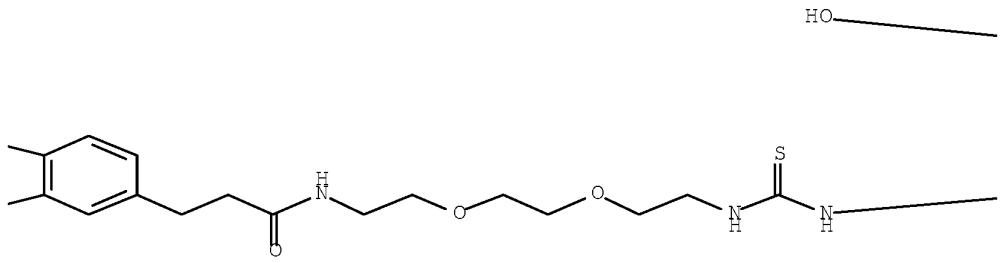
IT 1704199-08-5P
RL: DGN (Diagnostic use); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(double-labeled probes for tumor imaging)
RN 1704199-08-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

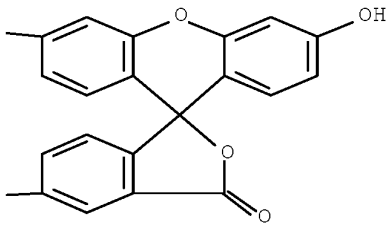
PAGE 1-A



PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.175



L132 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:690715 CAPLUS Full-text
DOCUMENT NUMBER: 162:564198
TITLE: Preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-lysines, their DOTA complexes and their radionuclides conjugates, their use as imaging agents and pharmaceutical agents for the treatment of prostate cancer
INVENTOR(S): Eder, Matthias; Kopka, Klaus; Schaefer, Martin; Bauder-Wust, Ulrike; Haberkorn, Uwe; Eisenhut, Michael; Mier, Walter; Benesova, Martina
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum, Germany; Ruprecht-Karls-Universitaet Heidelberg
SOURCE: Eur. Pat. Appl., 32pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

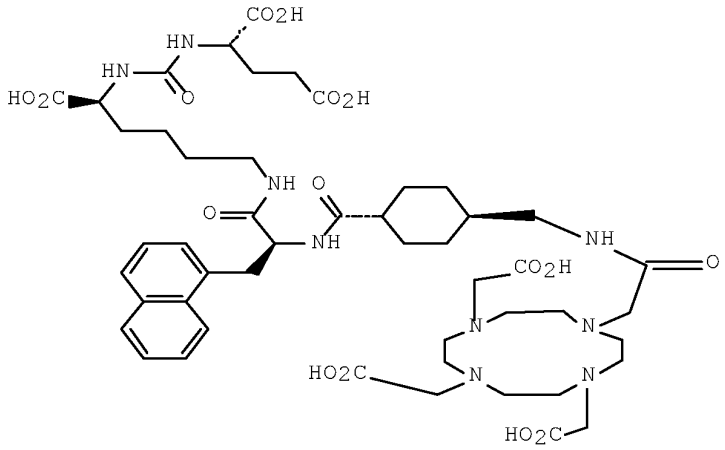
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2862857	A1	20150422	EP 2013-4991	20131018
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
CA 2924360	A1	20150423	CA 2014-2924360	20141017
WO 2015055318	A1	20150423	WO 2014-EP2808	20141017
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
AU 2014336638	A1	20160414	AU 2014-336638	20141017
IL 245113	A	20160531	IL 2014-245113	20141017
CN 105636924	A	20160601	CN 2014-80056250	20141017

Fusion Pharmaceuticals, Inc.
Exhibit 1004.176

KR 2016063398	A	20160603	KR 2016-7012314		20141017
EP 3038996	A1	20160706	EP 2014-799340		20141017
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME					
JP 2016535013	T	20161110	JP 2016-524427		20141017
IN 201617011691	A	20160812	IN 2016-17011691		20160401
US 20160228587	A1	20160811	US 2016-15131118		20160418
MX 2016005013	A	20170228	MX 2016-5013		20160418
PRIORITY APPLN. INFO.:			EP 2013-4991	A	20131018
			EP 2014-175612	A	20140703
			WO 2014-EP2808	W	20141017

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

GI



I

AB The invention is related to the preparation of glutamate-urea-lysines (GUL) in which a chelator group is conjugated to the GUL moiety via a linker, e.g., I, that are potent inhibitors of PSMA activity and to their radionuclides conjugates useful in nuclear medicine as tracers, imaging agents and for the treatment of various disease states of prostate cancer. Thus, the DOTA conjugated-PSMA inhibitor I was prepared via solid phase peptide synthesis using bis(tert-butyl)-L-glutamate hydrochloride, N-(9-fluorenylmethoxycarbonyl)-3-(2-naphthyl)-L-alanine, trans-4-(Fmoc-aminomethyl)cyclohexanecarboxylic acid tris(t-bu)-DOTA. I was evaluated in in vitro assays (affinity, internalization) and in vivo expts. (microPET screening and organ distribution). In the PET diagrams the compds. of the present invention, in particular I, showed a rapid background clearance as well as a substantial reduction of the enrichment in the kidney after 2 h while it is further accumulated and retained in the PSMA-expressing tumor.

IT 1702720-89-5P 1702720-91-9P 1702720-95-3P
1702720-97-5P 1702721-00-3P 1702721-02-5P
RL: DGN (Diagnostic use); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of radiolabeled prostate specific membrane antigen inhibitors

Fusion Pharmaceuticals, Inc.
Exhibit 1004.177

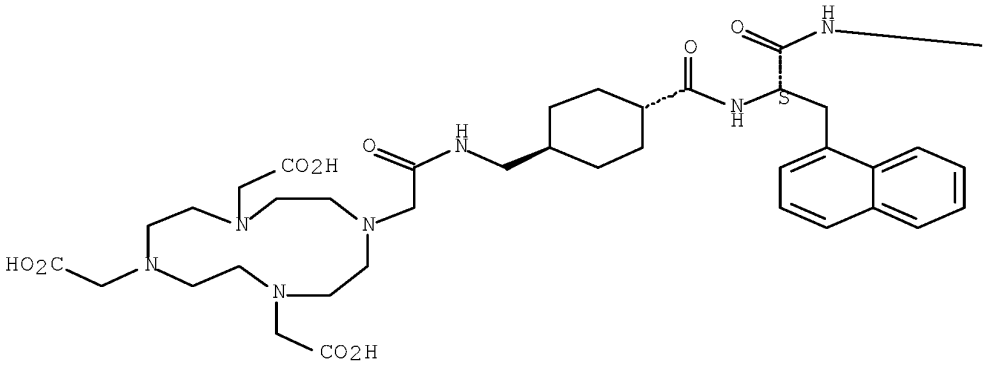
as tracers, imaging agents and for treating prostate cancer)

RN 1702720-89-5 CAPLUS

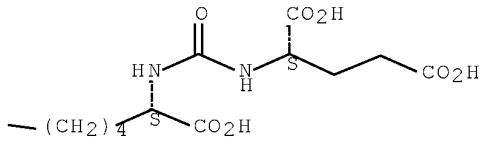
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(1-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



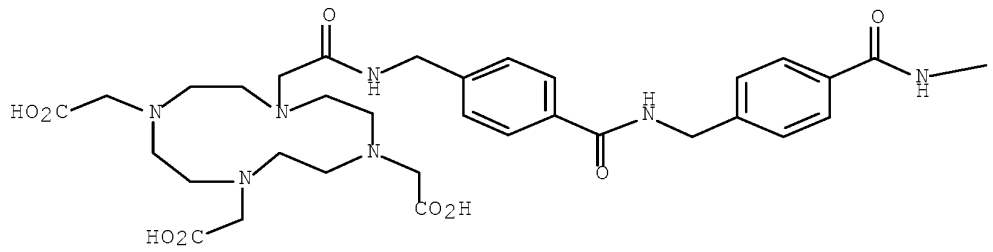
RN 1702720-91-9 CAPLUS

CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[[4-[[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

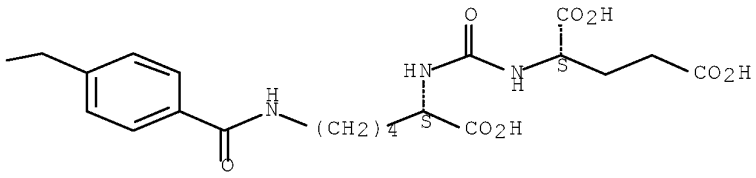
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.178

PAGE 1-A



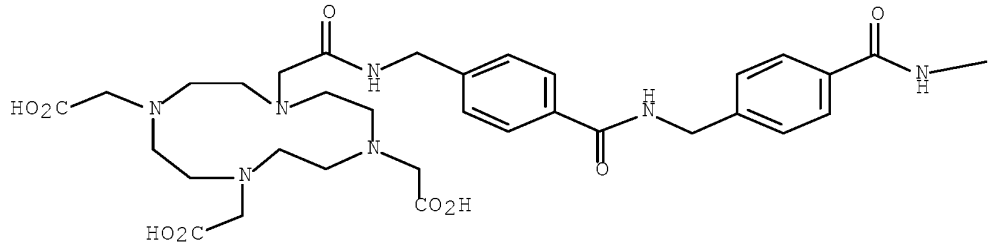
PAGE 1-B



RN 1702720-95-3 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[[4-[[[[4-[[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

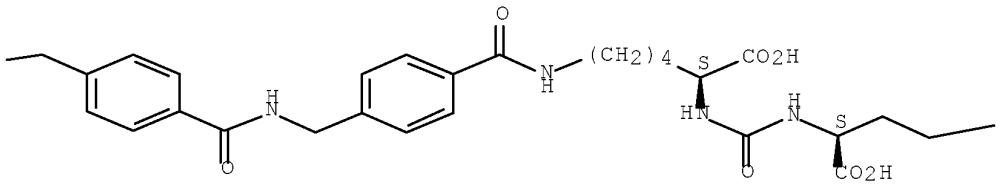
Absolute stereochemistry.

PAGE 1-A

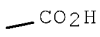


Fusion Pharmaceuticals, Inc.
Exhibit 1004.179

PAGE 1-B



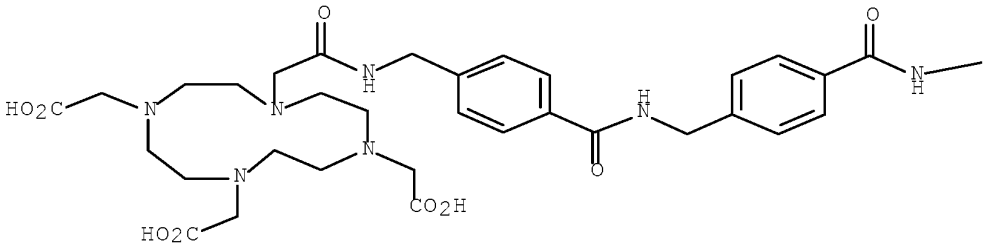
PAGE 1-C



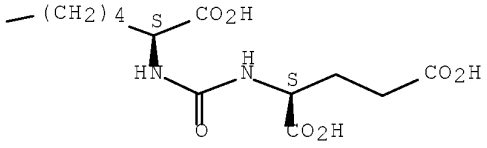
RN 1702720-97-5 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid,
10-[2-[[[4-[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-
dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]a
mino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



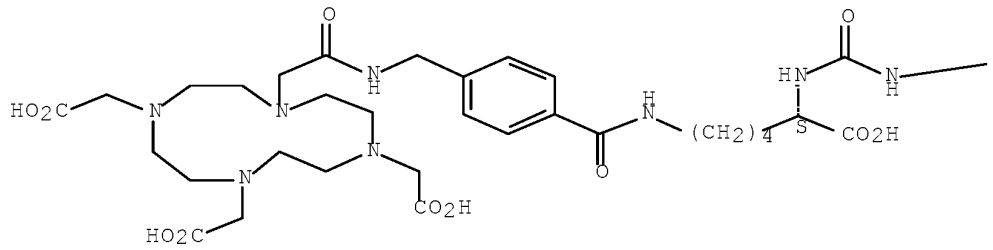
RN 1702721-00-3 CAPLUS

Fusion Pharmaceuticals, Inc.
Exhibit 1004.180

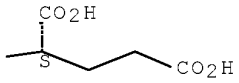
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

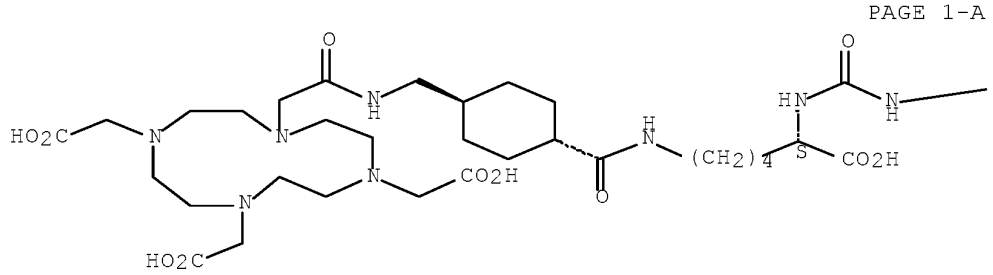


RN 1702721-02-5 CAPLUS

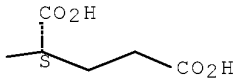
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[trans-4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]cyclohexyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.181

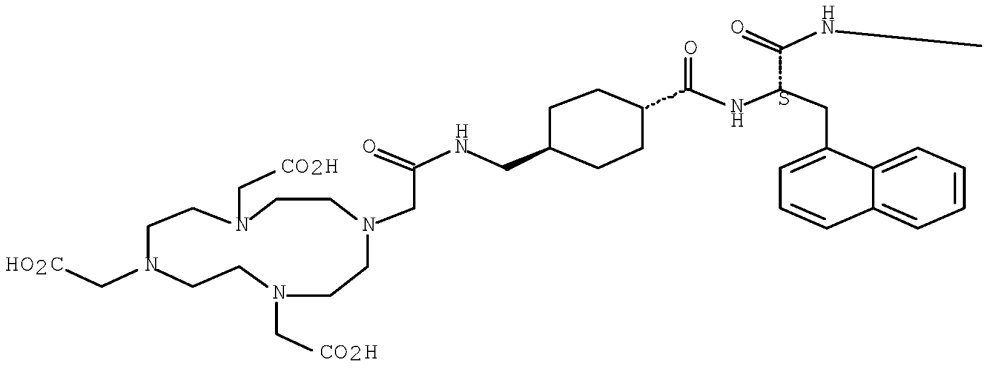
IT 1702720-89-5D, Gallium-68 complexes 1702720-91-9D, Gallium-68 complexes
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of radiolabeled prostate specific membrane antigen inhibitors as tracers, imaging agents and for treating prostate cancer)

RN 1702720-89-5 CAPLUS

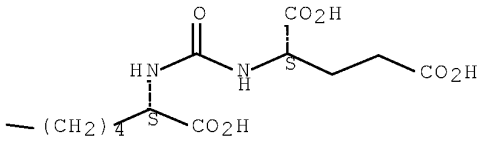
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(1-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



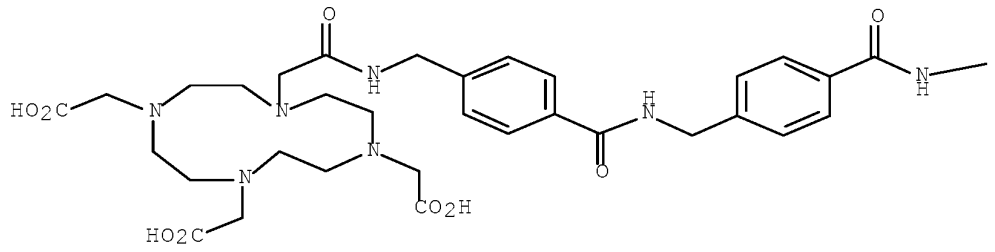
RN 1702720-91-9 CAPLUS

CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-[[[4-[[[4-[[[4-[[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]carbonyl]phenyl]methyl]amino]-2-oxoethyl]- (CA INDEX NAME)

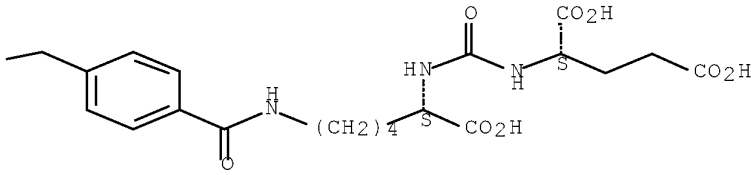
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.182

PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:2012102 CAPLUS Full-text
DOCUMENT NUMBER: 162:267785
TITLE: The diagnostic value of PET/CT imaging with the 68Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer
AUTHOR(S): Afshar-Oromieh, Ali; Avtzi, Eleni; Giesel, Frederik L.; Holland-Letz, Tim; Linhart, Heinz G.; Eder, Matthias; Eisenhut, Michael; Boxler, Silvan; Hadaschik, Boris A.; Kratochwil, Clemens; Weichert, Wilko; Kopka, Klaus; Debus, Juergen; Haberkorn, Uwe
CORPORATE SOURCE: Department of Nuclear Medicine, University Hospital of Heidelberg, Heidelberg, 69120, Germany
SOURCE: European Journal of Nuclear Medicine and Molecular Imaging (2015), 42(2), 197-209
CODEN: EJNMA6; ISSN: 1619-7070
DIGITAL OBJECT ID: 10.1007/s00259-014-2949-6
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Purpose: Since the introduction of positron emission tomog. (PET) imaging with 68Ga-PSMA-HBED-CC (=68Ga-DKFZ-PSMA-11), this method has been regarded as a significant step forward in the diagnosis of recurrent prostate cancer (PCa). However, published data exist for small patient cohorts only. The aim of this evaluation was to analyze the diagnostic value of 68Ga-PSMA-ligand PET/CT in a large cohort and the influence of several possibly interacting variables. Methods: We

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performed a retrospective anal. in 319 patients who underwent 68Ga-PSMA-ligand PET/CT from 2011 to 2014. Potential influences of several factors such as prostate-specific antigen (PSA) level and doubling time (DT), Gleason score (GSC), androgen deprivation therapy (ADT), age and amount of injected tracer were evaluated. Histol. verification was performed in 42 patients after the 68Ga-PSMA-ligand PET/CT. Tracer uptake was measured in 901 representative tumor lesions. Results: In 82.8 % of the patients at least one lesion indicative of PCa was detected. Tumor-detection was pos. associated with PSA level and ADT. GSC and PSA-DT were not associated with tumor-detection. The average maximum standardized uptake value (SUVmax) of tumor lesions was 13.3 ± 14.6 (0.7-122.5). Amongst lesions investigated by histol., 30 were false-neg. in 4 different patients, and all other lesions (n = 416) were true-pos. or true-neg. A lesion-based anal. of sensitivity, specificity, neg. predictive value (NPV) and pos. predictive value (PPV) revealed values of 76.6 %, 100 %, 91.4 % and 100 %. A patient-based anal. revealed a sensitivity of 88.1 %. Of 116 patients available for follow-up, 50 received local therapy after 68Ga-PSMA-ligand PET/CT. Conclusion: 68Ga-PSMA-ligand PET/CT can detect recurrent PCa in a high number of patients. In addition, the radiotracer is highly specific for PCa. Tumor detection is pos. associated with PSA and ADT. 68Ga-PSMA-ligand PET/CT can help delay systemic therapy of PCa.

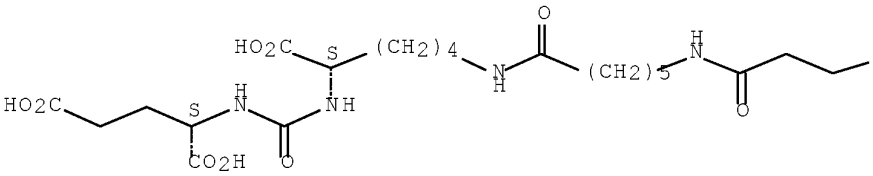
IT 1366302-52-4D, gallium-68 complex
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); BIOL (Biological study); USES (Uses)
(68Ga-DKFZ-PSMA-11; diagnostic value of PET/CT imaging with the 68Ga-labeled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer)

RN 1366302-52-4 CAPLUS

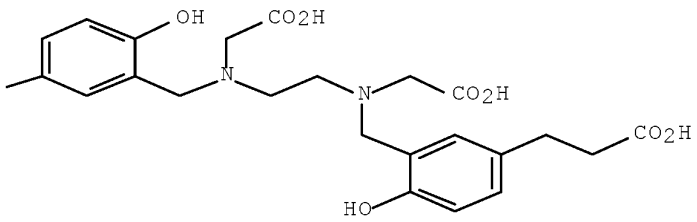
CN 4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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OS.CITING REF COUNT: 64 THERE ARE 64 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1890718 CAPLUS Full-text
DOCUMENT NUMBER: 162:420766
TITLE: Novel preclinical and radiopharmaceutical aspects of [68Ga]Ga-PSMA-HBED-CC: a new PET tracer for imaging of prostate cancer
AUTHOR(S): Eder, Matthias; Neels, Oliver; Mueller, Miriam; Bauder-Wuest, Ulrike; Remde, Yvonne; Schaefer, Martin; Hennrich, Ute; Eisenhut, Michael; Afshar-Oromieh, Ali; Haberkorn, Uwe; Kopka, Klaus
CORPORATE SOURCE: German Cancer Research Center, Division of Radiopharmaceutical Chemistry, Heidelberg, Germany
SOURCE: Pharmaceuticals (2014), 7(7), 779-796
CODEN: PHARH2; ISSN: 1424-8247
DIGITAL OBJECT ID: 10.3390/ph7070779
PUBLISHER: MDPI AG
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

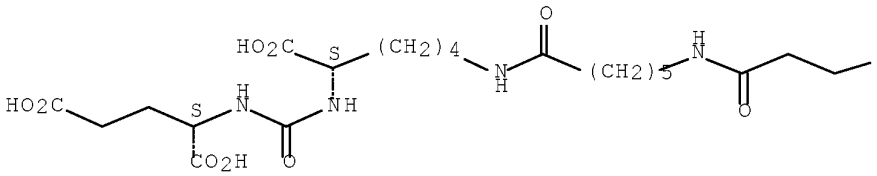
AB The detection of prostate cancer lesions by PET imaging of the prostate-specific membrane antigen (PSMA) has gained highest clin. impact during the last years. 68Ga-labeled Glu-urea-Lys(Ahx)-HBED-CC ([68Ga]Ga-PSMA-HBED-CC) represents a successful novel PSMA inhibitor radiotracer which has recently demonstrated its suitability in individual first-in-man studies. The radiometal chelator HBED-CC used in this mol. represents a rather rarely used acyclic complexing agent with chemical characteristics favorably influencing the biol. functionality of the PSMA inhibitor. The simple replacement of HBED-CC by the prominent radiometal chelator DOTA was shown to dramatically reduce the in vivo imaging quality of the resp. 68Ga-labeled PSMA-targeted tracer proving that HBED-CC contributes intrinsically to the PSMA binding of the Glu-urea-Lys(Ahx) pharmacophore. Owing to the obvious growing clin. impact, this work aims to reflect the properties of HBED-CC as acyclic radiometal chelator and presents novel preclin. data and relevant aspects of the radiopharmaceutical production process of [68Ga]Ga-PSMA-HBED-CC.

IT 1366302-52-4D, 68Ga-labeled
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(PSMA-HBED-CC; [68Ga]Ga-PSMA-HBED-CC, a new PET tracer for imaging of prostate cancer)
RN 1366302-52-4 CAPLUS
CN 4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)- (CA INDEX NAME)

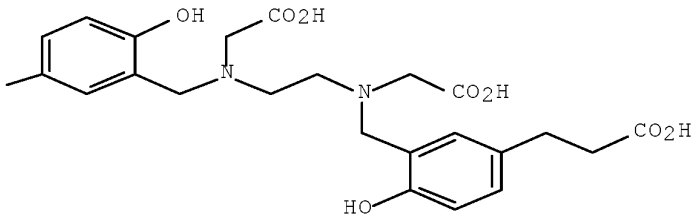
Absolute stereochemistry.

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PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 40 THERE ARE 40 CAPLUS RECORDS THAT CITE THIS RECORD (41 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:60214 CAPLUS Full-text
DOCUMENT NUMBER: 161:498316
TITLE: A dimerized urea-based inhibitor of the prostate-specific membrane antigen for 68Ga-PET imaging of prostate cancer
AUTHOR(S): Schaefer, Martin; Bauder-Wuest, Ulrike; Leotta, Karin; Zoller, Frederic; Mier, Walter; Haberkorn, Uwe; Eisenhut, Michael; Eder, Matthias
CORPORATE SOURCE: Radiopharmaceutical Chemistry, German Cancer Research Center, Heidelberg, 69120, Germany
SOURCE: EJNMMI Research (2012), 2(1), 23, 11 pp.
CODEN: ERJEAI; ISSN: 2191-219X
DIGITAL OBJECT ID: 10.1186/2191-219X-2-23
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 161:498316
AB Background: Alternative positron-emission tomog. (PET) probes like labeled inhibitors of the prostate-specific membrane antigen (PSMA) are of emerging clin. impact as they show the ability to image small lesions of recurrent prostate cancer. Here, the dimerization of the pharmacophore Glu-ureido-Lys via the 68Ga chelator N,N'-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic acid (HBED-CC) was investigated to further improve the binding characteristics and pharmacokinetics. Methods: The peptidomimetic structures were synthesized by solid-phase chemical and the resulting products were coupled with the resp. 2,3,5,6-tetrafluorophenol esters of HBED-CC to form the monomeric reference and

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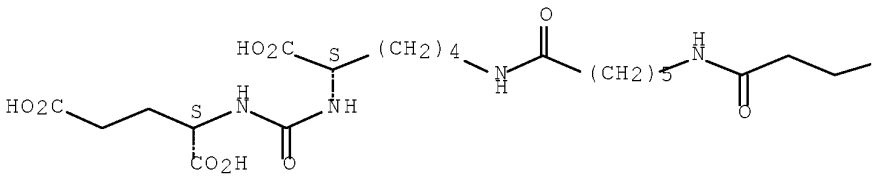
the dimeric Glu-ureido-Lys derivative The binding properties were analyzed in competitive binding, internalization and cell surface retention expts. PET images and biodistribution data were obtained 1 h after injection in BALB/c nu/nu mice bearing LNCaP tumor xenografts. Results: Cell binding data revealed significant better binding properties of the dimer (IC50 = 3.9 ± 1.8 nM; IC50 (monomer) = 12.1 ± 2.1 nM). The inhibition potency investigated by the enzyme-based NAALADase assay confirmed these results. Specific internalization in LNCaP cells was demonstrated for both, the monomer and dimer. As shown by efflux measurements, the dimeric compound was more effectively retained on the cell surface, resulting in advanced in vivo properties (T/BMonomer = 9.2; T/BDimer = 26.5). Conclusions: The dimeric [68Ga]7 is a promising imaging agent for PSMA-expressing tumors as it shows higher tumor uptake while observing more favorable background clearance. As compared to the resp. monomer, the higher affinity and prolonged tumor retention addnl. represent promising features and warrant further evaluation regarding 68Ga-PET imaging of PSMA expression.

IT 1366302-52-4DP, complexes with Fe and 68Ga
1644283-89-5P, DKFZ-PSMA 10
RL: DGN (Diagnostic use); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dimerized urea based inhibitor of prostate-specific membrane antigen for 68Ga-positron emission tomog. imaging of prostate cancer)

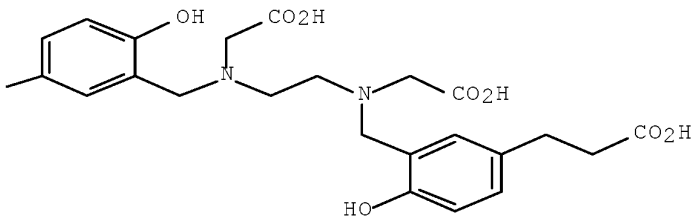
RN 1366302-52-4 CAPLUS
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



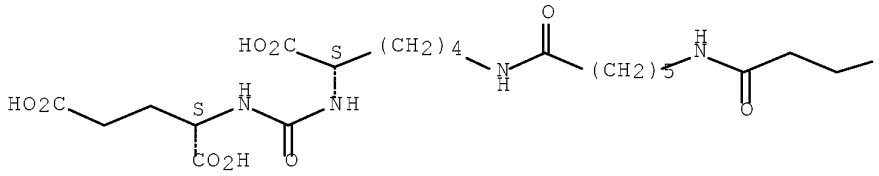
RN 1644283-89-5 CAPLUS
CN L-Glutamic acid, N,N'-[1,2-ethanediylbis[[(carboxymethyl)imino]methylene(4-hydroxy-3,1-phenylene)(1-oxo-3,1-propanediyl)imino(1-oxo-6,1-

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Exhibit 1004.187

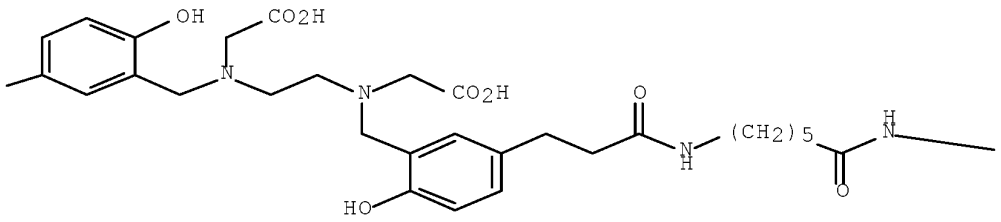
hexanediyl)imino[(1S)-1-carboxy-5,1-pentanediyl]iminocarbonyl]]bis- (CA INDEX NAME)

Absolute stereochemistry.

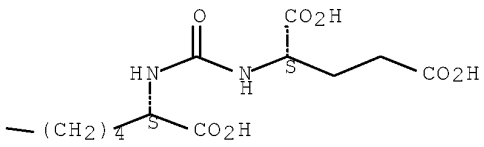
PAGE 1-A



PAGE 1-B

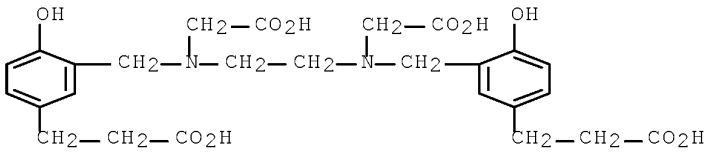


PAGE 1-C



IT 143557-99-7, complex with Fe
RL: RCT (Reactant); RACT (Reactant or reagent)
(dimerized urea based inhibitor of prostate-specific membrane antigen for 68Ga-positron emission tomog. imaging of prostate cancer)
RN 143557-99-7 CAPLUS
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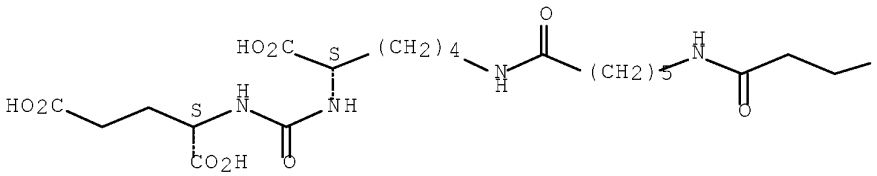
Fusion Pharmaceuticals, Inc.
Exhibit 1004.188



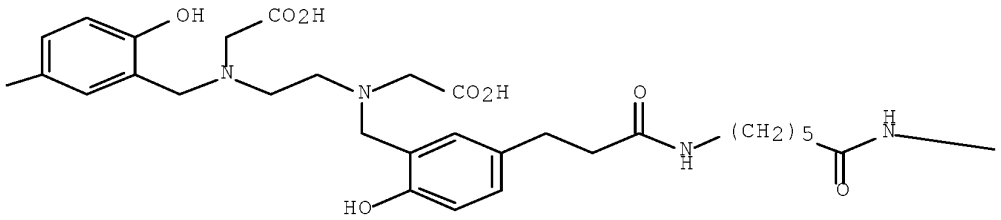
IT 1644283-89-5DP, complexes
RL: SPN (Synthetic preparation); PREP (Preparation)
(dimerized urea based inhibitor of prostate-specific membrane antigen for 68Ga-positron emission tomog. imaging of prostate cancer)
RN 1644283-89-5 CAPLUS
CN L-Glutamic acid, N,N'-[1,2-ethanediylbis[[(carboxymethyl)imino]methylene(4-hydroxy-3,1-phenylene)(1-oxo-3,1-propanediyl)imino(1-oxo-6,1-hexanediyl)imino[(1S)-1-carboxy-5,1-pentanediyl]iminocarbonyl]]bis- (CA INDEX NAME)

Absolute stereochemistry.

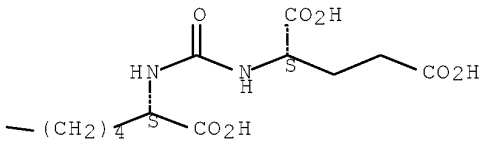
PAGE 1-A



PAGE 1-B



PAGE 1-C



Fusion Pharmaceuticals, Inc.
Exhibit 1004.189

OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:284564 CAPLUS Full-text
DOCUMENT NUMBER: 156:444417
TITLE: 68Ga-Complex Lipophilicity and the Targeting Property of a Urea-Based PSMA Inhibitor for PET Imaging
AUTHOR(S): Eder, Matthias; Schaefer, Martin; Bauder-Wuest, Ulrike; Hull, William-Edmund; Waengler, Carmen; Mier, Walter; Haberkorn, Uwe; Eisenhut, Michael
CORPORATE SOURCE: Radiopharmaceutical Chemistry, Molecular Structure Analysis, German Cancer Research Center, Heidelberg, Germany
SOURCE: Bioconjugate Chemistry (2012), 23(4), 688-697
CODEN: BCCHES; ISSN: 1043-1802
DIGITAL OBJECT ID: 10.1021/bc200279b
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 156:444417

AB Urea-based inhibitors of the prostate-specific membrane antigen (PSMA) represent low-mol.-weight pepidomimetics showing the ability to image PSMA-expressing prostate tumors. The highly efficient, acyclic Ga(III) chelator N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'- diacetic acid (HBED-CC) was introduced as a lipophilic side chain into the hydrophilic pharmacophore Glu-NH-CO-NH-Lys which was found favorable to interact with the PSMA "active binding site". This report describes the syntheses, in vitro binding analyses, and biodistribution data of the radiogallium labeled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC in comparison to the corresponding DOTA conjugate. The binding properties were analyzed using competitive cell binding and enzyme-based assays followed by internalization expts. Compared to the DOTA-conjugate, the HBED-CC derivative showed reduced unspecific binding and considerable higher specific internalization in LNCaP cells. The 68Ga complex of the HBED-CC ligand exhibited higher specificity for PSMA expressing tumor cells resulting in improved in vivo properties. 68Ga labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC showed fast blood and organ clearances, low liver accumulation, and high specific uptake in PSMA expressing organs and tumor. It could be demonstrated that the PET-imaging property of a urea-based PSMA inhibitor could significantly be improved with HBED-CC.

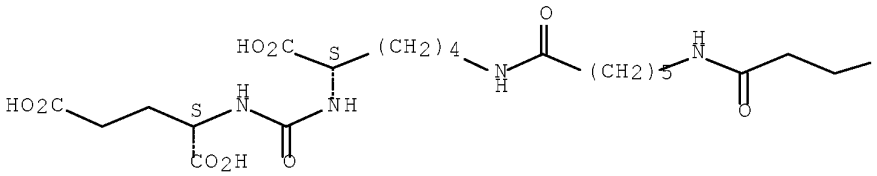
IT 1366302-52-4DP, complex with 68Ga 1366302-54-6DP, complex with 68Ga 1366302-57-9DP, complex with Gallium
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(lipophilic 68Ga-complex preparation and PSMA inhibition for PET imaging)

RN 1366302-52-4 CAPLUS
CN 4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)- (CA INDEX NAME)

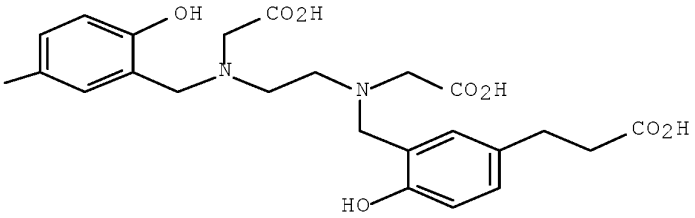
Absolute stereochemistry.

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Exhibit 1004.190

PAGE 1-A



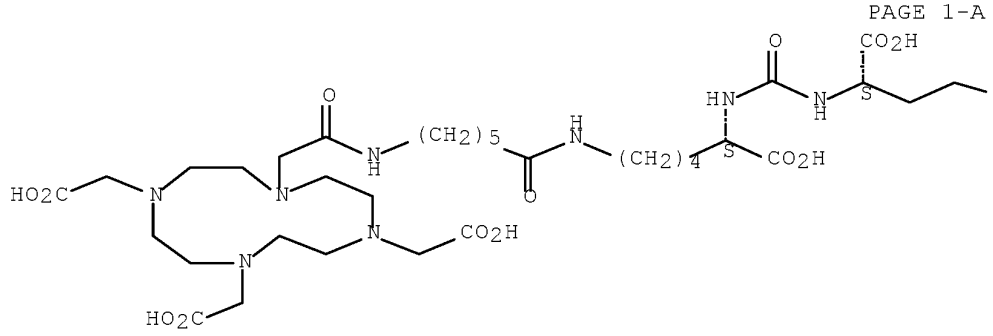
PAGE 1-B



RN 1366302-54-6 CAPLUS
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



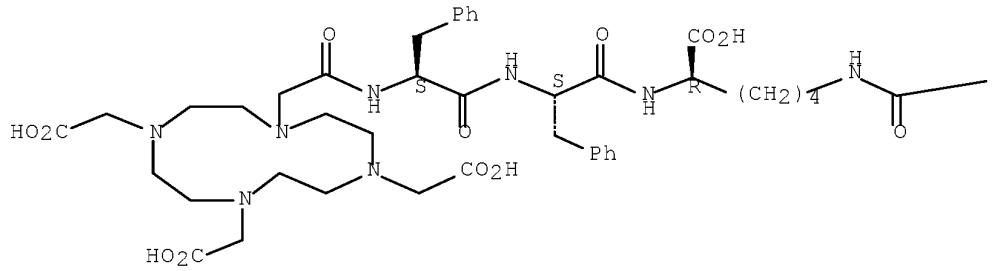
RN 1366302-57-9 CAPLUS

Fusion Pharmaceuticals, Inc.
Exhibit 1004.191

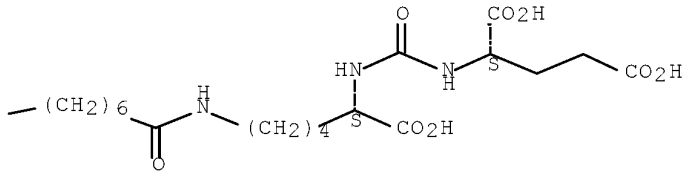
CN D-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

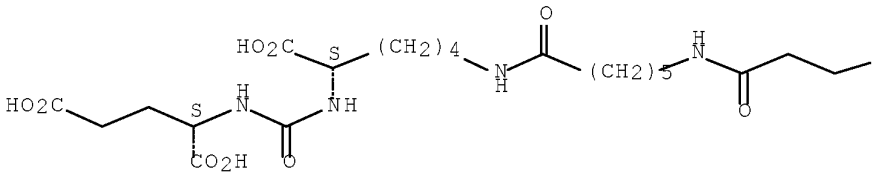


IT 1366302-52-4P 1366302-54-6P 1366302-57-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(lipophilic 68Ga-complex preparation and PSMA inhibition for PET imaging)
RN 1366302-52-4 CAPLUS
CN 4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)- (CA INDEX NAME)

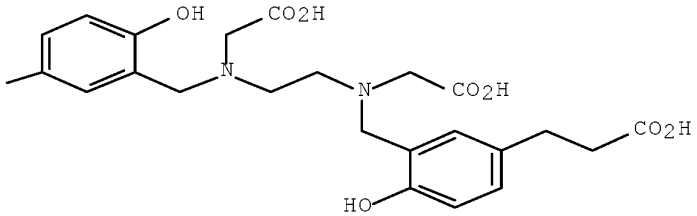
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.192

PAGE 1-A



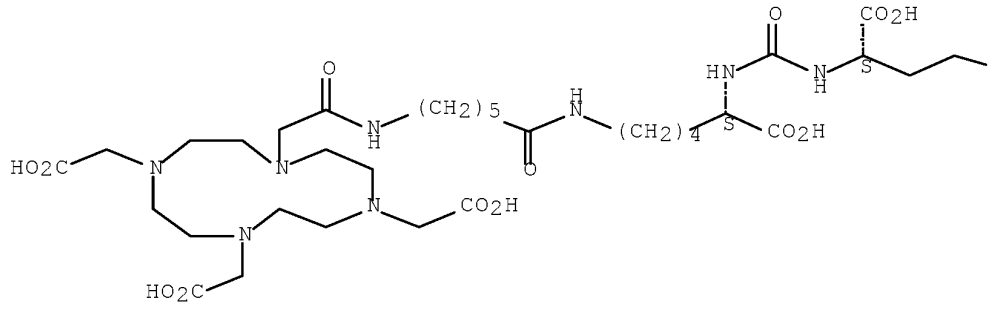
PAGE 1-B



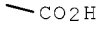
RN 1366302-54-6 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[(15S,19S)-15,19,21-tricarboxy-2,9,17-trioxo-3,10,16,18-tetraazaheneicos-1-yl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



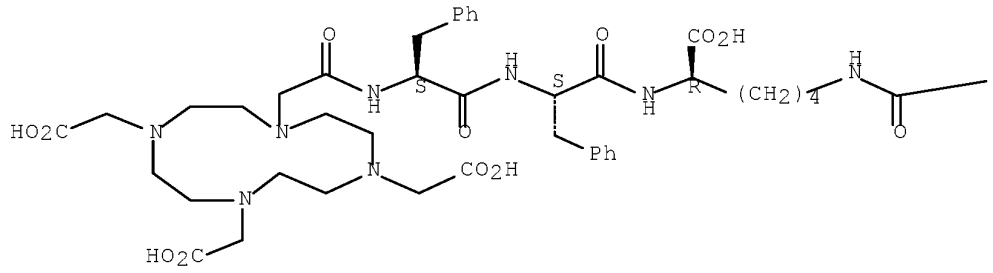
RN 1366302-57-9 CAPLUS

Fusion Pharmaceuticals, Inc.
Exhibit 1004.193

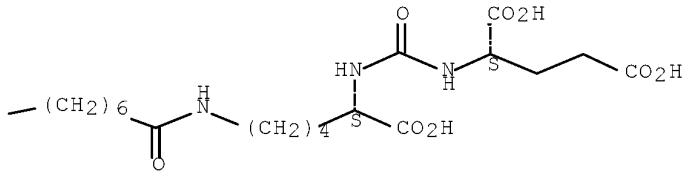
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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Fusion Pharmaceuticals, Inc.
Exhibit 1004.194

STRUCTURE SEARCH PART 1

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=> fil reg; d stat que l116; d stat que l119
FILE 'REGISTRY' ENTERED AT 15:32:24 ON 22 JUN 2017
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   21 JUN 2017  HIGHEST RN 2098835-24-4
DICTIONARY FILE UPDATES:  21 JUN 2017  HIGHEST RN 2098835-24-4

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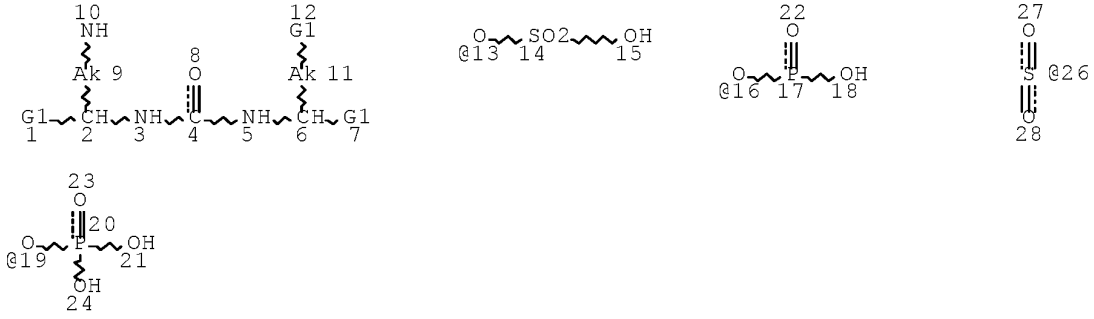
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 4, 2017

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific
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L99 STR



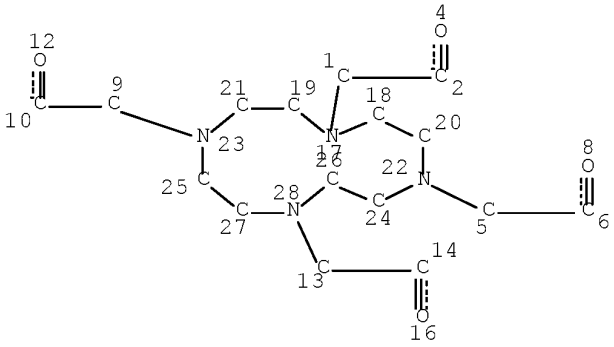

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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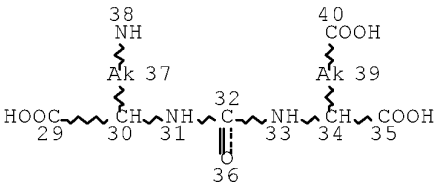

Fusion Pharmaceuticals, Inc.
Exhibit 1004.195

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L102   1093 SEA FILE=REGISTRY SSS FUL L99
L114   STR



Page 1-A



Page 2-A
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DEFAULT ECLEVEL IS LIMITED

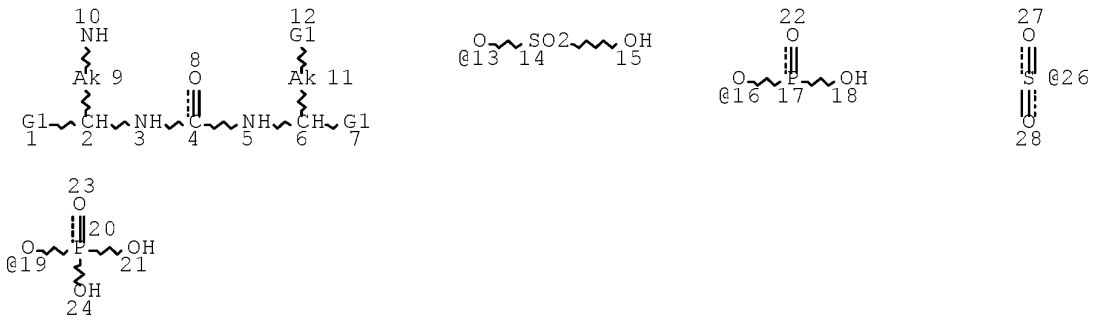
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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED   226 ITERATIONS   81 ANSWERS
SEARCH TIME: 00.00.01

L99   STR

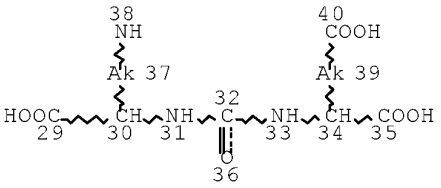
Fusion Pharmaceuticals, Inc.
Exhibit 1004.196



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DEFAULT MLEVEL IS ATOM
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L102   1093 SEA FILE=REGISTRY SSS FUL L99
L117   STR



NODE ATTRIBUTES:
CONNECT IS E2 RC AT 37
CONNECT IS E2 RC AT 39
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN LOC SAT AT 37
GGCAT   IS LIN LOC SAT AT 39
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L119   1093 SEA FILE=REGISTRY SUB=L102 SSS FUL L117

Fusion Pharmaceuticals, Inc.
Exhibit 1004.197

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100.0% PROCESSED      1093 ITERATIONS                          1093 ANSWERS
SEARCH TIME: 00.00.01


=> fil capl; d que nos l121; d que nos l122
FILE 'CAPLUS' ENTERED AT 15:32:32 ON 22 JUN 2017
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FILE COVERS 1907 - 22 Jun 2017 VOL 167 ISS 1
FILE LAST UPDATED: 21 Jun 2017 (20170621/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015

CAplus includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2017.

CAplus now includes the comprehensive Cooperative Patent Classification
(CPC).  See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L99             STR
L102       1093 SEA FILE=REGISTRY SSS FUL L99
L114            STR
L116         81 SEA FILE=REGISTRY SUB=L102 SSS FUL L114
L121         29 SEA FILE=CAPLUS SPE=ON  ABB=ON  L116



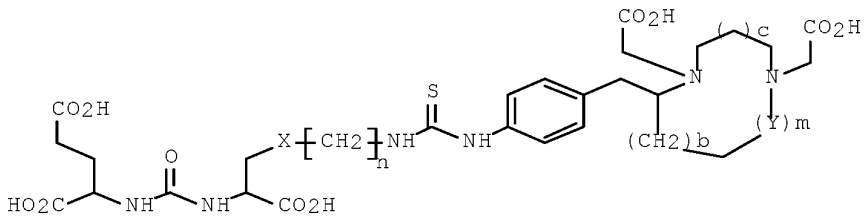
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L117            STR
L119       1093 SEA FILE=REGISTRY SUB=L102 SSS FUL L117
L122          6 SEA FILE=CAPLUS SPE=ON  ABB=ON  L119 AND L68
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.198

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=> s l121,l122 not l132
L133        27 (L121 OR L122) NOT L132
                       (L132=INVENTOR SEARCH, PREVIOUSLY DISPLAYED)

=> d ibib abs hitstr l133 1-27

L133 ANSWER 1 OF 27  CAPLUS  COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER:         2017:794046  CAPLUS  Full-text
DOCUMENT NUMBER:          166:546804
TITLE:                    Peptide thiourea derivative, radioisotope labeled
                          compound containing it and pharmaceutical composition
                          for treatment or diagnosis of prostate cancer
                          comprising the same as active ingredient
INVENTOR(S):              Jeong, Jae Min; Moon, Sung-Hyun; Lee, Yun-Sang
PATENT ASSIGNEE(S):       Cellbion Co,. Ltd, S. Korea
SOURCE:                   PCT Int. Appl., 38pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Korean
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:
     PATENT NO.           KIND  DATE        APPLICATION NO.          DATE
     ---------------      ----  --------    ---------------------    --------
     WO 2017082620         A1   20170518    WO 2016-KR12849          20161109
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
             BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC,
             EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN,
             IR, IS, JP, KE, KG, KN, KP, KW, KZ, LA, LC, LK, LR, LS, LU, LY,
             MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
             PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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
         RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM,
             ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW,
             SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
     KR 1639599            B1   20160714    KR 2015-156536           20151109
PRIORITY APPLN. INFO.:                      KR 2015-156536       A   20151109
GI
```



I

Fusion Pharmaceuticals, Inc.
Exhibit 1004.199

AB The present invention relates to a peptide thiourea derivative, shown as chemical formula (I)(X=single bond, -O-, -S-; n=integer of 1 to 5; y=-N(CH2COOH)(CH2)aCH2CH2-, m=1 or 2; a,b,c= 0 or 1), a pharmaceutically acceptable salt thereof, a radioisotope labeled compound containing the same, and a pharmaceutical composition containing the same as an active ingredient for treating and diagnosing prostate cancer. The peptide thiourea derivative, when administered into the body, has excellent stability in the human serum, favorably binds to PSMA which is competitively expressed in prostate cancer, exhibits an excellent PSMA inhibitory effect with a low concentration, and can obtain a clear image of a prostate cancer tumor site by being excreted into the kidney rather than the hepatobiliary route due to high water solubility thereof. Therefore, the peptide thiourea derivative can be favorably used as a pharmaceutical composition for treating or diagnosing prostate cancer.

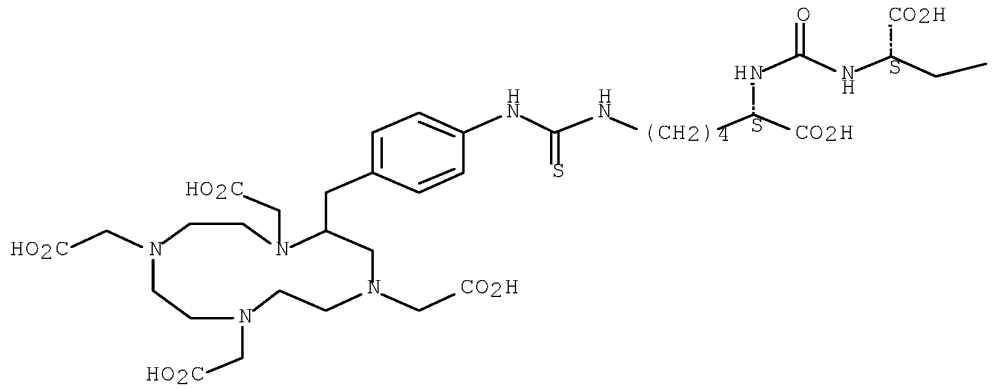
IT 1970173-58-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide thiourea derivative, radioisotope labeled compound containing it and pharmaceutical composition for treatment or diagnosis of prostate cancer comprising the same as active ingredient)

RN 1970173-58-0 CAPLUS

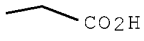
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L133 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1956168 CAPLUS Full-text
DOCUMENT NUMBER: 166:511542
TITLE: Labeled inhibitors of prostate specific membrane

Fusion Pharmaceuticals, Inc.
Exhibit 1004.200

antigen (psma), biological evaluation, and use as imaging agents

INVENTOR(S): Pomper, Martin G.; Sangeeta, Ray; Mease, Ronnie C.; Foss, Catherine

PATENT ASSIGNEE(S): The Johns Hopkins University, USA

SOURCE: U.S., No pp. given
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 9044468	B2	20150602	US 2010-666441	20101122
US 20110064657	A1	20110317		
CA 2926573	A1	20081231	CA 2008-2926573	20080626
WO 2009002529	A2	20081231	WO 2008-US7947	20080626
WO 2009002529	A3	20090212		
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CN 104774175	A	20150715	CN 2015-10067581	20080626
EP 2921482	A2	20150923	EP 2014-195837	20080626
EP 2921482	A3	20151104		
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US 20150246144	A1	20150903	US 2015-14715115	20150518
AU 2015203742	A1	20150730	AU 2015-203742	20150703
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PRIORITY APPLN. INFO.:	US 2007-60937242	P	20070626
	US 2008-61011111	P	20080115
	WO 2008-US7947	W	20080626
	AU 2008-269094	A3	20080626
	CA 2008-2694266	A3	20080626
	CN 2008-80104344	A3	20080626
	EP 2008-779786	A3	20080626
	US 2010-666441	A3	20101122

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The prostate-specific membrane antigen (PSMA) is increasingly recognized as a viable target for imaging and therapy of cancer. Various 99mTc/Re-labeled compds. were prepared by attaching known Tc/Re chelating agents to an amino-functionalized PSMA inhibitor with or without a variable length linker moiety. Ex vivo biodistribution and in vivo imaging demonstrated the degree of specific binding to engineered PSMA+ PC3 PIP tumors.

IT 1095118-43-6P 1095118-48-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.201

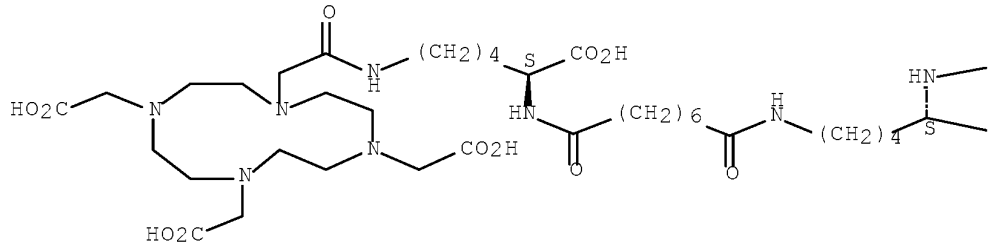
(labeled conjugates of PSMA inhibitors and evaluation and use as tumor imaging agents)

RN 1095118-43-6 CAPLUS

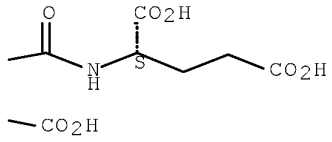
CN 4,6,12,21,27-Pentaazanonacosane-1,3,7,22-tetracarboxylic acid, 5,13,20,28-tetraoxo-29-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-, (3S,7S,22S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

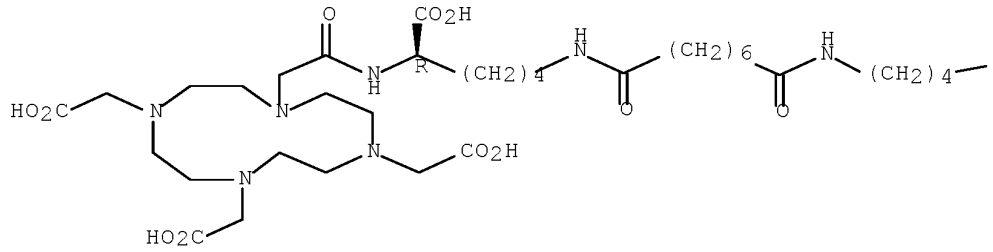


RN 1095118-48-1 CAPLUS

CN 4,6,12,21,27-Pentaazanonacosane-1,3,7,26-tetracarboxylic acid, 5,13,20,28-tetraoxo-29-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-, (3S,7S,26R)- (CA INDEX NAME)

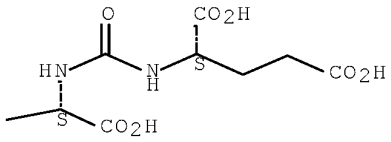
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.202

PAGE 1-B



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1942350 CAPLUS Full-text
DOCUMENT NUMBER: 166:490942
TITLE: Homomultivalent and heteromultivalent inhibitors of prostate specific membrane antigen (pmsa) and uses thereof
INVENTOR(S): Pomper, Martin Gilbert; Ray, Sangeeta; Mease, Ronnie C.
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20140341804	A1	20141120	US 2014-14362011	20140530
US 9371360	B2	20160621		
WO 2013082338	A1	20130606	WO 2012-US67162	20121130
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US 20170049912	A1	20170223	US 2016-15187274	20160908

PRIORITY APPLN. INFO.:
US 2011-61565179 P 20111130
WO 2012-US67162 W 20121130
US 2014-14362011 A1 20140530
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention provides bivalent and multivalent ligands with a view to improving the affinity and pharmacokinetic properties of a urea class of PSMA inhibitors. The compds. and their synthesis can be generalized to multivalent

Fusion Pharmaceuticals, Inc.
Exhibit 1004.203

compds. of other target antigens. Because they present multiple copies of the pharmacophore, multivalent ligands can bind to receptors with high avidity and affinity, thereby serving as powerful inhibitors. The modular multivalent scaffolds of the present invention, in one or more embodiments, contains a lysine-based (α-, ε-)dialkyne residue for incorporating two or more antigen binding moieties, such as PSMA binding Lys-Glu urea moieties, exploiting click chemical and one or more addnl. lysine residues for subsequent modification with an imaging and/or therapeutic nuclides or a cytotoxic ligands for tumor cell killing.

IT 1442110-14-6P

RL: DGN (Diagnostic use); PAC (Pharmacological activity); PKT (Pharmacokinetics); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

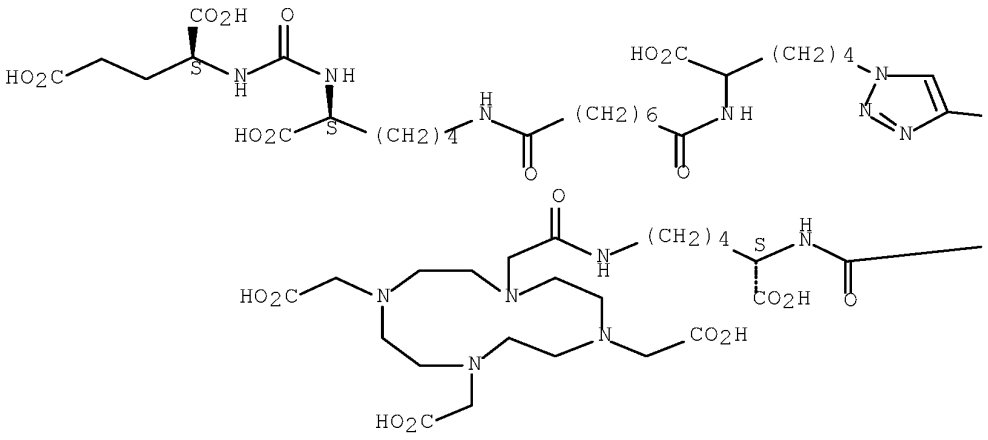
(preparation of compds. that are PSMA inhibitors useful in imaging, diagnosis, prophylaxis and treatment of cancer)

RN 1442110-14-6 CAPLUS

CN L-Lysine, N2,N6-bis[[1-[(20S,24S)-5,20,24,26-tetracarboxy-7,14,22-trioxo-6,15,21,23-tetraazahexacos-1-yl]-1H-1,2,3-triazol-4-yl]carbonyl]-L-lysyl-N6-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]- (CA INDEX NAME)

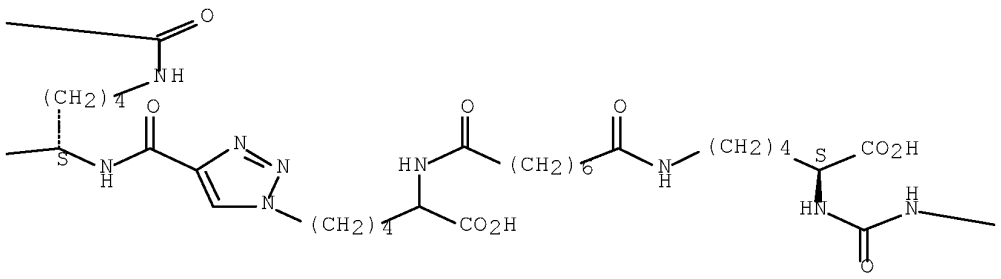
Absolute stereochemistry.

PAGE 1-A

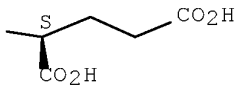


Fusion Pharmaceuticals, Inc.
Exhibit 1004.204

PAGE 1-B



PAGE 1-C



L133 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1796459 CAPLUS Full-text
DOCUMENT NUMBER: 165:600255
TITLE: Radionuclide labeled prostate specific membrane antigen targeting inhibitor and preparation method thereof
INVENTOR(S): Yang, Zhi; Han, Xuedi; Zhu, Hua; Liu, Chen; Liu, Fei; Xie, Qinghua
PATENT ASSIGNEE(S): Beijing Cancer Hospital, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 7pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

Fusion Pharmaceuticals, Inc.
Exhibit 1004.205

CN 106075484 A 20161109 CN 2016-10488183 20160628
PRIORITY APPLN. INFO.: CN 2016-10488183 20160628

AB A radionuclide labeled prostate specific membrane antigen targeting inhibitor is radionuclide labeled DKFZ-PSMA-617, the radionuclide includes one of 64Cu, 68Ga and 89Zr. The preparation method is as follows: adding sodium acetate and copper chloride or 89Zr4 leachate into DKFZ-PSMA-617, reacting at 80-110°C for 10-20 min, and obtaining 64Cu-PSMA-617 or 89Zr-PSMA-617. The inhibitor can be used for preparing tumor imaging agents and therapeutic drugs for targeting PSMA, and can also be used for preparing PET/CT mol. diagnosis imaging agents. The inhibitor has stable property, good imaging effect, high affinity and functional activity of prostate specific membrane antigen, which is conducive to the early diagnosis and accurate staging of prostatic cancer, and provide new ideas for the diagnosis of breast cancer and gastric cancer.

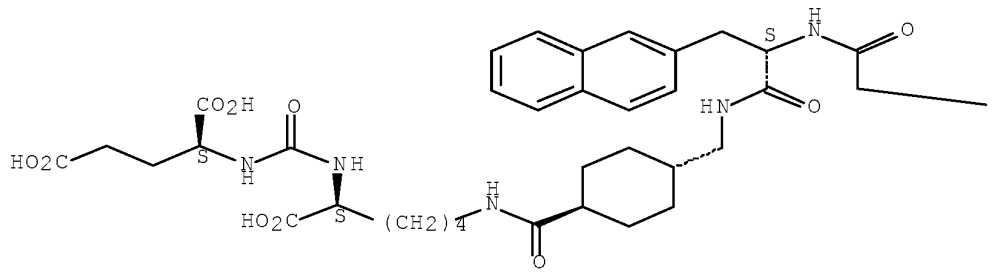
IT 1702967-55-2DP, PSMA-617, 64Cu-labeled
RL: DGN (Diagnostic use); MOA (Modifier or additive use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(radionuclide labeled prostate specific membrane antigen targeting inhibitor and preparation method thereof)

RN 1702967-55-2 CAPLUS

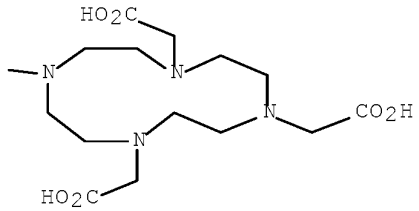
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-alanyl-trans-4-(aminomethyl)cyclohexanecarbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

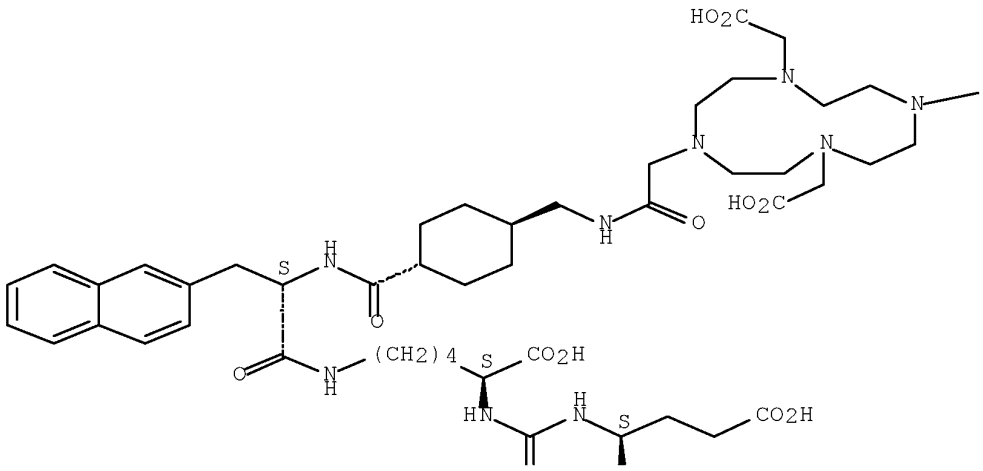


Fusion Pharmaceuticals, Inc.
Exhibit 1004.206

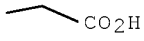
IT 1702967-37-0, DKFZ-PSMA-617
RL: DGN (Diagnostic use); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(radionuclide labeled prostate specific membrane antigen targeting inhibitor and preparation method thereof)
RN 1702967-37-0 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A



L133 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1542136 CAPLUS Full-text
DOCUMENT NUMBER: 165:448785
TITLE: 68Ga-Labeled NOTA-Chelated PSMA-Targeted Imaging and Therapeutic Agents

Fusion Pharmaceuticals, Inc.
Exhibit 1004.207

INVENTOR(S): Pomper, Martin G.; Mease, Ronnie; Ray, Sangeeta
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 74pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016149188	A1	20160922	WO 2016-US22309	20160314

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2015-62132955 P 20150313
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB PSMA-targeted PET/SPECT agents (I) for imaging PSMA-pos. cancer and or tumor neovasculature and PSMA-targeted radiotherapeutic agent for the treatment of PSMA-pos. cancer or tumor neovasculature are disclosed (Z is tetrazole or CO2Q;Q is H or a protecting group;X and A are each independently O or S;m is an integer selected from the group consisting of 1, 2, 3 and 4;n each independently an integer selected from the group consisting of 0, 1,2, 3, 4, 5, 6, 7, 8, 9, and 10; R1 is independently H or alkyl;each R2 is independently H or -COOR3, wherein each R3 is independently H or a alkyl;each R4 is independently H or alkyl;each R is independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkyaryl, arylakyl, and alkylheteroaryl). Methods of imaging PSMA expressing tumors, or cells and kits also are disclosed.

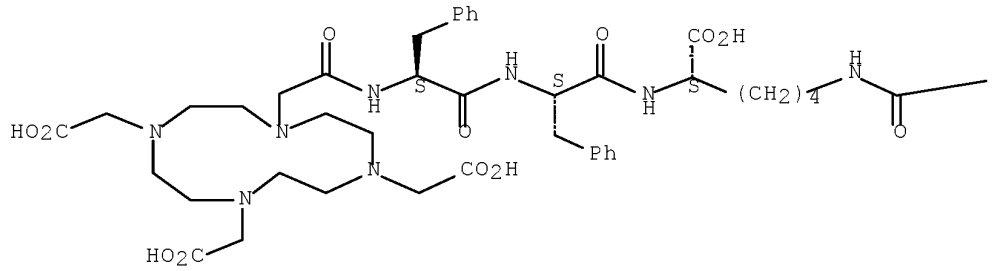
IT 1235548-82-9P
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation, antitumor, and biodistribution of 68Ga-labeled NOTA-chelated PSMA-targeted imaging and therapeutic agents)

RN 1235548-82-9 CAPLUS
CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

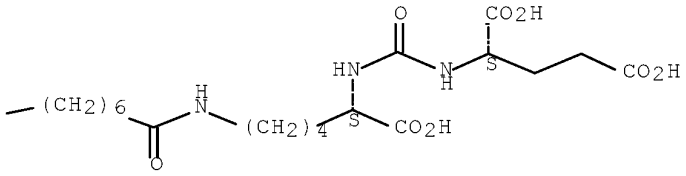
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.208

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

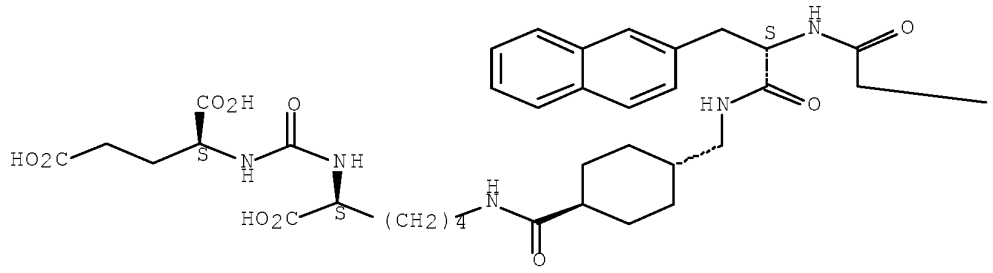
L133 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1479928 CAPLUS Full-text
DOCUMENT NUMBER: 165:568794
TITLE: Radioligand therapy with 177Lu-PSMA-617 of metastatic prostate cancer has already been arrived in clinical use
AUTHOR(S): Ahmadzadehfar, Hojjat; Essler, Markus; Schaefers, Michael; Rahbar, Kambiz
CORPORATE SOURCE: Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany
SOURCE: Nuclear Medicine and Biology (2016), 43(12), 835
CODEN: NMBIEO; ISSN: 0969-8051
DIGITAL OBJECT ID: 10.1016/j.nucmedbio.2016.08.003
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB Radioligand therapy with 177Lu-PSMA-617 of metastatic prostate cancer has already been arrived in clin. use.
IT 1702967-55-2, PSMA-617
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(radiolabeled with 177Lu; radioligand therapy with 177Lu-PSMA-617 of metastatic prostate cancer has already been arrived in clin. use)
RN 1702967-55-2 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-

Fusion Pharmaceuticals, Inc.
Exhibit 1004.209

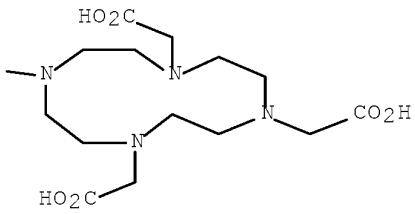
naphthalenyl)-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-alanyl-trans-4-(aminomethyl)cyclohexanecarbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1470304 CAPLUS Full-text
DOCUMENT NUMBER: 165:361286
TITLE: Method for labeling a prostate-specific membrane antigen ligand with a radioactive isotope
INVENTOR(S): Shalom, Eli
PATENT ASSIGNEE(S): Isotopia Molecular Imaging Ltd, Israel
SOURCE: Eur. Pat. Appl., 18pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 3064224	A1	20160907	EP 2016-158323	20160302
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO,				

Fusion Pharmaceuticals, Inc.
Exhibit 1004.210

RS, SE, SI, SK, SM, TR, BA, ME

IL 237525	A	20160929	IL 2015-237525	20150303
US 20160256579	A1	20160908	US 2016-15058537	20160302

PRIORITY APPLN. INFO.: IL 2015-237525 A 20150303
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 165:361286

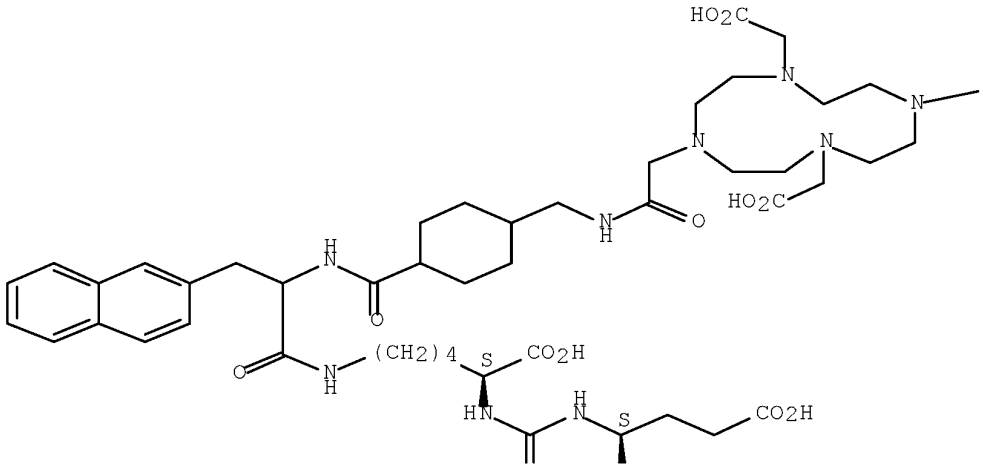
AB The present invention relates to a method for labeling a prostate-specific membrane antigen (PSMA) ligand with a radioactive isotope such as 68Ga, 177Lu, or 9Y, and to a kit for carrying out this method. Radiolabeled PSMA ligands prepared by this method can be used for both imaging and therapy purposes.

IT 1998102-65-0 1998102-66-1
RL: BUU (Biological use, unclassified); PRPH (Prophetic); BIOL (Biological study); USES (Uses)
(PSMA ligands radiolabeling for imaging and therapy)

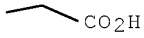
RN 1998102-65-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A

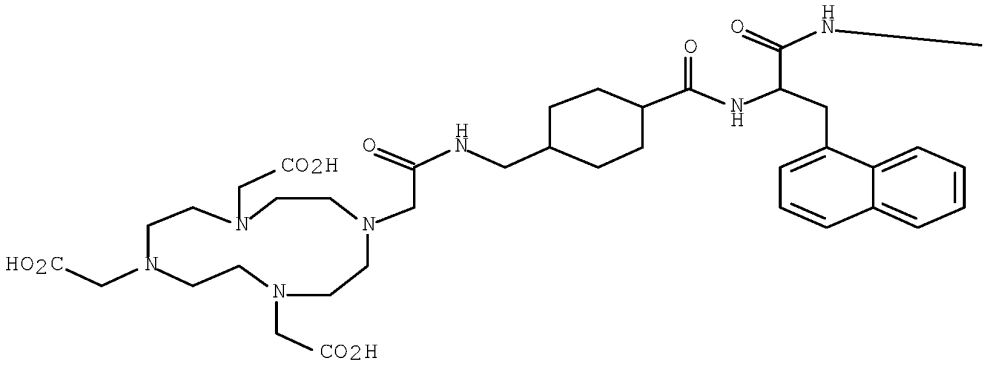


Fusion Pharmaceuticals, Inc.
Exhibit 1004.211

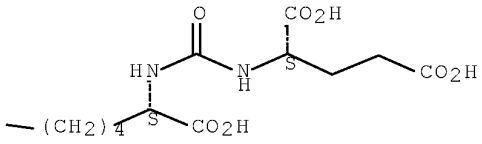
RN 1998102-66-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1223645 CAPLUS Full-text
DOCUMENT NUMBER: 165:527053
TITLE: Mechanochemical synthesis of mesoporous tin oxide: a new generation nanosorbent for 68Ge/68Ga generator technology
AUTHOR(S): Chakravarty, Rubel; Chakraborty, Sudipta; Shukla, Rakesh; Bahadur, Jitendra; Ram, Ramu; Mazumder, Subhasish; Dev Sarma, Haladhar; Tyagi, Avesh Kumar; Dash, Ashutosh
CORPORATE SOURCE: Isotope Production and Applications Division, Bhabha Atomic Research Centre, Mumbai, 400 085, India
SOURCE: Dalton Transactions (2016), 45(34), 13361-13372
CODEN: DTARAF; ISSN: 1477-9226
DIGITAL OBJECT ID: 10.1039/C6DT01921H
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal; (online computer file)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.212

LANGUAGE: English
OTHER SOURCE(S): CASREACT 165:527053

AB The present article reports the synthesis and characterization of mesoporous tin oxide (MTO) nanoparticles by a solid-state mechanochem. route. The synthesized material was used as an advanced sorbent material for 68Ge/68Ga radionuclide generator technol. Gallium-68 (t1/2 = 68 min) obtained from the 68Ge/68Ga generator is an important diagnostic radioisotope which holds tremendous potential in the non-invasive monitoring of various diseases, including cancer, using positron emission tomog. (PET). The crystallite size of the MTO nanoparticles was in the range of 6-12 nm with a large surface area of 265 ± 16 m2 g-1, while the mean pore radius was found to be 2.1 ± 0.6 nm. Determination of the zeta-potential of the MTO nanoparticles dispersed in solns. at different pH values aided in understanding the sorption and separation mechanisms, which were based on the surface charge developed on the nanosorbent. The sorption capacity observed under column-flow conditions was 85 ± 5 mg Ge per g of nanosorbent. A clin.-scale 68Ge/68Ga generator (740 MBq) was developed using this nanosorbent. Gallium-68 could be regularly eluted from this generator over a prolonged period of 1 yr with >70% elution yield and met all the requirements for clin. use. The suitability of 68Ga obtained from it was evaluated in preclin. settings by the preparation of a 68Ga-labeled peptide containing the arginine-glycine-aspartic acid (RGD) motif. To the best of our knowledge, this is the first report on the synthesis of MTO nanoparticles by a mechanochem. route which could be effectively utilized for the routine preparation of clin.-scale 68Ge/68Ga generators. The promising results obtained in this study would facilitate greater implementation of mechanochem. for the synthesis of nanosorbents for radionuclide generator technol. since this method is simple, economical and convenient.

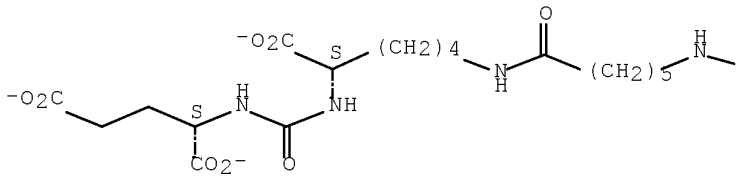
IT 1906894-20-9P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(mechanochem. synthesis of mesoporous tin oxide for a new generation nanosorbent for 68Ge/68Ga generator technol.)

RN 1906894-20-9 CAPLUS

CN Gallate(5-)-68Ga, [N-[[[(1S)-1-carboxy-5-[[6-[[3-[4-[[[2-[[[5-(2-carboxyethyl)-2-(hydroxy-κO)phenyl]methyl][(carboxy-κO)methyl]amino-κN]ethyl][(carboxy-κO)methyl]amino-κN]methyl]-3-(hydroxy-κO)phenyl]-1-oxopropyl]amino]-1-oxohexyl]amino]pentyl]amino]carbonyl]-L-glutamato(8-)]-, hydrogen (1:5) (CA INDEX NAME)

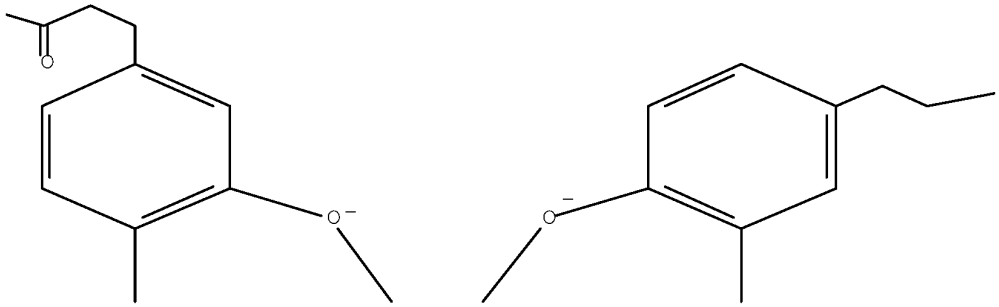
Absolute stereochemistry.

PAGE 1-A

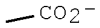


Fusion Pharmaceuticals, Inc.
Exhibit 1004.213

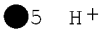
PAGE 1-B



PAGE 1-C

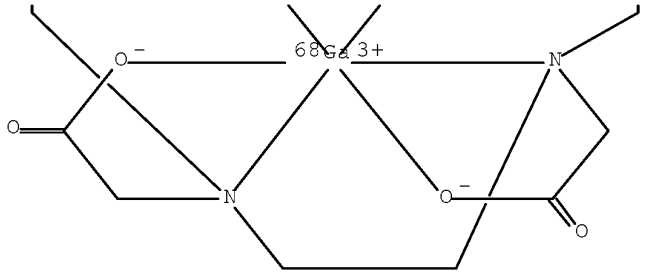


PAGE 2-A

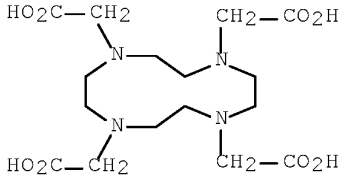


Fusion Pharmaceuticals, Inc.
Exhibit 1004.214

PAGE 2-B

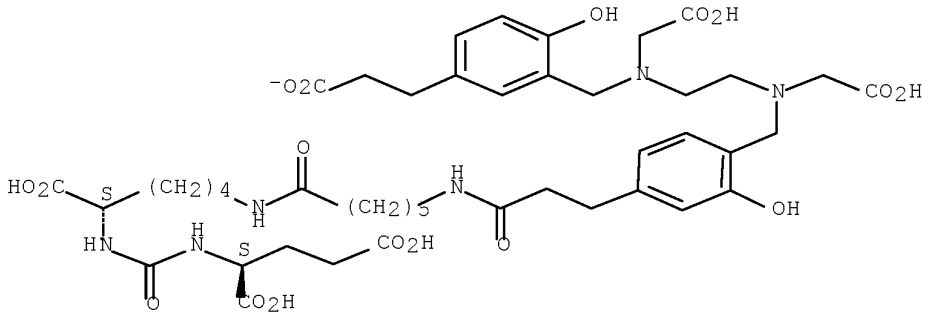


IT 60239-18-1, Dota 2027475-65-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(mechanochem. synthesis of mesoporous tin oxide for a new generation nanosorbent for 68Ge/68Ga generator technol.)
RN 60239-18-1 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (CA INDEX NAME)



RN 2027475-65-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

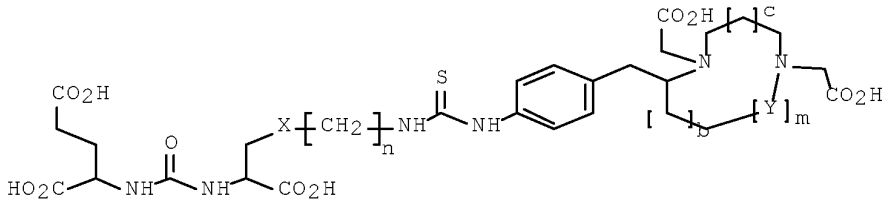
Fusion Pharmaceuticals, Inc.
Exhibit 1004.215

L133 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1174248 CAPLUS Full-text
DOCUMENT NUMBER: 165:209208
TITLE: Peptide thiourea derivative, radioisotope labeled compound containing it and pharmaceutical composition for treatment or diagnosis of prostate cancer comprising the same as active ingredient
INVENTOR(S): Jung, Jae Min; Moon, Seong Hyeon; Lee, Yun Sang
PATENT ASSIGNEE(S): SNU R&DB Foundation, S. Korea
SOURCE: Repub. Korea, 21pp.
CODEN: KRXXFC
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 1639599	B1	20160714	KR 2015-156536	20151109
WO 2017082620	A1	20170518	WO 2016-KR12849	20161109

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: KR 2015-156536 A 20151109
OTHER SOURCE(S): MARPAT 165:209208
GI



I

AB The invention relates to peptide thiourea derivative, shown as chemical formula (I)(X=0, -O-, -S-; n=integer of 1 to 5; y--N(CH2COOH)(CH2)aCH2CH2-, m=1 or 2; a,b,c= 0 or 1), its pharmaceutical acceptable salt, radioisotope labeled compound containing it and pharmaceutical composition for treatment or diagnosis of prostate cancer comprising the same as active ingredient. The derivative has good stability

Fusion Pharmaceuticals, Inc.
Exhibit 1004.216

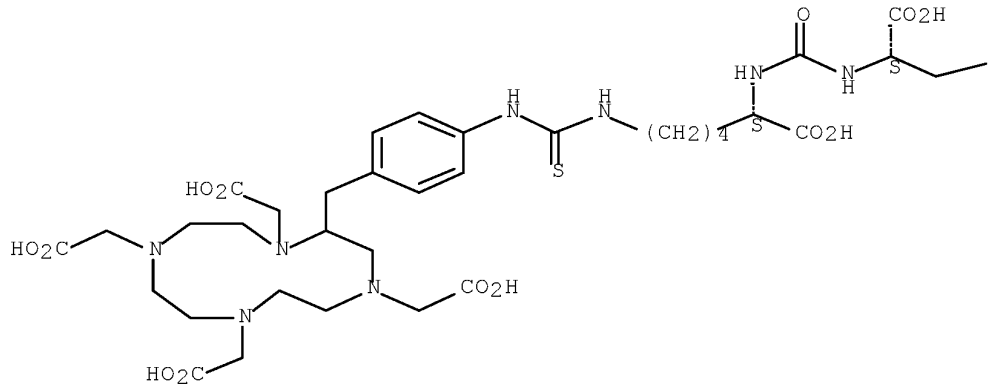
in human serum when it is administered, competitively binds to PSMA expressed in prostate cancer, and has good PSMA inhibition efficiency at low concentration It has high water solubility, and is discharged to kidney instead of liver, so clear prostate tumor image can be obtained.

IT 1970173-58-0DP, gallium complexes
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptide thiourea derivative, radioisotope labeled compound containing it and pharmaceutical composition for treatment or diagnosis of prostate cancer comprising the same as active ingredient)

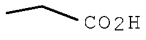
RN 1970173-58-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



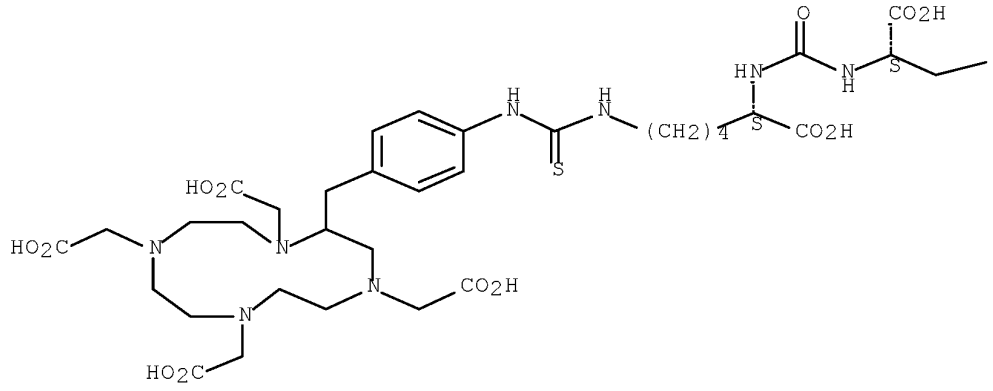
IT 1970173-58-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide thiourea derivative, radioisotope labeled compound containing it and pharmaceutical composition for treatment or diagnosis of prostate cancer comprising the same as active ingredient)

RN 1970173-58-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

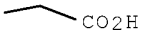
Absolute stereochemistry.

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Exhibit 1004.217

PAGE 1-A



PAGE 1-B



L133 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:925859 CAPLUS Full-text
DOCUMENT NUMBER: 165:96350
TITLE: Prospects of medium specific activity 177Lu in targeted therapy of prostate cancer using 177Lu-labeled PSMA inhibitor
AUTHOR(S): Chakraborty, Sudipta; Chakravarty, Rubel; Shetty, Priyalata; Vimalnath, K. V.; Sen, Ishita B.; Dash, Ashutosh
CORPORATE SOURCE: Isotope Production and Applications Division, Bhabha Atomic Research Centre, Mumbai, India
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (2016), 59(9), 364-371
CODEN: JLCRD4; ISSN: 0362-4803
DIGITAL OBJECT ID: 10.1002/jlcr.3414
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Targeted radionuclide therapy using 177Lu-labeled peptidomimetic inhibitor of prostate specific membrane antigen (PSMA) viz. PSMA-617 is emerging as one the most effective strategies for management of metastatic prostate cancer, which is one of the leading causes of cancer related death. The aim of the present study is to develop a robust and easily adaptable protocol for formulation of therapeutic dose of 177Lu-PSMA-617 at hospital radiopharmacy using moderate specific activity 177Lu available at an affordable cost. Extensive radiochem. studies were performed to optimize the required [PSMA-617] / [Lu] ratio and other parameters to formulate 7.4 GBq dose of 177Lu-PSMA-617. Based on these, 7.4 GBq therapeutic dose of 177Lu-PSMA-617 was formulated by incubating 160 μg of PSMA-617 with

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Exhibit 1004.218

indigenously produced 177LuCl3 (555 GBq/μg specific activity of 177Lu) at 90 °C for 30 min. The radiochem. purity of the formulation was 98.3 ± 0.6% (n = 7) which was retained to the extent of >95% after 7 d in normal saline at room temperature and >96% after 2 d in human serum at 37 °C. Preliminary clin. studies showed specific targeting of the agent in the lesion sites and similar physiol. distribution as in diagnostic 68Ga-PSMA-11 PET scans performed earlier. The developed optimized protocol for formulating therapeutic dose of 177Lu-PSMA-617 could be useful for large number of nuclear medicine therapy clinics across the world having access to moderate specific activity 177Lu at an affordable cost.

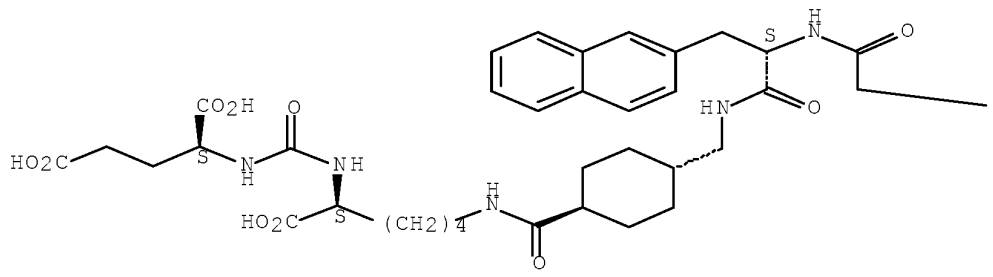
IT 1702967-55-2, PSMA-617
RL: RCT (Reactant); RACT (Reactant or reagent)
(targeted therapy of prostate cancer using 177Lu-labeled PSMA inhibitor)

RN 1702967-55-2 CAPLUS

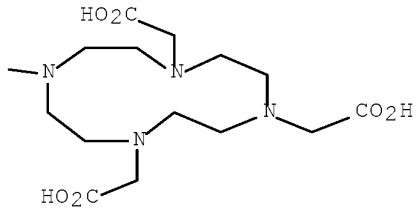
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-alanyl-trans-4-(aminomethyl)cyclohexanecarbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L133 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:599466 CAPLUS Full-text

Fusion Pharmaceuticals, Inc.
Exhibit 1004.219

DOCUMENT NUMBER: 165:2011
TITLE: Preclinical Comparative Study of 68Ga-Labeled DOTA, NOTA, and HBED-CC Chelated Radiotracers for Targeting PSMA
AUTHOR(S): Ray Banerjee, Sangeeta; Chen, Zhengping; Pullambhatla, Mrudula; Lisok, Ala; Chen, Jian; Mease, Ronnie C.; Pomper, Martin G.
CORPORATE SOURCE: Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA
SOURCE: Bioconjugate Chemistry (2016), 27(6), 1447-1455
CODEN: BCCHES; ISSN: 1043-1802
DIGITAL OBJECT ID: 10.1021/acs.bioconjchem.5b00679
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

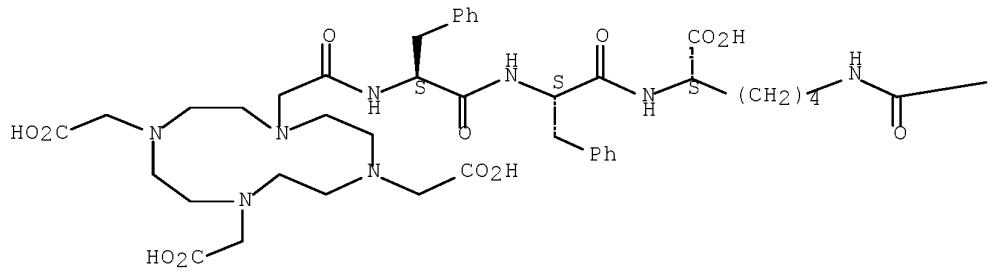
AB 68Ga-labeled, low-mol.-weight imaging agents that target the prostate-specific membrane antigen (PSMA) are increasingly used clin. to detect prostate and other cancers with positron emission tomog. (PET). The goal of this study was to compare the pharmacokinetics of three PSMA-targeted radiotracers: 68Ga-1, using DOTA-monoamide as the chelating agent; 68Ga-2, containing the macrocyclic chelating agent p-SCN-Bn-NOTA; and 68Ga-DKFZ-PSMA-11, currently in clin. trials, which uses the acyclic chelating agent, HBED-CC. The PSMA-targeting scaffold for all three agents utilized a similar Glu-urea-Lys-linker construct. Each radiotracer enabled visualization of PSMA+ PC3 PIP tumor, kidney, and urinary bladder as early as 15 min post-injection using small animal PET/computed tomog. (PET/CT). 68Ga-2 demonstrated the fastest rate of clearance from all tissues in this series and displayed higher uptake in PSMA+ PC3 PIP tumor compared to 68Ga-1 at 1 h post-injection. There was no significant difference in PSMA+ PC3 PIP tumor uptake for the three agents at 2 and 3 h post-injection. 68Ga-DKFZ-PSMA-11 demonstrated the highest uptake and retention in normal tissues, including kidney, blood, spleen, and salivary glands and PSMA-neg. PC3 flu tumors up to 3 h post-injection. In this preclin. evaluation 68Ga-2 had the most advantageous characteristics for PSMA-targeted PET imaging.

IT 1235548-82-9
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); BIOL (Biological study); USES (Uses)
(comparative study of 68Ga-labeled DOTA, NOTA and HBED-CC chelated radiotracers for PSMA targeting)
RN 1235548-82-9 CAPLUS
CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

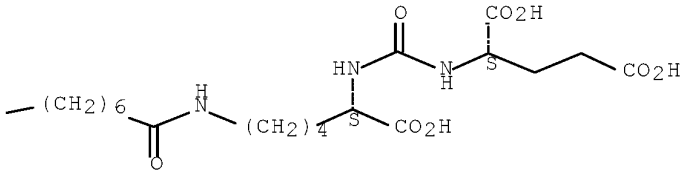
Absolute stereochemistry.

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Exhibit 1004.220

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:404750 CAPLUS Full-text
DOCUMENT NUMBER: 165:337321
TITLE: Clinical translation of 177Lu-labeled PSMA-617: Initial experience in prostate cancer patients
AUTHOR(S): Das, Tapas; Guleria, Mohini; Parab, Anil; Kale, Chanchala; Shah, Hina; Sarma, Haladhar D.; Lele, Vikram R.; Banerjee, Sharmila
CORPORATE SOURCE: Radiopharmaceuticals Chemistry Section, Radiochemistry and Isotope Group, Bhabha Atomic Research Centre, Mumbai, 400 085, India
SOURCE: Nuclear Medicine and Biology (2016), 43(5), 296-302
CODEN: NMBIEO; ISSN: 0969-8051
DIGITAL OBJECT ID: 10.1016/j.nucmedbio.2016.02.002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB PSMA-617 is reported to exhibit very high binding affinity towards PSMA receptors, over-expressed on prostate cancer cells and therefore, 177Lu-labeled PSMA-617 is expected to play a pivotal role in the clin. management of patients suffering from ca prostate. The objective of the present study is to formulate the patient dose of 177Lu-labeled PSMA-617, pre-clin. studies in animal model and clin. investigation in limited number of prostate cancer patients as well evaluating its potential for theranostic application.Patient dose of 7.4 GBq (200 mCi) of 177Lu-labeled PSMA-617 was prepared by incubating 100 μg of PSMA-617 with 177LuCl3

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Exhibit 1004.221

at 95 °C for 15 min. Radiochem. purity as well as in-vitro stability of the preparation was determined by PC and HPLC methods. The pharmacokinetic behavior and in-vivo distribution of the agent were studied by carrying out biodistribution studies in normal male Wistar rats. Preliminary clin. investigation was performed in 7 patients suffering from prostate cancer. The complex was prepared with > 98% radiochem. purity under the optimized reaction protocols and the preparation exhibited adequate in-vitro stability. Biodistribution studies revealed no significant uptake in any of the major organ/tissue along with major clearance through renal pathway. Clin. studies showed similar distribution in lesions and physiol. areas of uptake as seen in diagnostic 68Ga-PSMA-11 PET scans performed earlier. Preliminary clin. studies indicated the promising potential of the agent for theranostic applications. However, further investigations in large pool of patients are warranted to establish the theranostic potential of the agent.

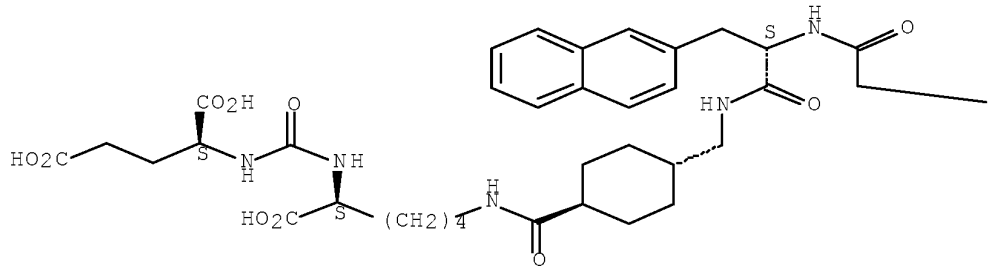
IT 1702967-55-2, PSMA617
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiolabeled with 177Lu; clin. translation of 177Lu-labeled PSMA-617)

RN 1702967-55-2 CAPLUS

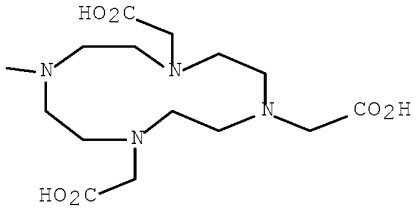
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-alanyl-trans-4-(aminomethyl)cyclohexanecarbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

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Exhibit 1004.222

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:390657 CAPLUS Full-text
DOCUMENT NUMBER: 164:386977
TITLE: Organ protection in prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy of prostate cancer
INVENTOR(S): Babich, John W.; Hillier, Shawn; Joyal, John
PATENT ASSIGNEE(S): Molecular Insight Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 22pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160067361	A1	20160310	US 2015-14846252	20150904
CA 2959726	A1	20160317	CA 2015-2959726	20150904
WO 2016040179	A1	20160317	WO 2015-US48651	20150904
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
AU 2015315465	A1	20170406	AU 2015-315465	20150904

PRIORITY APPLN. INFO.:

US 2014-62047546	P	20140908
WO 2015-US48651	W	20150904

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A method of reducing radiation exposure of a non-cancerous tissue of a patient diagnosed with a cancer includes administering to the patient an agent capable of competing for binding sites on a surface of the non-cancerous tissue, provided that the administration is carried out after a waiting period that follows administration of a compound including a radionuclide to the patient, the compound having affinity for both a cancerous tissue and the non-cancerous tissue, and, further provided that the binding sites have an affinity for both the agent and the compound Thus, overall, the study results indicated that with careful dose selection it is possible to meaningfully reduce kidney exposure by administering a cold MIP-1095 several hours post 125I-MIP-1095 dose while maintaining a reasonably high tumor exposure and keeping all other organs exposure relatively unchanged.

IT 1422159-00-9 1620171-96-1 1620171-97-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(organ protection in prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy of prostate cancer)

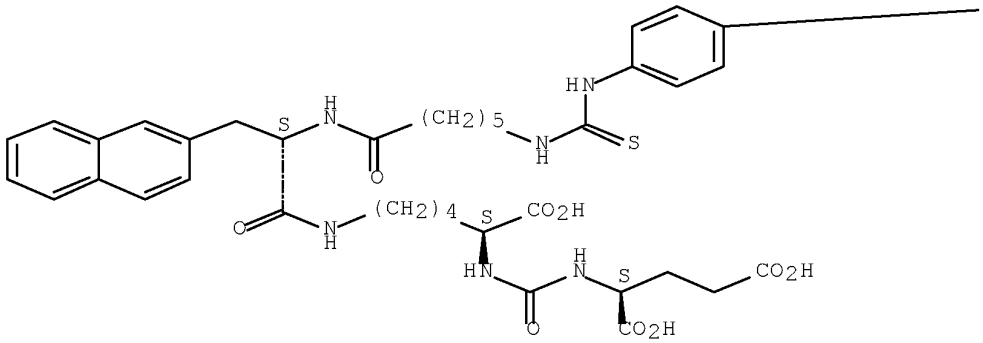
RN 1422159-00-9 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[1-oxo-6-[[[[4-[[1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-

Fusion Pharmaceuticals, Inc.
Exhibit 1004.223

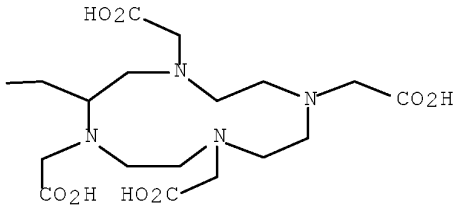
tetraazacyclododec-2-yl]methyl]phenyl]amino]thioxomethyl]amino]hexyl]-L-alanyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

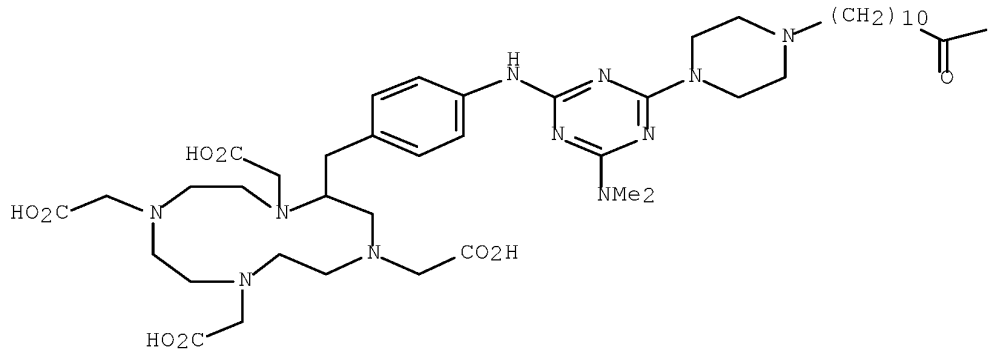


RN 1620171-96-1 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, 2-[[4-[[4-[4-[11-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-11-oxoundecyl]-1-piperazinyl]-6-(dimethylamino)-1,3,5-triazin-2-yl]amino]phenyl]methyl]- (CA INDEX NAME)

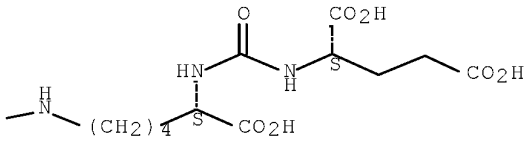
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.224

PAGE 1-A



PAGE 1-B

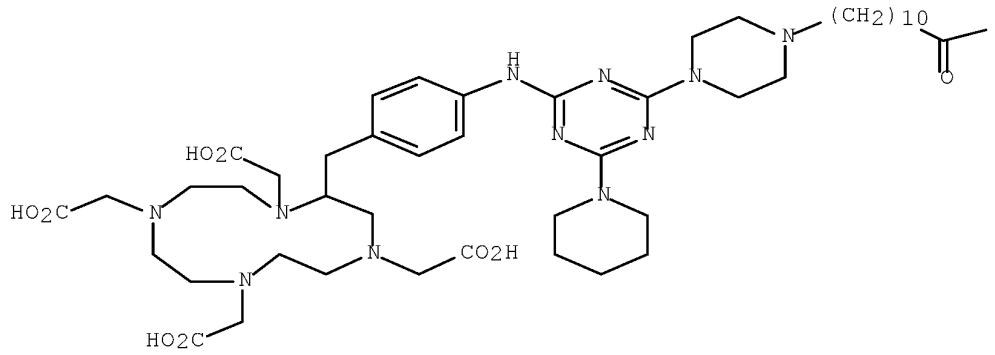


RN 1620171-97-2 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, 2-[[4-[[4-[4-[11-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-11-oxoundecyl]-1-piperazinyl]-6-(1-piperidinyl)-1,3,5-triazin-2-yl]amino]phenyl]methyl]- (CA INDEX NAME)

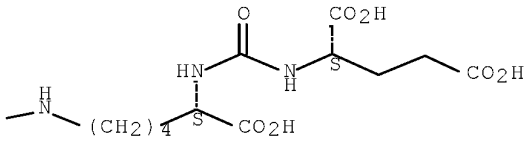
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.225

PAGE 1-A



PAGE 1-B

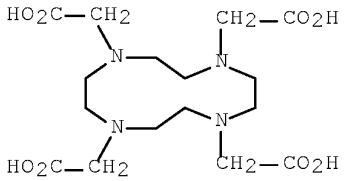


L133 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:109980 CAPLUS Full-text
DOCUMENT NUMBER: 164:369424
TITLE: Development of a complementary PET/MR dual-modal imaging probe for targeting prostate-specific membrane antigen (PSMA)
AUTHOR(S): Moon, Sung-Hyun; Yang, Bo Yeun; Kim, Young Ju; Hong, Mee Kyung; Lee, Yun-Sang; Lee, Dong Soo; Chung, June-Key; Jeong, Jae Min
CORPORATE SOURCE: Department of Nuclear Medicine and Institute of Radiation Medicine, Seoul National University College of Medicine, Seoul, S. Korea
SOURCE: Nanomedicine (New York, NY, United States) (2016), 12(4), 871-879
CODEN: NANOBF; ISSN: 1549-9634
DIGITAL OBJECT ID: 10.1016/j.nano.2015.12.368
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB We tried to develop a dual-modal PET/MR imaging probe using a straightforward one-pot method by encapsulation with specific amphiphiles. In this study, iron oxide (IO) nanoparticles were encapsulated with three amphiphiles containing PEG, DOTA and the prostate-specific membrane antigen (PSMA)-targeting ligand in aqueous medium. The diameter of the prepared nanoparticle DOTA-IO-GUL was 11.01 ± 1.54

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Exhibit 1004.226

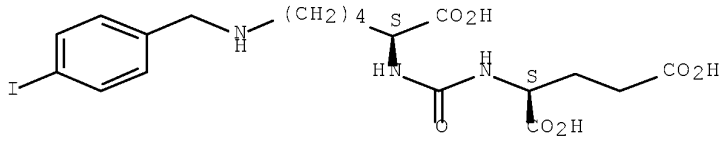
nm. DOTA-IO-GUL was labeled with 68Ga in high efficiency. The DOTA-IO-GUL showed a dose-dependent binding to LNCaP (PSMA pos.) cells via a competitive binding study against 125I-labeled MIP-1072 (PSMA-targeting agent). Addnl., PET and MR imaging results showed PSMA selective uptake by only 22Rv1 (PSMA pos.) but not PC-3 (PSMA neg.) in dual-tumor xenograft mouse model study. MR imaging showed high resolution, and PET imaging enabled quantification and confirmation of the specificity. In conclusion, we have successfully developed the specific PSMA-targeting IO nanoparticle, DOTA-IO-GUL, as a dual-modality probe for complementary PET/MR imaging.

IT 60239-18-1, DOTA
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(development of a complementary PET/MR dual-modal imaging probe for targeting prostate-specific membrane antigen (PSMA))
RN 60239-18-1 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (CA INDEX NAME)



IT 949575-20-6, MIP-1072
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(125I-labeled; development of a complementary PET/MR dual-modal imaging probe for targeting prostate-specific membrane antigen (PSMA))
RN 949575-20-6 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-1-carboxy-5-[[(4-iodophenyl)methyl]amino]pentyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1883478 CAPLUS Full-text
DOCUMENT NUMBER: 165:112235
TITLE: Radio-synthesis and mass spectrometry analysis of 68Ga-DKFZ-PSMA-617 for non-invasive prostate cancer

Fusion Pharmaceuticals, Inc.
Exhibit 1004.227

PET imaging

AUTHOR(S): Zhu, Hua; Xie, Qing; Li, Nan; Tian, Huifang; Liu, Fei; Yang, Zhi

CORPORATE SOURCE: Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Nuclear Medicine, Beijing Cancer Hospital and Institute, Peking University Cancer Hospital and Institute, Beijing, 100142, Peop. Rep. China

SOURCE: Journal of Radioanalytical and Nuclear Chemistry (2016), 309(2), 575-581
CODEN: JRNCDM; ISSN: 0236-5731

DIGITAL OBJECT ID: 10.1007/s10967-015-4623-2

PUBLISHER: Springer

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

OTHER SOURCE(S): CASREACT 165:112235

AB Abstract: The focus of this paper in on quality control and decay property anal. of 68Ga-DKFZ-PSMA-617 for positron emission tomog. (PET) imaging of prostate cancer. 68Ga-DKFZ-PSMA-617 was synthesized in high radiochem. yield and specific activity (77 GBq/μmol) under optimized conditions. The decayed tracer was characterized by MADLI-TOF to support its decay and coordination characterization. Contrast PET imaging studies were performed using normal nude mice after i.v. injection of 18.5 MBq of 68Ga-DKFZ-PSMA-617 and 18F-FDG resp. These results warrant the further clin. application of 68Ga-DKFZ-PSMA-617 in prostate cancer PET imaging. Graphical Abstract: 68Ga-DKFZ-PSMA-617 was synthesized in high radiochem. yield and specific activity (77 GBq/μmol) under optimized conditions. The corresponding decay tracer was firstly characterized by MADLI-TOF. Pre-clin. PET imaging studies were performed using normal nude mice after i.v. injection of 18.5 MBq of 68Ga-DKFZ-PSMA-617 which showed the typical enterohepatic metabolism All these results warrant the further clin. application of 68Ga- DKFZ-PSMA-617.[Figure not available: see full text.].

IT 1702967-37-0, DKFZ-PSMa-617
RL: RCT (Reactant); RACT (Reactant or reagent)
(DKFZ-PSMa-617; radiosynthesis and mass spectrometry of 68Ga-DKFZ-PSMA-617 for prostate cancer PET imaging)

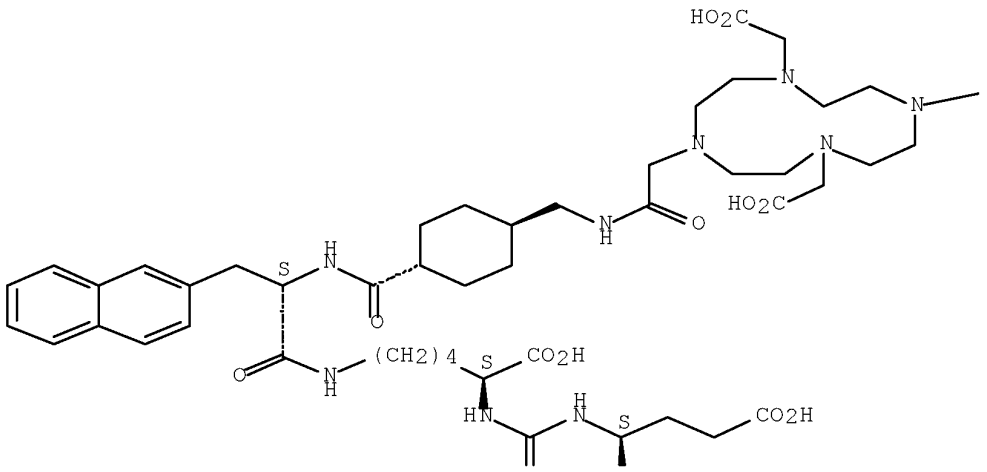
RN 1702967-37-0 CAPLUS

CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[[trans-4-[[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]methyl]cyclohexyl]carbonyl]-L-alanyl]- (CA INDEX NAME)

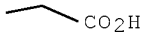
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.228

PAGE 1-A



PAGE 1-B



PAGE 2-A



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:1803879 CAPLUS Full-text
DOCUMENT NUMBER: 163:702635
TITLE: Preparation of metal or radiometal-labeled urea- and carbamate-based PSMA inhibitors for PSMA-targeted imaging and radiotherapy
INVENTOR(S): Ray, Sangeeta; Pomper, Martin G.; Meade, Thomas J.; Mease, Ronnie C.; Chen, Ying; Yang, Xing
PATENT ASSIGNEE(S): The Johns Hopkins University, USA; Northwestern University
SOURCE: PCT Int. Appl., 144pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

Fusion Pharmaceuticals, Inc.
Exhibit 1004.229

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2015171792	A1	20151112	WO 2015-US29504		20150506
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2950892	A1	20151112	CA 2015-2950892		20150506
AU 2015256002	A1	20161222	AU 2015-256002		20150506
EP 3140282	A1	20170315	EP 2015-790006		20150506
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CN 106660943	A	20170510	CN 2015-80036857		20150506
US 20170081298	A1	20170323	US 2016-15309009		20161104
PRIORITY APPLN. INFO.:			US 2014-61989428	P	20140506
			US 2015-62117603	P	20150218
			WO 2015-US29504	W	20150506

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 163:702635; MARPAT 163:702635

AB Three new low-mol. weight gadolinium (Gd)-based MR contrast agents for PSMA-specific T1-weighted MR imaging containing one to three GdIII chelates per mol. were prepared The (Gd)-based MR contrast agents exhibited high binding affinity for PSMA and specific Ti contrast enhancement at PSMA+ cells. The PSMA-targeted Gd-based MR contrast agents can be used for PSMA-targeted imaging in vivo. 86Y-labeled PSMA-binding ureas were prepared for dosimetry ests. suitable for use with other radiotherapeutics. 111In-, 177Lu- and 203Pb-labeled ureas and carbamates were prepared for PSMA-based targeted radionuclide therapy.

IT 1235548-82-9P 1823122-56-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of metal or radiometal-labeled urea- and carbamate-based PSMA inhibitors for PSMA-targeted imaging and radiotherapy)

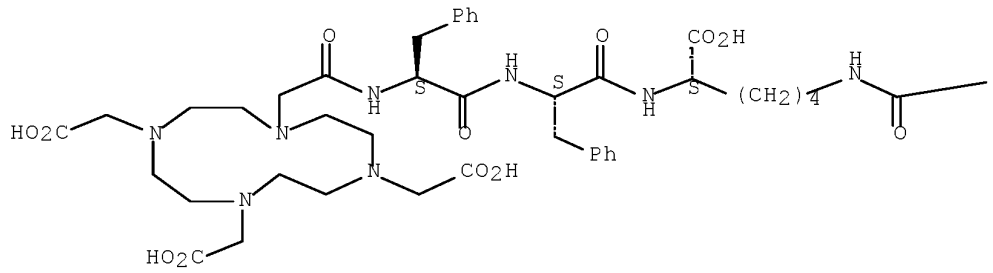
RN 1235548-82-9 CAPLUS

CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

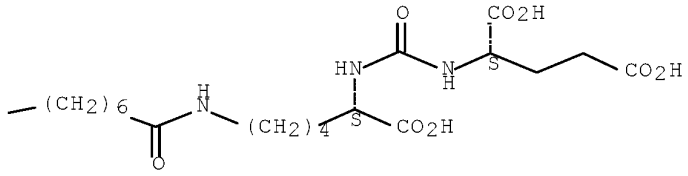
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.230

PAGE 1-A



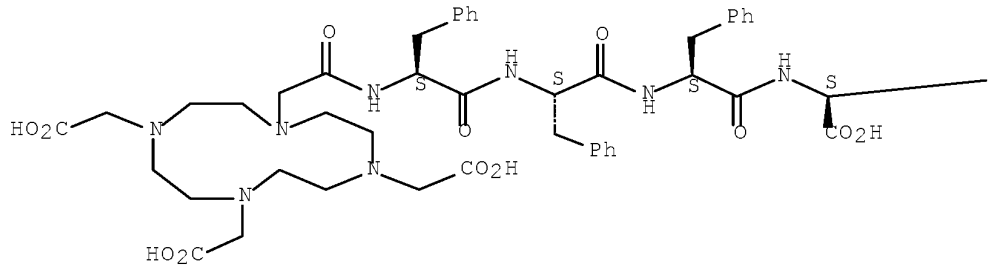
PAGE 1-B



RN 1823122-56-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

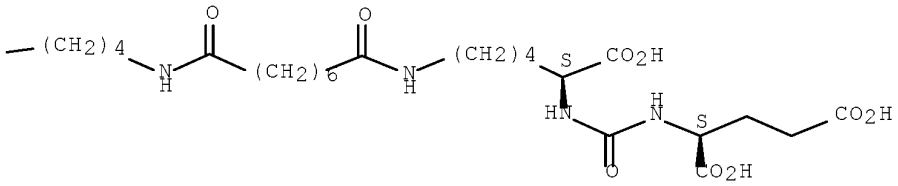
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.231

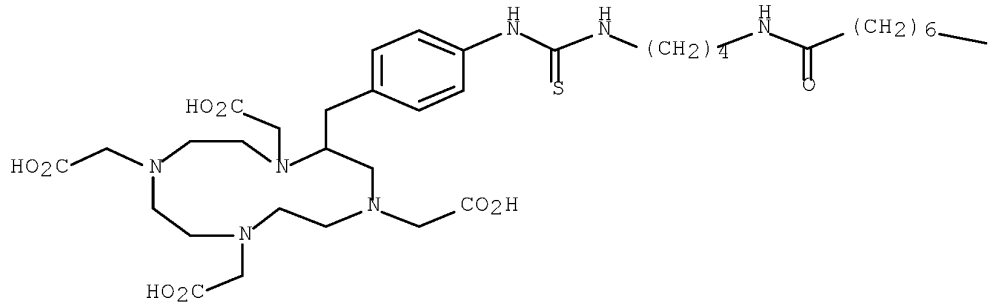
PAGE 1-B



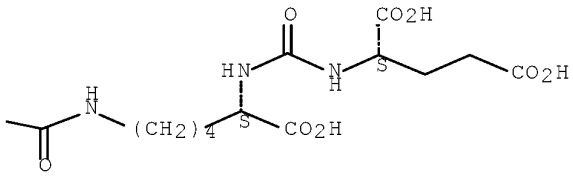
IT 1823122-66-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of metal or radiometal-labeled urea- and carbamate-based PSMA inhibitors for PSMA-targeted imaging and radiotherapy)
RN 1823122-66-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Fusion Pharmaceuticals, Inc.
Exhibit 1004.232

L133 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:1157312 CAPLUS Full-text
DOCUMENT NUMBER: 161:241161
TITLE: Triazine based radiopharmaceuticals and radioimaging agents
INVENTOR(S): Babich, John W.; Zimmerman, Craig; Joyal, John; Lu, Genliang
PATENT ASSIGNEE(S): Molecular Insight Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 119pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014110372	A1	20140717	WO 2014-US11047	20140110
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
CA 2897437	A1	20140717	CA 2014-2897437	20140110
US 20140255306	A1	20140911	US 2014-14152864	20140110
US 9447121	B2	20160920		
AU 2014205304	A1	20150813	AU 2014-205304	20140110
KR 2015115797	A	20151014	KR 2015-7021666	20140110
CN 105025933	A	20151104	CN 2014-80011222	20140110
EP 2943227	A1	20151118	EP 2014-738117	20140110
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BA, ME				
JP 2016511231	T	20160414	JP 2015-552805	20140110
MX 2015008993	A	20160404	MX 2015-8993	20150710
US 20160346410	A1	20161201	US 2016-15233096	20160810

PRIORITY APPLN. INFO.:

US 2013-61752350	P	20130114
US 2013-61785788	P	20130314
US 2014-14152864	A3	20140110
WO 2014-US11047	W	20140110

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 161:241161; MARPAT 161:241161
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Fusion Pharmaceuticals, Inc.
Exhibit 1004.233

AB Compds. according to Formula (I) are potent inhibitors of PSMA. The proposed pharmaceutical compns may include a complex of a radionuclide with either formula compds. Methods include using the radionuclide complex of either formula compds. for treating or diagnosis of a disease or a condition associated with PSMA activity.

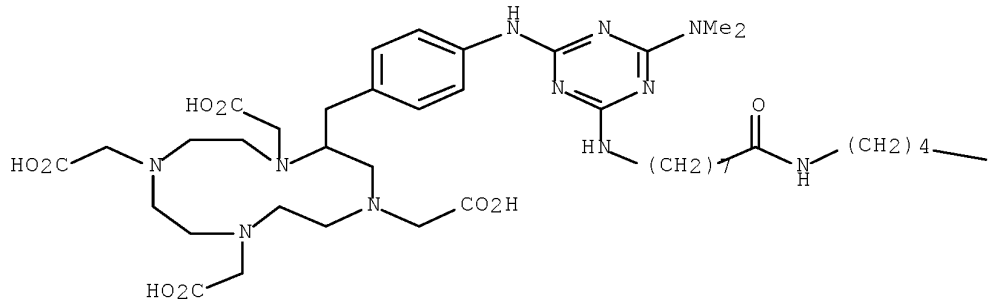
IT 1620171-90-5P 1620171-91-6P 1620171-92-7P
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1620171-96-1P 1620171-97-2P 1620171-98-3P
1620171-99-4P 1620172-00-0P 1620172-01-1P
1620172-02-2P 1620172-03-3P 1620172-04-4P
1620172-05-5P
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(triazine-based radiopharmaceuticals and radioimaging agents)

RN 1620171-90-5 CAPLUS

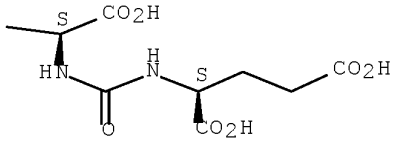
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, 2-[[4-[[4-[[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-8-oxooctyl]amino]-6-(dimethylamino)-1,3,5-triazin-2-yl]amino]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RN 1620171-91-6 CAPLUS

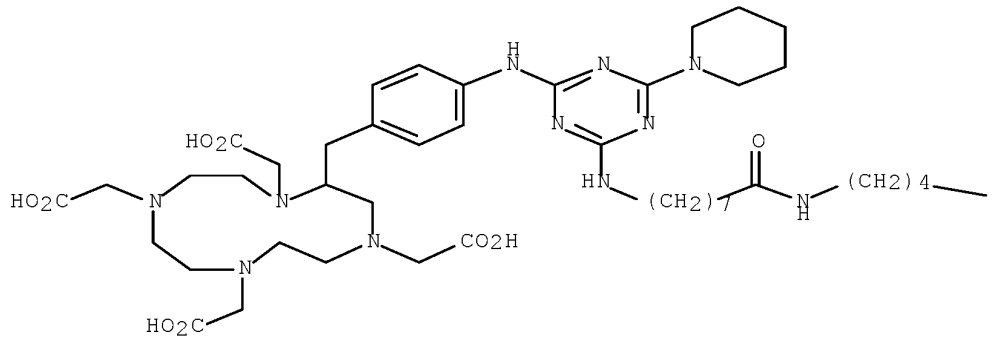
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Exhibit 1004.234

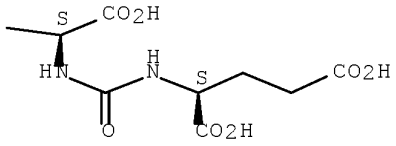
dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-8-oxooctyl]amino]-6-(1-piperidinyl)-1,3,5-triazin-2-yl]amino]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

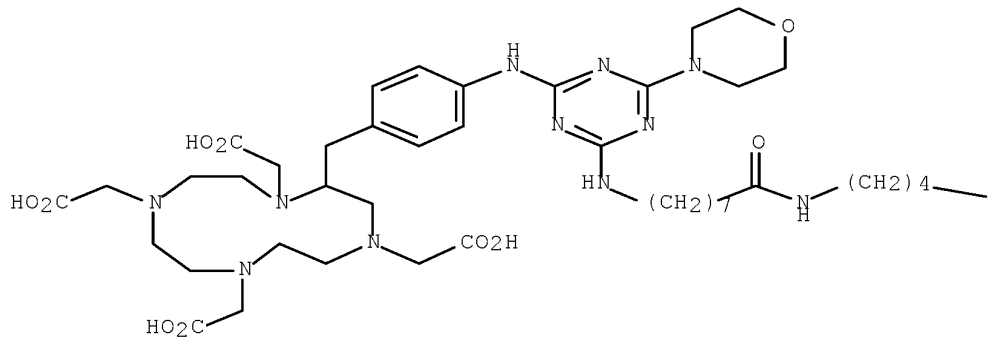


RN 1620171-92-7 CAPLUS
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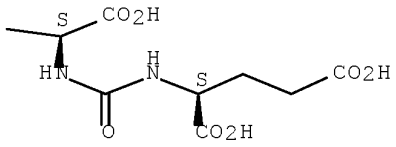
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.235

PAGE 1-A



PAGE 1-B

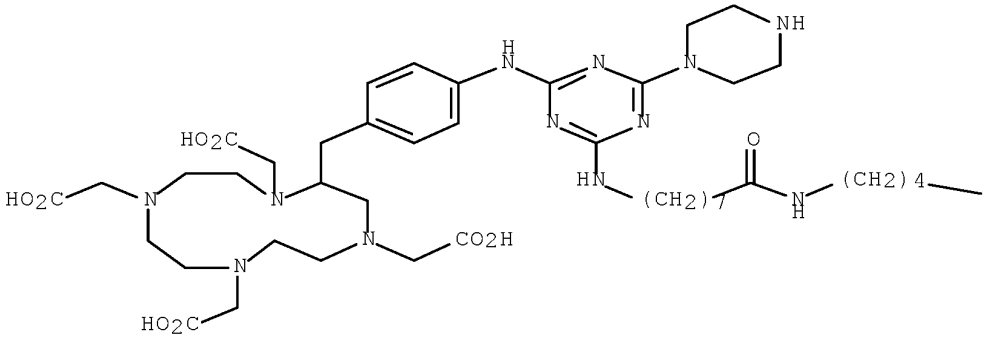


RN 1620171-93-8 CAPLUS
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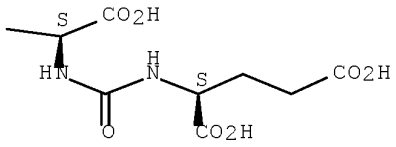
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.236

PAGE 1-A



PAGE 1-B

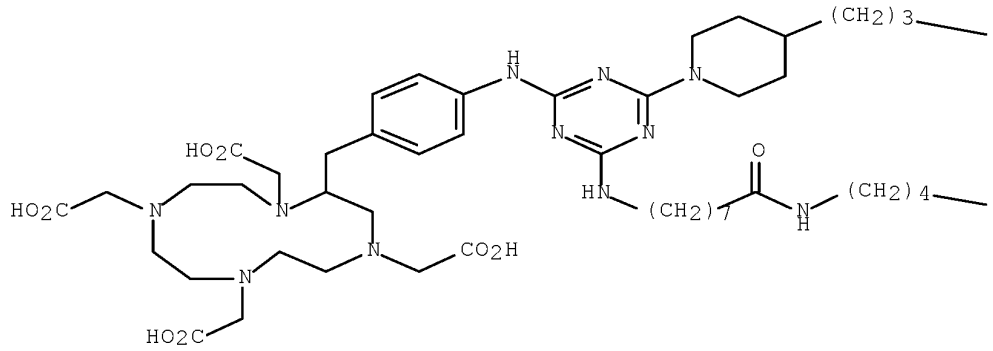


RN 1620171-94-9 CAPLUS
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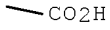
Absolute stereochemistry.

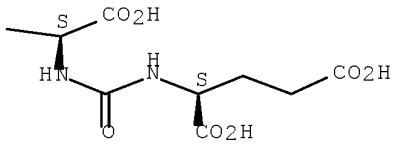
Fusion Pharmaceuticals, Inc.
Exhibit 1004.237

PAGE 1-A



PAGE 1-B

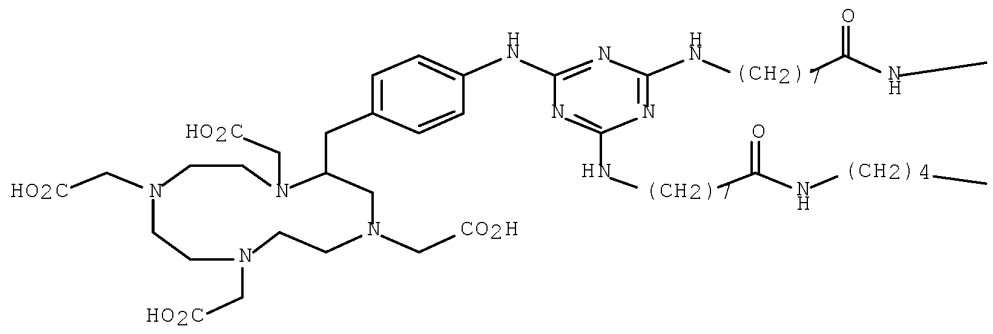




RN 1620171-95-0 CAPLUS
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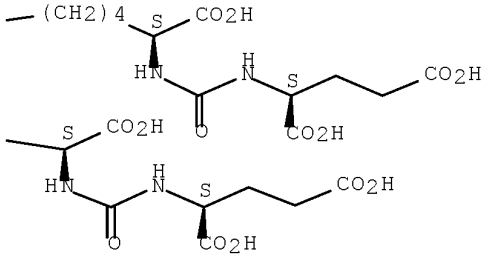
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.238

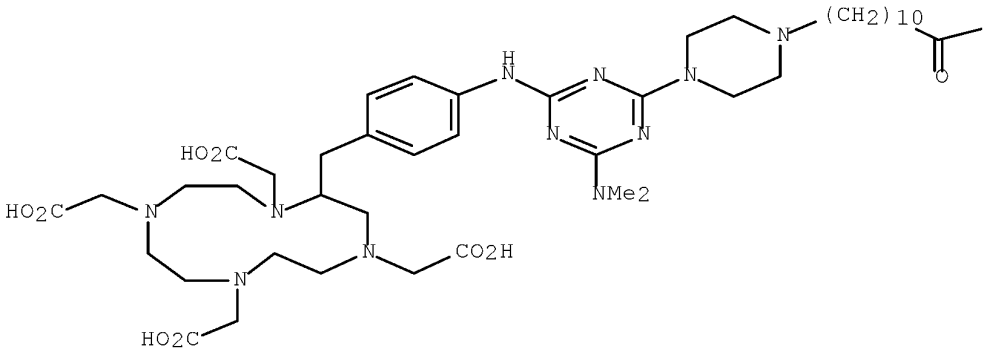
PAGE 1-B



RN 1620171-96-1 CAPLUS
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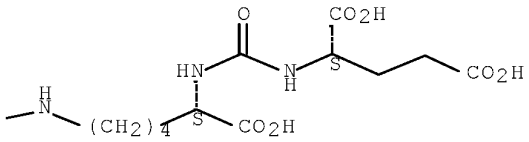
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.239

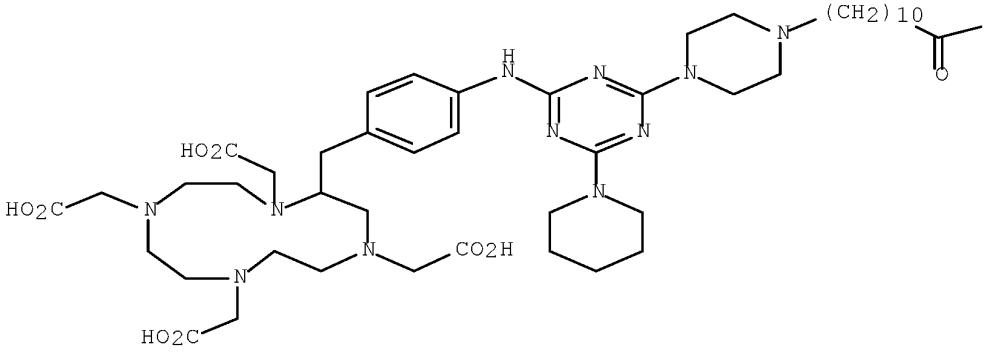
PAGE 1-B



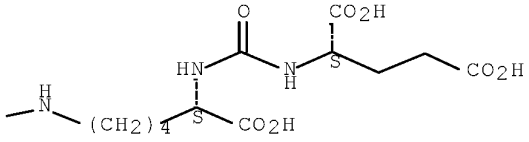
RN 1620171-97-2 CAPLUS
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

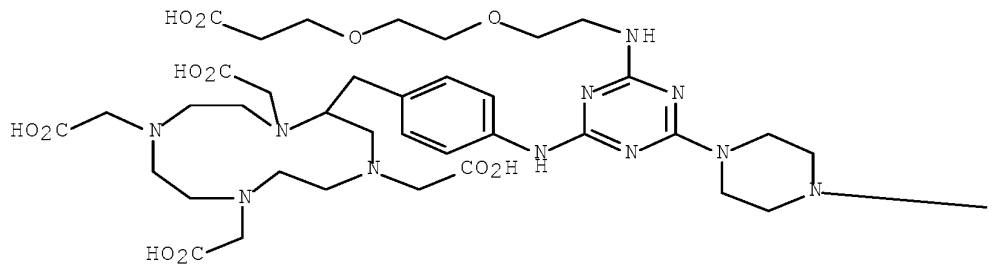


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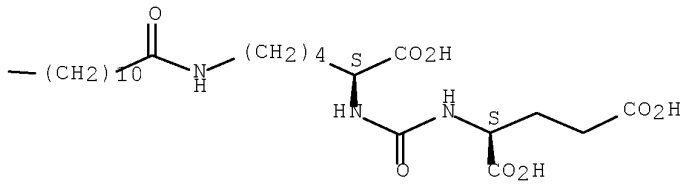
Fusion Pharmaceuticals, Inc.
Exhibit 1004.240

Absolute stereochemistry.

PAGE 1-A



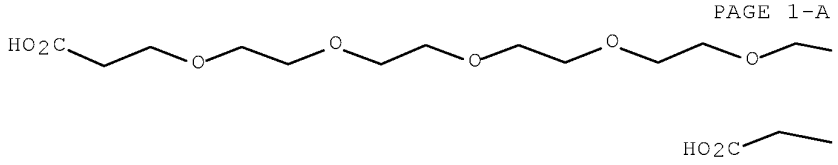
PAGE 1-B



RN 1620171-99-4 CAPLUS
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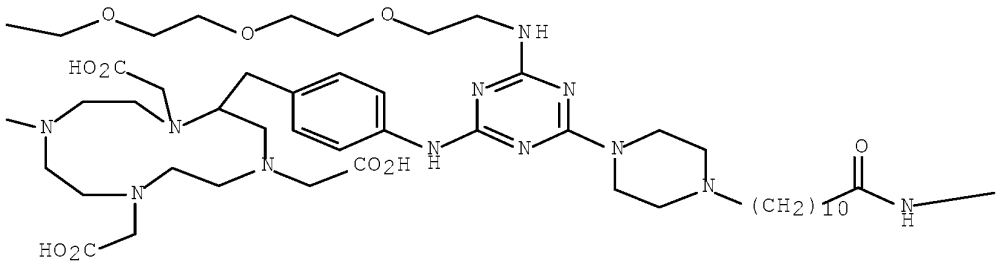
Absolute stereochemistry.

PAGE 1-A

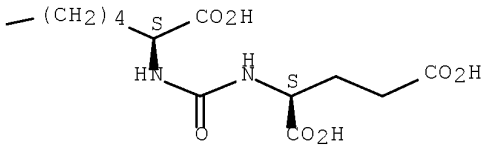


Fusion Pharmaceuticals, Inc.
Exhibit 1004.241

PAGE 1-B



PAGE 1-C

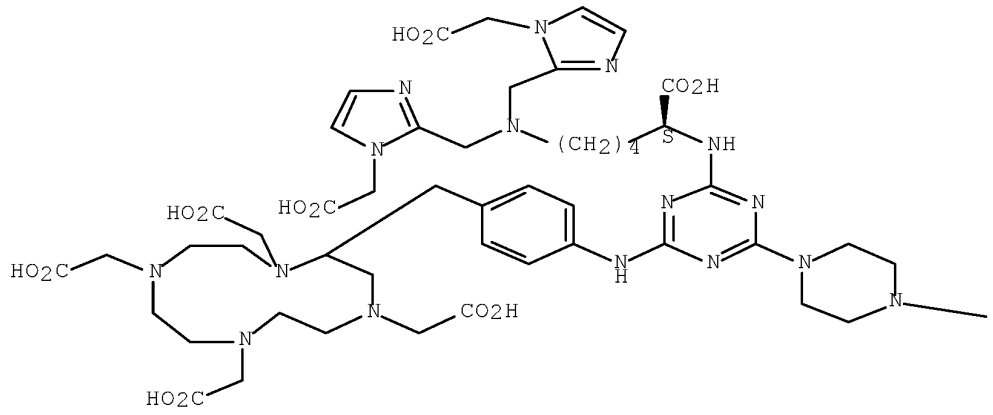


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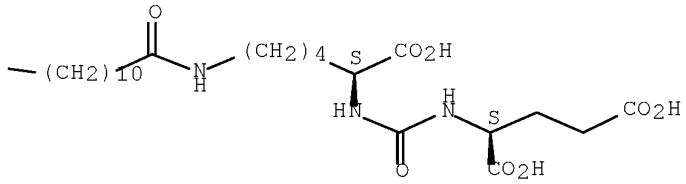
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.242

PAGE 1-A



PAGE 1-B

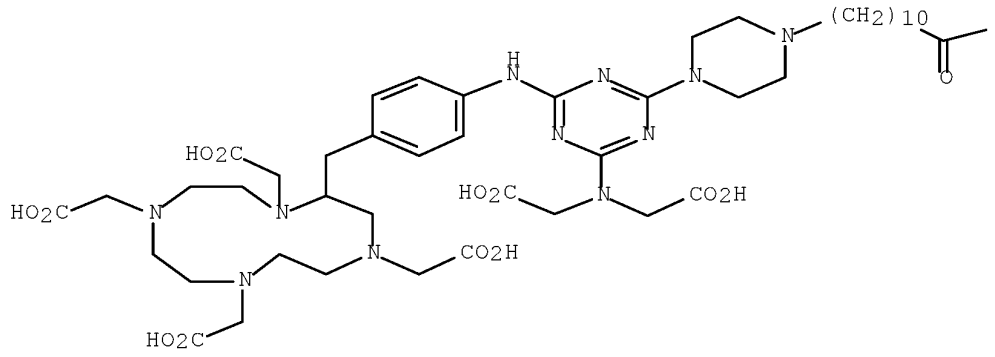


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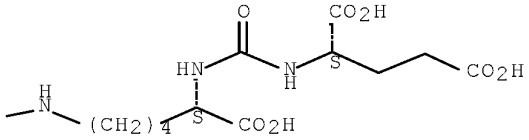
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.243

PAGE 1-A



PAGE 1-B

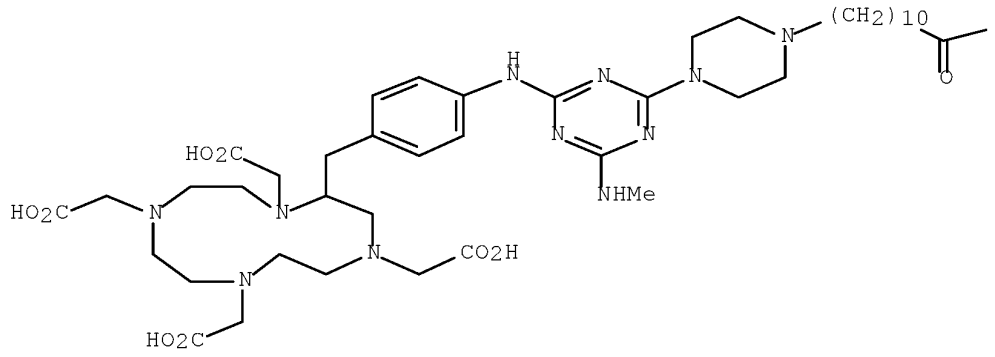


RN 1620172-02-2 CAPLUS
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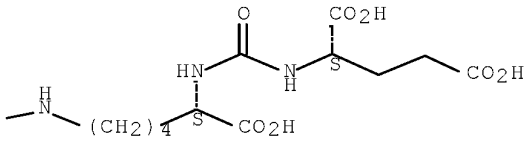
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.244

PAGE 1-A



PAGE 1-B

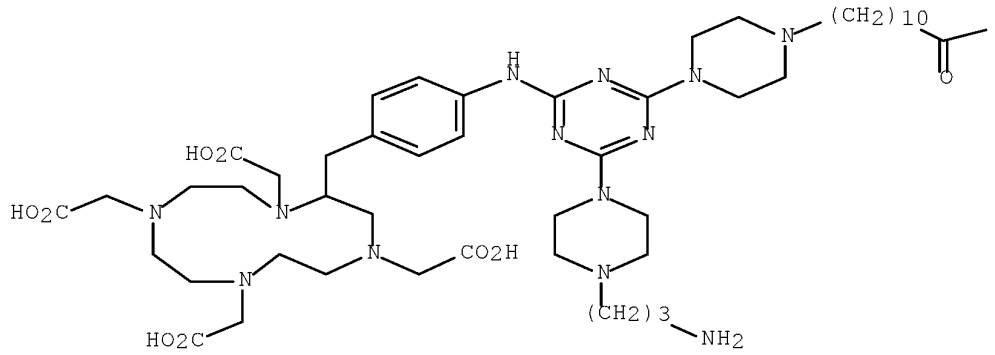


RN 1620172-03-3 CAPLUS
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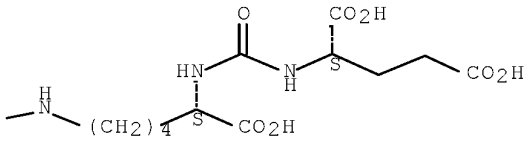
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.245

PAGE 1-A



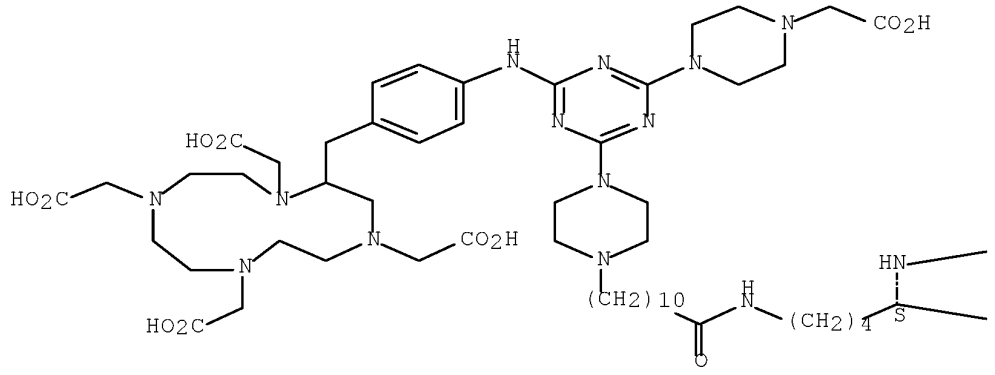
PAGE 1-B



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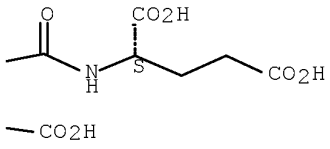
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.246

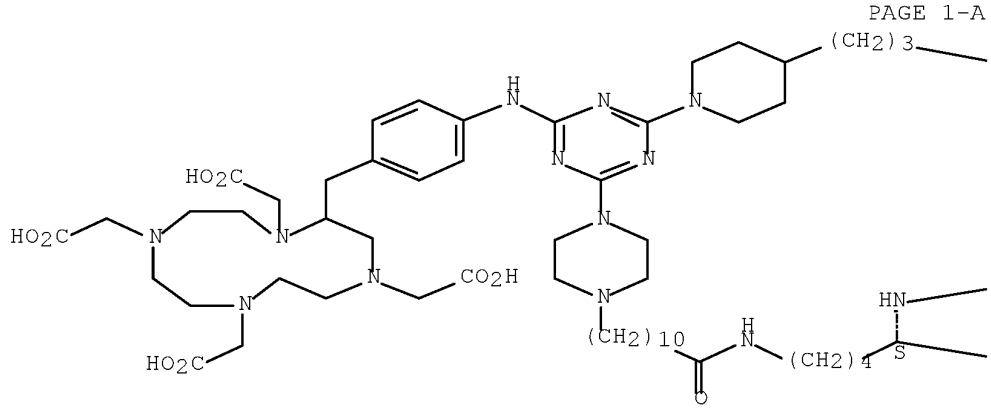
PAGE 1-B



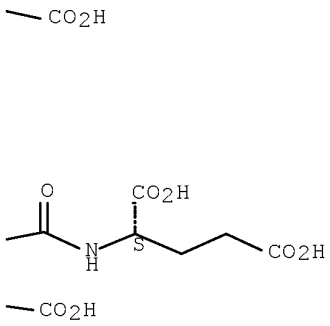
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Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.247



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:256171 CAPLUS Full-text
DOCUMENT NUMBER: 160:422629
TITLE: 64Cu-Labeled Inhibitors of Prostate-Specific Membrane Antigen for PET Imaging of Prostate Cancer
AUTHOR(S): Banerjee, Sangeeta Ray; Pullambhatla, Mrudula; Foss, Catherine A.; Nimmagadda, Sridhar; Ferdani, Riccardo; Anderson, Carolyn J.; Mease, Ronnie C.; Pomper, Martin G.
CORPORATE SOURCE: Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA
SOURCE: Journal of Medicinal Chemistry (2014), 57(6), 2657-2669
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/jm401921j
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 160:422629

AB Prostate-specific membrane antigen (PSMA) is a well-recognized target for identification and therapy of a variety of cancers. Here we report five 64Cu-labeled inhibitors of PSMA, [64Cu]3-7, which are based on the lysine-glutamate urea scaffold and utilize a variety of macrocyclic chelators, namely NOTA(3), PCTA(4), Oxo-DO3A(5), CB-TE2A(6), and DOTA(7), in an effort to determine which provides the most suitable pharmacokinetics for in vivo PET imaging. [64Cu]3-7 were prepared in high radiochem. yield (60-90%) and purity (>95%). Positron emission tomog. (PET) imaging studies of [64Cu]3-7 revealed specific accumulation in PSMA-expressing xenografts (PSMA+ PC3 PIP) relative to isogenic control tumor (PSMA- PC3 flu) and background tissue. The favorable kinetics and high image contrast provided by CB-TE2A chelated [64Cu]6 suggest it as the most promising among the candidates tested. That could be due to the higher stability of [64Cu]CB-TE2A as compared with [64Cu]NOTA, [64Cu]PCTA, [64Cu]Oxo-DO3A, and [64Cu]DOTA chelates in vivo.

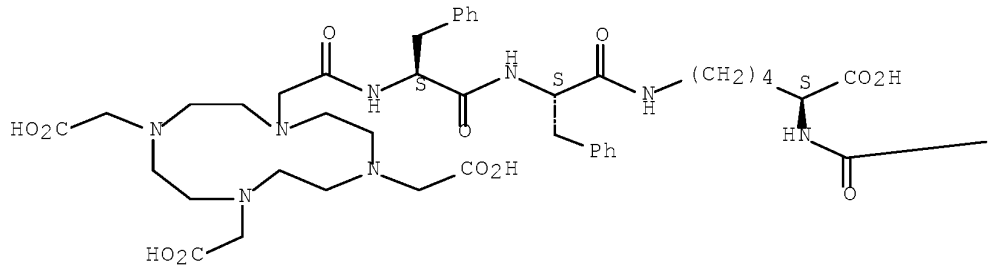
IT 1575386-77-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.248

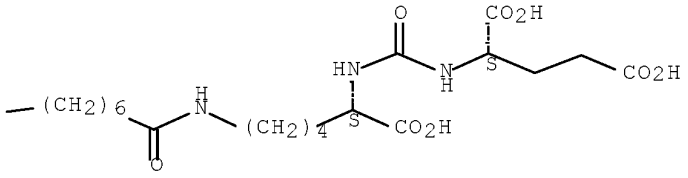
(64Cu-labeled PSMA inhibitors for PET imaging of prostate cancer)
RN 1575386-77-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2014:64039 CAPLUS Full-text
DOCUMENT NUMBER: 160:243341
TITLE: Heterobivalent Agents Targeting PSMA and Integrin-αvβ3
AUTHOR(S): Shallal, Hassan M.; Minn, Il; Banerjee, Sangeeta R.; Lisok, Ala; Mease, Ronnie C.; Pomper, Martin G.
CORPORATE SOURCE: Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA
SOURCE: Bioconjugate Chemistry (2014), 25(2), 393-405
CODEN: BCCHES; ISSN: 1043-1802
DIGITAL OBJECT ID: 10.1021/bc4005377
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 160:243341

Fusion Pharmaceuticals, Inc.
Exhibit 1004.249

AB Differential expression of surface proteins on normal vs malignant cells provides the rationale for the development of receptor-, antigen-, and transporter-based, cancer-selective imaging and therapeutic agents. However, tumors are heterogeneous, and do not always express what can be considered reliable, tumor-selective markers. That suggests development of more flexible targeting platforms that incorporate multiple moieties enabling concurrent targeting to a variety of putative markers. We report the synthesis, biochem., in vitro, and preliminary in vivo evaluation of a new heterobivalent (HtBv) imaging agent targeting both the prostate-specific membrane antigen (PSMA) and integrin-αvβ3 surface markers, each of which can be overexpressed in certain tumor epithelium and/or neovasculature. The HtBv agent was functionalized with either 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) or the com. available IRDye800CW. DOTA-conjugated HtBv probe 9 bound to PSMA or αvβ3 with affinities similar to those of monovalent (Mnv) compds. designed to bind to their targets independently. In situ energy minimization expts. support a model describing the conformations adapted by 9 that enable it to bind both targets. IRDye800-conjugated HtBv probe 10 demonstrated target-specific binding to either PSMA or integrin-αvβ3 overexpressing xenografts. HtBv agents 9 and 10 may enable dual-targeted imaging of malignant cells and tissues in an effort to address heterogeneity that confounds many cancer-targeted imaging agents.

IT 1537185-99-1P

RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)

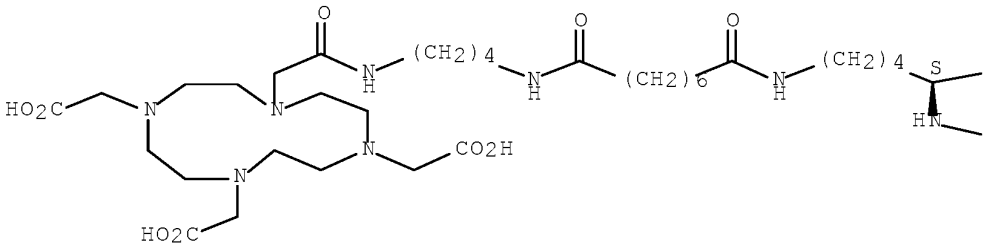
(heterobivalent imaging agents preparation and targeting PSMA and integrin-αvβ3)

RN 1537185-99-1 CAPLUS

CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[(22S,26S)-22,26,28-tricarboxy-2,9,16,24-tetraoxo-3,8,17,23,25-pentaazaoctacos-1-yl]- (CA INDEX NAME)

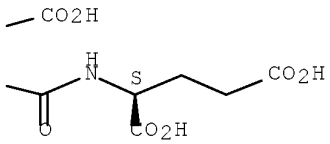
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.250

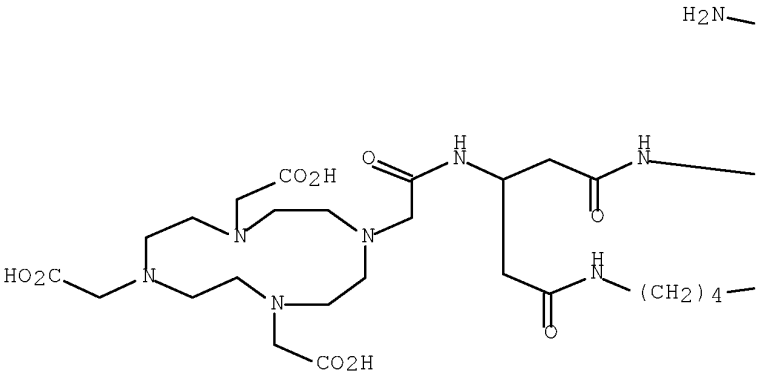
PAGE 1-B



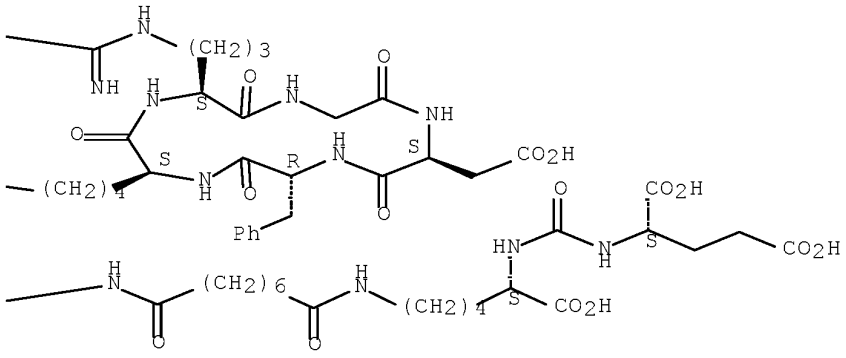
IT 1537186-03-0P
RL: DGN (Diagnostic use); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heterobivalent imaging agents preparation and targeting PSMA and integrin-αvβ3)
RN 1537186-03-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.251

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:882367 CAPLUS Full-text
DOCUMENT NUMBER: 159:76086
TITLE: Preparation of homomultivalent and heteromultivalent ligand-containing lysine-glutamate urea moieties as prostate specific membrane antigen (PMSA) inhibitors for therapeutic and imaging use
INVENTOR(S): Pomper, Martin Gilbert; Ray, Sangeeta; Mease, Ronnie C.; Shallal, Hassan
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 54pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013082338	A1	20130606	WO 2012-US67162	20121130
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, 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, PA, 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2785712	A1	20141008	EP 2012-853926	20121130
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				
CN 104203942	A	20141210	CN 2012-80068163	20121130
CN 104203942	B	20170412		
US 20140341804	A1	20141120	US 2014-14362011	20140530
US 9371360	B2	20160621		
US 20170049912	A1	20170223	US 2016-15187274	20160908

PRIORITY APPLN. INFO.:
US 2011-61565179 P 20111130
WO 2012-US67162 W 20121130
US 2014-14362011 A1 20140530
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 159:76086; MARPAT 159:76086
GI

Fusion Pharmaceuticals, Inc.
Exhibit 1004.252

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides bivalent and multivalent ligands with improved affinity and pharmacokinetic properties of a urea class of PSMA inhibitors. The compds. and their synthesis can be generalized to multivalent compds. of other target antigens. The modular multivalent scaffolds of the present invention, in ≥1 embodiments, contain a lysine-based (α-, ε-) dialkyne residue for incorporating two or more antigen binding moieties, such as PSMA binding Lys-Glu urea moieties, exploiting click chemical and ≥1 addnl. lysine residues for subsequent modification with an imaging and/or therapeutic nuclides or a cytotoxic ligands for tumor cell killing. Thus, I, prepared via solid phase peptide synthesis and Huisgen 1,3-dipolar cycloaddn., displayed a PSMA inhibition constant Ki value of 0.08 nM.

IT 1442110-14-6P

RL: DGN (Diagnostic use); PAC (Pharmacological activity); PKT (Pharmacokinetics); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

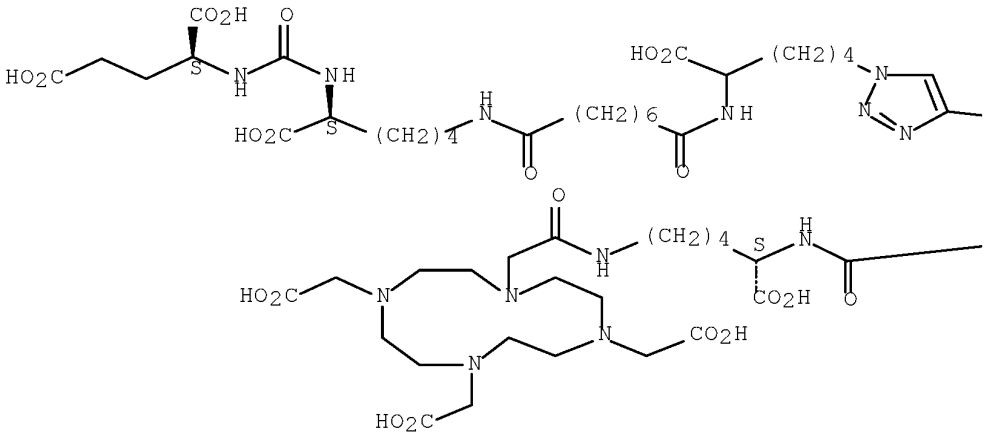
(preparation of compds. that are PSMA inhibitors useful in imaging, diagnosis, prophylaxis and treatment of cancer)

RN 1442110-14-6 CAPLUS

CN L-Lysine, N2,N6-bis[[1-[(20S,24S)-5,20,24,26-tetracarboxy-7,14,22-trioxo-6,15,21,23-tetraazahexacos-1-yl]-1H-1,2,3-triazol-4-yl]carbonyl]-L-lysyl-N6-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]- (CA INDEX NAME)

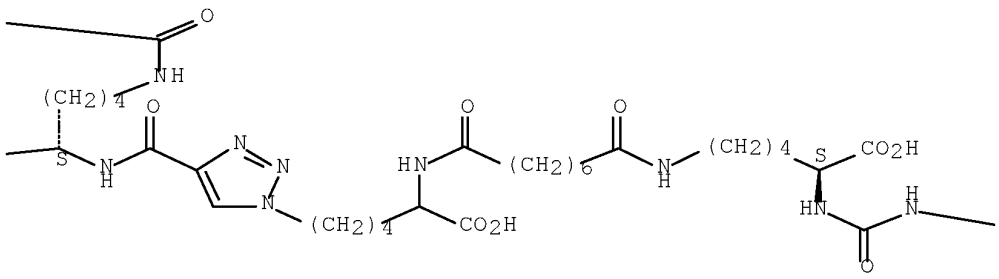
Absolute stereochemistry.

PAGE 1-A

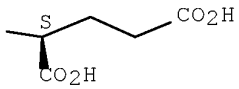


Fusion Pharmaceuticals, Inc.
Exhibit 1004.253

PAGE 1-B



PAGE 1-C



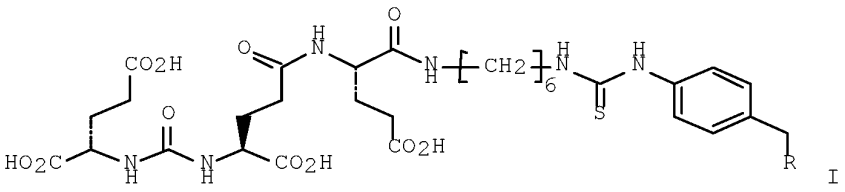
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:206841 CAPLUS Full-text
DOCUMENT NUMBER: 158:302408
TITLE: Preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-glutamates and glutamate-urea-lysines and their radionuclides conjugates, for diagnosis and treatment of diseases
INVENTOR(S): Babich, John W.; Zimmerman, Craig; Joyal, John L.; Lu, Genliang
PATENT ASSIGNEE(S): Molecular Insight Pharmaceuticals, USA
SOURCE: U.S. Pat. Appl. Publ., 107pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

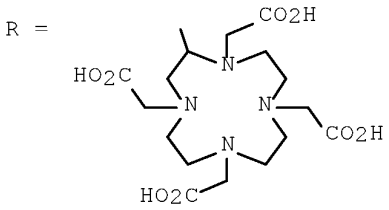
Fusion Pharmaceuticals, Inc.
Exhibit 1004.254

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     US 20130034494       A1   20130207    US 2012-13566849         20120803
     US 8926944           B2   20150106
     CA 2844151           A1   20130214    CA 2012-2844151          20120803
     WO 2013022797        A1   20130214    WO 2012-US49644          20120803
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     US 9388144           B2   20160712
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                                           US 2012-13566849     A3  20120803
                                           WO 2012-US49644      W   20120803
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S):         CASREACT 158:302408; MARPAT 158:302408
GI
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.255



I



AB The invention is related to the preparation of glutamate-urea-lysine (GUL) or glutamate-urea-glutamate (GUG) analogs in which a chelator group is conjugated to the GUL or GUG moiety via a linker, e.g., I, that are potent inhibitors of PSMA activity and to their radionuclides conjugates useful for treating or diagnosis of a disease or a condition associated with PSMA activity. Thus, I and its 111Lu-complex were prepared Biodistribution studies and affinity binding tests were conducted for the 111Lu complex.

IT 1422158-73-3P 1422158-84-6P 1422158-89-1P
1422158-91-5P 1422158-98-2P 1422159-00-9P
1422159-07-6P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(claimed; preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-glutamates and glutamate-urea-lysines and their radionuclides conjugates, for diagnosis and treatment of diseases)

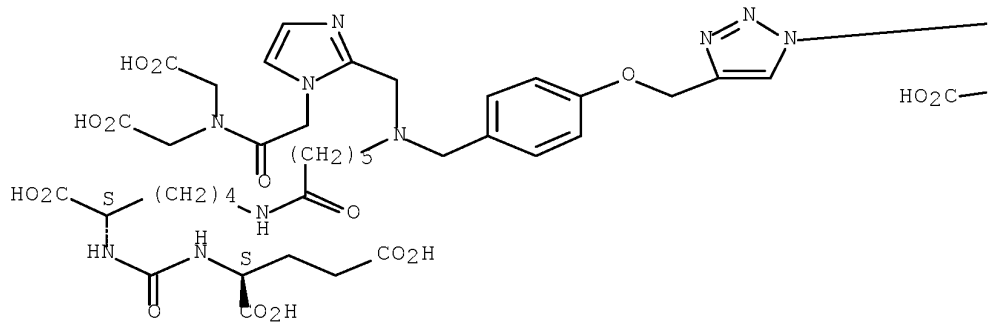
RN 1422158-73-3 CAPLUS

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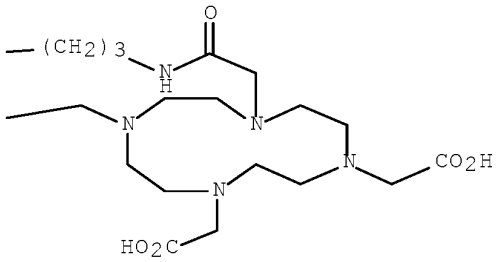
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.256

PAGE 1-A



PAGE 1-B

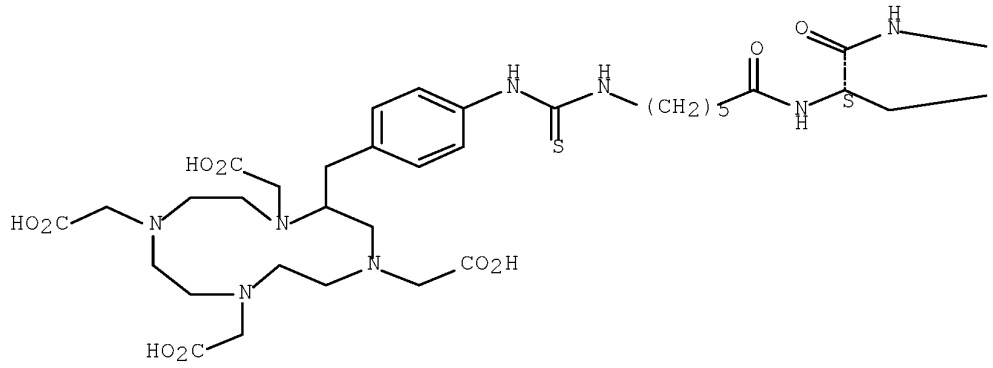


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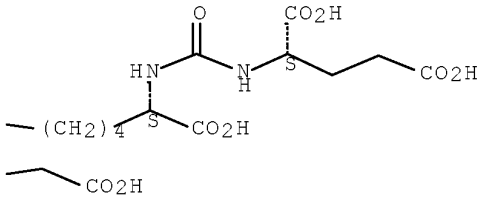
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.257

PAGE 1-A



PAGE 1-B

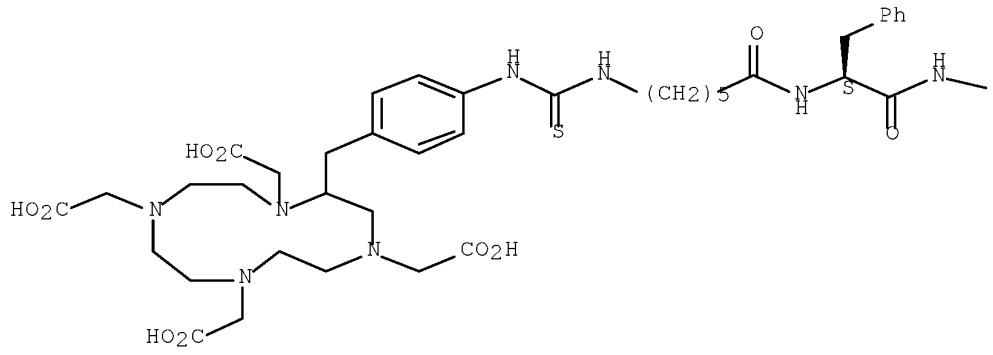


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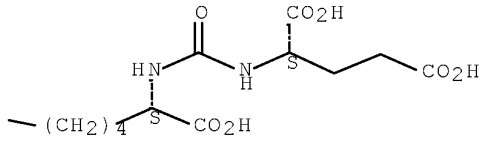
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.258

PAGE 1-A



PAGE 1-B

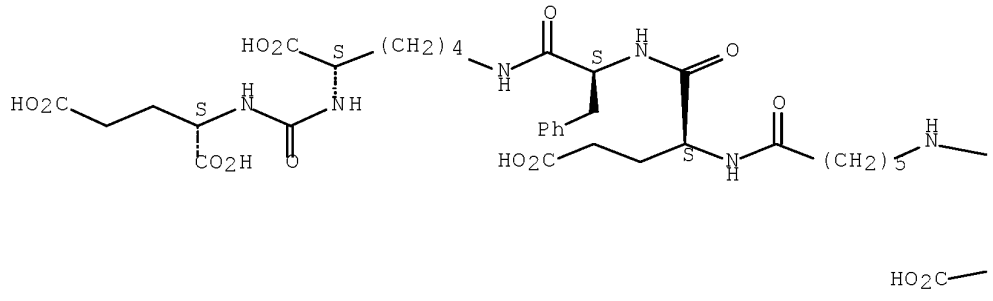


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CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[N-[1-oxo-6-[[[4-[[(2S)-1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododec-2-yl]methyl]phenyl]amino]thioxomethyl]amino]hexyl]-L-α-glutamyl-L-phenylalanyl]- (CA INDEX NAME)

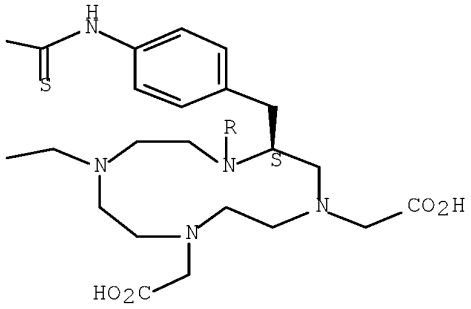
Absolute stereochemistry.

PAGE 1-A

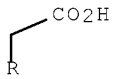


Fusion Pharmaceuticals, Inc.
Exhibit 1004.259

PAGE 1-B



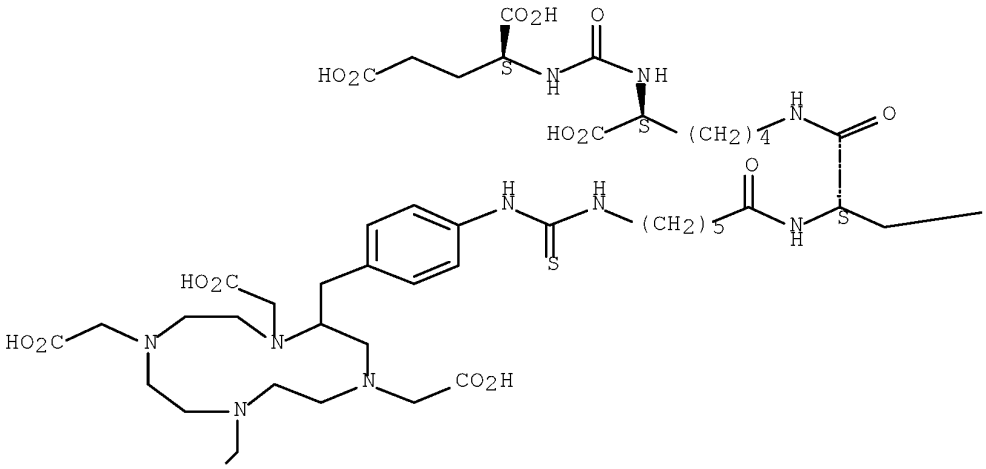
PAGE 2-A



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CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, 2-[[4-[[(10S,17S,21S)-17,21,23-tricarboxy-10-[(4-fluorophenyl)methyl]-8,11,19-trioxo-1-thioxo-2,9,12,18,20-pentaazatricos-1-yl]amino]phenyl]methyl]- (CA INDEX NAME)

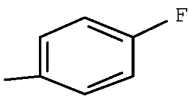
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.260

PAGE 1-B



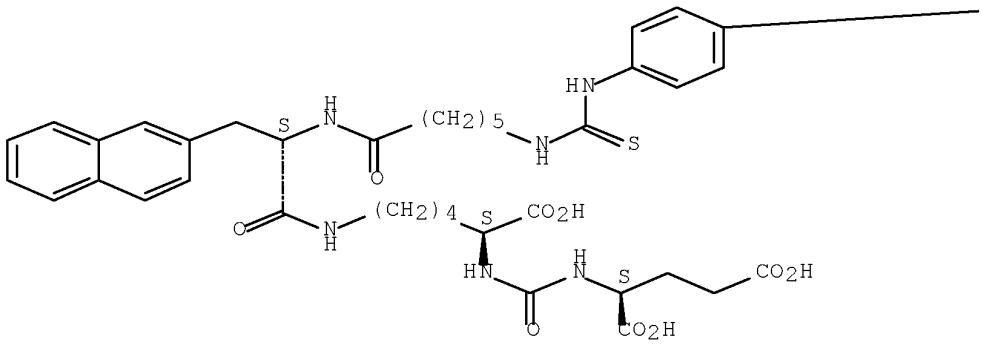
PAGE 2-A



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CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[3-(2-naphthalenyl)-N-[1-oxo-6-[[[[4-[[1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododec-2-yl]methyl]phenyl]amino]thioxomethyl]amino]hexyl]-L-alanyl]- (CA INDEX NAME)

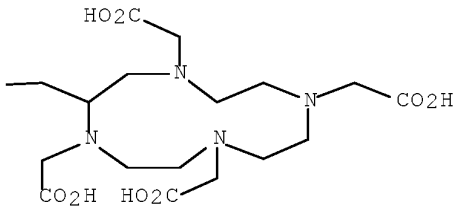
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.261

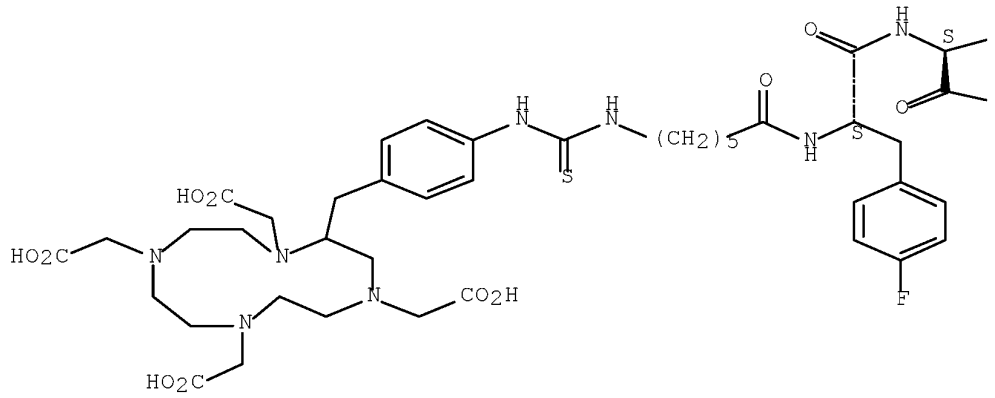
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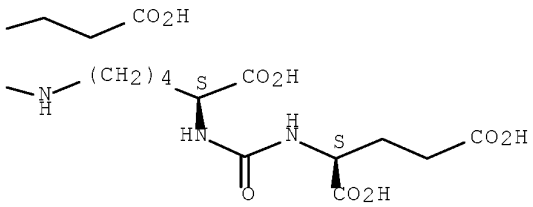
RN 1422159-07-6 CAPLUS
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 1422158-82-4P 1422159-38-3P 1422159-39-4P
1422159-40-7P 1422159-41-8P 1422159-42-9P
1422159-43-0P 1422159-44-1P 1422159-45-2P

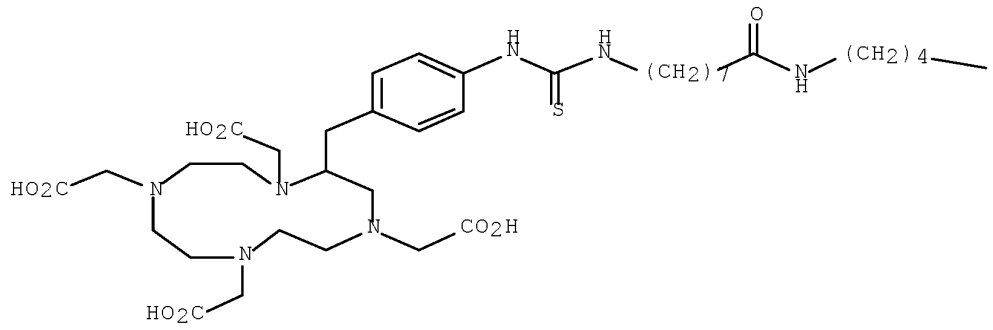
Fusion Pharmaceuticals, Inc.
Exhibit 1004.262

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1422159-49-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed; preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-glutamates and glutamate-urea-lysines and their radionuclides conjugates, for diagnosis and treatment of diseases)

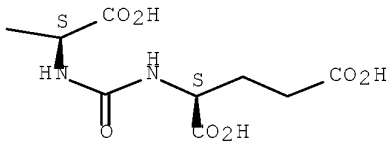
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

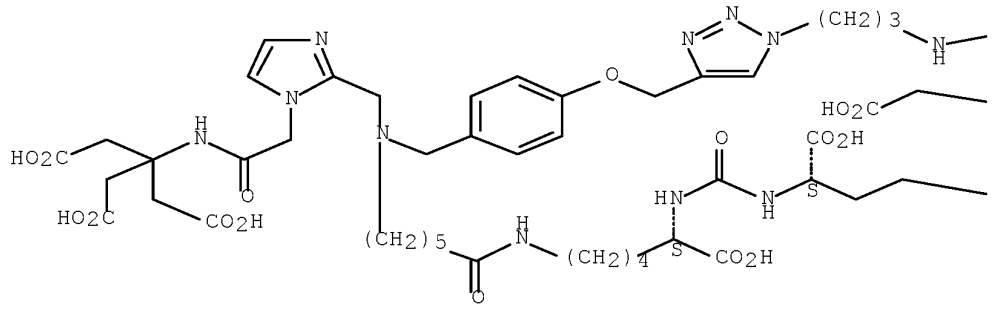


RN 1422159-38-3 CAPLUS
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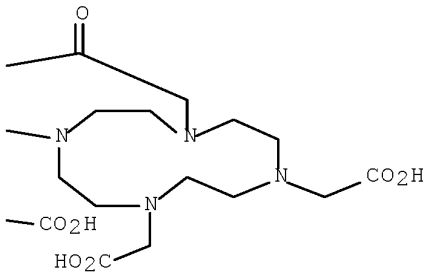
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.263

PAGE 1-A



PAGE 1-B

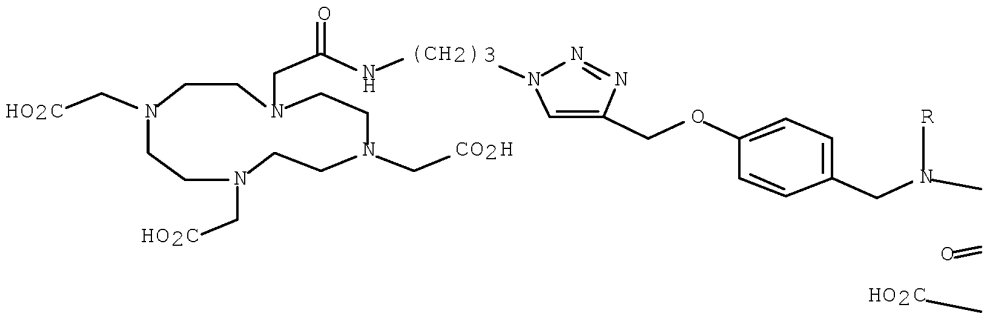


RN 1422159-39-4 CAPLUS
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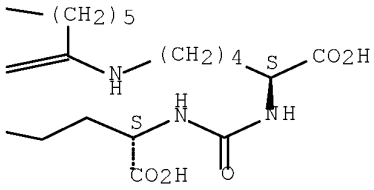
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.264

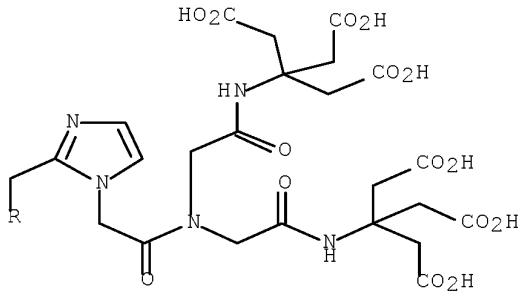
PAGE 1-A



PAGE 1-B



PAGE 2-A



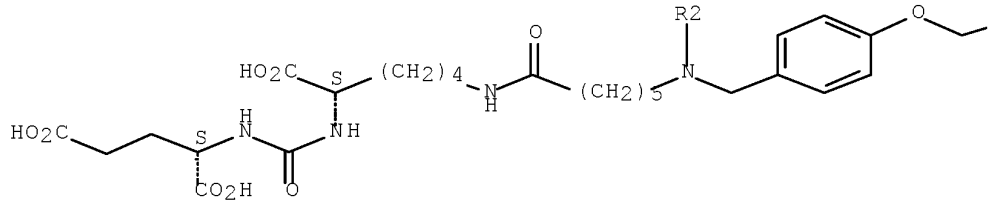
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.265

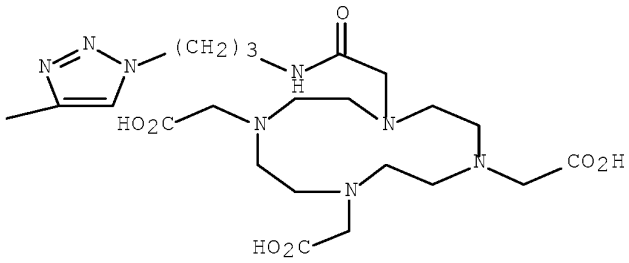
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Absolute stereochemistry.

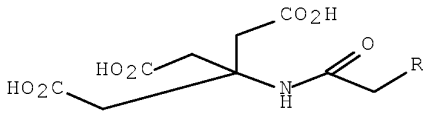
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PAGE 1-B

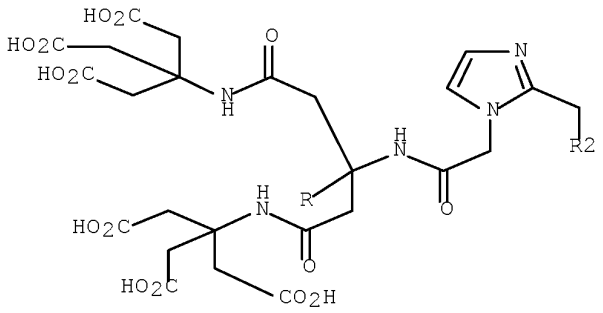


PAGE 2-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.266

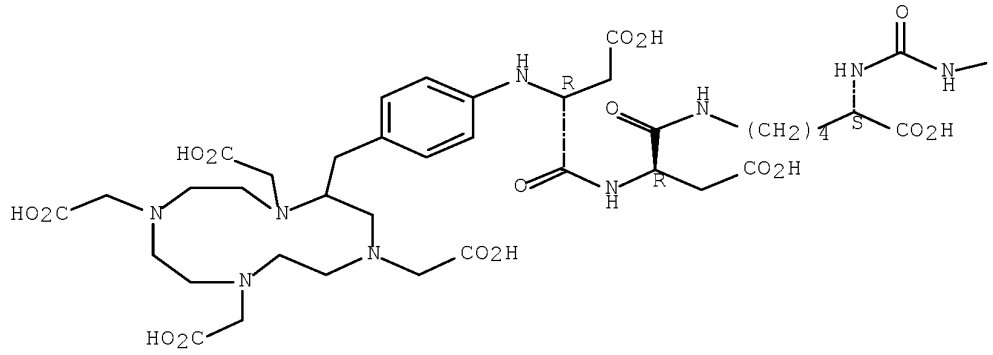
PAGE 3-A



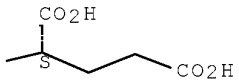
RN 1422159-41-8 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[N-[4-[[1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododec-2-yl]methyl]phenyl]-D-α-aspartyl-D-α-aspartyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



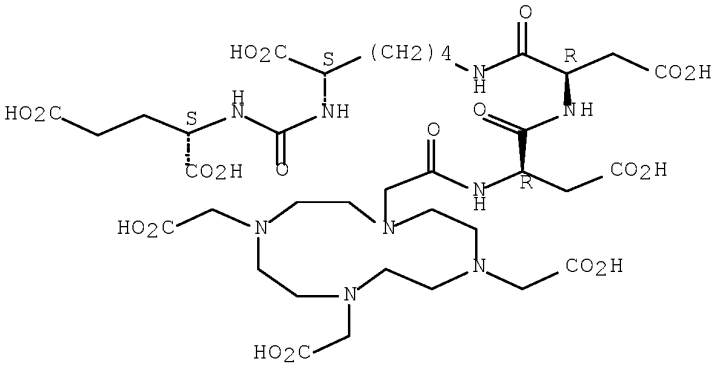
PAGE 1-B



RN 1422159-42-9 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-D-α-aspartyl-D-α-aspartyl]- (CA INDEX NAME)

Absolute stereochemistry.

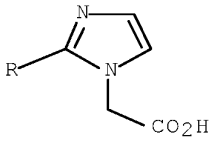
Fusion Pharmaceuticals, Inc.
Exhibit 1004.267



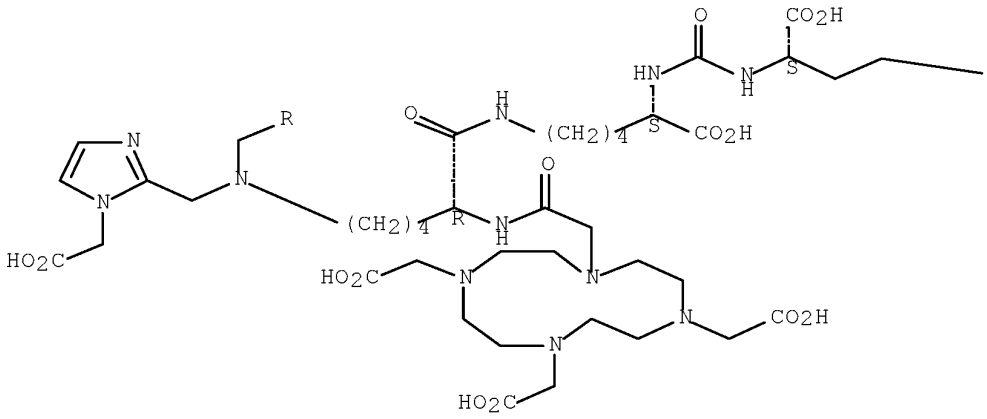
RN 1422159-43-0 CAPLUS
CN L-Lysine, N6-[N6,N6-bis[[1-(carboxymethyl)-1H-imidazol-2-yl]methyl]-N2-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-lysyl]-N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

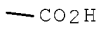


PAGE 2-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.268

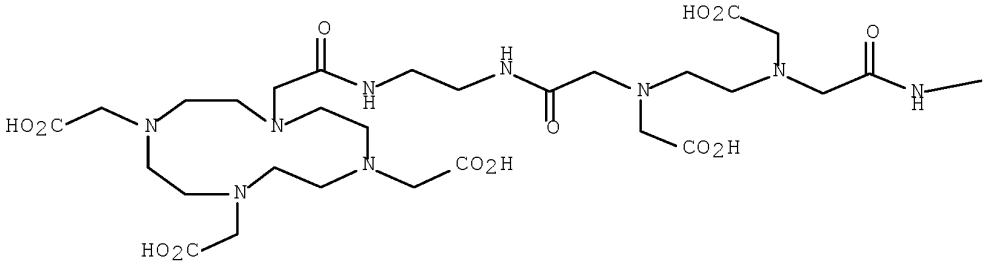
PAGE 2-B



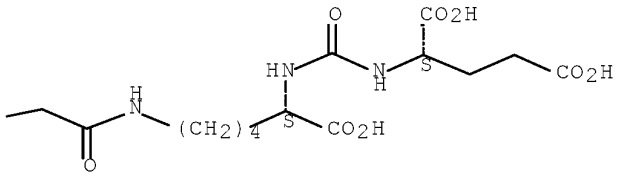
RN 1422159-44-1 CAPLUS
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

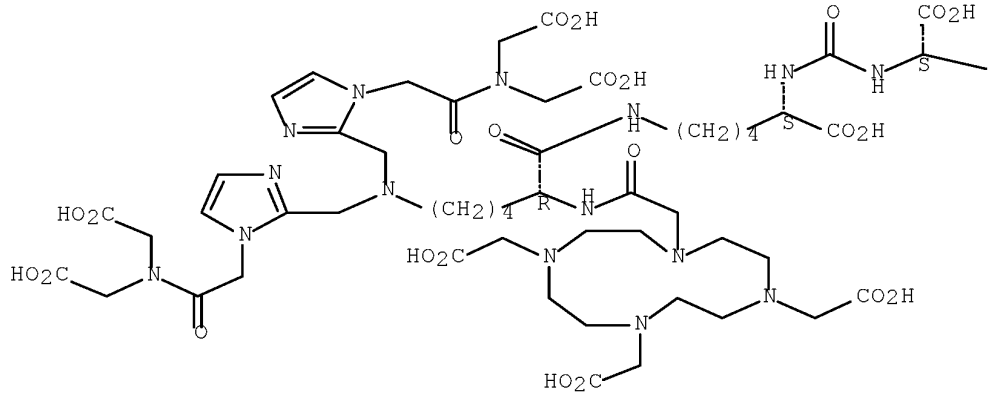


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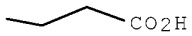
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.269

PAGE 1-A



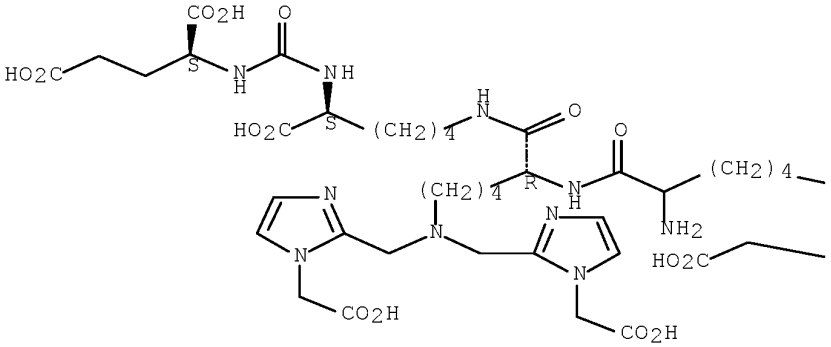
PAGE 1-B



RN 1422159-46-3 CAPLUS
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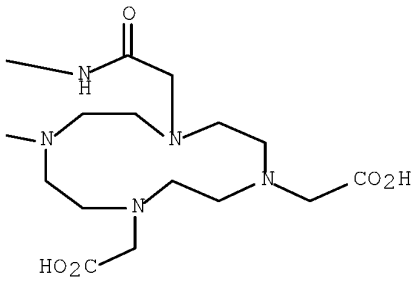
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.270

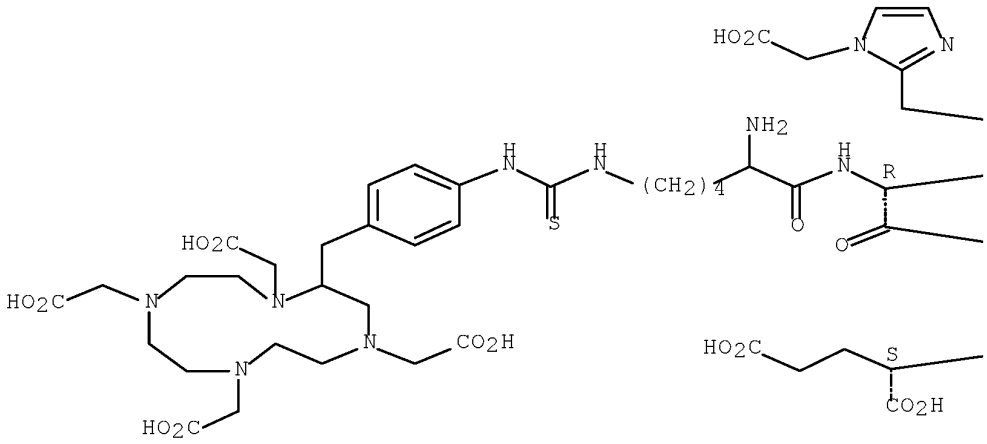
PAGE 1-B



RN 1422159-47-4 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[N6-[[[4-[[1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododec-2-yl]methyl]phenyl]amino]thioxomethyl]lysyl-N6,N6-bis[[1-(carboxymethyl)-1H-imidazol-2-yl]methyl]-D-lysyl]- (CA INDEX NAME)

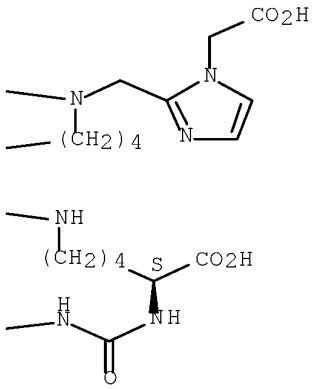
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.271

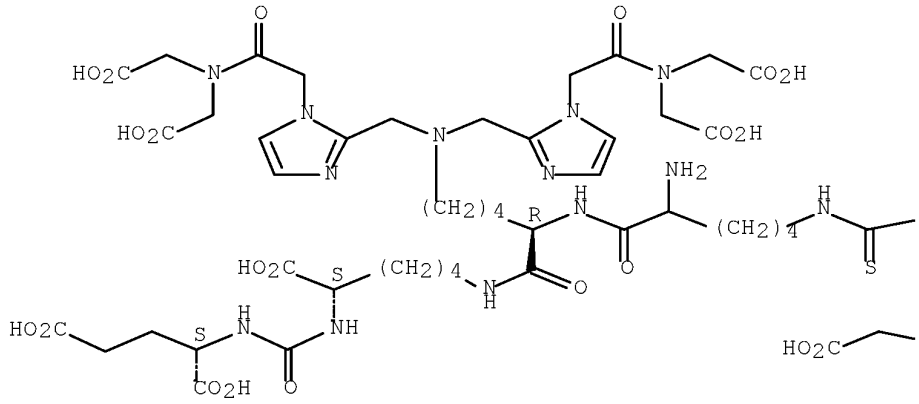
PAGE 1-B



RN 1422159-48-5 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[N6-[[[4-[[1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododec-2-yl]methyl]phenyl]amino]thioxomethyl]lysyl-N6,N6-bis[[1-[2-[bis(carboxymethyl)amino]-2-oxoethyl]-1H-imidazol-2-yl]methyl]-D-lysyl]- (CA INDEX NAME)

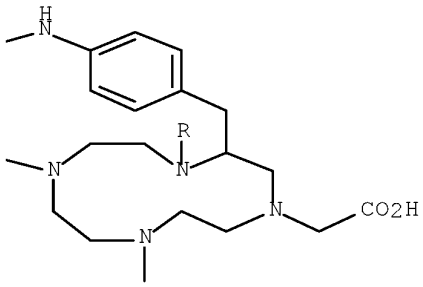
Absolute stereochemistry.

PAGE 1-A

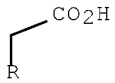


Fusion Pharmaceuticals, Inc.
Exhibit 1004.272

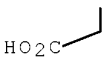
PAGE 1-B



PAGE 2-A



PAGE 2-B

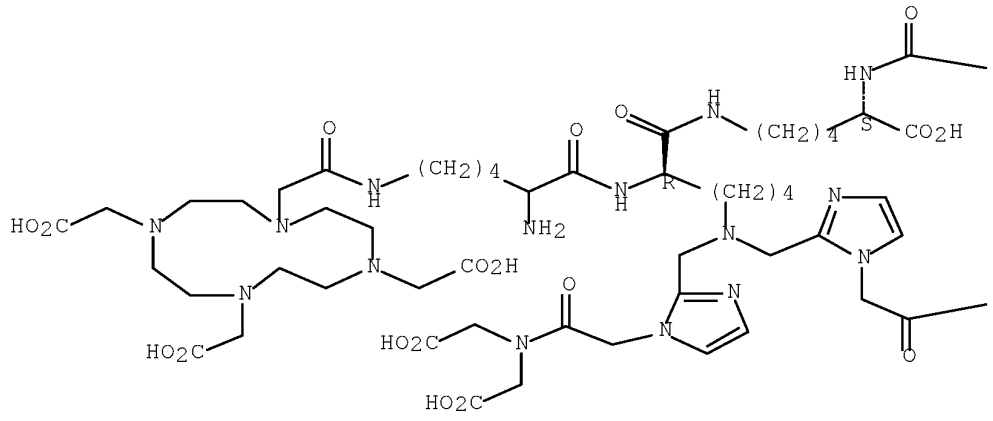


RN 1422159-49-6 CAPLUS
CN L-Lysine, N2-[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]-N6-[N6-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]lysyl-N6,N6-bis[[1-[2-[bis(carboxymethyl)amino]-2-oxoethyl]-1H-imidazol-2-yl]methyl]-D-lysyl]- (CA INDEX NAME)

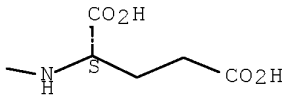
Absolute stereochemistry.

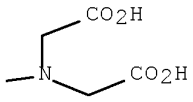
Fusion Pharmaceuticals, Inc.
Exhibit 1004.273

PAGE 1-A



PAGE 1-B



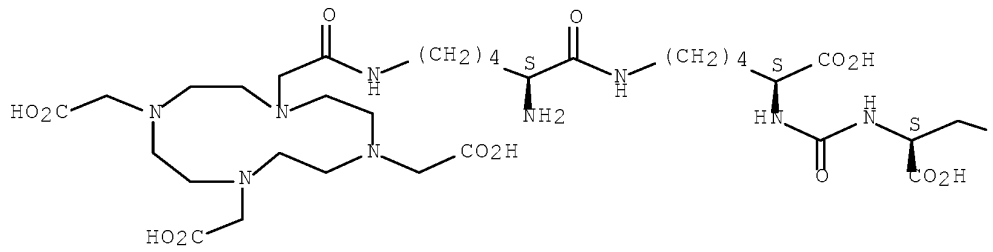


IT 1422158-81-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-glutamates and glutamate-urea-lysines and their radionuclides conjugates, for diagnosis and treatment of diseases)
RN 1422158-81-3 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[(8S,15S,19S)-8-amino-15,19,21-tricarboxy-2,9,17-trioxo-3,10,16,18-tetraazaheneicos-1-yl]- (CA INDEX NAME)

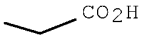
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.274

PAGE 1-A



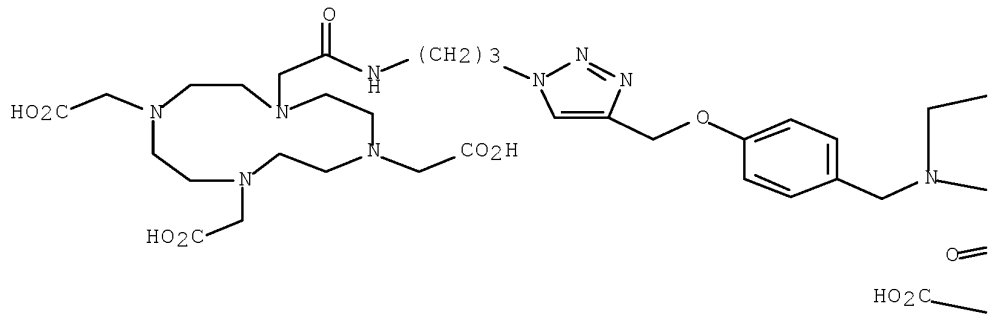
PAGE 1-B



IT 1422158-79-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of radiolabeled prostate specific membrane antigen inhibitors, particularly glutamate-urea-glutamates and glutamate-urea-lysines and their radionuclides conjugates, for diagnosis and treatment of diseases)
RN 1422158-79-9 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[2-oxo-2-[[3-[4-[[4-[(14S,18S)-14,18,20-tricarboxy-2-[[1-(carboxymethyl)-1H-imidazol-2-yl]methyl]-8,16-dioxo-2,9,15,17-tetraazaeicos-1-yl]phenoxy]methyl]-1H-1,2,3-triazol-1-yl]propyl]amino]ethyl]- (CA INDEX NAME)

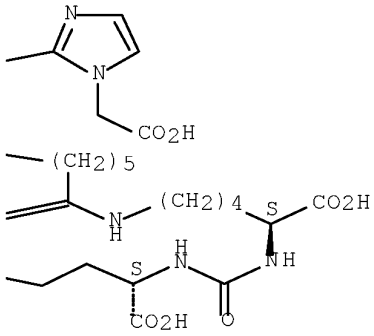
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.275

PAGE 1-B



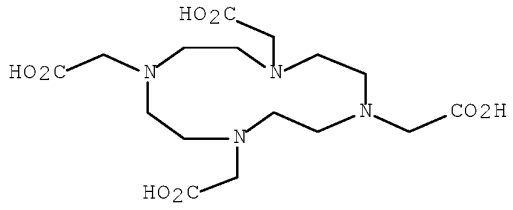
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L133 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:847089 CAPLUS Full-text
DOCUMENT NUMBER: 157:77076
TITLE: Preparation of PSMA targeting compounds, particularly glutamate-urea-lysines, their conjugates to dendrimers and radionuclide-dendrimer complexes useful in imaging and treatment of prostate cancer or cancer of other tissue where protein is expressed
INVENTOR(S): Babich, John W.; Joyal, John L.; Zimmerman, Craig
PATENT ASSIGNEE(S): Molecular Insight Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012078534	A1	20120614	WO 2011-US63361	20111206
W: 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				
RW: 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, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2819850	A1	20120614	CA 2011-2819850	20111206

Fusion Pharmaceuticals, Inc.
Exhibit 1004.276

EP 2648766 A1 20131016 EP 2011-797287 20111206
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR
JP 2014510015 T 20140424 JP 2013-542250 20111206
US 20130336888 A1 20131219 US 2013-13991812 20130820
PRIORITY APPLN. INFO.: US 2010-61420265 P 20101206
WO 2011-US63361 W 20111206
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:77076; MARPAT 157:77076
GI

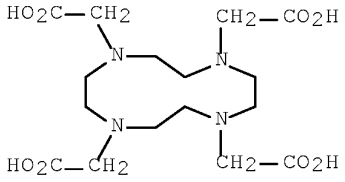


AB The invention is related to PSMA targeting compds., particularly glutamate-urea homodimers and glutamate-urea heterodimers, their conjugates to dendrimers and radionuclide-dendrimer complexes [wherein the radionuclide is selected from rhenium, technetium, yttrium, lutetium, etc.] useful imaging tissues or for the radiotherapeutic treatment of cancer tissue. Such complexes are specific to PSMA protein and can therefore be used in imaging or treating cancer of the prostate and other tissue where the protein is expressed. Thus, (3S,7S,26S,30S)-15,18-bis[2-[[(S)-5-carboxy-5-[3-((S)-1,3-dicarboxypropyl)ureido]pentyl]amino]-2-oxoethyl]-5,13,20,28-tetraoxo-4,6,12,15,18,21,27,29-octaazadotriacontane-1,3,7,26,30,32-hexacarboxylic acid (I) was prepared by reaction of 4,4'-(ethane-1,2-diyl)dimorpholino-2,6-dione with di-tert-Bu (S)-2-[3-((S)-6-amino-1-tert-butoxy-1-oxohexan-2-yl)ureido]pentanedioate (II), activation of (14S,18S)-3-[(7S,11S)-7,11-bis(tert-butoxycarbonyl)-2,2-dimethyl-4,9,17-trioxo-3-oxa-8,10,16-triazaoctadecan-18-yl]-14,18-bis(tert-butoxycarbonyl)-6-(carboxymethyl)-23,23-dimethyl-8,16,21-trioxo-22-oxa-3,6,9,15,17-pentaazatetracosan-1-oic acid with DDCI/HOBt in the presence of DIPEA, reaction of the activated dimer (no data) with II and cleavage of the tert-butoxycarbonyl groups. The analogs and radiolabeled dendrimer conjugates of I were screened in a human prostate cancer cell binding assay at a concentration of 3 nM using PSMA pos. LnCap cells.

IT 60239-18-1DP, DOTA, complexes with dendrimers and radionuclides
1380613-66-0DP, analogs and radiolabeled dendrimer conjugates
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of PSMA targeting compds., particularly glutamate-urea-lysines, their conjugates to dendrimers and radionuclide-dendrimer complexes useful in imaging and treatment of prostate cancer)

RN 60239-18-1 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (CA INDEX NAME)

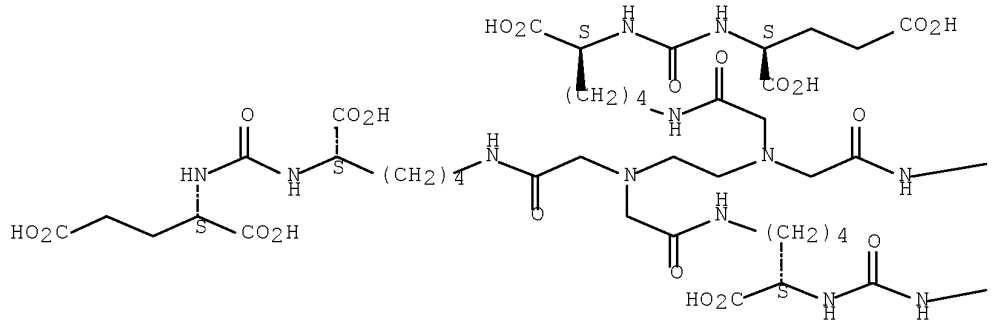
Fusion Pharmaceuticals, Inc.
Exhibit 1004.277



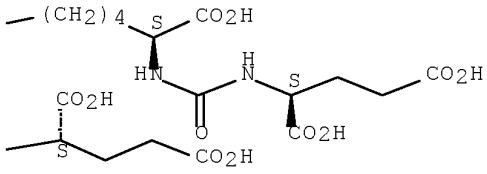
RN 1380613-66-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of PSMA targeting compds., particularly glutamate-urea-lysines, their conjugates to dendrimers and radionuclide-dendrimer complexes useful in imaging and treatment of prostate cancer

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.278

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2011:1051338 CAPLUS Full-text
DOCUMENT NUMBER: 155:598525
TITLE: Sequential SPECT and Optical Imaging of Experimental Models of Prostate Cancer with a Dual Modality Inhibitor of the Prostate-Specific Membrane Antigen
AUTHOR(S): Banerjee, Sangeeta Ray; Pullambhatla, Mrudula; Byun, Youngjoo; Nimmagadda, Sridhar; Foss, Catherine A.; Green, Gilbert; Fox, James J.; Lupold, Shawn E.; Mease, Ronnie C.; Pomper, Martin G.
CORPORATE SOURCE: The Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, MD, 21231, USA
SOURCE: Angewandte Chemie, International Edition (2011), 50(39), 9167-9170, S9167/1-S9167/20
CODEN: ACIEF5; ISSN: 1433-7851
DIGITAL OBJECT ID: 10.1002/anie.201102872
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 155:598525

AB The authors have developed an efficient chemical and radiochem. synthesis of a dual modality, prostate-specific membrane antigen (PSMA)-binding compound, which provides sequential imaging by SPECT and NIRF at radiotracer levels. Concurrent, rather than sequential, imaging will be possible with this agent once a corresponding dual modality imaging device becomes available.

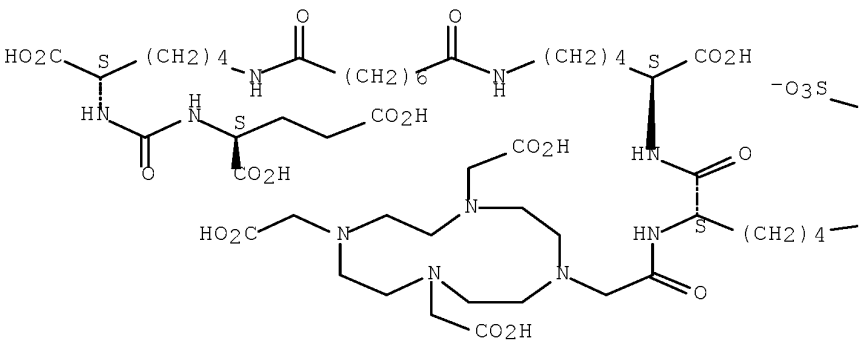
IT 1345090-91-6P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(PSMA inhibitor; sequential SPECT and optical imaging of exptl. models of prostate cancer with a dual modality inhibitor of prostate-specific membrane antigen)

RN 1345090-91-6 CAPLUS
CN L-Lysine, N6-[6-[2-[(1E)-2-[(3E)-3-[(2E)-2-[1,3-dihydro-3,3-dimethyl-5-sulfo-1-(4-sulfobutyl)-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-5-sulfo-3H-indolio]-1-oxohexyl]-N2-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-lysyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-, inner salt (CA INDEX NAME)

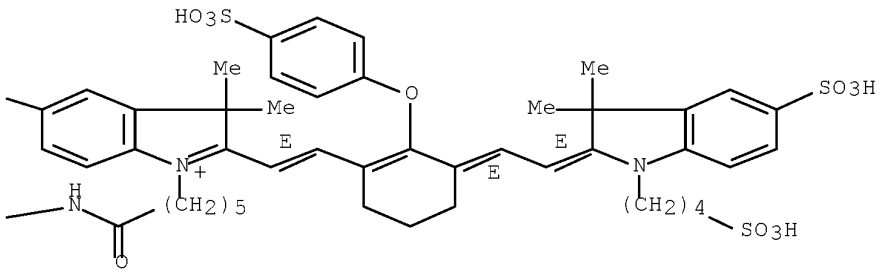
Absolute stereochemistry.
Double bond geometry as shown.

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Exhibit 1004.279

PAGE 1-A



PAGE 1-B

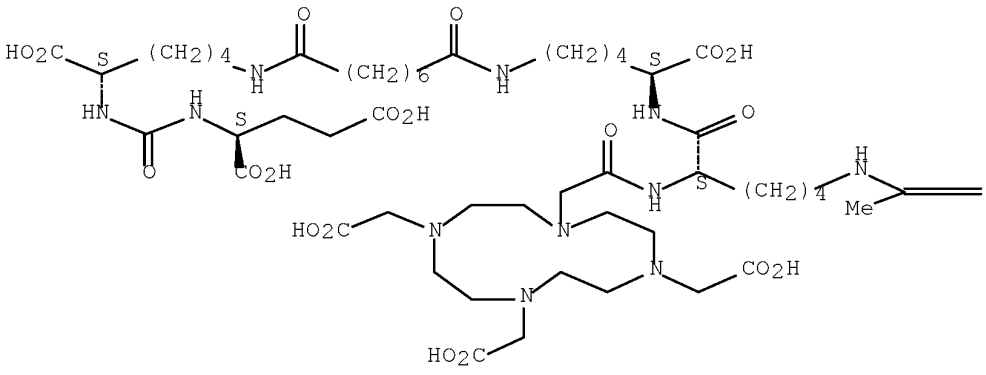


IT 1345090-93-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(sequential SPECT and optical imaging of exptl. models of prostate cancer with a dual modality inhibitor of prostate-specific membrane antigen)
RN 1345090-93-8 CAPLUS
CN L-Lysine, N6-[1-(4,4-dimethyl-3,5-dioxocyclohexylidene)ethyl]-N2-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-lysyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

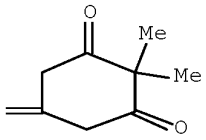
Absolute stereochemistry.

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Exhibit 1004.280

PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 33 THERE ARE 33 CAPLUS RECORDS THAT CITE THIS RECORD (33 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2010:1191992 CAPLUS Full-text
DOCUMENT NUMBER: 153:450806
TITLE: Psma-targeting compounds and uses thereof
INVENTOR(S): Pomper, Martin G.; Mease, Ronnie C.; Ray, Sangeeta; Chen, Ying
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 159pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010108125	A2	20100923	WO 2010-US28020	20100319
WO 2010108125	A3	20110324		

W: 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,

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Exhibit 1004.281

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, RO, RS, RU, 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
RW: 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, SE, SI,
SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

CA 2755965	A1	20100923	CA 2010-2755965		20100319
EP 2408755	A2	20120125	EP 2010-754194		20100319
EP 2408755	B1	20170503			
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US 20120009121	A1	20120112	US 2011-13257499		20110919
US 9056841	B2	20150616			
US 20150104387	A1	20150416	US 2014-14243535		20140402

PRIORITY APPLN. INFO.:

US 2009-61161484	P	20090319
US 2009-61161485	P	20090319
US 2009-61248067	P	20091002
US 2009-61248934	P	20091006
WO 2010-US28020	W	20100319
US 2011-13257499	A3	20110919

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 153:450806; MARPAT 153:450806

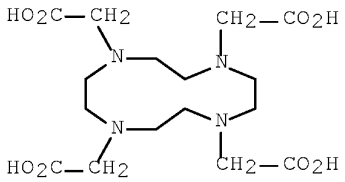
AB Prostate-specific membrane antigen (PSMA) targeting compds. are described. Uses of the compds. for imaging, therapy, cell sorting, and tumor mapping are also described.

IT 60239-18-1D, Dota, complexes 1235548-80-7D, complexes 1235548-82-9D, complexes 1246261-01-7D, complexes 1246261-02-8D, complexes 1246261-03-9D, complexes 1246261-04-0D, complexes 1246261-05-1D, complexes 1246261-06-2D, complexes 1246261-07-3D, complexes 1246261-08-4D, complexes 1246261-09-5D, complexes 1246261-10-8D, complexes 1246261-13-1 1246261-14-2 1246261-15-3 1246261-16-4 1246261-17-5 1246261-18-6 1246261-19-7 1246261-20-0 1246261-21-1 1246261-22-2 1246261-23-3 1246300-45-7 1246300-46-8 1246300-47-9

RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(PSMA-targeting compds. preparation and use for cancer imaging)

RN 60239-18-1 CAPLUS

CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (CA INDEX NAME)

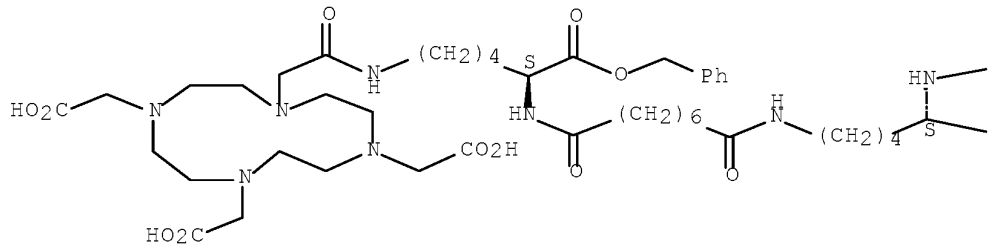


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Exhibit 1004.282

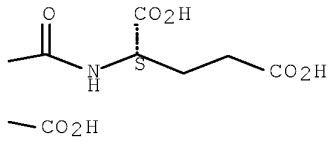
RN 1235548-80-7 CAPLUS
CN 4,6,12,21-Tetraazahexacosane-1,3,7,22-tetracarboxylic acid, 5,13,20-trioxo-26-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]-, 22-(phenylmethyl) ester, (3S,7S,22S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



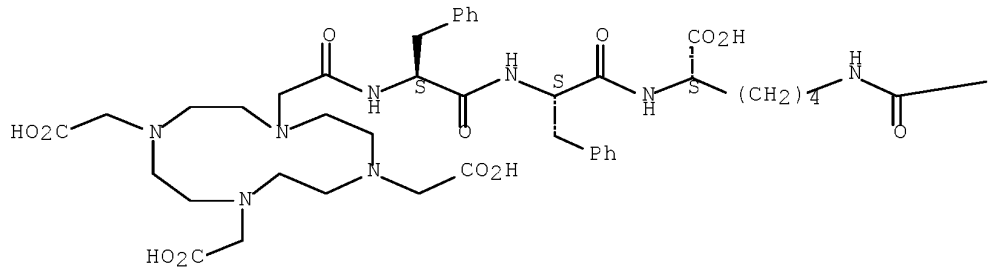
PAGE 1-B



RN 1235548-82-9 CAPLUS
CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

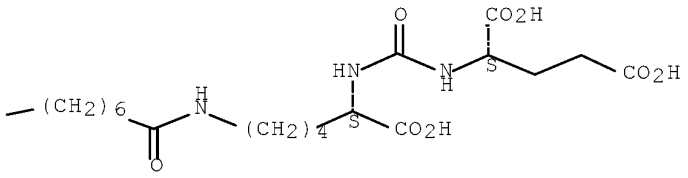
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.283

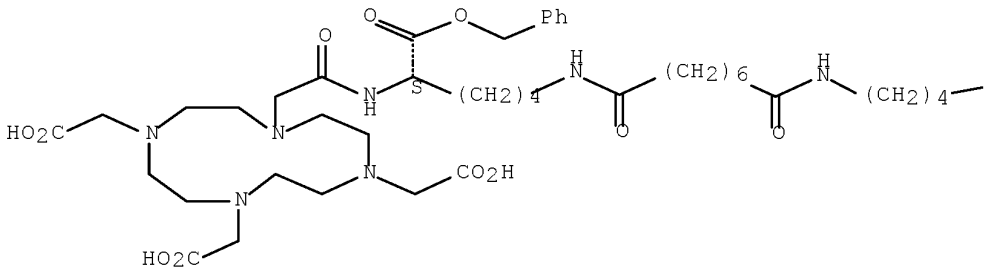
PAGE 1-B



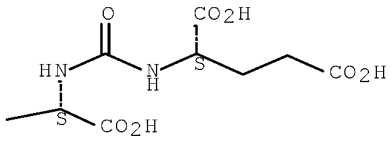
RN 1246261-01-7 CAPLUS
CN 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, 10-[(4S,23S,27S)-23,27,29-tricarboxy-2,10,17,25-tetraoxo-4-[(phenylmethoxy)carbonyl]-3,9,18,24,26-pentaazanonacosan-1-yl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

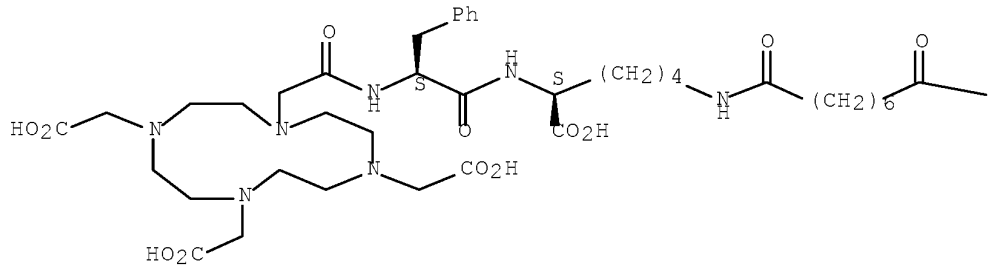


RN 1246261-02-8 CAPLUS
CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

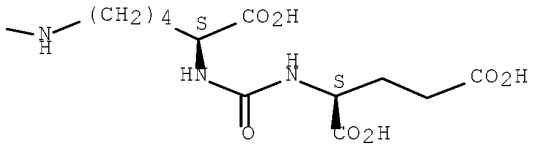
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.284

PAGE 1-A



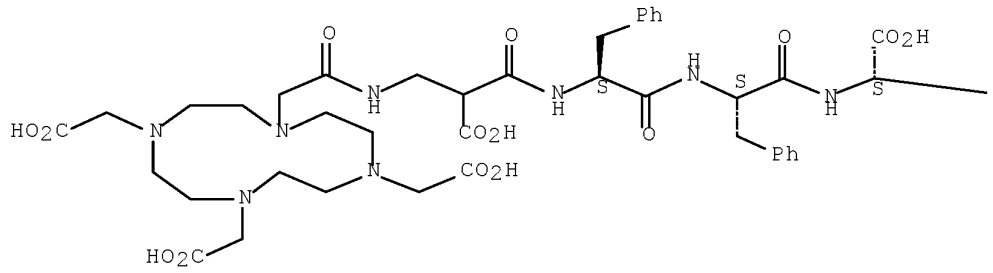
PAGE 1-B



RN 1246261-03-9 CAPLUS
CN L-Lysine, 2-carboxy-N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-β-alanyl-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

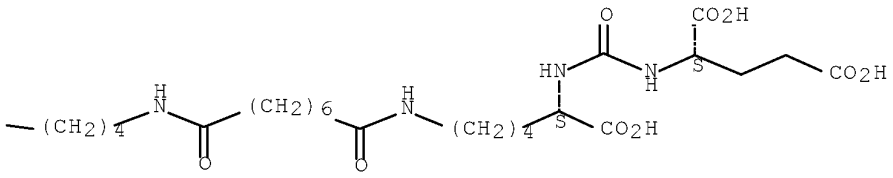
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.285

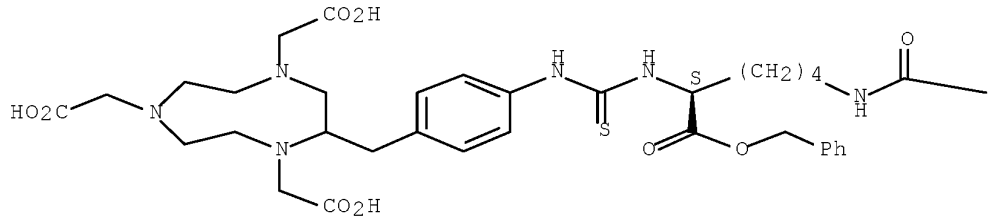
PAGE 1-B



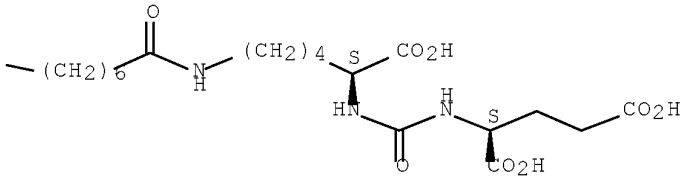
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

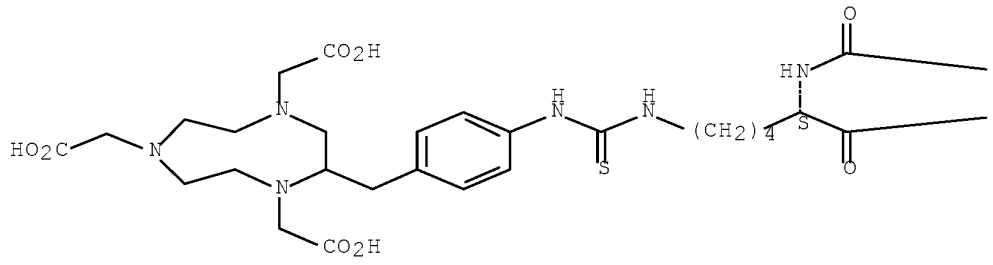


RN 1246261-05-1 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, hexahydro-8-[[4-[[(7S,22S,26S)-22,26,28-tricarboxy-9,16,24-trioxo-7-[(phenylmethoxy)carbonyl]-1-thioxo-2,8,17,23,25-pentaazaoctacos-1-yl]amino]phenyl]methyl]- (CA INDEX NAME)

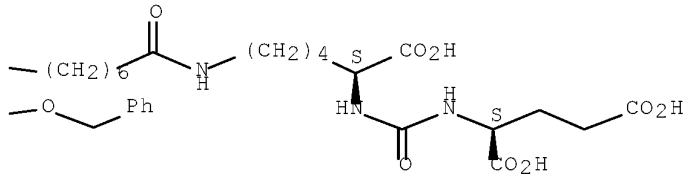
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.286

PAGE 1-A



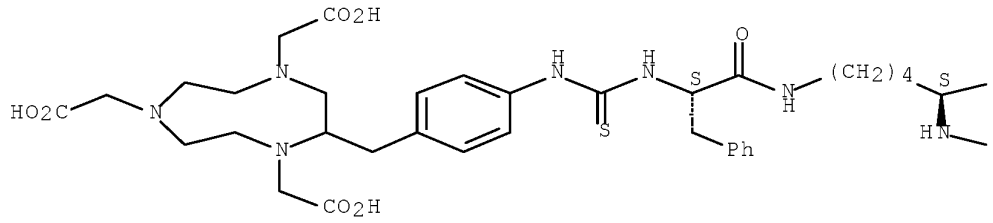
PAGE 1-B



RN 1246261-06-2 CAPLUS
CN L-Lysine, N2-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-N6-[N-[thioxo[[4-[[1,4,7-tris(carboxymethyl)octahydro-1H-1,4,7-triazonin-2-yl]methyl]phenyl]amino]methyl]-L-phenylalanyl]- (CA INDEX NAME)

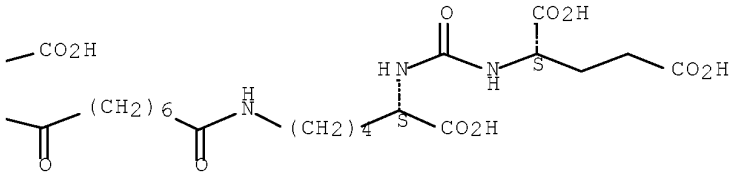
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.287

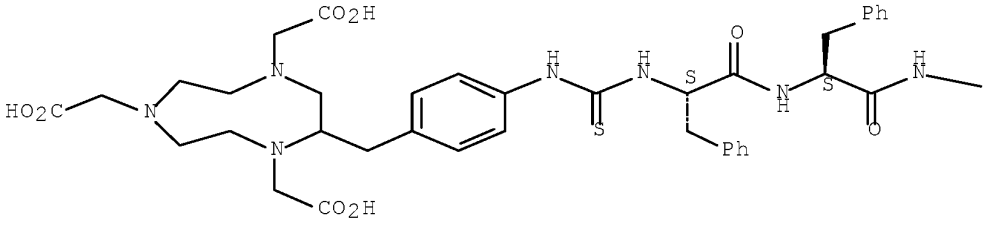
PAGE 1-B



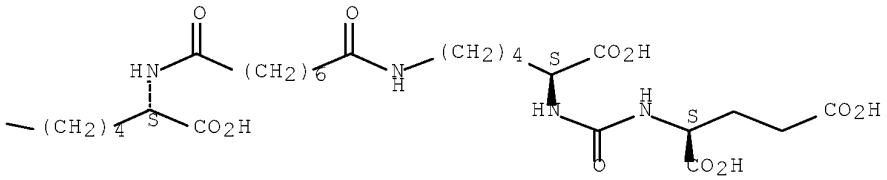
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

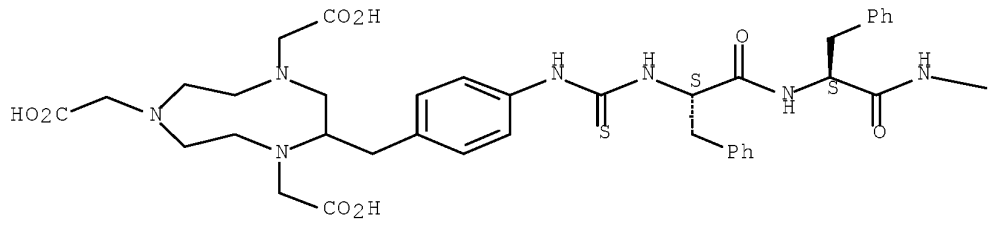


RN 1246261-08-4 CAPLUS
CN L-Lysine, N2-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-N6-[N-[thioxo[[4-[[1,4,7-tris(carboxymethyl)octahydro-1H-1,4,7-triazonin-2-yl]methyl]phenyl]amino]methyl]-L-phenylalanyl-L-phenylalanyl-L-phenylalanyl]- (CA INDEX NAME)

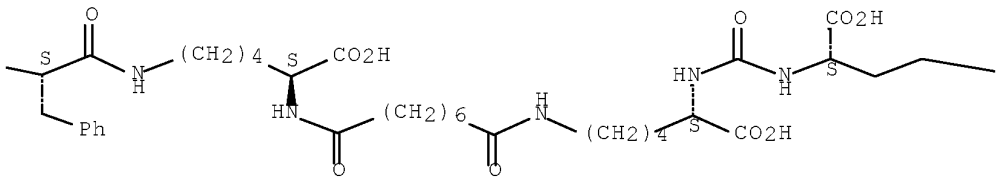
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.288

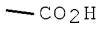
PAGE 1-A



PAGE 1-B



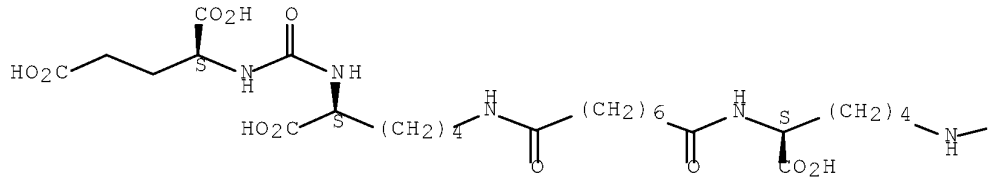
PAGE 1-C



RN 1246261-09-5 CAPLUS
CN L-Lysine, N2-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-N6-[N-[2-[(triphenylmethyl)thio]acetyl]glycylglycylglycyl-L-phenylalanyl-L-phenylalanyl]- (CA INDEX NAME)

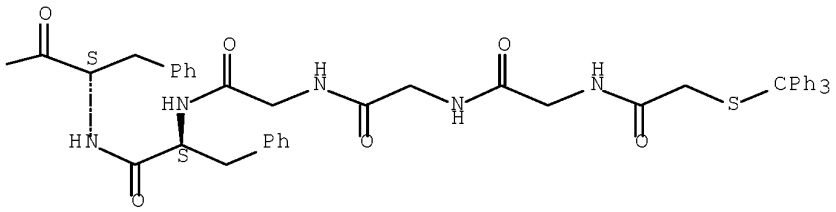
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.289

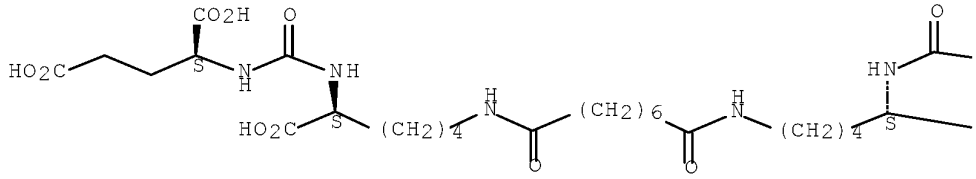
PAGE 1-B



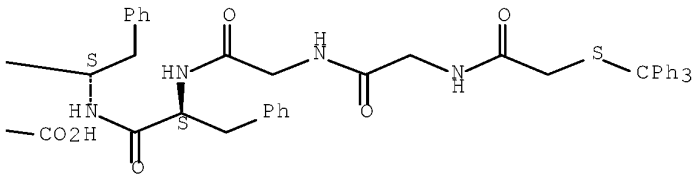
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CN L-Lysine, N-[2-[(triphenylmethyl)thio]acetyl]glycylglycyl-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

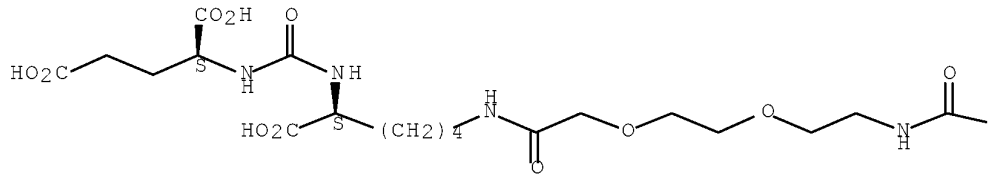


RN 1246261-13-1 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-(1-ethyl-1,3-dihydro-3,3-dimethyl-2H-indol-2-ylidene)ethylidene]-2-phenoxy-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-1-(3-sulfopropyl)-5-[(16S,20S)-16,20,22-tricarboxy-1,10,18-trioxo-5,8-dioxa-2,11,17,19-tetraazadocos-1-yl]-, inner salt (CA INDEX NAME)

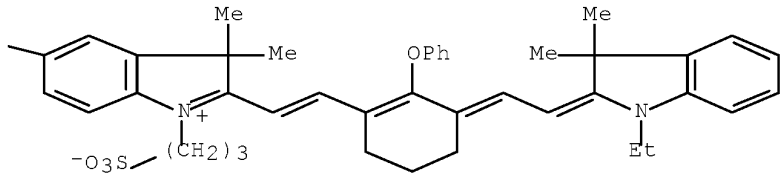
Absolute stereochemistry.
Double bond geometry unknown.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.290

PAGE 1-A



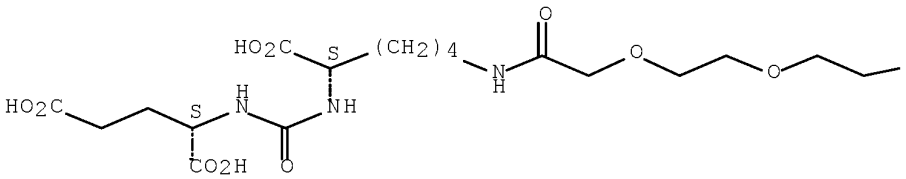
PAGE 1-B



RN 1246261-14-2 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-[1,3-dihydro-3,3-dimethyl-1-(4-sulfobutyl)-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-1-[(21S,25S)-21,25,27-tricarboxy-6,15,23-trioxo-10,13-dioxa-7,16,22,24-tetraazaheptacos-1-yl]-, inner salt (CA INDEX NAME)

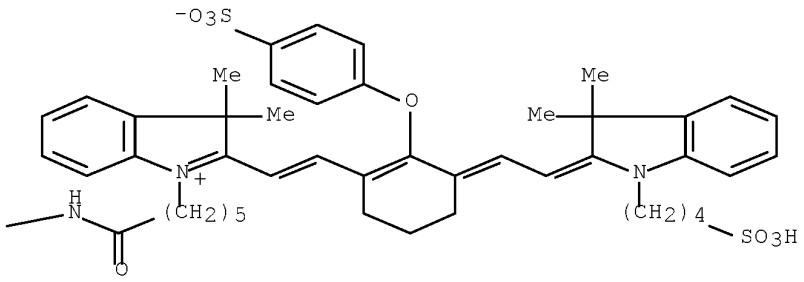
Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.291

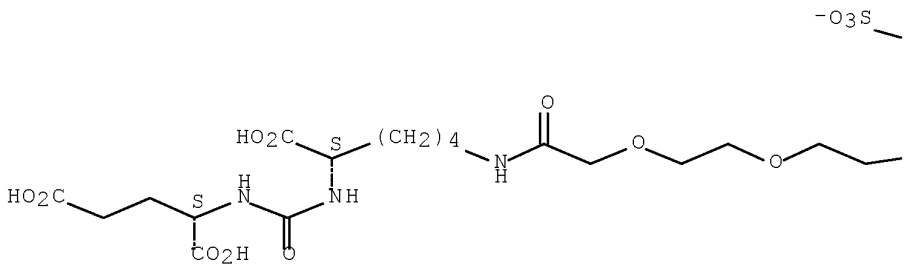
PAGE 1-B



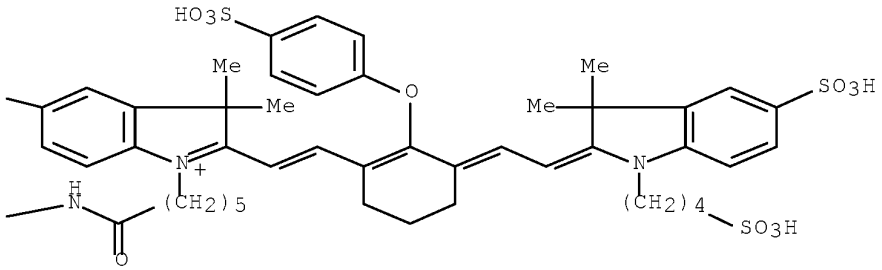
RN 1246261-15-3 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-[1,3-dihydro-3,3-dimethyl-5-sulfo-1-(4-sulfobutyl)-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-5-sulfo-1-[(21S,25S)-21,25,27-tricarboxy-6,15,23-trioxo-10,13-dioxa-7,16,22,24-tetraazaheptacos-1-yl]-, inner salt (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

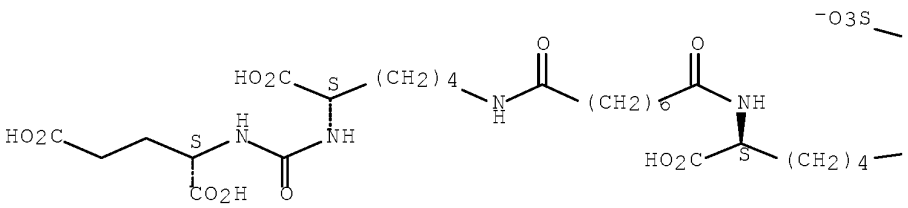


Fusion Pharmaceuticals, Inc.
Exhibit 1004.292

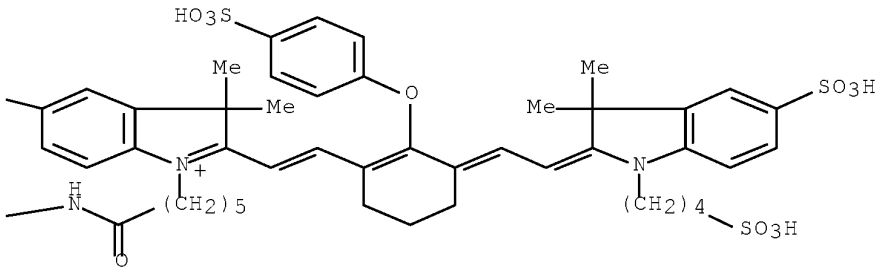
RN 1246261-16-4 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-[1,3-dihydro-3,3-dimethyl-5-sulfo-1-(4-sulfobutyl)-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-5-sulfo-1-[(12S,27S,31S)-12,27,31,33-tetracarboxy-6,14,21,29-tetraoxo-7,13,22,28,30-pentaazatritriacont-1-yl]-, inner salt (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

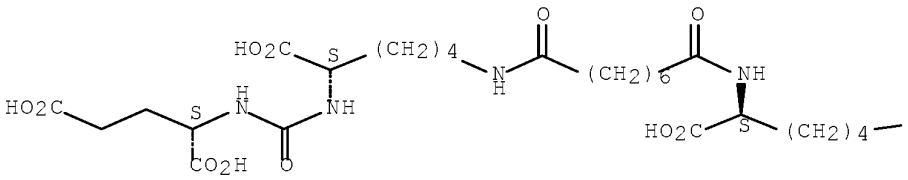


RN 1246261-17-5 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-[1,3-dihydro-3,3-dimethyl-1-(4-sulfobutyl)-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-1-[(12S,27S,31S)-12,27,31,33-tetracarboxy-6,14,21,29-tetraoxo-7,13,22,28,30-pentaazatritriacont-1-yl]-, inner salt (CA INDEX NAME)

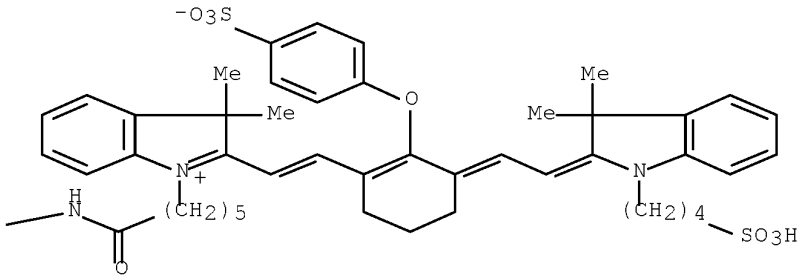
Absolute stereochemistry.
Double bond geometry unknown.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.293

PAGE 1-A



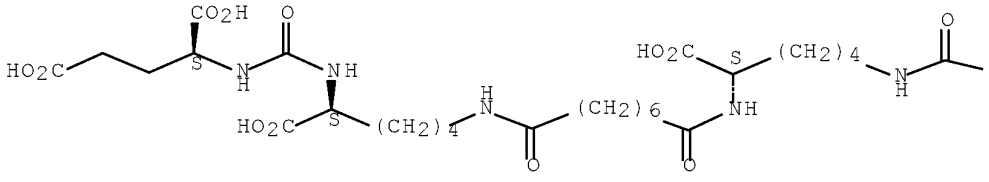
PAGE 1-B



RN 1246261-18-6 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-(1-ethyl-1,3-dihydro-3,3-dimethyl-2H-indol-2-ylidene)ethylidene]-2-phenoxy-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-1-(3-sulfopropyl)-5-[(7S,22S,26S)-7,22,26,28-tetracarboxy-1,9,16,24-tetraoxo-2,8,17,23,25-pentaazaoctacos-1-yl]-, inner salt (CA INDEX NAME)

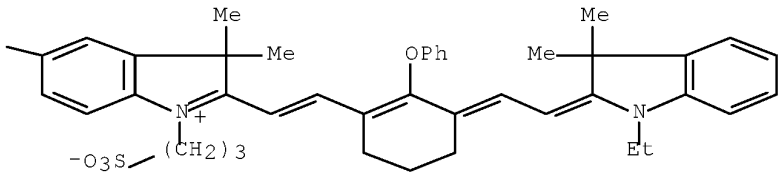
Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.294

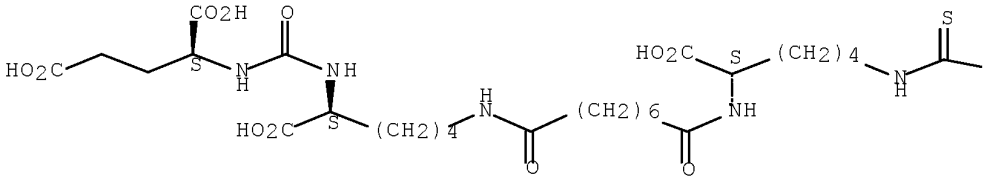
PAGE 1-B



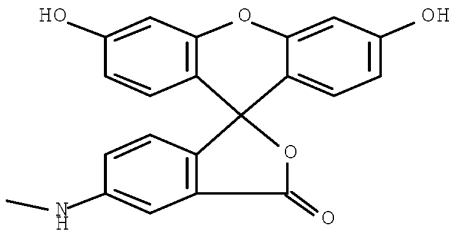
RN 1246261-19-7 CAPLUS
CN 3,12,18,20-Tetraazatetracosanedioic acid, 17,21-dicarboxy-2-[4-[[[(3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-5-yl)amino]thioxomethyl]amino]butyl]-4,11,19-trioxo-, (2S,17S,21S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



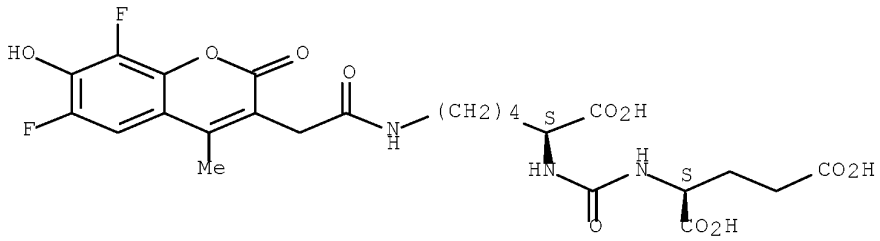
PAGE 1-B



RN 1246261-20-0 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-1-carboxy-5-[[2-(6,8-difluoro-7-hydroxy-4-methyl-2-oxo-2H-1-benzopyran-3-yl)acetyl]amino]pentyl]amino]carbonyl]- (CA INDEX NAME)

Absolute stereochemistry.

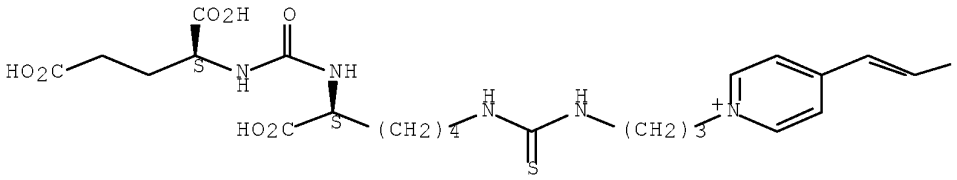
Fusion Pharmaceuticals, Inc.
Exhibit 1004.295



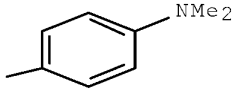
RN 1246261-21-1 CAPLUS
CN Pyridinium, 4-[2-[4-(dimethylamino)phenyl]ethenyl]-1-[(11S,15S)-11,15,17-tricarboxy-13-oxo-5-thioxo-4,6,12,14-tetraazaheptadec-1-yl]- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

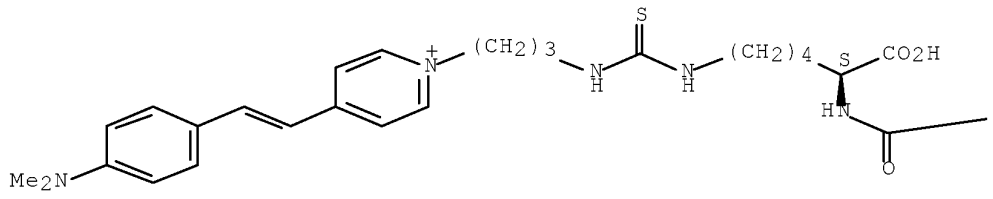


RN 1246261-22-2 CAPLUS
CN Pyridinium, 4-[2-[4-(dimethylamino)phenyl]ethenyl]-1-[(11S,26S,30S)-11,26,30,32-tetracarboxy-13,20,28-trioxo-5-thioxo-4,6,12,21,27,29-hexaazadotriacont-1-yl]- (CA INDEX NAME)

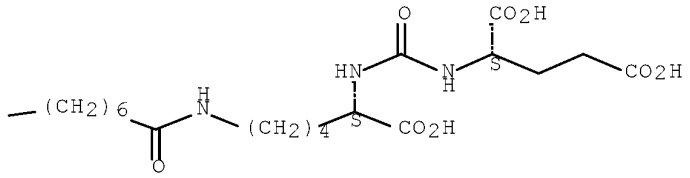
Absolute stereochemistry.
Double bond geometry unknown.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.296

PAGE 1-A



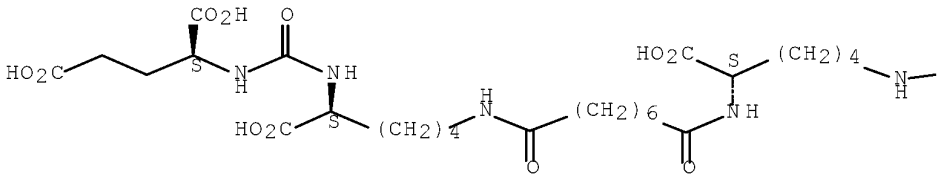
PAGE 1-B



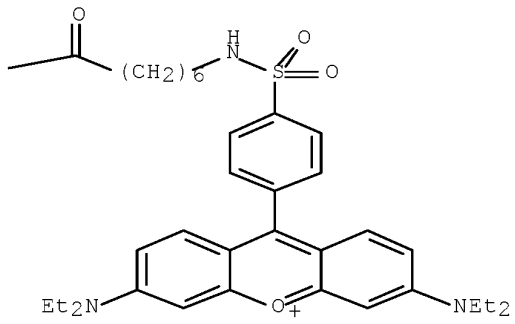
RN 1246261-23-3 CAPLUS
CN Xanthylium, 3,6-bis(diethylamino)-9-[4-[[[(13S,28S,32S)-13,28,32,34-tetracarboxy-7,15,22,30-tetraoxo-8,14,23,29,31-pentaazatetratriacont-1-yl]amino]sulfonyl]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



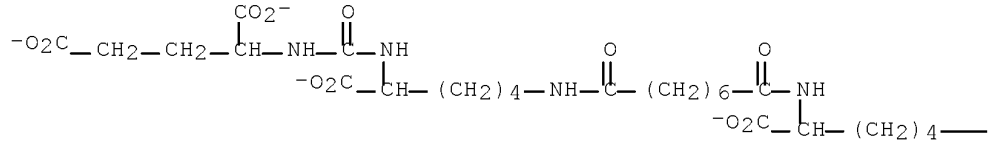
PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.297

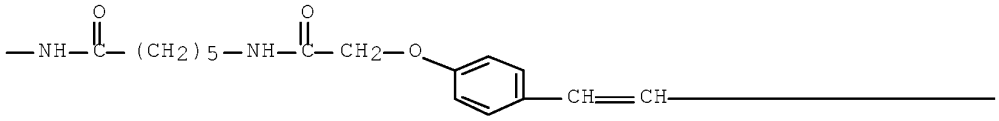
RN 1246300-45-7 CAPLUS
CN Borate(4-), [(3S,7S,22S)-36-[4-[2-[2-[([2,2'-bi-1H-pyrrol]-5-yl-κN1)methylene]-2H-pyrrol-5-yl-κN]ethenyl]phenoxy]-5,13,20,28,35-pentaoxo-4,6,12,21,27,34-hexaazahexacontane-1,3,7,22-tetracarboxylato(5-)]difluoro-, hydrogen (1:4), (T-4)- (CA INDEX NAME)

PAGE 1-A

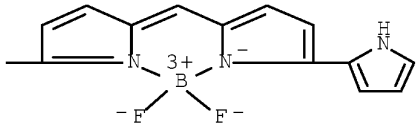


●4 H+

PAGE 1-B



PAGE 1-C

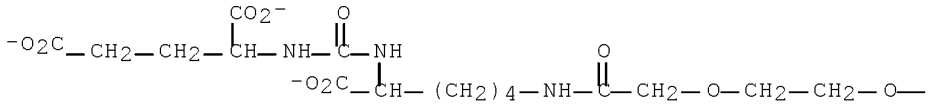


RN 1246300-46-8 CAPLUS
CN Borate(3-), [(3S,7S)-30-[4-[2-[2-[([2,2'-bi-1H-pyrrol]-5-yl-

Fusion Pharmaceuticals, Inc.
Exhibit 1004.298

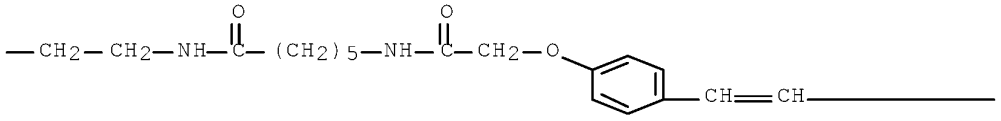
κN1)methylene]-2H-pyrrol-5-yl-κN]ethenyl]phenoxy]-5,13,22,29-tetraoxo-15,18-dioxa-4,6,12,21,28-pentaazatriacontane-1,3,7-tricarboxylato(4-)]difluoro-, hydrogen (1:3), (T-4)- (CA INDEX NAME)

PAGE 1-A

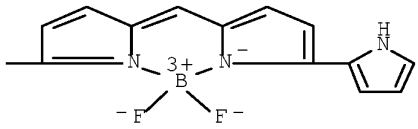


3 H+

PAGE 1-B



PAGE 1-C

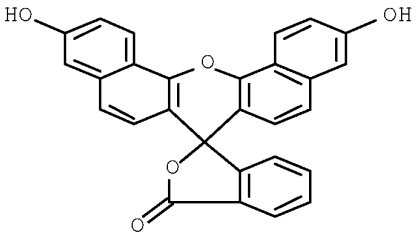


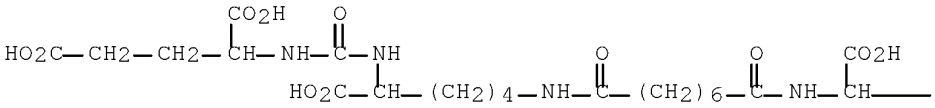
RN 1246300-47-9 CAPLUS

CN 4,6,12,21,27-Pentaazaoctacosane-1,3,7,22-tetracarboxylic acid, 28-[3,11-dihydroxy-3'-oxospiro[7H-dibenzo[c,h]xanthene-7,1'(3'H)-isobenzofuran]-5'(or 6')-yl]-5,13,20,28-tetraoxo- (CA INDEX NAME)

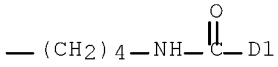
Fusion Pharmaceuticals, Inc.
Exhibit 1004.299

PAGE 1-A





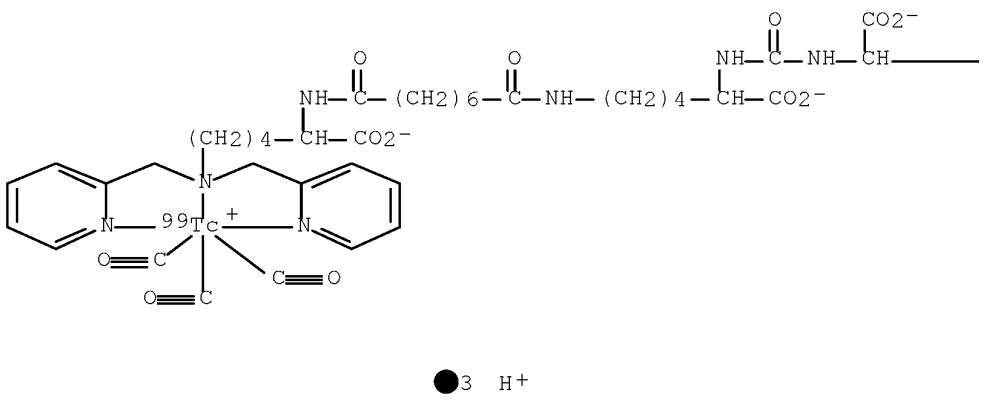
PAGE 1-B



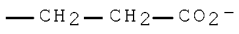
IT 1048338-01-7 1246300-40-2 1246300-42-4
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); BIOL (Biological study); USES (Uses)
(PSMA-targeting compds. preparation and use for cancer imaging)
RN 1048338-01-7 CAPLUS
CN Technetate(3-)-99Tc, tricarbonyl[(3S,7S,22R)-5,13,20-trioxo-28-(2-pyridinyl-κN)-27-[(2-pyridinyl-κN)methyl]-4,6,12,21,27-pentaazaoctacosane-1,3,7,22-tetracarboxylato(4-)-κN27]-, hydrogen (1:3) (CA INDEX NAME)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.300

PAGE 1-A



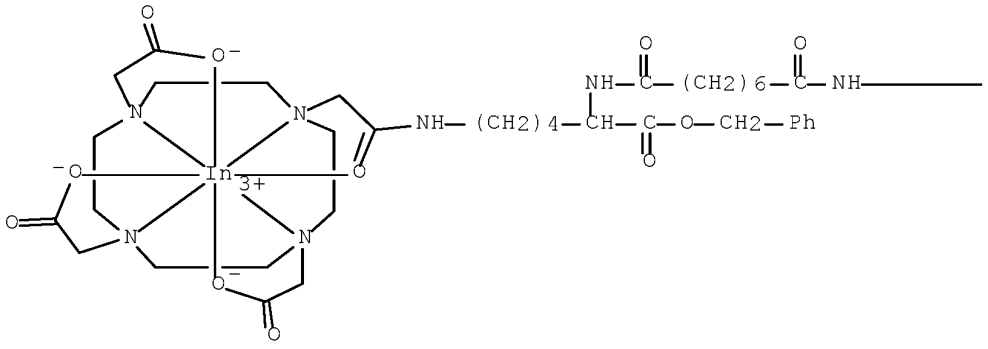
PAGE 1-B



RN 1246300-40-2 CAPLUS

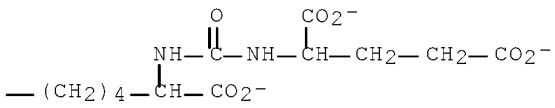
CN Indate(3-), [N-[[[1-carboxy-5-[[1,8-dioxo-8-[[1-[(phenylmethoxy)carbonyl]-5-[[2-[4,7,10-tris[(carboxy-κO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κN1,κN4,κN7,κN10]acetyl-κO]amino]pentyl]amino]octyl]amino]pentyl]amino]carbonyl]glutamato(6-)]-, hydrogen (1:3) (CA INDEX NAME)

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.301

PAGE 1-B

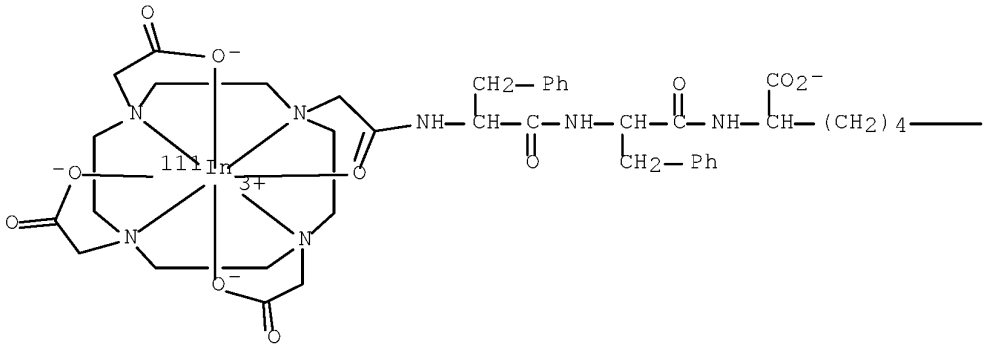


●3 H^+

RN 1246300-42-4 CAPLUS

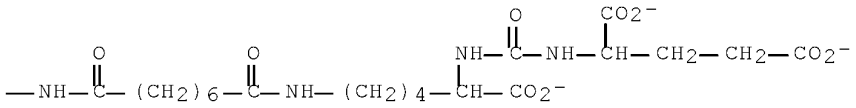
CN Indate(4-)-111In, [N-[2-[4,7,10-tris[(carboxy-κO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κN1,κN4,κN7,κN10]acetyl-κO]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-L-lysinato(7-)]-, hydrogen (1:4) (CA INDEX NAME)

PAGE 1-A



●4 H^+

PAGE 1-B



IT 1246261-00-6P, Tc-99m-labeled 1246300-37-7P 1246300-43-5P 1246300-44-6P

RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)

(PSMA-targeting compds. preparation and use for cancer imaging)

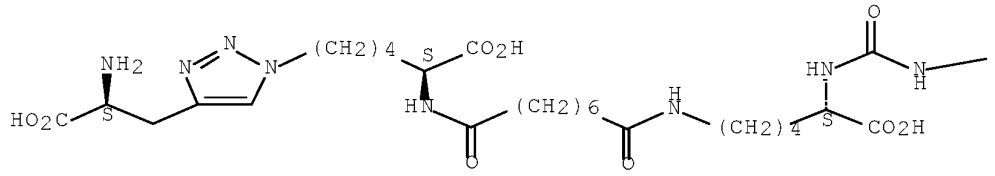
RN 1246261-00-6 CAPLUS

Fusion Pharmaceuticals, Inc.
Exhibit 1004.302

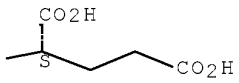
CN 3,12,18,20-Tetraazatetracosanedioic acid, 2-[4-[4-[(2S)-2-amino-2-carboxyethyl]-1H-1,2,3-triazol-1-yl]butyl]-17,21-dicarboxy-4,11,19-trioxo-, (2S,17S,21S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

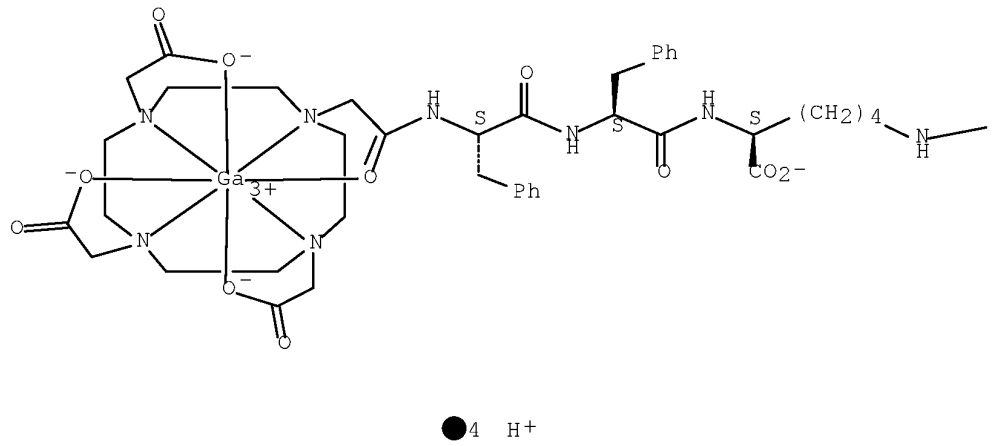


RN 1246300-37-7 CAPLUS

CN Gallate(4-), [N-[2-[4,7,10-tris[(carboxy-κO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κN1,κN4,κN7,κN10]acetyl-κO]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-L-lysinato(7-)]-, hydrogen (1:4) (CA INDEX NAME)

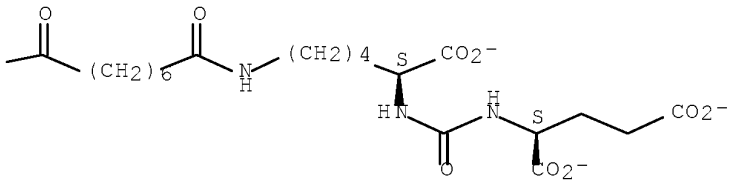
Absolute stereochemistry.

PAGE 1-A



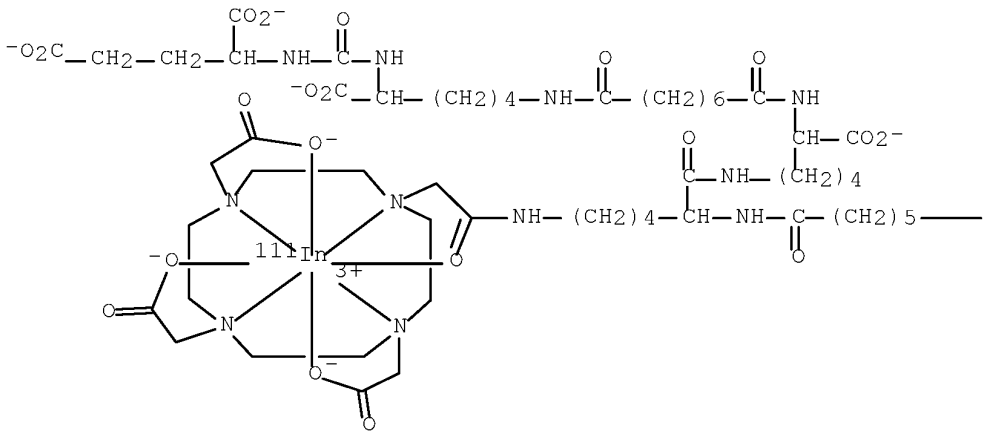
Fusion Pharmaceuticals, Inc.
Exhibit 1004.303

PAGE 1-B



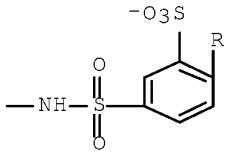
RN 1246300-43-5 CAPLUS
CN Indate(4-)-111In, [N6-[N2-[6-[[[4-[3,6-bis(diethylamino)xanthylium-9-yl]-3-sulfophenyl]sulfonyl]amino]-1-oxohexyl]-N6-[2-[4,7,10-tris[(carboxy-κO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κN1,κN4,κN7,κN10]acetyl-κO]-L-lysyl]-N2-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-L-lysinato(8-)]-, hydrogen (1:4) (CA INDEX NAME)

PAGE 1-A

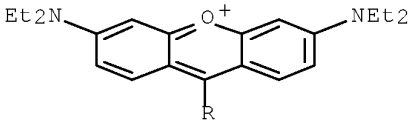


Fusion Pharmaceuticals, Inc.
Exhibit 1004.304

PAGE 1-B



PAGE 2-A

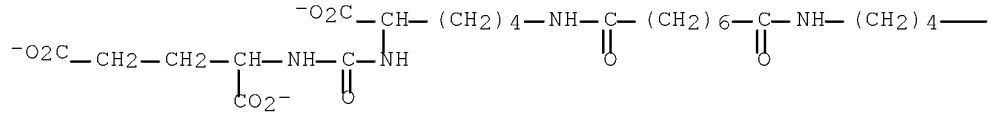


● 4 H+

RN 1246300-44-6 CAPLUS

CN Technetate(5-)-99Tc, [N-[2-(mercapto-κS)acetyl]glycyl-κN-glycyl-κN-L-phenylalanyl-κN-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-L-lysinato(8-)]oxo-, hydrogen (1:4), (SP-5-25)- (CA INDEX NAME)

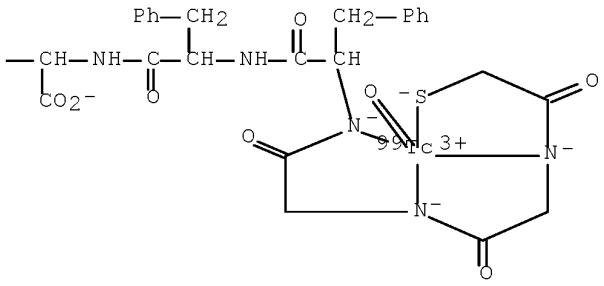
PAGE 1-A



● 4 H+

Fusion Pharmaceuticals, Inc.
Exhibit 1004.305

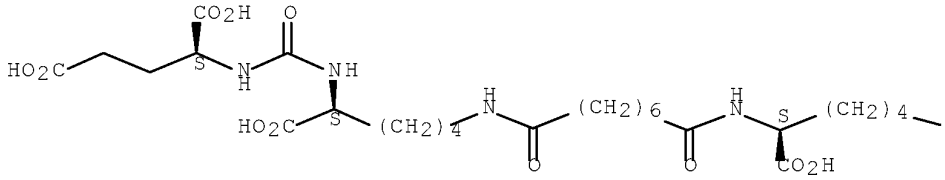
PAGE 1-B



IT 1095118-46-9P 1246261-11-9P 1246261-26-6P
1246300-34-4P
RL: DGN (Diagnostic use); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(PSMA-targeting compds. preparation and use for cancer imaging)
RN 1095118-46-9 CAPLUS
CN 4,6,12,21-Tetraazahexacosane-1,3,7,22-tetracarboxylic acid, 26-amino-5,13,20-trioxo-, (3S,7S,22S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

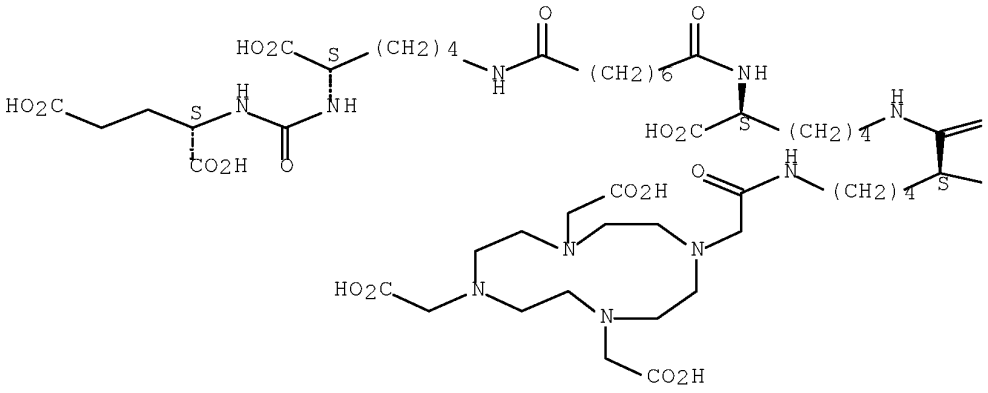


RN 1246261-11-9 CAPLUS
CN Xanthylium, 3,6-bis(diethylamino)-9-[2-sulfo-4-[[[(8S,15S,30S,34S)-15,30,34,36-tetracarboxy-6,9,17,24,32-pentaoxo-8-[4-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]butyl]-7,10,16,25,31,33-hexaazahexatriacont-1-yl]amino]sulfonyl]phenyl]-, inner salt (CA INDEX NAME)

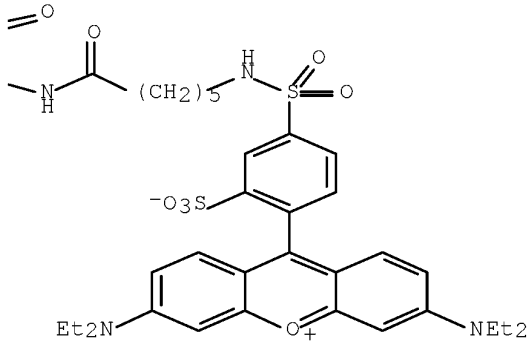
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.306

PAGE 1-A



PAGE 1-B

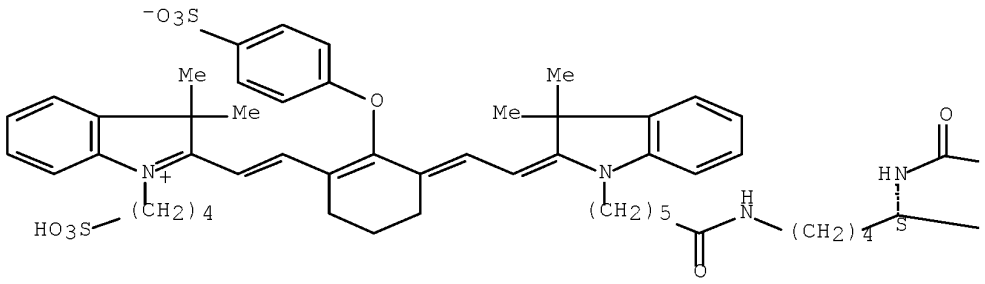


RN 1246261-26-6 CAPLUS
CN 3H-Indolium, 2-[2-[3-[2-[1-[6-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-6-oxohexyl]-1,3-dihydro-3,3-dimethyl-2H-indol-2-ylidene]ethylidene]-2-(4-sulfophenoxy)-1-cyclohexen-1-yl]ethenyl]-3,3-dimethyl-1-(4-sulfobutyl)-, inner salt (CA INDEX NAME)

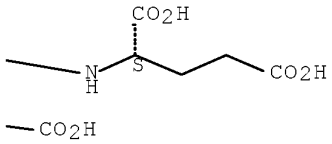
Absolute stereochemistry.
Double bond geometry unknown.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.307

PAGE 1-A

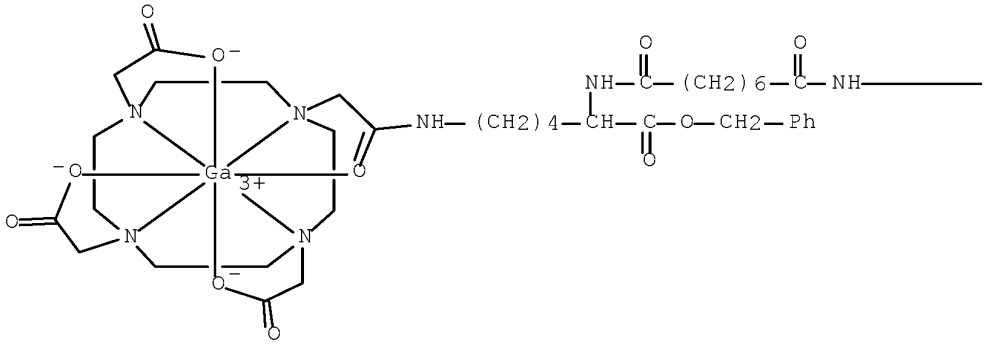


PAGE 1-B



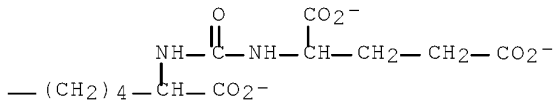
RN 1246300-34-4 CAPLUS
CN Gallate(3-), [22-(phenylmethyl) (3S,7S,22S)-5,13,20-trioxo-26-[[2-[4,7,10-tris[(carboxy-κO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-κN1,κN4,κN7,κN10]acetyl-κO]amino]-4,6,12,21-tetraazahexacosane-1,3,7,22-tetracarboxylato(6-)]-, hydrogen (1:3) (CA INDEX NAME)

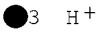
PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.308

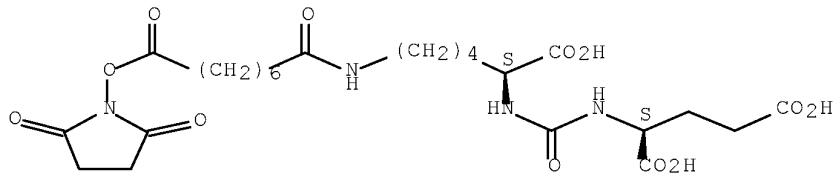
PAGE 1-B





IT 1159849-86-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(PSMA-targeting compds. preparation and use for cancer imaging)
RN 1159849-86-1 CAPLUS
CN L-Glutamic acid, N-[[[(1S)-1-carboxy-5-[[8-[(2,5-dioxo-1-pyrrolidinyl)oxy]-1,8-dioxooctyl]amino]pentyl]amino]carbonyl]- (CA INDEX NAME)

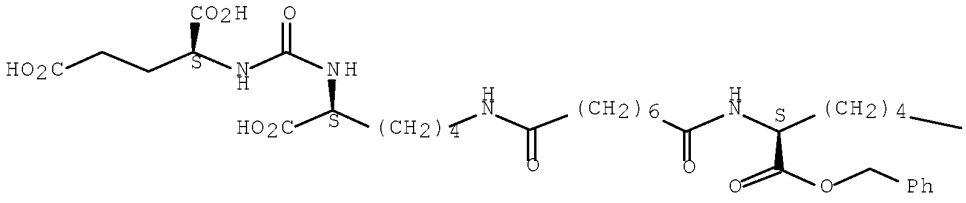
Absolute stereochemistry.



IT 1235548-79-4P 1235548-80-7P 1235548-82-9P
1246261-00-6P 1246261-25-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(PSMA-targeting compds. preparation and use for cancer imaging)
RN 1235548-79-4 CAPLUS
CN 3,12,18,20-Tetraazatetracosanedioic acid, 2-(4-aminobutyl)-17,21-dicarboxy-4,11,19-trioxo-, 1-(phenylmethyl) ester, (2S,17S,21S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.309

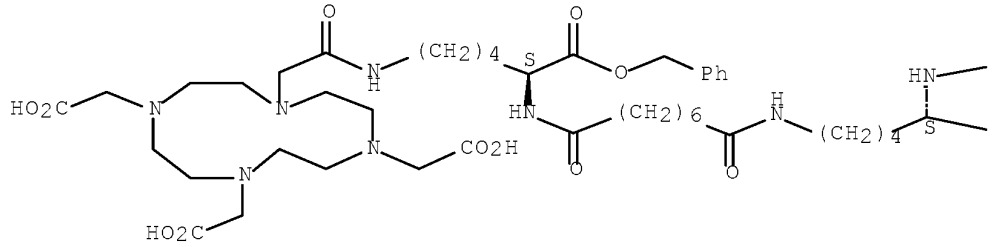
PAGE 1-B



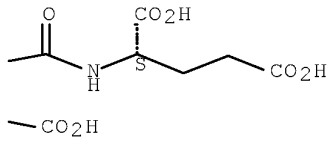
RN 1235548-80-7 CAPLUS
CN 4,6,12,21-Tetraazahexacosane-1,3,7,22-tetracarboxylic acid, 5,13,20-trioxo-26-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]-, 22-(phenylmethyl) ester, (3S,7S,22S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

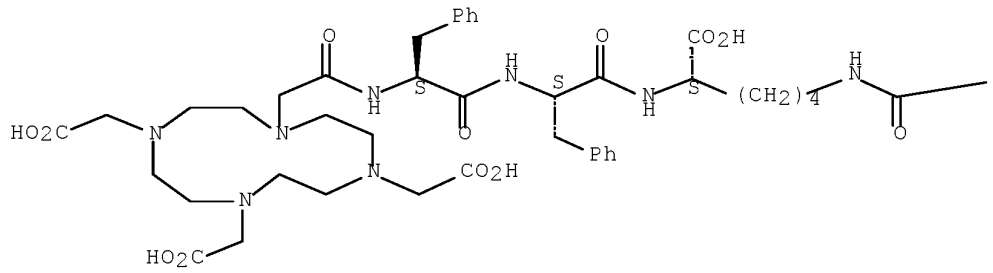


RN 1235548-82-9 CAPLUS
CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

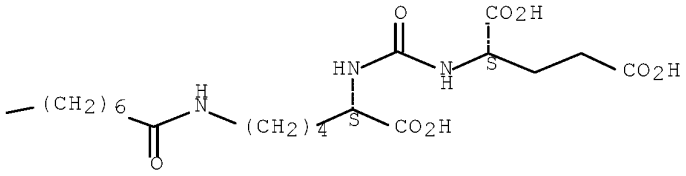
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.310

PAGE 1-A



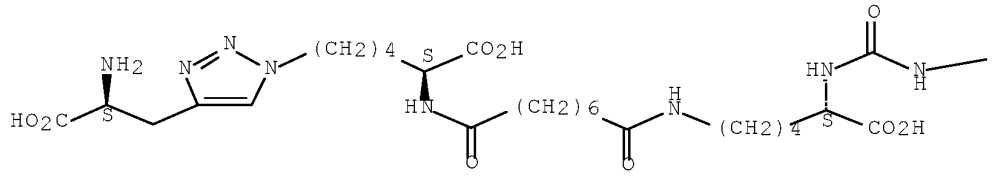
PAGE 1-B



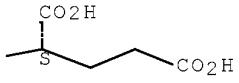
RN 1246261-00-6 CAPLUS
CN 3,12,18,20-Tetraazatetracosanedioic acid,
2-[4-[4-[(2S)-2-amino-2-carboxyethyl]-1H-1,2,3-triazol-1-yl]butyl]-17,21-dicarboxy-4,11,19-trioxo-, (2S,17S,21S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

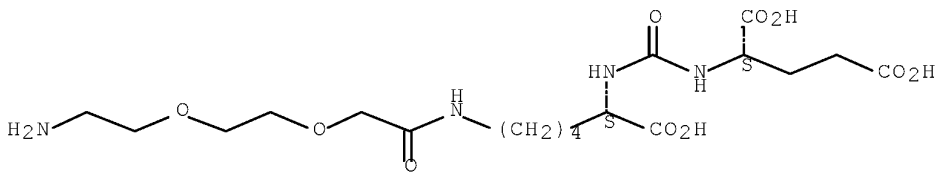


RN 1246261-25-5 CAPLUS
CN 15,18-Dioxa-4,6,12-triazaeicosane-1,3,7-tricarboxylic acid,

Fusion Pharmaceuticals, Inc.
Exhibit 1004.311

20-amino-5,13-dioxo-, (3S,7S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L133 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2010:786919 CAPLUS Full-text
DOCUMENT NUMBER: 153:196131
TITLE: 68Ga-Labeled Inhibitors of Prostate-Specific Membrane Antigen (PSMA) for Imaging Prostate Cancer
AUTHOR(S): Banerjee, Sangeeta Ray; Pullambhatla, Mrudula; Byun, Youngjoo; Nimmagadda, Sridhar; Green, Gilbert; Fox, James J.; Horti, Andrew; Mease, Ronnie C.; Pomper, Martin G.
CORPORATE SOURCE: Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins Medical Institutions, Baltimore, MD, 21231, USA
SOURCE: Journal of Medicinal Chemistry (2010), 53(14), 5333-5341
CODEN: JMCMAR; ISSN: 0022-2623
DIGITAL OBJECT ID: 10.1021/jm100623e
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 153:196131

AB Gallium-68 is a generator-produced radionuclide for positron emission tomog. (PET) that is being increasingly used for radiolabeling of tumor-targeting peptides. Compds. [68Ga]3 and [68Ga]6 are high-affinity urea-based inhibitors of the prostate-specific membrane antigen (PSMA) that were synthesized in decay-uncorrected yields ranging from 60% to 70% and radiochem. purities of more than 99%. Compound [68Ga]3 demonstrated 3.78 ± 0.90% injected dose per g of tissue (%ID/g) within PSMA+ PIP tumor at 30 min postinjection, while [68Ga]6 showed a 2 h PSMA+ PIP tumor uptake value of 3.29 ± 0.77 %ID/g. Target (PSMA+ PIP) to nontarget (PSMA- flu) ratios were 4.6 and 18.3, resp., at those time points. Both compds. delineated tumor clearly by small animal PET. The urea series of imaging agents for PSMA can be radiolabeled with 68Ga, a cyclotron-free isotope useful for clin. PET studies, with maintenance of target specificity.

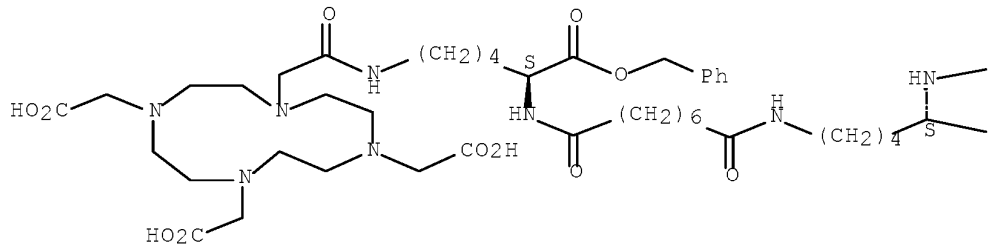
IT 1235548-80-7P 1235548-82-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(68Ga-labeled inhibitors of PSMA for imaging of prostate cancer)

RN 1235548-80-7 CAPLUS
CN 4,6,12,21-Tetraazahexacosane-1,3,7,22-tetracarboxylic acid, 5,13,20-trioxo-26-[[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]amino]-, 22-(phenylmethyl) ester, (3S,7S,22S)- (CA INDEX NAME)

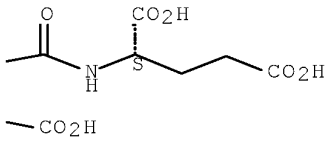
Fusion Pharmaceuticals, Inc.
Exhibit 1004.312

Absolute stereochemistry.

PAGE 1-A



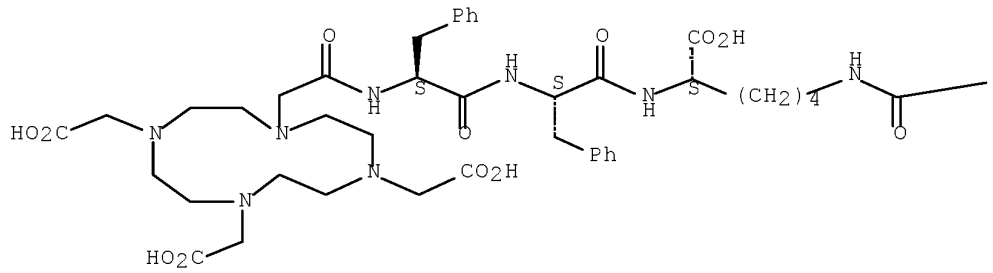
PAGE 1-B



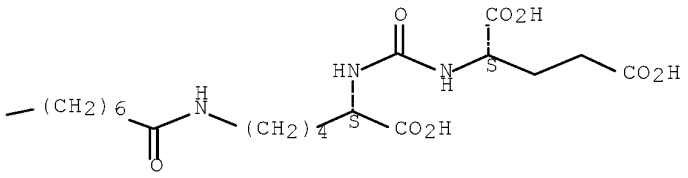
RN 1235548-82-9 CAPLUS
CN L-Lysine, N-[2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-L-phenylalanyl-N6-[8-[[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.313



OS.CITING REF COUNT: 76 THERE ARE 76 CAPLUS RECORDS THAT CITE THIS RECORD (78 CITINGS)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L133 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2010:721186 CAPLUS Full-text
DOCUMENT NUMBER: 153:75798
TITLE: Synthesis of technetium- and rhenium-bis(heteroaryl) complexes and methods of use thereof for inhibiting PSMA
INVENTOR(S): Babich, John W.; Zimmerman, Craig; Joyal, John; Maresca, Kevin P.; Lu, Genliang; Hillier, Shawn
PATENT ASSIGNEE(S): Molecular Insight Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010065902	A2	20100610	WO 2009-US66836	20091204
WO 2010065902	A3	20110217		
W: 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, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: 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, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
CA 2745955	A1	20100610	CA 2009-2745955	20091204
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US 20100178246	A1	20100715	US 2009-631337	20091204
US 8211401	B2	20120703		
AU 2009322167	A1	20110707	AU 2009-322167	20091204
AU 2009322167	B2	20141120		
EP 2389361	A2	20111130	EP 2009-775429	20091204
EP 2389361	B1	20160824		
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.314

CN 102272100	A	20111207	CN 2009-80153722	20091204
CN 102272100	B	20160817		
JP 2012511023	T	20120517	JP 2011-539755	20091204
JP 5220203	B2	20130626		
EP 2759535	A1	20140730	EP 2014-155382	20091204
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RU 2532912	C2	20141120	RU 2011-127468	20091204
ES 2595128	T3	20161227	ES 2009-775429	20091204

PRIORITY APPLN. INFO.:

US 2008-61120226	P	20081205
US 2009-61180341	P	20090521
EP 2009-775430	A3	20091204
WO 2009-US66836	W	20091204

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 153:75798; MARPAT 153:75798
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

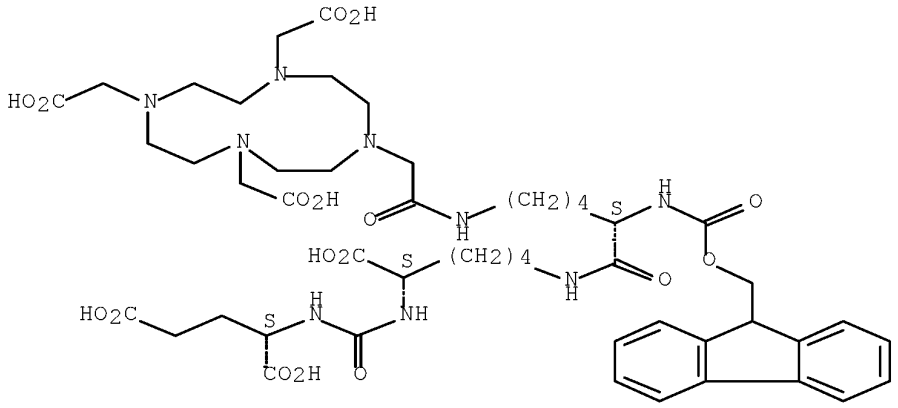
AB The synthesis is described for glutamate derivs. with nitrogen chelating groups (I; R = H, ammonium ion, alkylammonium ion, alkaline earth metal ion, rare earth metal ion or an alkyl group; Z and W are bonds or linking groups; NRaRb is a chelating group), a pharmaceutically acceptable salt, or solvate thereof, complexes with metals such as rhenium, technetium, and others to provide a complex for imaging tissues or treating disease, particularly where the metal is radioactive. Such complexes are specific to PSMA protein and can therefore be used in imaging or treating cancer of the prostate and other tissue where the protein is expressed. Thus the rhenium chelate (II) and related complexes were prepared and biodistribution imaging studies performed with related 99mTc complexes.

IT 1228969-25-2P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of rhenium and technetium complexes with glutamic acid derivs. with bis(heteroaryl) chelating groups for use in imaging and treating prostate cancer)

RN 1228969-25-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.315



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L133 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2009:1755 CAPLUS Full-text
DOCUMENT NUMBER: 150:92568
TITLE: Labeled inhibitors of prostate specific membrane antigen (psma), biological evaluation, and use as imaging agents
INVENTOR(S): Pomper, Martin Gilbert; Ray, Sangeeta; Mease, Ronnie C.; Foss, Catherine
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 91pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009002529	A2	20081231	WO 2008-US7947	20080626
WO 2009002529	A3	20090212		
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AU 2008269094	B2	20150409		
CA 2694266	A1	20081231	CA 2008-2694266	20080626
CA 2694266	C	20160614		
CA 2926573	A1	20081231	CA 2008-2926573	20080626

Fusion Pharmaceuticals, Inc.
Exhibit 1004.316

EP 2170075	A2	20100407	EP 2008-779786		20080626
EP 2170075	B1	20141203			
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CN 101784192	B	20150318			
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JP 5680409	B2	20150304			
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EP 2921482	A2	20150923	EP 2014-195837		20080626
EP 2921482	A3	20151104			
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US 20150246144	A1	20150903	US 2015-14715115		20150518
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			EP 2008-779786	A3	20080626
			WO 2008-US7947	W	20080626
			US 2010-666441	A3	20101122

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 150:92568

AB The prostate-specific membrane antigen (PSMA) is increasingly recognized as a viable target for imaging and therapy of cancer. Various 99mTc/Re-labeled compds. were prepared by attaching known Tc/Re chelating agents to an amino- functionalized PSMA inhibitor with or without a variable length linker moiety. Ex vivo biodistribution and in vivo imaging demonstrated the degree of specific binding to engineered PSMA+ PC3 PIP tumors.

IT 1095118-43-6P 1095118-40-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(labeled conjugates of PSMA inhibitors and evaluation and use as tumor imaging agents)

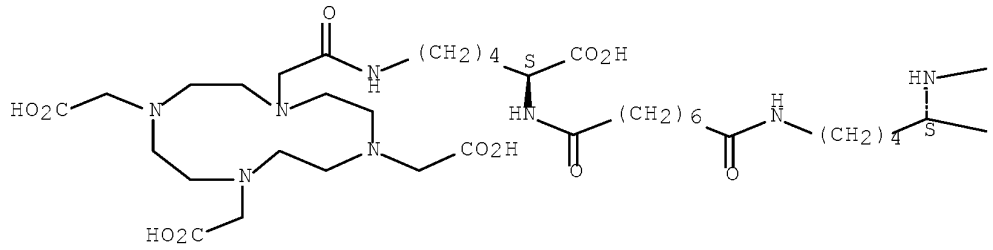
RN 1095118-43-6 CAPLUS

CN 4,6,12,21,27-Pentaazanonacosane-1,3,7,22-tetracarboxylic acid, 5,13,20,28-tetraoxo-29-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-, (3S,7S,22S)- (CA INDEX NAME)

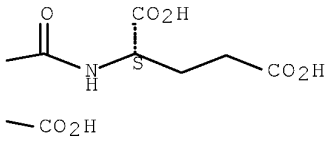
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.317

PAGE 1-A



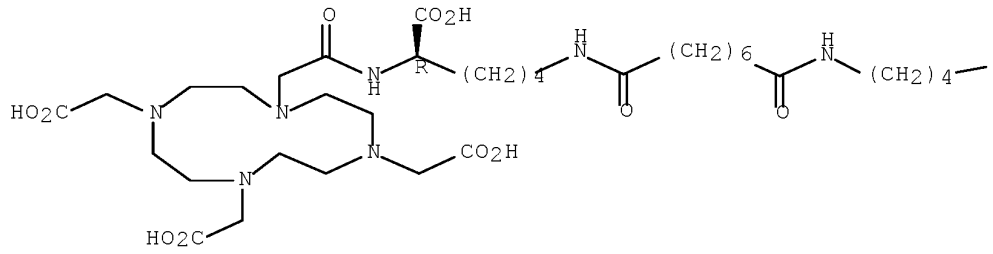
PAGE 1-B



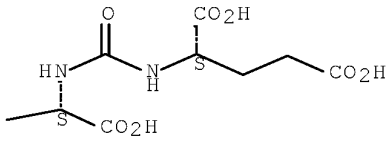
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CN 4,6,12,21,27-Pentaazanonacosane-1,3,7,26-tetracarboxylic acid, 5,13,20,28-tetraoxo-29-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-, (3S,7S,26R)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.318

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.319

STRUCTURE SEARCH PART 2

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FILE 'REGISTRY' ENTERED AT 15:33:28 ON 22 JUN 2017
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   21 JUN 2017  HIGHEST RN 2098835-24-4
DICTIONARY FILE UPDATES:  21 JUN 2017  HIGHEST RN 2098835-24-4

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

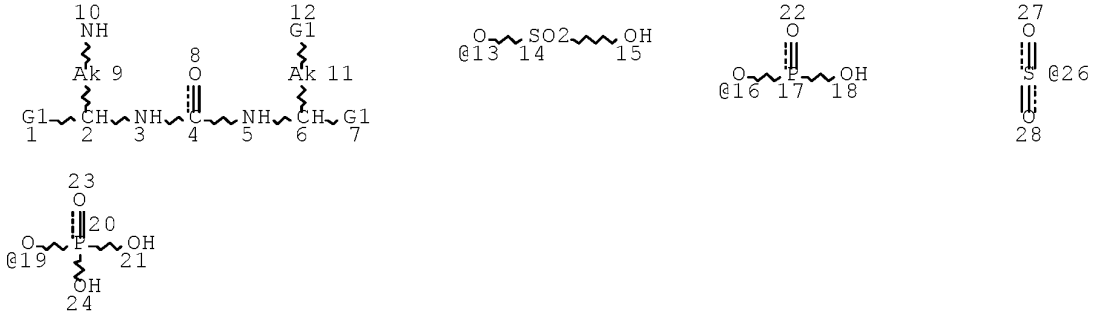
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 4, 2017

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific
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L99 STR



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CONNECT IS E2  RC AT  11
CONNECT IS E3  RC AT  26
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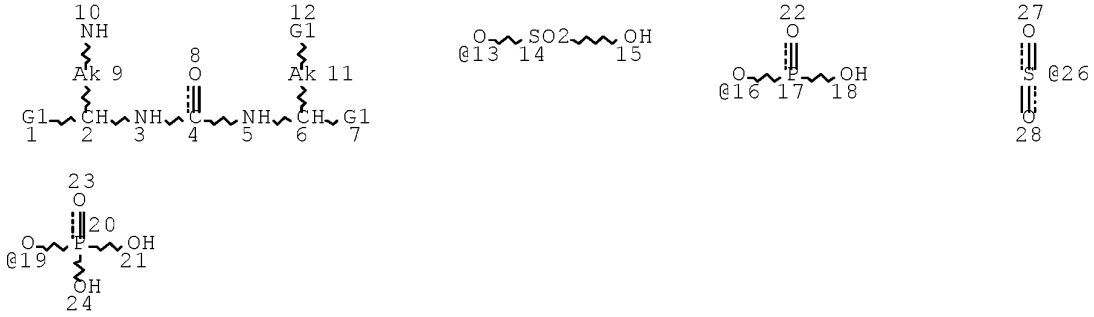

Fusion Pharmaceuticals, Inc.
Exhibit 1004.320

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

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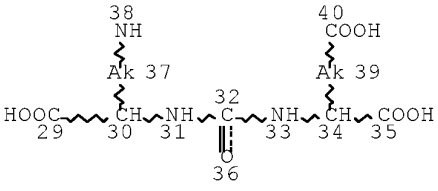
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.321

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L122          6 SEA FILE=CAPLUS SPE=ON  ABB=ON  L119 AND L68



FILE 'CAPLUS' ENTERED AT 15:33:28 ON 22 JUN 2017
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FILE COVERS 1907 - 22 Jun 2017 VOL 167 ISS 1
FILE LAST UPDATED: 21 Jun 2017 (20170621/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015

CAplus includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2017.

CAplus now includes the comprehensive Cooperative Patent Classification
(CPC).  See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


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Fusion Pharmaceuticals, Inc.
Exhibit 1004.322

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L134 ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER:         2017:78526  CAPLUS  Full-text
DOCUMENT NUMBER:          166:152904
TITLE:                    Preparation of gallium complex with
                          HBED-bisphosphonates conjugates as theranostic agents
INVENTOR(S):              Kung, Hank F.; Wu, Zehui; Choi, Seok Rye; Ploessl,
                          Karl; Zha, Zhihao
PATENT ASSIGNEE(S):       Five Eleven Pharma Inc., USA
SOURCE:                   PCT Int. Appl., 69pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
     PATENT NO.           KIND  DATE        APPLICATION NO.          DATE
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     WO 2017007790         A1   20170112    WO 2016-US41040          20160706
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             BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.323

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SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
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US 20170022224 A1 20170126 US 2016-15203602 20160706
PRIORITY APPLN. INFO.: US 2015-62189652 P 20150707
US 2016-62320296 P 20160408
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 166:152904; MARPAT 166:152904
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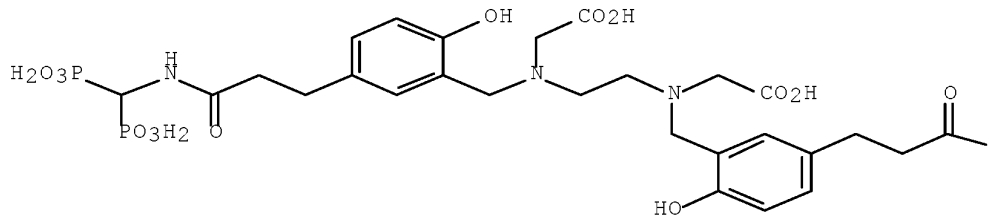
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to preparation of radiometal complexes with compds. (I), which are potential bone imaging agents and therapeutic agents for treating bone tumors and metastases (A is a divalent linking moiety comprising 1 to 10 carbon atoms in a chain, a ring, or a combination thereof, wherein at least one carbon atom is optionally replaced with O, -NR3-, or -C(O)-; E is CR4R5; X = amino acid, DOTA or sugar derivs., Z = independently CH or N; R1 = H or alkyl; R2 = H or a carboxylic acid protecting group; R3 = independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, alkylaryl, arylalkyl and heteroaryl; R4 and R5 = independently H, alkyl, ethylene glycolyl, or a propylene glycolyl). Certain compds. labeled with 68Ga displayed excellent bone uptake and retention. The present invention also relates to pharmaceutical compns. comprising a pharmaceutical acceptable carrier and a compound of (I) or a pharmaceutically acceptable salt thereof.

IT 2058323-15-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, biodistribution and PET imaging of gallium complex with HBED-bisphosphonates conjugates as theranostic agents)
RN 2058323-15-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

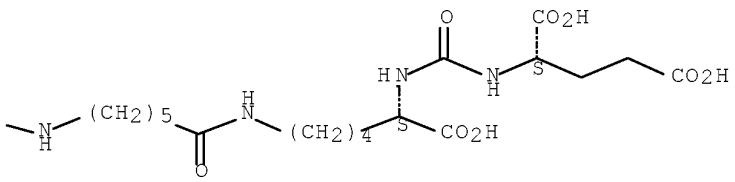
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.324

PAGE 1-B



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L134 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:1111486 CAPLUS Full-text
DOCUMENT NUMBER: 165:172513
TITLE: Conjugates for imaging
INVENTOR(S): Vlahov, Iontcho R.; Leamon, Christopher P.; Santhapuram, Hari Krishna R.
PATENT ASSIGNEE(S): Endocyte, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

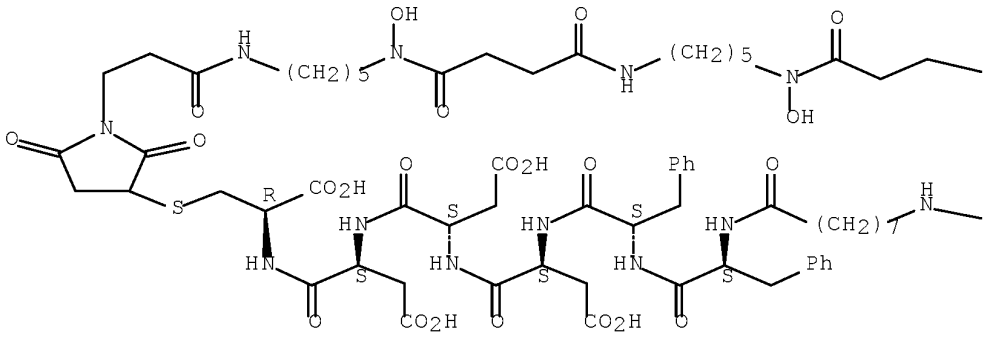
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160193371	A1	20160707	US 2016-14989498	20160106
PRIORITY APPLN. INFO.:			US 2015-62100677 P	20150107

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 165:172513
AB The invention described herein relates to conjugates and compns. for imaging, diagnosing, and/or monitoring diseases using radionuclide-based imaging. In particular, the invention described herein relates to conjugates and compns. for imaging, diagnosing, and/or monitoring diseases using positron emission tomog.
IT 1961308-17-7P, EC 2450 1961309-40-6P, EC 2458
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates for imaging)
RN 1961308-17-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

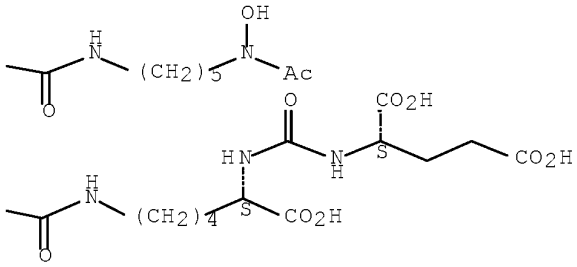
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.325

PAGE 1-A



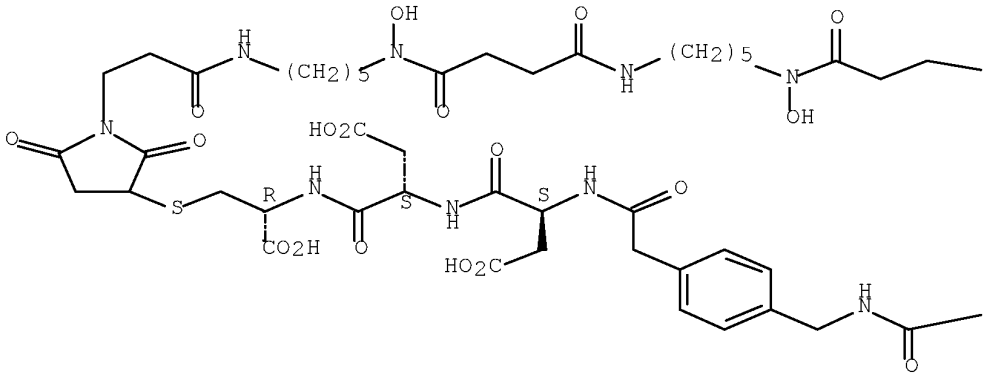
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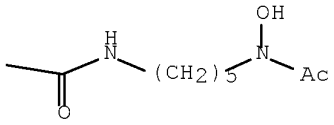
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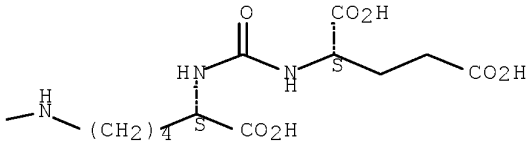
PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.326

PAGE 1-B





L134 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:891009 CAPLUS Full-text
DOCUMENT NUMBER: 165:133566
TITLE: Design of a Small-Molecule Drug Conjugate for Prostate Cancer Targeted Theranostics
AUTHOR(S): Kumar, Amit; Mastren, Tara; Wang, Bin; Hsieh, Jer-Tsong; Hao, Guiyang; Sun, Xiankai
CORPORATE SOURCE: Department of Radiology, Department of Urology, and Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: Bioconjugate Chemistry (2016), 27(7), 1681-1689
CODEN: BCCHES; ISSN: 1043-1802
DIGITAL OBJECT ID: 10.1021/acs.bioconjchem.6b00222
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASREACT 165:133566

AB Targeted therapy has become an effective strategy of precision medicine for cancer treatment. Based on the success of antibody-drug conjugates (ADCs), here we report a theranostic design of small-mol. drug conjugates (T-SMDCs) for targeted imaging and chemotherapy of prostate cancer. The structure of T-SMDCs built upon a polyethylene glycol (PEG) scaffold consists of (i) a chelating moiety for positron emission tomog. (PET) imaging when labeled with 68Ga, a positron-emitting radioisotope; (ii) a prostate specific membrane antigen (PSMA) specific ligand for prostate cancer targeting; and (iii) a cytotoxic drug (DM1) for chemotherapy. For proof-of-concept, such a T-SMDC, NO3A-DM1-Lys-Urea-Glu, was synthesized and evaluated. The chemical modification of Lys-Urea-Glu for the construction of the conjugate did not compromise its specific binding affinity to PSMA. The PSMA-mediated internalization of 68Ga-labeled NO3A-DM1-Lys-Urea-Glu displayed a time-dependent manner, allowing the desired drug delivery and release within tumor cells. The antiproliferative activity of the T-SMDC showed a pos. correlation with the PSMA expression level. Small animal PET imaging with 68Ga-labeled NO3A-DM1-Lys-Urea-Glu exhibited significantly higher uptake ($p < 0.01$) in the PSMA pos. PC3-PIP tumors (4.30 ± 0.20%ID/g) at 1 h postinjection than in the PSMA neg. PC3-Flu tumors (1.12 ± 0.42%ID/g). Taken together, we have successfully designed and synthesized a T-SMDC system for prostate cancer targeted imaging and therapy.

IT 1945992-74-4DP, gallium-68 complex

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Exhibit 1004.327

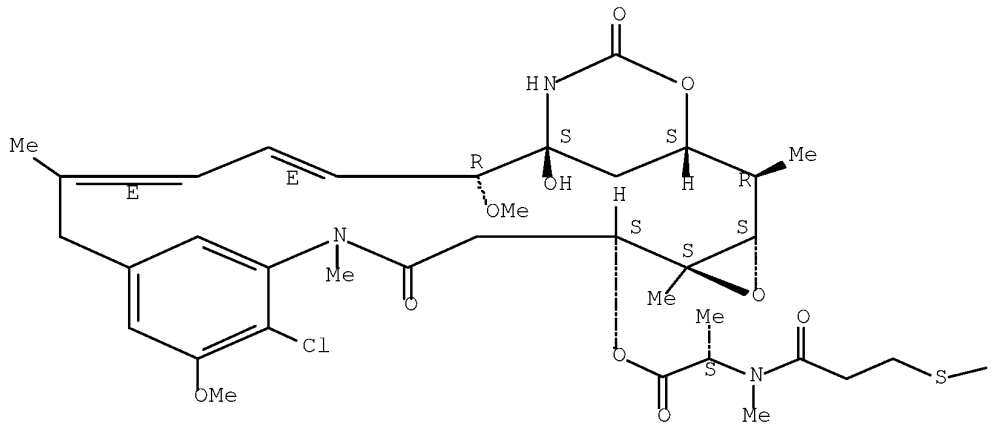
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(design of a small-mol. drug conjugate for prostate cancer targeted theranostics)

RN 1945992-74-4 CAPLUS

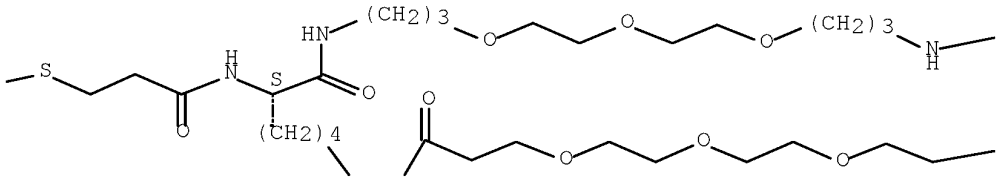
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

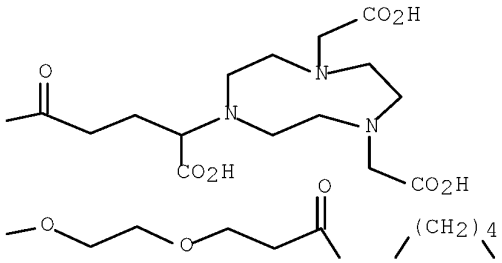


PAGE 1-B



Fusion Pharmaceuticals, Inc.
Exhibit 1004.328

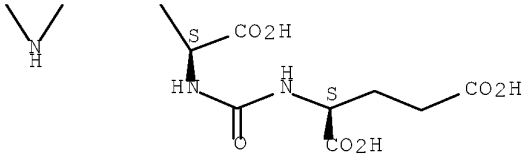
PAGE 1-C



PAGE 2-B



PAGE 2-C



RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design of a small-mol. drug conjugate for prostate cancer targeted theranostics

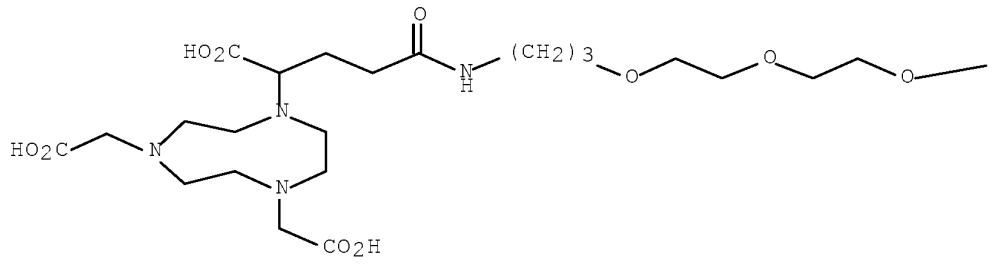
IT 1945992-79-9P 1945992-82-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design of a small-mol. drug conjugate for prostate cancer targeted theranostics)

RN 1945992-79-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

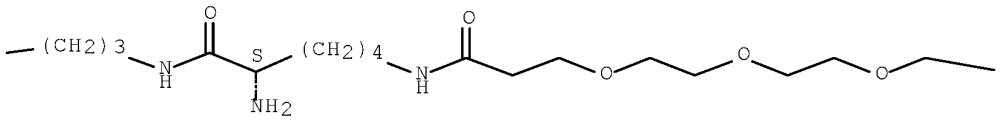
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.329

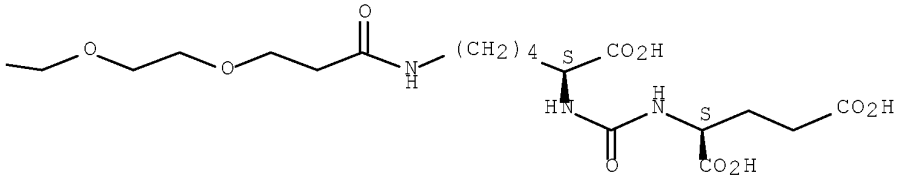
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PAGE 1-B



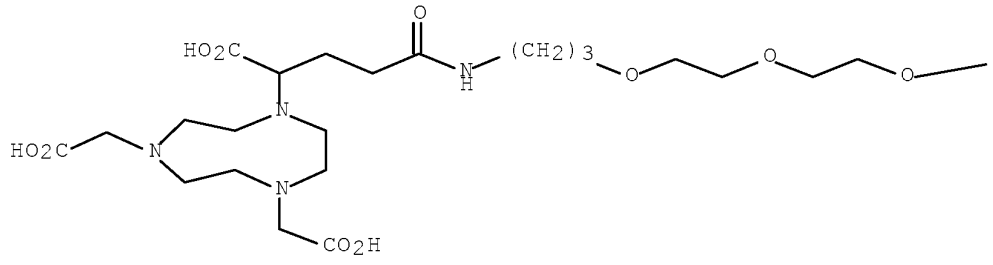
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RN 1945992-82-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

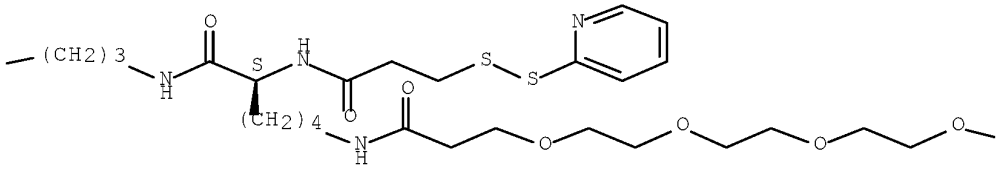
Absolute stereochemistry.

PAGE 1-A

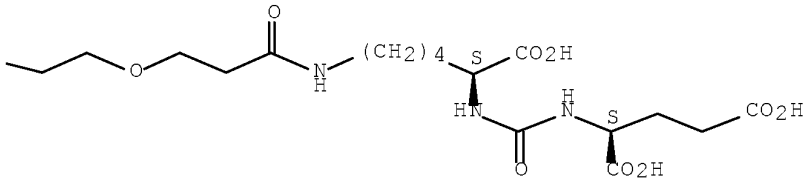


Fusion Pharmaceuticals, Inc.
Exhibit 1004.330

PAGE 1-B



PAGE 1-C



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L134 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2016:265455 CAPLUS Full-text
DOCUMENT NUMBER: 164:326784
TITLE: Methods and compositions for improved labeling of targeting peptides useful in detection, diagnosis, imaging and therapy of tumors
INVENTOR(S): McBride, William J.; Goldenberg, David M.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 99pp., Cont.-in-part of U.S. Ser. No. 755,712.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 92
PATENT INFORMATION:

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US 20160045626	A1	20160218	US 2015-14922619	20151026
US 20080170989	A1	20080717	US 2007-960262	20071219
US 7597876	B2	20091006		
AU 2007343600	A1	20080724	AU 2007-343600	20071219
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CA 2675202	A1	20080724	CA 2007-2675202	20071219
CA 2675202	C	20140916		

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Exhibit 1004.331

CN 101568352 A 20091028 CN 2007-80048376 20071219
CN 101568352 B 20130821
EP 2117604 A2 20091118 EP 2007-869485 20071219
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JP 2010515732 T 20100513 JP 2009-545555 20071219
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CN 103372221 A 20131030 CN 2013-10302558 20071219
CN 103372221 B 20160824
US 20080253964 A1 20081016 US 2008-112289 20080430
US 7563433 B2 20090721
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US 20150057432 A1 20150226 US 2014-14509679 20141008
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Exhibit 1004.332

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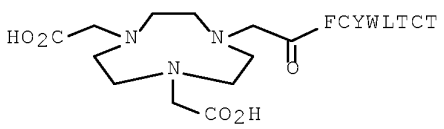
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WO	2015-US57350	W 20151026

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 164:326784

GI



I

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Exhibit 1004.333

AB The invention discloses compns. and methods of synthesis and use of labeled targeting peptides, such as octreotide, octreotate, or other somatostatin analogs or derivs., e.g., I. The targeting peptide may be labeled with a therapeutic or diagnostic isotope, such as 61Cu, 62Cu, 64Cu, 67Cu, 18F, 19F, 66Ga, 67Ga, 68Ga, 72Ga, 111In, 177Lu, 44Sc, 47Sc, 86Y, 88Y, 90Y, 45Ti or 89Zr, preferably 18F or 19F. More preferably, the targeting peptide is NOTA-octreotate, NOTA-MPAA-octreotate, pyridine-NOTA-octreotate or triazole-NOTA-octreotate. The labeled targeting peptides may be used for detection, diagnosis, imaging and/or treatment of sst2+ tumors, such as neuroendocrine tumors. The invention also discloses compns. and methods of synthesis and use of 18F or 19F-labeled mols., e.g., NODA-MPAA-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH2 [NODA = 1,4,7-triazacyclononane-1,4-diacetate; ; MPAA = methylphenylacetic acid; HSG = histamine succinylglycine] labeled with 18F by Al18F chelation, for use in PET, SPECT and/or MR imaging.

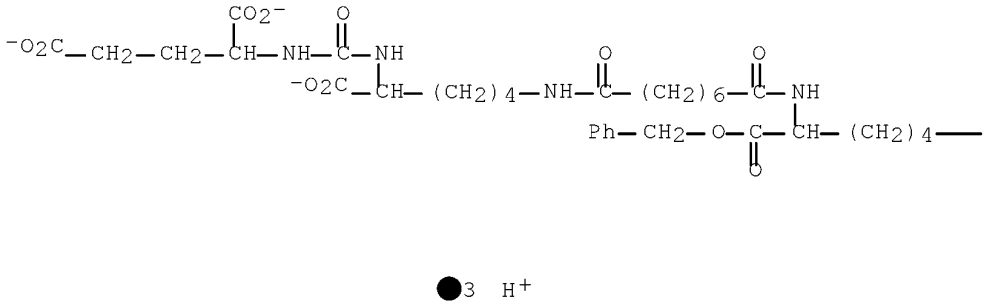
IT 1379601-63-4P 1379601-64-5P

RL: DGN (Diagnostic use); PRPH (Prophetic); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of labeled targeting peptides useful in detection, diagnosis, imaging and therapy of tumors)

RN 1379601-63-4 CAPLUS

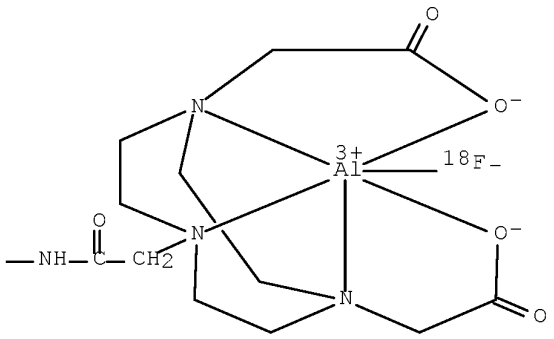
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PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.334

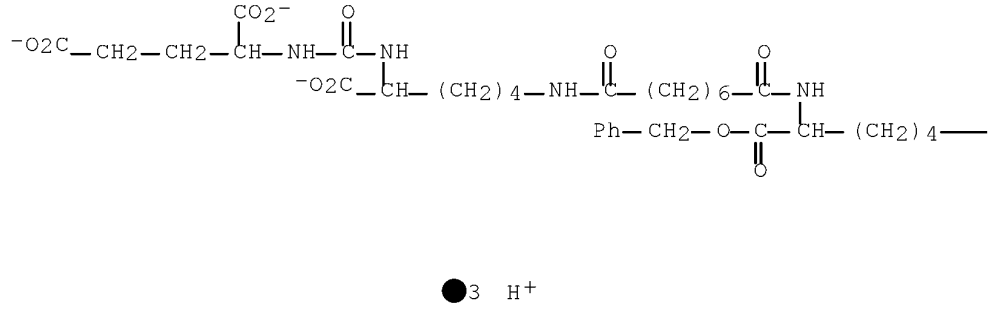
PAGE 1-B



RN 1379601-64-5 CAPLUS

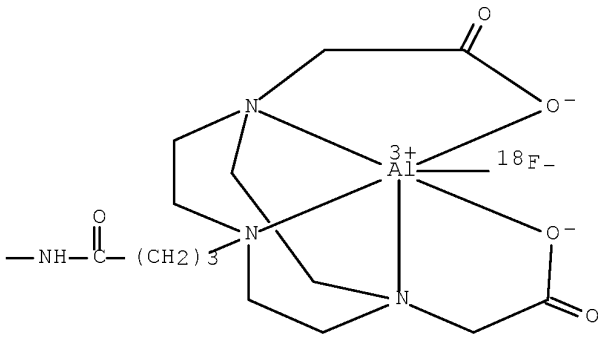
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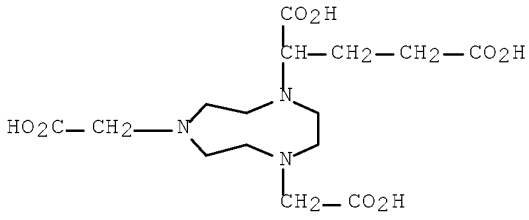


Fusion Pharmaceuticals, Inc.
Exhibit 1004.335

PAGE 1-B



IT 1092370-12-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of labeled targeting peptides useful in detection, diagnosis, imaging and therapy of tumors)
RN 1092370-12-1 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, α1-(2-carboxyethyl)hexahydro- (CA INDEX NAME)



L134 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:866259 CAPLUS Full-text
DOCUMENT NUMBER: 163:2276
TITLE: Compounds for positron emission tomography
INVENTOR(S): Vlahov, Iontcho R.; Leamon, Christopher P.; Low, Philip S.; Parham, Garth L.; Chen, Qingshou
PATENT ASSIGNEE(S): Endocyte, Inc., USA; Purdue Research Foundation
SOURCE: PCT Int. Appl., 109pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015073678	A1	20150521	WO 2014-US65467	20141113

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Fusion Pharmaceuticals, Inc.
Exhibit 1004.336

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HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
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KR 2016079887	A	20160706	KR 2016-7015740		20141113
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JP 2016540747	T	20161228	JP 2016-529948		20141113
US 20160287731	A1	20161006	US 2016-15035936		20160511
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IN 201617019424	A	20160831	IN 2016-17019424		20160606
PRIORITY APPLN. INFO.:			US 2013-61904387	P	20131114
			US 2013-61904400	P	20131114
			US 2013-61909822	P	20131127
			WO 2014-US65467	W	20141113

OTHER SOURCE(S): CASREACT 163:2276; MARPAT 163:2276

AB Described herein are compds., compns., and methods for diagnosing and/or monitoring pathogenic disease using positron emission tomog. Also described are conjugates of the formula B-L-P, wherein B is a radical of a targeting agent selected from vitamin receptor binding ligands (such as folate), PSMA binding ligands, or PSMA inhibitors; L is a divalent linker comprising aspartic acid, lysine, or arginine, and P is a radical of an imaging agent or radiotherapy agent, such as a radionuclide or radionuclide containing group, or a radical of a compound capable of binding a radionuclide, such as a metal chelating group.

IT 1778692-80-0P 1778692-92-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compds. for positron emission tomog.)

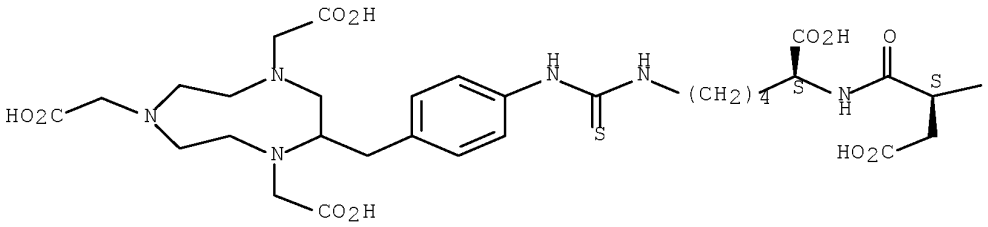
RN 1778692-80-0 CAPLUS

CN L-Lysine, N-[2-[4-[(9S,13S)-9,13,15-tricarboxy-3,11-dioxo-2,4,10,12-tetraazapentadec-1-yl]phenyl]acetyl]-L-α-aspartyl-L-α-aspartyl-N6-[thioxo[[4-[[1,4,7-tris(carboxymethyl)octahydro-1H-1,4,7-triazonin-2-yl]methyl]phenyl]amino]methyl]- (CA INDEX NAME)

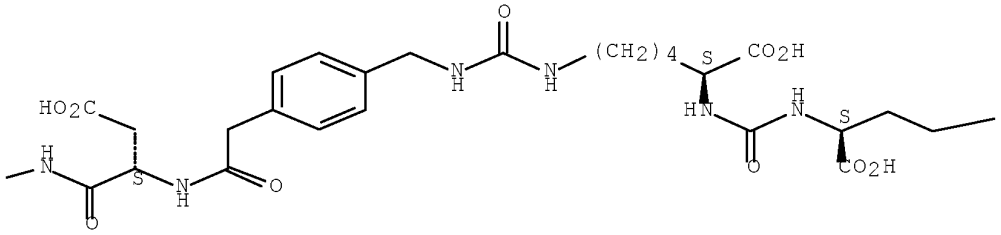
Absolute stereochemistry.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.337

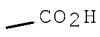
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PAGE 1-B



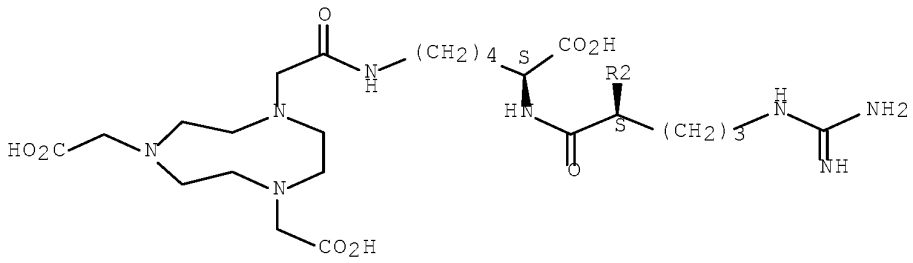
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RN 1778692-92-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

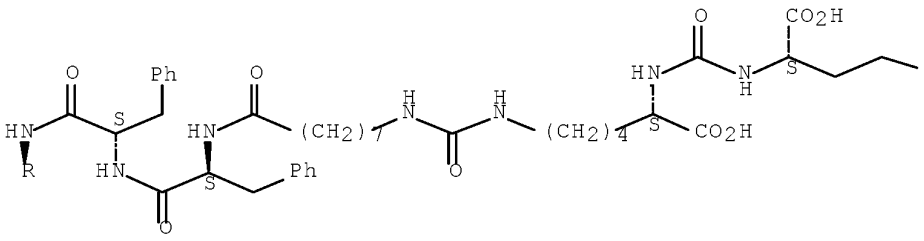
Absolute stereochemistry.

PAGE 1-A

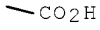


Fusion Pharmaceuticals, Inc.
Exhibit 1004.338

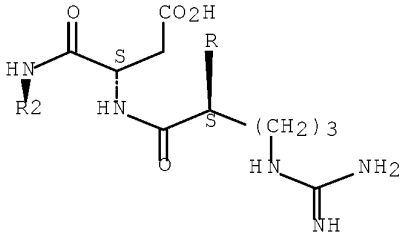
PAGE 2-A



PAGE 2-B



PAGE 3-A



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L134 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2015:731142 CAPLUS Full-text
DOCUMENT NUMBER: 164:136945
TITLE: Evaluation of PSMA PET/CT imaging using a 68Ga-HBED-CC ligand in patients with prostate cancer and the value of early pelvic imaging
AUTHOR(S): Kabasakal, Levent; Demirci, Emre; Ocak, Meltem; Akyel, Resit; Nematyazar, Jamal; Aygun, Aslan; Halac, Metin; Talat, Zubeyir; Araman, Ahmet
CORPORATE SOURCE: Department of Nuclear Medicine, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turk.
SOURCE: Nuclear Medicine Communications (2015), 36(6), 582-587 CODEN: NMCODC; ISSN: 0143-3636
DIGITAL OBJECT ID: 10.1097/MNM.0000000000000290

Fusion Pharmaceuticals, Inc.
Exhibit 1004.339

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

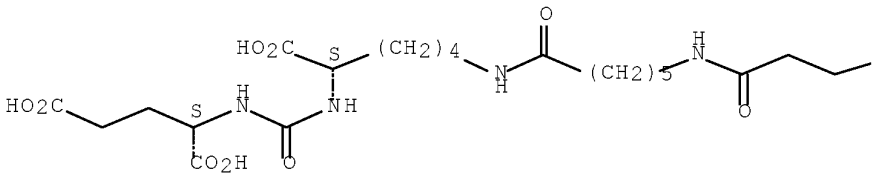
AB Purpose: The aim of the study was to evaluate the diagnostic value of the prostate-specific membrane antigen (PSMA) ligand Ga-HBED-CC (PSMA PET/CT) in patients with prostate cancer and evaluate the value of early imaging of the pelvis. Materials and methods: The files of 28 patients were retrospectively evaluated. All patients had a histopatol. confirmation of prostate cancer. PSMA PET/CT images were obtained at 5 and 60 min after injection from all patients. Results: Intense pathol. radiotracer uptake was observed in 23 patients (77%) at the site of primary tumor. Lymph node metastases were detected in 10 patients (36%) and bone metastases were detected in seven patients (25%). Bone scan (n=25) results revealed metastatic bone lesions in four patients, equivocal results in nine patients and normal results in 12 patients. PSMA PET/CT confirmed bone metastases in all four patients. Pathol. radiotracer uptake in PSMA PET/CT scans was observed only in one patient among those who had equivocal bone scans. PSMA PET/CT showed addnl. bone lesions in two patients who had a normal bone scan. When we compared early and late pelvic images we found no difference in the number of lesions detected. The maximum standardized uptake value (SUVmax) for primary tumor, lymph nodes and bone metastases was significantly higher in late images. Conclusion: PSMA PET/CT imaging seems to be a valuable imaging modality for evaluation of primary prostate cancer and it seems to have potential for the detection of lymph node and bone metastases. Early images 5 min p.i. can help to better distinguish between urinary bladder (before tracer accumulation occurs) and tumor lesions.

IT 1366302-52-4
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(complex with Ga68; evaluation of PSMA PET/CT imaging using 68Ga-HBED-CC ligand in patients with prostate cancer and value of early pelvic imaging)

RN 1366302-52-4 CAPLUS
CN 4,6,12,19-Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-, (3S,7S)- (CA INDEX NAME)

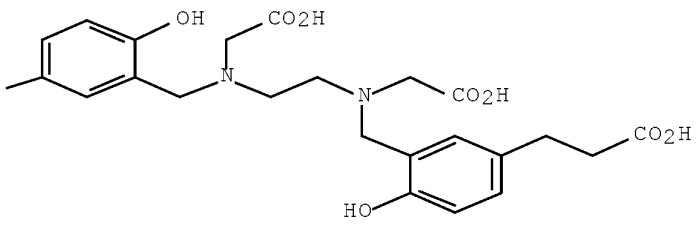
Absolute stereochemistry.

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.340

PAGE 1-B



OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L134 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2013:1840175 CAPLUS Full-text
DOCUMENT NUMBER: 160:29532
TITLE: Methods and compositions for improved F-18 labeling of proteins, peptides and other molecules via Al18F chelation
INVENTOR(S): D'Souza, Christopher A.; McBride, William J.; Goldenberg, David M.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 120 pp., Cont.-in-part of U.S. Ser. No. 850,591.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 92
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20130315821	A1	20131128	US 2013-13897849	20130520
US 8709382	B2	20140429		
US 20080170989	A1	20080717	US 2007-960262	20071219
US 7597876	B2	20091006		
AU 2007343600	A1	20080724	AU 2007-343600	20071219
AU 2007343600	B2	20120628		
CA 2675202	A1	20080724	CA 2007-2675202	20071219
CA 2675202	C	20140916		
CN 101568352	A	20091028	CN 2007-80048376	20071219
CN 101568352	B	20130821		
EP 2117604	A2	20091118	EP 2007-869485	20071219
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US 20080253964	A1	20081016	US 2008-112289	20080430
US 7563433	B2	20090721		
US 20090155166	A1	20090618	US 2008-343655	20081224
US 7993626	B2	20110809		
US 20090246130	A1	20091001	US 2009-433212	20090430

Fusion Pharmaceuticals, Inc.
Exhibit 1004.341

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CA 2782223	A1	20110609	CA 2010-2782223	20101202	
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US 8398956	B2	20130319			
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US 20120134920	A1	20120531	US 2011-13323139	20111212	
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US 8496912	B2	20130730			
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US 20140228541	A1	20140814	US 2014-14199625	20140306	
US 8889100	B2	20141118			
US 20150057432	A1	20150226	US 2014-14509679	20141008	
US 9115172	B2	20150825			
JP 2015110561	A	20150618	JP 2014-225253	20141105	
JP 5853292	B2	20160209			
AU 2014259570	A1	20141127	AU 2014-259570	20141107	

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Exhibit 1004.342

AU 2014259570	B2	20160609			
US 20150086482	A1	20150326	US 2014-14564243		20141209
AU 2015201433	A1	20150409	AU 2015-201433		20150318
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			US 2014-14509679	A2	20141008
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present application discloses compns. and methods of synthesis and use of 18F or 19F-labeled mols. of use in PET, SPECT and/or MR imaging. Preferably, the 18F or 19F is conjugated to a targeting mol. by formation of a complex with a group IIIA metal and binding of the complex to a bifunctional chelating agent, which may be directly or indirectly attached to the targeting mol. In other embodiments, the 18F or 19F labeled moiety may comprise a targetable construct used in combination with a bispecific antibody to target a disease-associated antigen.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.343

The disclosed methods and compns. allow the simple and reproducible labeling of mols. at very high efficiency and specific activity in 30 min or less. In preferred embodiments, the labeled mol. may be used for imaging in a subject without purification after labeling. Thus, NODA-MPAA-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH2 (I, IMP-485) [NODA =1,4,7-triazacyclononane-1,4-diacetate; MPAA = methylphenylacetic acid; HSG = histamine succinylglycine] was prepared and labeled with 18F by Al18F chelation. For 18F labeling studies in water, to I formulated with trehalose, ascorbic acid and AlCl3 was added a solution of 18F and heated to 101° for 15 min. Biodistribution studies showed that in the presence of TF2 antibody, Al18F-I is found primarily in the tumor and the kidney radiolabeling is substantially decreased.

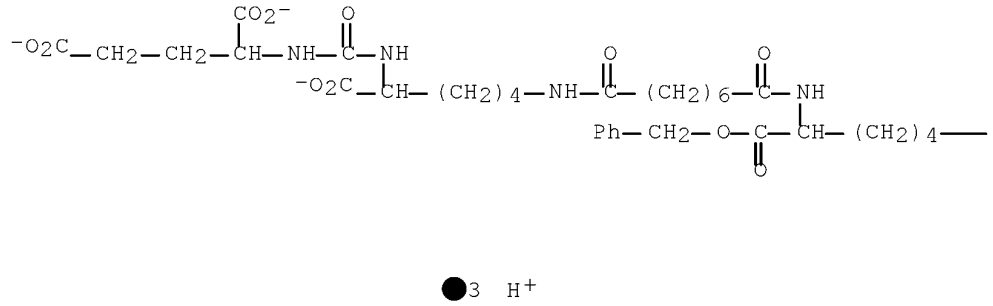
IT 1379601-63-4P 1379601-64-5P

RL: DGN (Diagnostic use); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods and compns. for improved F-18 labeling of proteins, peptides and other mols. via Al18F chelation)

RN 1379601-63-4 CAPLUS

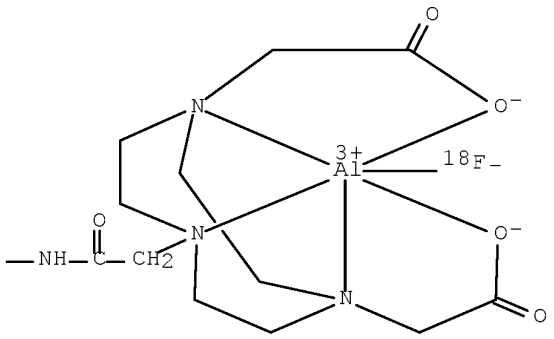
CN Aluminate(3-), [(3S,7S)-29-[4,7-bis[(carboxy-κO)methyl]octahydro-1H-1,4,7-triazonin-1-yl-κN1,κN4,κN7]-5,13,20,28-tetraoxo-22-[(phenylmethoxy)carbonyl]-4,6,12,21,27-pentaazanonacosane-1,3,7-tricarboxylato(5-)]fluoro-18F-, hydrogen (1:3) (CA INDEX NAME)

PAGE 1-A



Fusion Pharmaceuticals, Inc.
Exhibit 1004.344

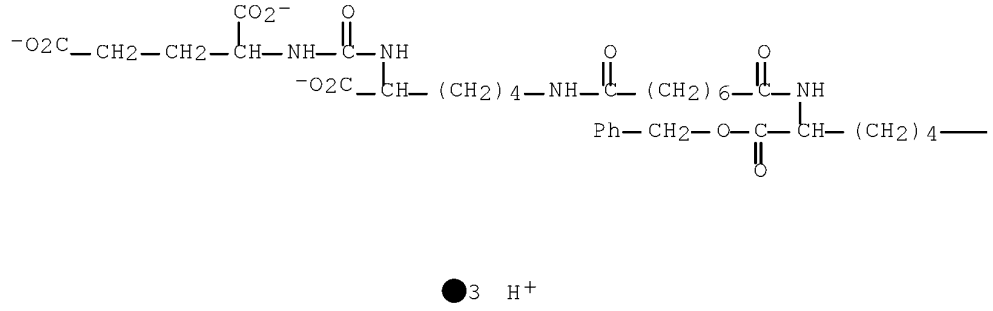
PAGE 1-B



RN 1379601-64-5 CAPLUS

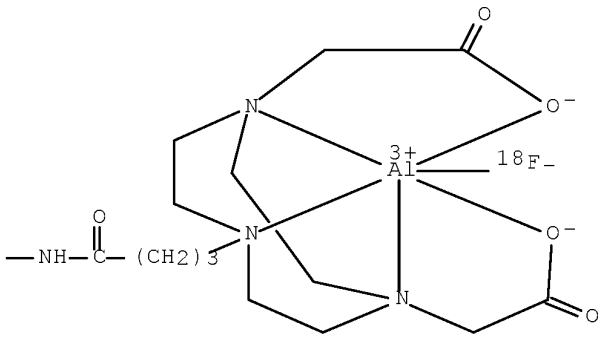
CN Aluminate(3-), [(3S,7S)-31-[4,7-bis[(carboxy-κO)methyl]octahydro-1H-1,4,7-triazonin-1-yl-κN1,κN4,κN7]-5,13,20,28-tetraoxo-22-[(phenylmethoxy)carbonyl]-4,6,12,21,27-pentaazahentriacontane-1,3,7-tricarboxylato(5-)]fluoro-18F-, hydrogen (1:3) (CA INDEX NAME)

PAGE 1-A

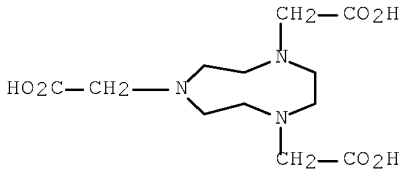


Fusion Pharmaceuticals, Inc.
Exhibit 1004.345

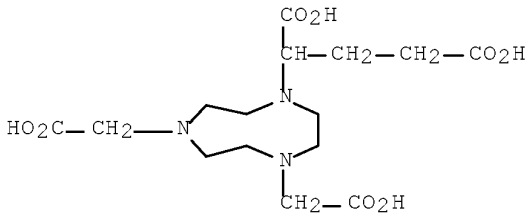
PAGE 1-B



IT 56491-86-2 1092370-12-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(methods and compns. for improved F-18 labeling of proteins, peptides and other mols. via Al18F chelation)
RN 56491-86-2 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, hexahydro- (CA INDEX NAME)



RN 1092370-12-1 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, α1-(2-carboxyethyl)hexahydro- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L134 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:885281 CAPLUS Full-text
DOCUMENT NUMBER: 157:125429

Fusion Pharmaceuticals, Inc.
Exhibit 1004.346

TITLE: Methods and compositions for improved F-18 labeling of proteins, peptides and other molecules via Al18F chelation
INVENTOR(S): D'Souza, Christopher A.; Mcbride, William J.; Goldenberg, David M.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 188pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 92
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012082618	A2	20120621	WO 2011-US64407	20111212
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.347

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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:125429
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present application discloses compns. and methods of synthesis and use of 18F or 19F-labeled mols. of use in PET, SPECT and/or MR imaging. Preferably, the 18F or 19F is conjugated to a targeting mol. by formation of a complex with a group IIIA metal and binding of the complex to a bifunctional chelating agent, which may be directly or indirectly attached to the targeting mol. In other embodiments, the 18F or 19F labeled moiety may comprise a targetable construct used in combination with a bispecific antibody to target a disease-associated antigen. The disclosed methods and compns. allow the simple and reproducible labeling of mols. at very high efficiency and specific activity in 30 min or less. In preferred embodiments, the labeled mol. may be used for imaging in a subject without purification after labeling. Thus, NODA-MPAA-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH2 (I, IMP-485) [NODA =1,4,7-triazacyclononane-1,4-diacetate; MPAA = methylphenylacetic acid; HSG = histamine succinylglycine] was prepared and labeled with 18F by Al18F chelation. For 18F labeling studies in water, to I formulated with trehalose, ascorbic acid and AlCl3 was added a solution of 18F and heated to 101° for 15 min. Biodistribution studies showed that in the presence of TF2 antibody, Al18F-I is found primarily in the tumor and the kidney radiolabeling is substantially decreased.

IT 1379601-63-4P 1379601-64-5P
RL: DGN (Diagnostic use); PRPH (Prophetic); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods and compns. for improved F-18 labeling of proteins, peptides and other mols. via Al18F chelation)

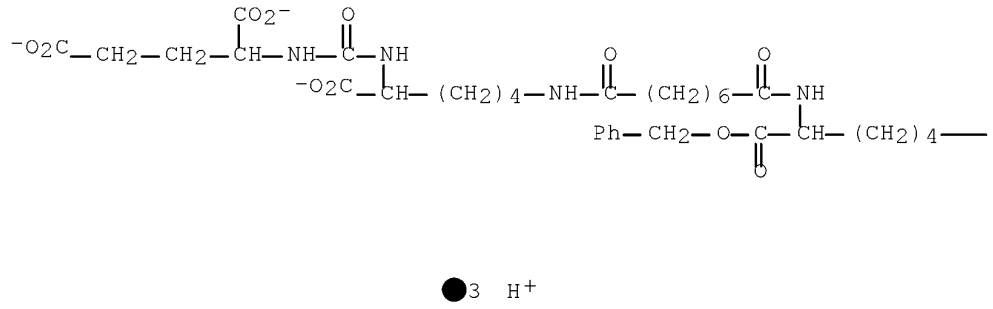
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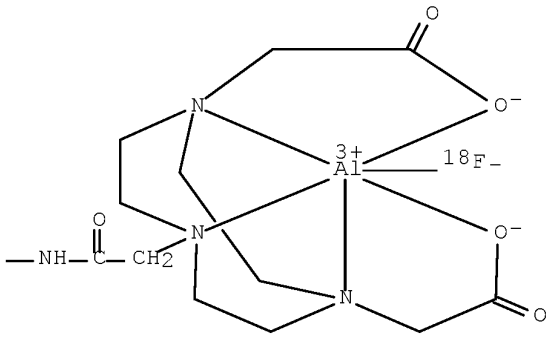
Fusion Pharmaceuticals, Inc.
Exhibit 1004.348

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PAGE 1-B

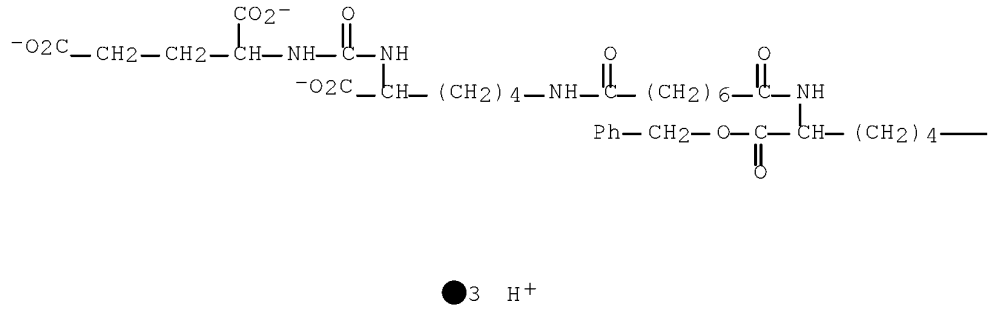


RN 1379601-64-5 CAPLUS

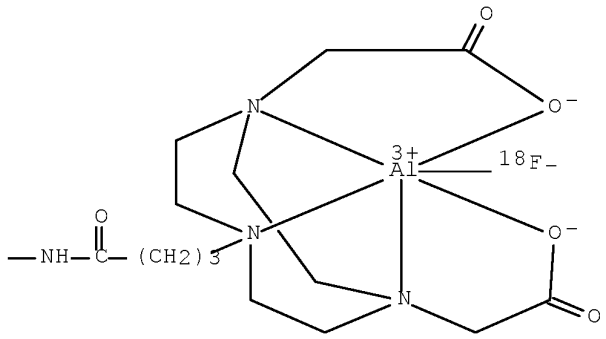
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.349

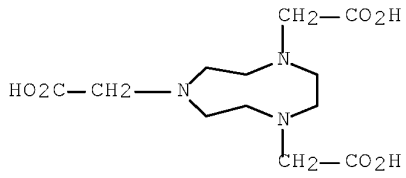
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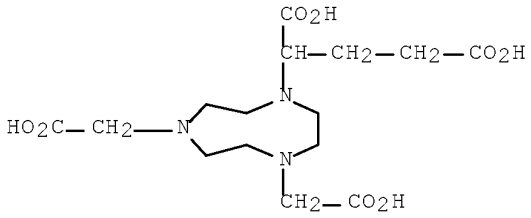


IT 56491-86-2 1092370-12-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(methods and compns. for improved F-18 labeling of proteins, peptides and other mols. via Al18F chelation)
RN 56491-86-2 CAPLUS
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.350

RN 1092370-12-1 CAPLUS
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OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L134 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2017 ACS on STN
ACCESSION NUMBER: 2012:775612 CAPLUS Full-text
DOCUMENT NUMBER: 157:45463
TITLE: Methods and compositions for fluorine-18 labeling of proteins, peptides and other molecules via Al18F chelation
INVENTOR(S): D'Souza, Christopher A.; McBride, William J.; Goldenberg, David M.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 117pp., Cont.-in-part of U.S. Ser. No. 309,714.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 92
PATENT INFORMATION:

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Fusion Pharmaceuticals, Inc.
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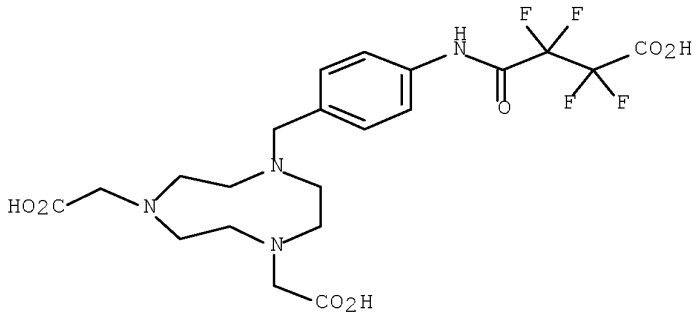
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.352

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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:45463; MARPAT 157:45463
GI

Fusion Pharmaceuticals, Inc.
Exhibit 1004.353



AB The present application discloses compns. and methods of synthesis and use of 18F or 19F-labeled mols. of use in PET, SPECT and/or MR imaging. Preferably, the 18F or 19F is conjugated to a targeting mol. by formation of a complex with a group IIIA metal and binding of the complex to a bifunctional chelating agent, which may be directly or indirectly attached to the targeting mol. The 18F or 19F labeled moiety may comprise a targetable construct used in combination with a bispecific antibody to target a disease-associated antigen. The disclosed methods and compns. allow the simple and reproducible labeling of mols. at high efficiency and specific activity in 30 min or less. The labeled mol. may be used for imaging in a subject without purification after labeling. Thus, NODA-MPAA-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH2 (I) [NODA = 1,4,7-triazacyclononane-1,4-diacetate; ; MPAA = methylphenylacetic acid; HSG = histamine succinylglycine] was prepared and labeled with 18F by Al18F chelation. For 18F labeling studies in water, to I formulated with trehalose, ascorbic acid and AlCl3 was added a solution of 18F and heated to 101° for 15 min. Biodistribution studies showed that in the presence of TF2 antibody, Al18F-I is found primarily in the tumor and the kidney radiolabeling is substantially decreased.

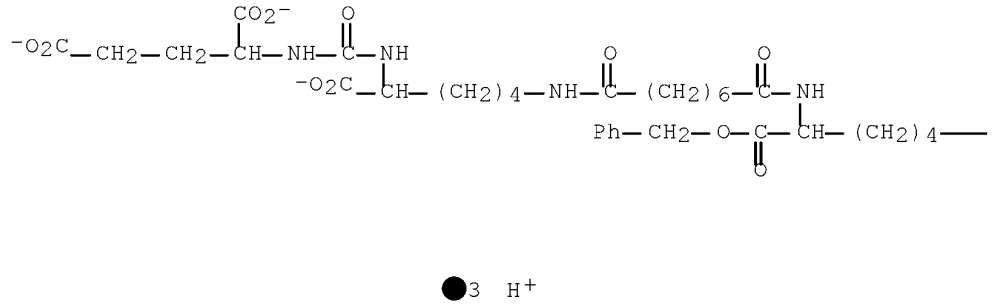
IT 1379601-63-4P 1379601-64-5P
RL: DGN (Diagnostic use); PRPH (Prophetic); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fluorine-18 labeling of proteins and peptides via Al18F chelation)

RN 1379601-63-4 CAPLUS

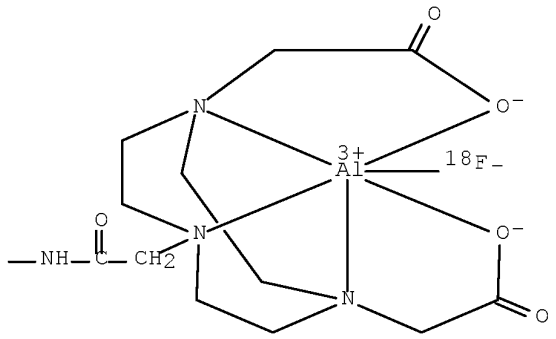
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Fusion Pharmaceuticals, Inc.
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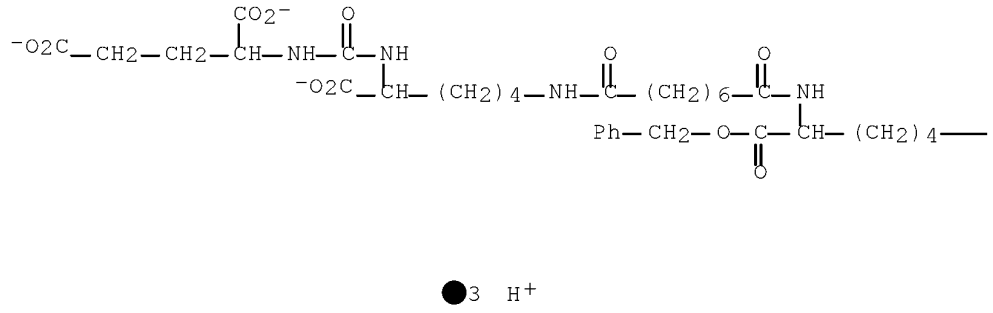


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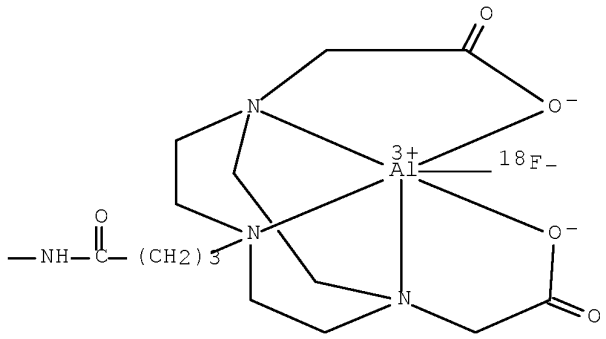
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.355

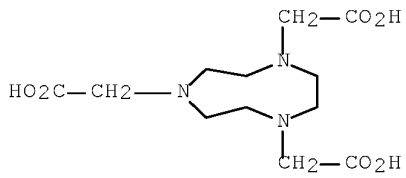
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PAGE 1-B



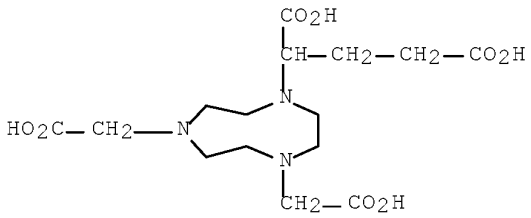
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RL: RCT (Reactant); RACT (Reactant or reagent)
(fluorine-18 labeling of proteins and peptides via Al18F chelation)
RN 56491-86-2 CAPLUS
CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid, hexahydro- (CA INDEX NAME)



RN 1092370-12-1 CAPLUS

Fusion Pharmaceuticals, Inc.
Exhibit 1004.356

CN 1H-1,4,7-Triazonine-1,4,7-triacetic acid,
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.357

STRUCTURE SEARCH PART 3

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http://www.cas.org/legal/infopolicy

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 4, 2017

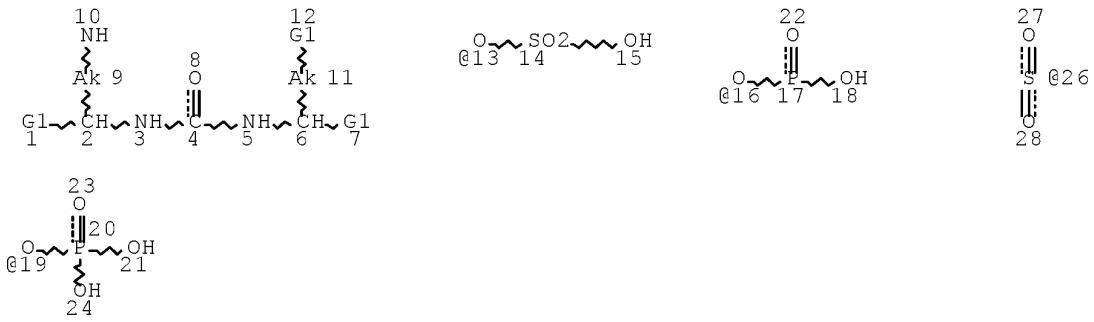
  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific


L83          27 SEA FILE=REGISTRY SPE=ON  ABB=ON  60239-18-1/CRN
L84          10 SEA FILE=REGISTRY SPE=ON  ABB=ON  56491-86-2/CRN
L85         357 SEA FILE=REGISTRY SPE=ON  ABB=ON  67-43-6/CRN
L86           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  143557-99-7/CRN
L87           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  1092370-12-1/CRN
L88           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  656242-49-8/CRN
L89           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  164858-91-7/CRN
L90           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  1397275-76-1/CRN
L91           5 SEA FILE=REGISTRY SPE=ON  ABB=ON  129162-88-5/CRN
L92          30 SEA FILE=REGISTRY SPE=ON  ABB=ON  70-51-9/CRN
L93         357 SEA FILE=REGISTRY SPE=ON  ABB=ON  67-43-6/CRN
L94           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  3565-84-2/CRN
L95           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  112193-74-5/CRN
L96           3 SEA FILE=REGISTRY SPE=ON  ABB=ON  (121806-83-5 OR  117499-23-7
                  OR  102650-30-6)/CRN
L97           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  376370-26-2/CRN
L98           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  (121806-84-6 OR  121806-83-5
                  OR  108414-96-6 OR  108414-95-5 OR  105359-63-5)/CRN
                        L83-L98=CHELATORS AS PART OF A MULTI-COMPONENT SUBSTANCE
L99               STR
```


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Exhibit 1004.358



VAR G1=COOH/SO3H/13/16/19/26
NODE ATTRIBUTES:
CONNECT IS E2 RC AT   9
CONNECT IS E2 RC AT 11
CONNECT IS E3 RC AT 26
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN LOC SAT AT   9
GGCAT   IS LIN LOC SAT AT 11
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L102   1093 SEA FILE=REGISTRY SSS FUL L99
L103   3 SEA FILE=REGISTRY SPE=ON ABB=ON (L83 OR L84 OR L85 OR L86 OR
                L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR L93 OR L94 OR L95 OR
                L96 OR L97 OR L98) AND L102

=> fil capl; d que nos l104
FILE 'CAPLUS' ENTERED AT 15:34:21 ON 22 JUN 2017
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FILE COVERS 1907 - 22 Jun 2017 VOL 167 ISS 1
FILE LAST UPDATED: 21 Jun 2017 (20170621/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015

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```
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015

CAplus includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2017.

CAplus now includes the comprehensive Cooperative Patent Classification
(CPC).  See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L83          27 SEA FILE=REGISTRY SPE=ON  ABB=ON  60239-18-1/CRN
L84          10 SEA FILE=REGISTRY SPE=ON  ABB=ON  56491-86-2/CRN
L85         357 SEA FILE=REGISTRY SPE=ON  ABB=ON  67-43-6/CRN
L86           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  143557-99-7/CRN
L87           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  1092370-12-1/CRN
L88           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  656242-49-8/CRN
L89           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  164858-91-7/CRN
L90           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  1397275-76-1/CRN
L91           5 SEA FILE=REGISTRY SPE=ON  ABB=ON  129162-88-5/CRN
L92          30 SEA FILE=REGISTRY SPE=ON  ABB=ON  70-51-9/CRN
L93         357 SEA FILE=REGISTRY SPE=ON  ABB=ON  67-43-6/CRN
L94           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  3565-84-2/CRN
L95           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  112193-74-5/CRN
L96           3 SEA FILE=REGISTRY SPE=ON  ABB=ON  (121806-83-5 OR  117499-23-7
                OR  102650-30-6)/CRN
L97           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  376370-26-2/CRN
L98           0 SEA FILE=REGISTRY SPE=ON  ABB=ON  (121806-84-6 OR  121806-83-5
                OR  108414-96-6 OR  108414-95-5 OR  105359-63-5)/CRN
L99             STR
L102       1093 SEA FILE=REGISTRY SSS FUL L99
L103          3 SEA FILE=REGISTRY SPE=ON  ABB=ON  (L83 OR L84 OR L85 OR L86 OR
                L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR L93 OR L94 OR L95 OR
                L96 OR L97 OR L98) AND L102
L104          1 SEA FILE=CAPLUS SPE=ON  ABB=ON  L103

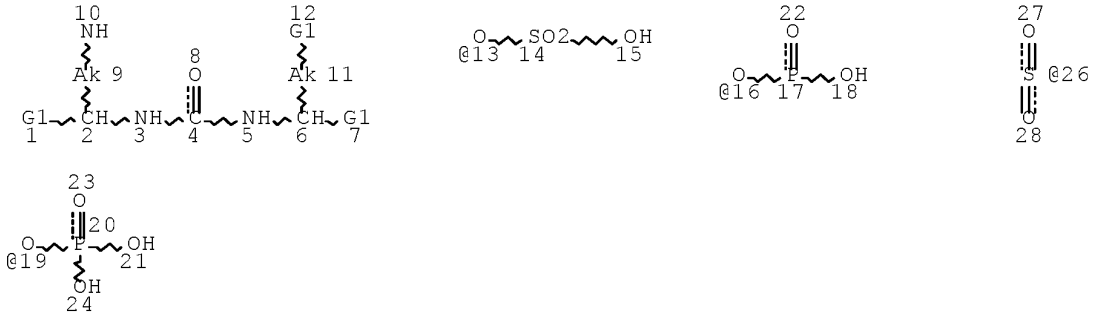

=> s l104 not l133,l132,l134
L135          0 L104 NOT (L133 OR L132 OR L134)
                            (L133,L132,L134 WERE PREVIOUSLY DISPLAYED)

=> fil hom
FILE 'HOME' ENTERED AT 15:34:43 ON 22 JUN 2017
```


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SEARCH HISTORY

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L85          357 SEA FILE=REGISTRY SPE=ON  ABB=ON  67-43-6/CRN
L86            0 SEA FILE=REGISTRY SPE=ON  ABB=ON  143557-99-7/CRN
L87            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  1092370-12-1/CRN
L88            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  656242-49-8/CRN
L89            0 SEA FILE=REGISTRY SPE=ON  ABB=ON  164858-91-7/CRN
L90            0 SEA FILE=REGISTRY SPE=ON  ABB=ON  1397275-76-1/CRN
L91            5 SEA FILE=REGISTRY SPE=ON  ABB=ON  129162-88-5/CRN
L92           30 SEA FILE=REGISTRY SPE=ON  ABB=ON  70-51-9/CRN
L93          357 SEA FILE=REGISTRY SPE=ON  ABB=ON  67-43-6/CRN
L94            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  3565-84-2/CRN
L95            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  112193-74-5/CRN
L96            3 SEA FILE=REGISTRY SPE=ON  ABB=ON  (121806-83-5 OR  117499-23-7
                 OR  102650-30-6)/CRN
L97            0 SEA FILE=REGISTRY SPE=ON  ABB=ON  376370-26-2/CRN
L98            0 SEA FILE=REGISTRY SPE=ON  ABB=ON  (121806-84-6 OR  121806-83-5
                 OR  108414-96-6 OR  108414-95-5 OR  105359-63-5)/CRN
L99              STR
```



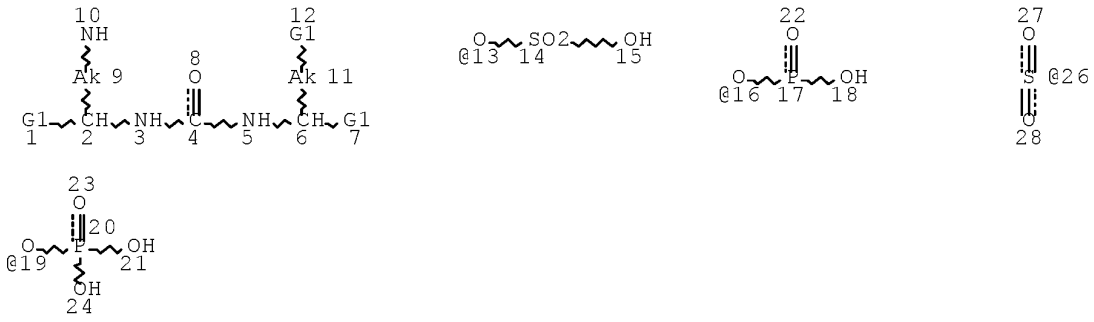

```
VAR G1=COOH/SO3H/13/16/19/26
NODE ATTRIBUTES:
CONNECT IS E2  RC AT   9
CONNECT IS E2  RC AT  11
CONNECT IS E3  RC AT  26
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN  LOC  SAT  AT   9
GGCAT   IS LIN  LOC  SAT  AT  11
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  27

STEREO ATTRIBUTES: NONE
L102       1093 SEA FILE=REGISTRY SSS FUL L99
L103          3 SEA FILE=REGISTRY SPE=ON  ABB=ON  (L83 OR L84 OR L85 OR L86 OR
                L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR L93 OR L94 OR L95 OR
                L96 OR L97 OR L98) AND L102
```


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Exhibit 1004.361

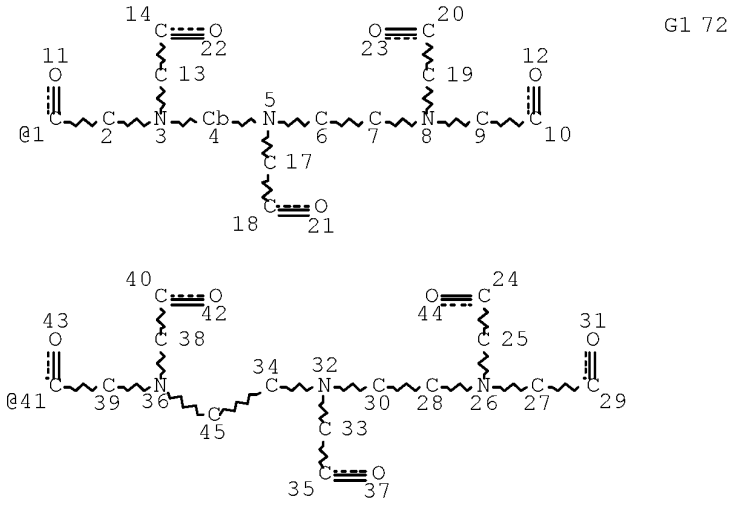
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=> d stat que l112
L99             STR
```



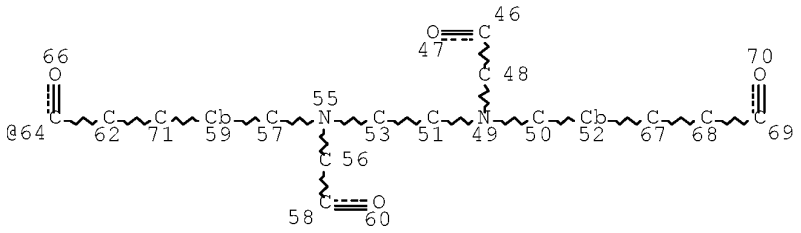
```
VAR G1=COOH/SO3H/13/16/19/26
NODE ATTRIBUTES:
CONNECT IS E2  RC AT   9
CONNECT IS E2  RC AT  11
CONNECT IS E3  RC AT  26
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN  LOC  SAT  AT   9
GGCAT   IS LIN  LOC  SAT  AT  11
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  27

STEREO ATTRIBUTES: NONE
L102       1093 SEA FILE=REGISTRY SSS FUL L99
L109            STR
```



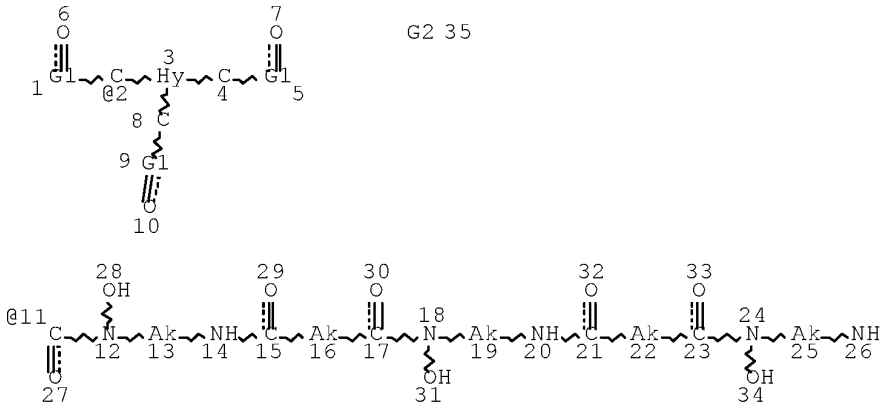
Fusion Pharmaceuticals, Inc.
Exhibit 1004.362



Page 2-A
VAR G1=1/41/64
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY LOC SAT AT 4
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 66

STEREO ATTRIBUTES: NONE
L110 STR



VAR G1=C/P
VAR G2=2/11
NODE ATTRIBUTES:
CONNECT IS E2 RC AT 13
CONNECT IS E2 RC AT 16
CONNECT IS E2 RC AT 19
CONNECT IS E2 RC AT 22
CONNECT IS E2 RC AT 25
DEFAULT MLEVEL IS ATOM
GGCAT IS LIN LOC SAT AT 13
GGCAT IS LIN LOC SAT AT 16
GGCAT IS LIN LOC SAT AT 19
GGCAT IS LIN LOC SAT AT 22
GGCAT IS LIN LOC SAT AT 25
DEFAULT ECLEVEL IS LIMITED

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Exhibit 1004.363

```
ECOUNT  IS M6-X11 C  M3-X4 N  AT   3

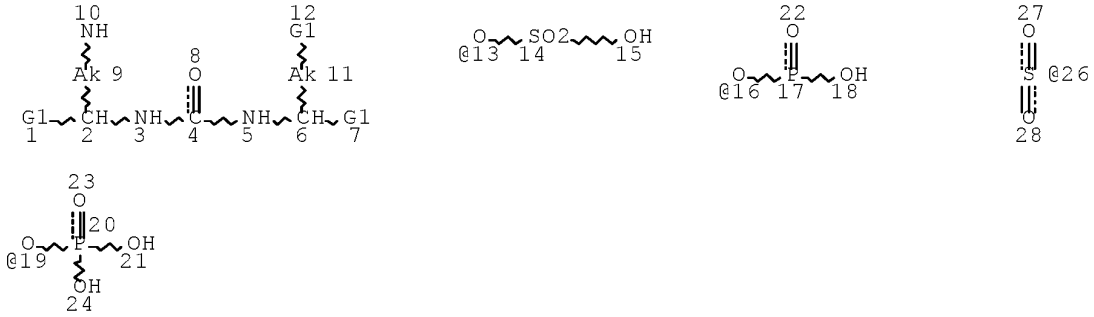
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  35

STEREO ATTRIBUTES: NONE
L112        128 SEA FILE=REGISTRY SUB=L102 SSS FUL (L109 OR L110)

100.0% PROCESSED      1093 ITERATIONS                          128 ANSWERS
SEARCH TIME: 00.00.01



=> d stat que l116
L99             STR
```

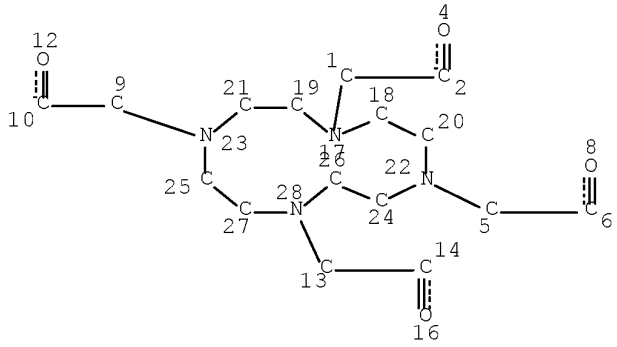



```
VAR G1=COOH/SO3H/13/16/19/26
NODE ATTRIBUTES:
CONNECT IS E2  RC AT   9
CONNECT IS E2  RC AT  11
CONNECT IS E3  RC AT  26
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN  LOC  SAT  AT   9
GGCAT   IS LIN  LOC  SAT  AT  11
DEFAULT ECLEVEL IS LIMITED

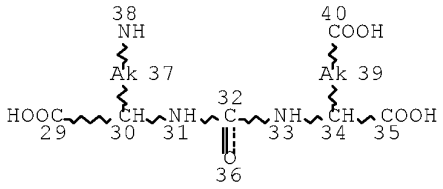
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  27

STEREO ATTRIBUTES: NONE
L102       1093 SEA FILE=REGISTRY SSS FUL L99
L114            STR
```


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Exhibit 1004.364



Page 1-A



Page 2-A
NODE ATTRIBUTES:
CONNECT IS E2 RC AT 37
CONNECT IS E2 RC AT 39
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN LOC SAT AT 37
GGCAT   IS LIN LOC SAT AT 39
DEFAULT ECLEVEL IS LIMITED

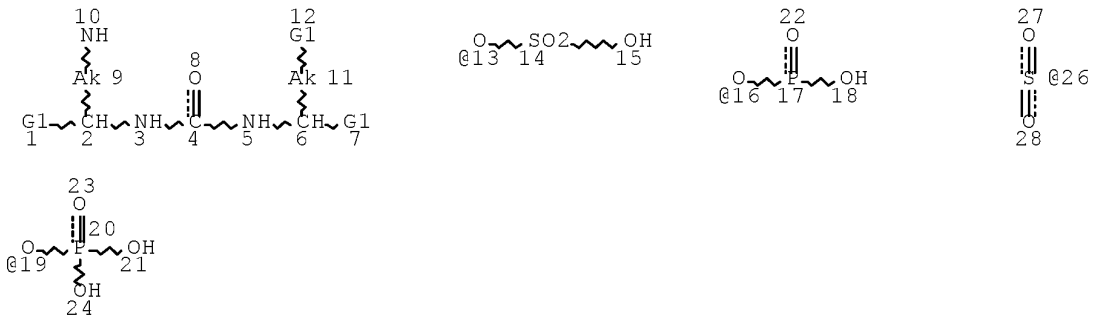
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE
L116   81 SEA FILE=REGISTRY SUB=L102 SSS FUL L114

100.0% PROCESSED   226 ITERATIONS   81 ANSWERS
SEARCH TIME: 00.00.01

=> d stat que l119
L99   STR

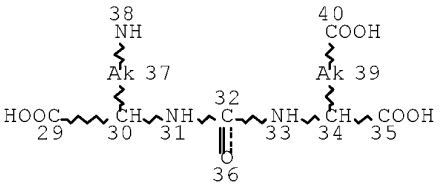
Fusion Pharmaceuticals, Inc.
Exhibit 1004.365



VAR G1=COOH/SO3H/13/16/19/26
NODE ATTRIBUTES:
CONNECT IS E2 RC AT   9
CONNECT IS E2 RC AT 11
CONNECT IS E3 RC AT 26
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN LOC SAT AT   9
GGCAT   IS LIN LOC SAT AT 11
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L102   1093 SEA FILE=REGISTRY SSS FUL L99
L117   STR



NODE ATTRIBUTES:
CONNECT IS E2 RC AT 37
CONNECT IS E2 RC AT 39
DEFAULT MLEVEL IS ATOM
GGCAT   IS LIN LOC SAT AT 37
GGCAT   IS LIN LOC SAT AT 39
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L119   1093 SEA FILE=REGISTRY SUB=L102 SSS FUL L117

Fusion Pharmaceuticals, Inc.
Exhibit 1004.366

```
100.0% PROCESSED      1093 ITERATIONS                          1093 ANSWERS
SEARCH TIME: 00.00.01


=> d his nofile

     (FILE 'HOME' ENTERED AT 12:10:53 ON 22 JUN 2017)

     FILE 'CAPLUS' ENTERED AT 12:11:03 ON 22 JUN 2017
                E US2016-15131118/APPS
L1              3 SEA SPE=ON  ABB=ON  US2016-15131118/AP
                D SCA

     FILE 'STNGUIDE' ENTERED AT 12:11:26 ON 22 JUN 2017

     FILE 'REGISTRY' ENTERED AT 12:15:43 ON 22 JUN 2017
L2              1 SEA SPE=ON  ABB=ON  67-43-6
L3              1 SEA SPE=ON  ABB=ON  3565-84-2
L4              1 SEA SPE=ON  ABB=ON  3565-84-2
L5              1 SEA SPE=ON  ABB=ON  114873-37-9
L6              1 SEA SPE=ON  ABB=ON  129162-88-5
L7              1 SEA SPE=ON  ABB=ON  1092370-12-1
                D SCA L2
                D SCA L3

     FILE 'STNGUIDE' ENTERED AT 12:17:17 ON 22 JUN 2017

     FILE 'REGISTRY' ENTERED AT 12:18:10 ON 22 JUN 2017
                D SCA L4
                D SCA L5
                D SCA L6
                D SCA L7

     FILE 'STNGUIDE' ENTERED AT 12:18:27 ON 22 JUN 2017

     FILE 'CAPLUS' ENTERED AT 12:20:57 ON 22 JUN 2017
                SEL RN L1

     FILE 'REGISTRY' ENTERED AT 12:21:06 ON 22 JUN 2017
L8             56 SEA SPE=ON  ABB=ON  (1702720-91-9/BI OR 1702720-95-3/BI OR
                  1702720-97-5/BI OR 1702721-00-3/BI OR 1702721-02-5/BI OR
                  112883-43-9/BI OR 137076-54-1/BI OR 1622455-85-9/BI OR
                  164470-64-8/BI OR 167690-53-1/BI OR 1702720-89-5/BI OR
                  1702967-37-0/BI OR 1702967-48-3/BI OR 1702967-50-7/BI OR
                  1702967-52-9/BI OR 1702967-62-1/BI OR 32677-01-3/BI OR
                  10098-91-6/BI OR 1092370-12-1/BI OR 129162-88-5/BI OR 138774-94
                  -4/BI OR 13981-25-4/BI OR 14133-76-7/BI OR 14265-75-9/BI OR
                  14265-85-1/BI OR 14276-65-4/BI OR 14333-34-7/BI OR 14391-32-3/B
                  I OR 15750-15-9/BI OR 15757-14-9/BI OR 15776-20-2/BI OR
                  1702967-44-9/BI OR 1702967-55-2/BI OR 1703768-76-6/BI OR
                  180839-17-2/BI OR 32315-10-9/BI OR 56491-86-2/BI OR 6298-03-9/B
                  I OR 67-43-6/BI OR 7439-89-6/BI OR 96402-49-2/BI OR 114873-37-9
                  /BI OR 16434-14-3/BI OR 1703749-62-5/BI OR 1703768-73-3/BI OR
                  1703768-75-5/BI OR 1703768-77-7/BI OR 1703768-78-8/BI OR
                  1703768-79-9/BI OR 1983142-60-4/BI OR 1983142-61-5/BI OR
                  1983142-62-6/BI OR 1983157-53-4/BI OR 1983157-54-5/BI OR
```


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Exhibit 1004.367

```
                1983157-55-6/BI OR 3565-84-2/BI)
L9           51 SEA SPE=ON  ABB=ON  L8 NOT (L2 OR L3 OR L4 OR L5 OR L6 OR L7)
                D SCA

     FILE 'STNGUIDE' ENTERED AT 12:21:40 ON 22 JUN 2017

     FILE 'LREGISTRY' ENTERED AT 12:24:45 ON 22 JUN 2017
L10           1 SEA SPE=ON  ABB=ON  DOTA/CN
L11           0 SEA SPE=ON  ABB=ON  HBED-CC/CN
L12           1 SEA SPE=ON  ABB=ON  NOTA/CN
L13           0 SEA SPE=ON  ABB=ON  NODAGA/CN
L14           0 SEA SPE=ON  ABB=ON  DOTAGA/CN
L15           0 SEA SPE=ON  ABB=ON  TRAP/CN
L16           0 SEA SPE=ON  ABB=ON  NOPO/CN
L17           1 SEA SPE=ON  ABB=ON  PCTA/CN
L18           0 SEA SPE=ON  ABB=ON  DFO/CN
L19           1 SEA SPE=ON  ABB=ON  DTPA/CN
L20           0 SEA SPE=ON  ABB=ON  CHX-DTPA/CN
L21           0 SEA SPE=ON  ABB=ON  OXO-DO3A/CN
L22           0 SEA SPE=ON  ABB=ON  SCN-BZ-DTPA/CN
L23           0 SEA SPE=ON  ABB=ON  1B3M/CN
L24           0 SEA SPE=ON  ABB=ON  1M3B/CN
L25           0 SEA SPE=ON  ABB=ON  MX-DTPA/CN
                D IDE L10
                D IDE L12
                D IDE L17
                D IDE L19

     FILE 'REGISTRY' ENTERED AT 12:29:49 ON 22 JUN 2017
                E HBED-CC/CN
L26           1 SEA SPE=ON  ABB=ON  HBED-CC/CN
                D SCA
                D RN
                E NODAGA/CN
L27           1 SEA SPE=ON  ABB=ON  NODAGA/CN
                D SCA
                D IDE
                E DOTAGA/CN
L28           1 SEA SPE=ON  ABB=ON  DOTAGA/CN
                D SCA
                D RN
                E TRAP/CN
                E CHEL TRAP/CN

     FILE 'LCA' ENTERED AT 12:34:27 ON 22 JUN 2017
L29           0 SEA SPE=ON  ABB=ON  TRAP (L)CHELAT?

     FILE 'CAPLUS' ENTERED AT 12:34:43 ON 22 JUN 2017
L30          51 SEA SPE=ON  ABB=ON  TRAP/OBI (L)CHELAT?/OBI

     FILE 'REGISTRY' ENTERED AT 12:35:10 ON 22 JUN 2017
L31           1 SEA SPE=ON  ABB=ON  164858-91-7
                D SCA
                E NOPO/CN
L32           1 SEA SPE=ON  ABB=ON  NOPO/CN
                D SCA
                D RN
```


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Exhibit 1004.368

```
                E PCTA/CN
L33           2 SEA SPE=ON  ABB=ON  PCTA/CN
                D SCA
                D SCA L6
                D RN L6
                E DFO/CN
L34           1 SEA SPE=ON  ABB=ON  DFO/CN
                D SCA
                E CHEL DFO/CN
                E CHELATOR/CN
                E C25H48N6O8/MF
L35          18 SEA SPE=ON  ABB=ON  C25H48N6O8/MF
L36           0 SEA SPE=ON  ABB=ON  L35 AND L8
L37          15 SEA SPE=ON  ABB=ON  L35 NOT RSD/FA
                D SCA
                E BUTANEDIAMIDE, N4-(5-((4-((5-(ACETYLHYDROXYAMINO)PENTYL)AMINO
L38           1 SEA SPE=ON  ABB=ON  "BUTANEDIAMIDE, N4-(5-((4-((5-(ACETYLHYDROX
                YAMINO)PENTYL)AMINO)-1,4-DIOXOBUTYL)HYDROXYAMINO)PENTYL)-N1-(5-
                AMINOPENTYL)-N1-HYDROXY-"/CN
                D RN

     FILE 'LREGISTRY' ENTERED AT 12:43:38 ON 22 JUN 2017
                D SCA L19

     FILE 'REGISTRY' ENTERED AT 12:43:38 ON 22 JUN 2017

     FILE 'LREGISTRY' ENTERED AT 12:44:17 ON 22 JUN 2017
                D RN L19

     FILE 'REGISTRY' ENTERED AT 12:44:48 ON 22 JUN 2017
                D SCA L3
                D QUE L3
                E OXO-DO3A/CN

     FILE 'CAPLUS' ENTERED AT 12:45:58 ON 22 JUN 2017
L39             3 SEA SPE=ON  ABB=ON  OXO DO3A/OBI
                D SCA HITIND

     FILE 'REGISTRY' ENTERED AT 12:47:08 ON 22 JUN 2017
L40             1 SEA SPE=ON  ABB=ON  2012539-31-8
L41             1 SEA SPE=ON  ABB=ON  2012539-32-9
L42             1 SEA SPE=ON  ABB=ON  2012539-33-0
                D SCA L40
                D SCA L41
                D SCA L42

     FILE 'CAPLUS' ENTERED AT 12:47:48 ON 22 JUN 2017
L43             0 SEA SPE=ON  ABB=ON  OXO D03A/OBI

     FILE 'LREGISTRY' ENTERED AT 12:48:06 ON 22 JUN 2017
L44               STR
L45             0 SEA SSS FUL L44

     FILE 'REGISTRY' ENTERED AT 12:49:17 ON 22 JUN 2017
L46            11 SEA SSS SAM L44
                D SCA
                E 1-OXA-4,7,10-TRIAZACYCLODODECANE-4,7,10-TRIACETIC ACID/CN
```


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Exhibit 1004.369

```
L47           1 SEA SPE=ON  ABB=ON  "1-OXA-4,7,10-TRIAZACYCLODODECANE-4,7,10-TR
                IACETIC ACID"/CN
                D SCA
                D RN
                E SCN-BZ-DTPA/CN

     FILE 'CAPLUS' ENTERED AT 12:51:47 ON 22 JUN 2017
L48           7 SEA SPE=ON  ABB=ON  SCN-BZ-DTPA/OBI
                D SCA HITIND

     FILE 'REGISTRY' ENTERED AT 12:54:01 ON 22 JUN 2017
L49           1 SEA SPE=ON  ABB=ON  121806-83-5
L50           1 SEA SPE=ON  ABB=ON  117499-23-7
L51           1 SEA SPE=ON  ABB=ON  102650-30-6
L52           1 SEA SPE=ON  ABB=ON  913300-33-1
L53           1 SEA SPE=ON  ABB=ON  102650-30-6
L54           1 SEA SPE=ON  ABB=ON  1258784-06-3
                D SCAN L49
                D SCAN L50

     FILE 'LREGISTRY' ENTERED AT 12:55:45 ON 22 JUN 2017
                D SCA L19

     FILE 'REGISTRY' ENTERED AT 12:55:46 ON 22 JUN 2017
                D SCA L51
                D SCA L52
                D SCA L53
                D SCA L54
L55           3 SEA SPE=ON  ABB=ON  (L49 OR L50 OR L51 OR L53)
                D SCA
                E GLYCINE, N-(2-(BIS(CARBOXYMETHYL)AMINO)ETHYL)-N-((2R)-2-(BIS(
                D RN L55 1-3
                E 1B3M/CN
                E 1M3B/CN
                E 1-(P-ISOTHIOCYANATOBENZYL)-3-METHYL-DTPA/CN

     FILE 'HCAPLUS' ENTERED AT 13:01:28 ON 22 JUN 2017
L56           0 SEA SPE=ON  ABB=ON  "1-(P-ISOTHIOCYANATOBENZYL)-3-METHYL-DTPA"/
                OBI

     FILE 'CAPLUS' ENTERED AT 13:02:07 ON 22 JUN 2017
L57           1 SEA SPE=ON  ABB=ON  1B3M/OBI
                D SCA

     FILE 'REGISTRY' ENTERED AT 13:02:27 ON 22 JUN 2017
L58           1 SEA SPE=ON  ABB=ON  376370-26-2
                D SCA

     FILE 'CAPLUS' ENTERED AT 13:03:06 ON 22 JUN 2017
L59           0 SEA SPE=ON  ABB=ON  1M3B/OBI
L60           4 SEA SPE=ON  ABB=ON  1M3B/BI
                D KWIC
                D SCA
                SEL RN

     FILE 'REGISTRY' ENTERED AT 13:03:55 ON 22 JUN 2017
L61          12 SEA SPE=ON  ABB=ON  (121806-84-6/BI OR 108414-95-5/BI OR
```


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Exhibit 1004.370

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                108414-96-6/BI OR 121806-83-5/BI OR 105359-63-5/BI OR 15750-15-
                9/BI OR 10098-91-6/BI OR 105394-74-9/BI OR 122367-02-6/BI OR
                13982-36-0/BI OR 23911-26-4/BI OR 67023-60-3/BI)
L62             6 SEA SPE=ON  ABB=ON  L61 AND S/ELS
                D SCA
                D SCA L58
L63             6 SEA SPE=ON  ABB=ON  L62 NOT L58
L64             0 SEA SPE=ON  ABB=ON  L8 AND S/ELS
                D SCA L58
                D SCA L62
L65             5 SEA SPE=ON  ABB=ON  L62 AND 4/N
                D RN 1-5
                D SCA L58
                E MX-DTPA/CN
L66             1 SEA SPE=ON  ABB=ON  MX-DTPA/CN
                D SCA
L67             1 SEA SPE=ON  ABB=ON  L66 AND L65
L68             1 SEA SPE=ON  ABB=ON  60239-18-1
L69             1 SEA SPE=ON  ABB=ON  56491-86-2
L70             1 SEA SPE=ON  ABB=ON  67-43-6
L71             1 SEA SPE=ON  ABB=ON  143557-99-7
L72             1 SEA SPE=ON  ABB=ON  1092370-12-1
L73             1 SEA SPE=ON  ABB=ON  656242-49-8
L74             1 SEA SPE=ON  ABB=ON  164858-91-7
L75             1 SEA SPE=ON  ABB=ON  1397275-76-1
L76             1 SEA SPE=ON  ABB=ON  129162-88-5
L77             1 SEA SPE=ON  ABB=ON  70-51-9
L78             1 SEA SPE=ON  ABB=ON  67-43-6
L79             1 SEA SPE=ON  ABB=ON  3565-84-2
L80             1 SEA SPE=ON  ABB=ON  112193-74-5
L81             3 SEA SPE=ON  ABB=ON  121806-83-5 OR  117499-23-7 OR  102650-30-6
L82             5 SEA SPE=ON  ABB=ON  121806-84-6 OR  121806-83-5 OR  108414-96-6
                  OR  108414-95-5 OR  105359-63-5
L83            27 SEA SPE=ON  ABB=ON  60239-18-1/CRN
L84            10 SEA SPE=ON  ABB=ON  56491-86-2/CRN
L85           357 SEA SPE=ON  ABB=ON  67-43-6/CRN
L86             0 SEA SPE=ON  ABB=ON  143557-99-7/CRN
L87             1 SEA SPE=ON  ABB=ON  1092370-12-1/CRN
L88             1 SEA SPE=ON  ABB=ON  656242-49-8/CRN
L89             0 SEA SPE=ON  ABB=ON  164858-91-7/CRN
L90             0 SEA SPE=ON  ABB=ON  1397275-76-1/CRN
L91             5 SEA SPE=ON  ABB=ON  129162-88-5/CRN
L92            30 SEA SPE=ON  ABB=ON  70-51-9/CRN
L93           357 SEA SPE=ON  ABB=ON  67-43-6/CRN
L94             1 SEA SPE=ON  ABB=ON  3565-84-2/CRN
L95             1 SEA SPE=ON  ABB=ON  112193-74-5/CRN
L96             3 SEA SPE=ON  ABB=ON  (121806-83-5 OR  117499-23-7 OR  102650-30-
                6)/CRN
L97             0 SEA SPE=ON  ABB=ON  376370-26-2/CRN
L98             0 SEA SPE=ON  ABB=ON  (121806-84-6 OR  121806-83-5 OR  108414-96-
                6 OR  108414-95-5 OR  105359-63-5)/CRN
L99               STR
L100           50 SEA SSS SAM L99
L101            1 SEA SPE=ON  ABB=ON  L8 AND L100
                D SCA
L102         1093 SEA SSS FUL L99
                SAVE TEMP L102 SAM118FULL/A
```


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Exhibit 1004.371

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L103          3 SEA SPE=ON  ABB=ON  (L83 OR L84 OR L85 OR L86 OR L87 OR L88 OR
                L89 OR L90 OR L91 OR L92 OR L93 OR L94 OR L95 OR L96 OR L97 OR
                L98) AND L102

     FILE 'CAPLUS' ENTERED AT 14:49:23 ON 22 JUN 2017
L104          1 SEA SPE=ON  ABB=ON  L103
L105      17007 SEA SPE=ON  ABB=ON  (L68 OR L69 OR L70 OR L71 OR L72 OR L73 OR
                L74 OR L75 OR L76 OR L77 OR L78 OR L79 OR L80 OR L81 OR L82)
L106        155 SEA SPE=ON  ABB=ON  L102
L107         15 SEA SPE=ON  ABB=ON  L105 AND L106

     FILE 'REGISTRY' ENTERED AT 14:49:56 ON 22 JUN 2017
L108         19 SEA SPE=ON  ABB=ON  (L68 OR L69 OR L70 OR L71 OR L72 OR L73 OR
                L74 OR L75 OR L76 OR L77 OR L78 OR L79 OR L80 OR L81 OR L82)
                D SCA
L109            STR
L110            STR
L111         10 SEA SUB=L102 SSS SAM (L109 OR L110)
L112        128 SEA SUB=L102 SSS FUL (L109 OR L110)
                SAVE TEMP L112 SAM118SUB2/A

     FILE 'CAPLUS' ENTERED AT 15:17:04 ON 22 JUN 2017
L113         41 SEA SPE=ON  ABB=ON  L112

     FILE 'REGISTRY' ENTERED AT 15:18:00 ON 22 JUN 2017
                D QUE L10
                D SCA L68
L114            STR 60239-18-1
L115          8 SEA SUB=L102 SSS SAM L114
L116         81 SEA SUB=L102 SSS FUL L114
                SAVE TEMP L116 SAM118SUB3/A
L117            STR L114
L118         50 SEA SUB=L102 SSS SAM L117
L119       1093 SEA SUB=L102 SSS FUL L117
                SAVE TEMP L119 SAM118SUB4/A
L120          0 SEA SPE=ON  ABB=ON  L119 AND L83

     FILE 'CAPLUS' ENTERED AT 15:26:58 ON 22 JUN 2017
L121         29 SEA SPE=ON  ABB=ON  L116
L122          6 SEA SPE=ON  ABB=ON  L119 AND L68
                D BIB L1
L123        414 SEA SPE=ON  ABB=ON  EDER M?/AU
L124        120 SEA SPE=ON  ABB=ON  KOPKA K?/AU
L125       2614 SEA SPE=ON  ABB=ON  SCHAFER M?/AU OR SCHAEFER M?/AU
L126         49 SEA SPE=ON  ABB=ON  BAUDER-WUEST U?/UA OR BAUDER U?/AU OR
                WUEST U?/AU OR WUST U?/AU
L127        271 SEA SPE=ON  ABB=ON  HABERKORN U?/AU
L128        248 SEA SPE=ON  ABB=ON  EISENHUT M?/AU
L129        173 SEA SPE=ON  ABB=ON  MIER W?/AU
L130         67 SEA SPE=ON  ABB=ON  BENESOVA M?/AU
L131         31 SEA SPE=ON  ABB=ON  BAUDER-WUEST U?/AU
L132         12 SEA SPE=ON  ABB=ON  (L123 OR L124 OR L125 OR L126 OR L127 OR
                L128 OR L129 OR L130 OR L131) AND (L107 OR L113 OR L104 OR
                L121 OR L122)

     FILE 'STNGUIDE' ENTERED AT 15:31:20 ON 22 JUN 2017
```


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Exhibit 1004.372

```
     FILE 'CAPLUS' ENTERED AT 15:31:43 ON 22 JUN 2017
                D QUE NOS L132
                D IBIB ABS HITSTR L132 1-12

     FILE 'REGISTRY' ENTERED AT 15:32:24 ON 22 JUN 2017
                D STAT QUE L116
                D STAT QUE L119

     FILE 'CAPLUS' ENTERED AT 15:32:32 ON 22 JUN 2017
                D QUE NOS L121
                D QUE NOS L122
L133         27 SEA SPE=ON  ABB=ON  (L121 OR L122) NOT L132
                D IBIB ABS HITSTR L133 1-27

     FILE 'REGISTRY' ENTERED AT 15:33:28 ON 22 JUN 2017
                D STAT QUE L102
                D STAT QUE L122

     FILE 'CAPLUS' ENTERED AT 15:33:28 ON 22 JUN 2017
                D QUE NOS L107
                D QUE NOS L113
L134          9 SEA SPE=ON  ABB=ON  (L107 OR L113) NOT (L133 OR L132)
                D IBIB ABS HITSTR 1-9

     FILE 'HOME' ENTERED AT 15:33:54 ON 22 JUN 2017

     FILE 'REGISTRY' ENTERED AT 15:34:16 ON 22 JUN 2017
                D STAT QUE L103

     FILE 'CAPLUS' ENTERED AT 15:34:21 ON 22 JUN 2017
                D QUE NOS L104
L135          0 SEA SPE=ON  ABB=ON  L104 NOT (L133 OR L132 OR L134)

     FILE 'HOME' ENTERED AT 15:34:43 ON 22 JUN 2017
                D STAT QUE L103
                D STAT QUE L112
                D STAT QUE L116
                D STAT QUE L119

=>
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Exhibit 1004.373

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BIB DATA SHEET

CONFIRMATION NO. 9416

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/470,104	06/14/2019 RULE	424	1618	173545 (304773-00005)

APPLICANTS

THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION, Brussels, BELGIUM;
UNIVERSITÄT HEIDELBERG, Heidelberg, GERMANY;

INVENTORS

Alfred MORGENSTERN, Karlsruhe, GERMANY;
Frank BRUCHERTSEIFER, Stutensee, GERMANY;
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Uwe HABERKORN, Schwetzingen, GERMANY;
Frederik GIESEL, Heidelberg, GERMANY;
Clemens KRATOCHWIL, Hirschberg a.d.B., GERMANY;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2016/081313 12/15/2016

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

10/04/2019

Foreign Priority claimed	❑ Yes ☑ No	❑ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	❑ Yes ☑ No		GERMANY	8	13	1
Verified and Acknowledged	/JAGADISHWAR RAO SAMALA/ Examiner's Signature	Initials				

ADDRESS

Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001
UNITED STATES

TITLE

TREATMENT OF PMSA EXPRESSING CANCERS

FILING FEE RECEIVED		
1720	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Fusion Pharmaceuticals, Inc.
Exhibit 1004.374

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on October 26, 2020 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Jennifer Guerra/
Jennifer Guerra

Appl No.	: 16/470,104	Confirmation No. 9416
Inventor	: Alfred Morgenstern, et al.	
Filed	: June 14, 2019	
Title	: TREATMENT OF PMSA EXPRESSING CANCERS	
TC/A.U.	: 1618	
Examiner	: Jagadishwar Rao Samala	
Docket No.	: 173545 (304773-00005)	
Customer No.	: 23363	

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
October 26, 2020

Commissioner:

In response to the Office action dated June 24, 2020, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 12 of this paper.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.375

Electronic Patent Application Fee Transmittal

Application Number:	16470104
Filing Date:	14-Jun-2019
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Filer:	Lauren E. Schneider/Jennifer Guerra
Attorney Docket Number:	173545 (304773-00005)

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	220	220
Miscellaneous:				
		Total in USD ($)		**220**

Electronic Acknowledgement Receipt

EFS ID:	40948999
Application Number:	16470104
International Application Number:	
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Lauren E. Schneider/Jennifer Guerra
Filer Authorized By:	Lauren E. Schneider
Attorney Docket Number:	173545 (304773-00005)
Receipt Date:	26-OCT-2020
Filing Date:	14-JUN-2019
Time Stamp:	17:03:40
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$220
RAM confirmation Number	E20200PH04014966
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		173545_Amentment_10-26-2020.pdf	1411402 f767ba77415048abd8a240bf8977487c0c6428d6	yes	16

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	12	16
	Claims	2	11
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30818 caacdc91af07afb642eab166840075befd848bb2	no	2

Warnings:

Information:

Total Files Size (in bytes):	1442220

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS/ARGUMENTS

In the Office action dated June 24, 2020, the Examiner rejected claims 13-24 and 36 on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-30 of U.S. Patent No. 10,398,791 ("the '791 patent") and claims 1-28 of U.S. Patent No. 10,471,160 ("the '160 patent"). In making these rejections, the Examiner asserts that while "the claims at issue are not identical" to the earlier issued claims, they are not patentably distinct because the claims are "directed to the same art specific subject-matter." Office action, pages 4 and 8. Additionally, the Examiner asserts that any differences between the present claims and those of the cited patents are "in scope only," and concludes that a hypothetical infringer of the earlier patents would necessarily be an infringer of the present claims. Office action, pages 7-8 and 12. Applicant respectfully traverses.

While the Examiner appears to base the double patenting rejection on the premise that the hypothetical infringer would necessarily infringe the claims of all three patents, this is not the correct standard for sustaining a double patenting rejection. Instead, as noted in the MPEP, "A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is **not patentably distinct** from the reference claim(s) **because** the examined application claim is **either anticipated by, or would have been obvious over**, the reference claim(s)." MPEP §804 (citing In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)). And when the rationale for making a nonstatutory double patenting rejection is based on obviousness, the MPEP notes that the analysis is "'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. [§]103' except that the patent disclosure principally underlying the double patenting rejection is not considered prior art." MPEP §804 (citing In re Braithwaite, 379 F.2d 594, 154 USPQ 29 (CCPA 1967)).

Fusion Pharmaceuticals, Inc.
Exhibit 1004.381

Contrary to the Examiner's assertion, claims that are directed to similar subject matter in the same art are not necessarily patentably indistinct or obvious over each other. And as will be evident from the analysis below, a hypothetical infringer of the '791 and '160 patents would **not** necessarily be an infringer of the current claims, and the current claims are not obvious over the claims of the '791 and '160 patents.

The '791 and '160 patents focus on the provision of a targeted chelator to which multiple different radionuclides can be complexed. The '160 patent claims a metal complex including "a radionuclide," and in separate claims list 14 different illustrative radionuclides. '160 patent, claims 6, 7, 17 and 18. And the '791 patent claims only ^{177}Lu complexed to the chelator compound. '791 patent, claims 12, 16 and 27. In contrast, the present claims recite only ^{225}Ac.

Additionally, while the '791 and '160 patents are not prior art for the purposes of these double patenting rejections, Applicant notes that these patents disclose twenty eight illustrative radionuclides, eleven of which are presented separately. '791 patent, column 22, lines 1-7; '160 patent, column 20, lines 49-55. These lists with various radionuclides include Ac-225. However, in the examples of the '791 and '160 patents, radionuclide Ga-68 is used for imaging and radionuclide Lu-177 is used for cancer therapy. '791 patent, Examples 9 and 10; '160 Patent, Examples 9 and 10. Notably, both the claims and the disclosures of the '791 and '160 patents are relatively silent about dosages. For instance, the '791 and '160 patents suggest a general broad dosage range of about 1.0-100 millicuries for imaging or therapeutic purposes. '791 patent, column 22, lines 39-40; '160 patent, column 21, lines 24-25. 1.0 to 100 millicuries corresponds to 37 MBq to 3.7 GBq. In the examples in the '791 and '160 patents, 3.3 GBq of the Lu-177 labeled chelator is used for the treatment of cancer. '791 patent, FIG. 18 and corresponding description; '160 patent, FIG. 18 and corresponding description.

In contrast to the claims (and description) of the '791 and '160 patents, the current claims recite methods for treating specific cancers by administering one or more **Ac-225**-radiopharmaceuticals, wherein the effective amount of said one or more Ac-225-

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Exhibit 1004.382

radiopharmaceuticals is administered as a dosage of from **25 kBq to 400 kBq/kg** of body weight of said patient, or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from **3 MBq to 30 MBq** to said patient. To arrive at the method and dosage recited in the present claims from either the description or claims of the '791 and '160 patents, the ordinary artisan would have needed to specifically select radionuclide Ac-225 and a dose that is **significantly lower** than the broadest range suggested in the '791 and '160 patents. Indeed, compared to the dosage actually used in the examples of cancer therapy in the '791 and '160 patents, the unitary dose suggested in the '791 and '160 patents is over 100-fold higher than the dosage recited in the present claims (i.e., 3.3 **G**Bq in the '791 and '160 patents compared to 3 to 30 **M**Bq recited in the present claims). Also, when expressed in bodyweight, there is the same marked difference between the cancer treatment dosage suggested in the '791 and '160 patents and that recited in the current claims. For example, in order for the unitary dose of 3.3 GBq (suggested in the '791 and '160 patents) to correspond to a dose at the upper limit recited in the present claims (i.e., 400 kBq/kg of body weight), the patient should weigh 8.250 kg.

It can be seen from the above, therefore, that a hypothetical infringer of the '791 and '160 patents would not necessarily be a hypothetical infringer of present claims. And as the present claims are not obvious over the claims of the '791 and '160 patents, even when considered in light of the '791 and '160 disclosures, the current claims are patentably distinct from '791 and '160 patents.

As further evidence that the present claims are patentably distinct from the claims of the '791 and '160 patents, Applicant directs the examiner's attention to comparative examples A6 to B2 in the present application. These examples compare treatment with a chelator with radionuclide Lu-177 at a dose as used in the '791 and '160 patents to treatment with a chelator with radionuclide Ac-225 at a dose as recited in the current claims. As described in [0094] of the present application, "[t]he group treated with Lu-177-PSMA-617 had a **lower response rate** in comparison to the one treated with Ac-

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Exhibit 1004.383

225-PSMA-617." Paragraph [0094] goes on to state that "[t]his is a remarkable difference taking into account similar hematological toxicity and the more advanced patients selected for Ac-225-radiopharmaceutical therapy."

Additionally, Fig. 14 of the present application pictures the partial response of a patient to treatment with 7.4 GBq of the Lu-177-comprising chelator and subsequent remission after treatment with 6.4 MBq (100 kBq per kg body weight) of the Ac-225 comprising chelator. Those of ordinary skill in the art would not have expected such a strong response to be obtainable for Ac-225-radiopharmaceuticals at the low dosages recited in the present claims. Accordingly, the current claims are patentably distinct from, and are not obvious over the claims of the '791 and '160 patents, and withdrawal of the nonstatutory double patenting rejections is respectfully requested.

Claims 13-24 and 36 remain pending in this application. By this amendment, Applicant has amended claim 1 solely to correct a minor and inadvertent grammatical error. The amendment finds full support in the original specification, claims and drawings, and no new matter is presented. In light of the above amendments and remarks, Applicant submits that all of pending claims 13-24 and 36 are in condition for allowance. Applicant therefore, respectfully requests reconsideration and a timely indication of allowance. However, if any issues remain that can be addressed over the telephone, Applicant invites the Examiner to contact Applicant's counsel at the number indicated below.

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Exhibit 1004.384

Payment of any fee required to enter and process this response is provided. The Director is authorized to charge any underpayment of fees or credit any overpayment of fees to Deposit Account No. 03-1728.

Respectfully submitted,

LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Lauren Schneider/
Lauren E. Schneider
Reg. No. 63,712
626/795-9900

LES/jhg

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Exhibit 1004.385

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

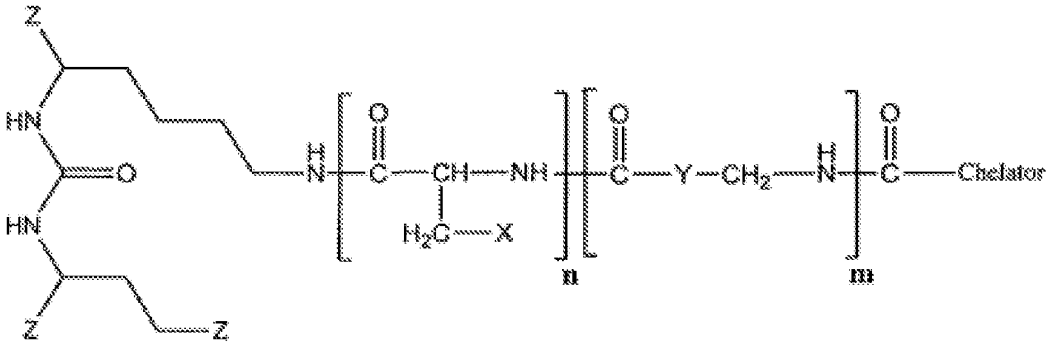
Listing of Claims:

Please amend claim 13.

1-12. (Canceled)

13. (Currently Amended) A method for treating PSMA expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

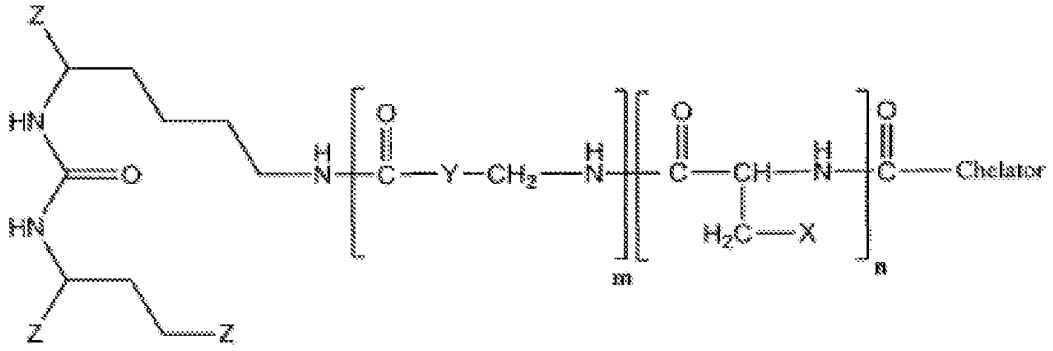
Formula (A)



or

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Exhibit 1004.386

Formula (B)



with:

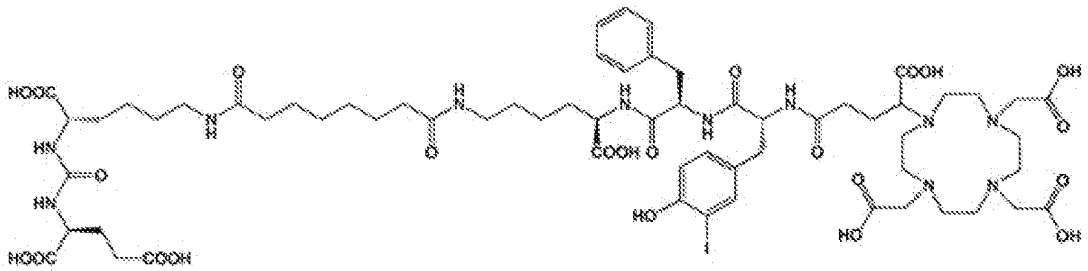
n:	0,1
m:	1,2,3,4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N''-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA), 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA), 1,4,7-triazacyclononane phosphinic acid (TRAP), 1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),

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Exhibit 1004.387

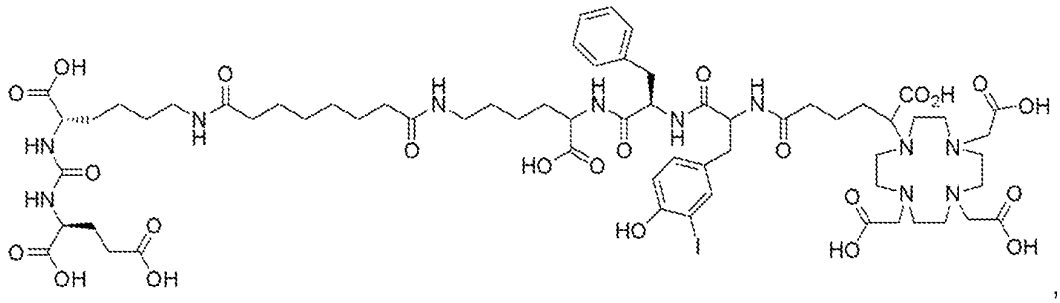
3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),
N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),
diethylenetriaminepentaacetic acid (DTPA),
Trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A)
p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA)

or

Formula (C)



Formula (D)



,

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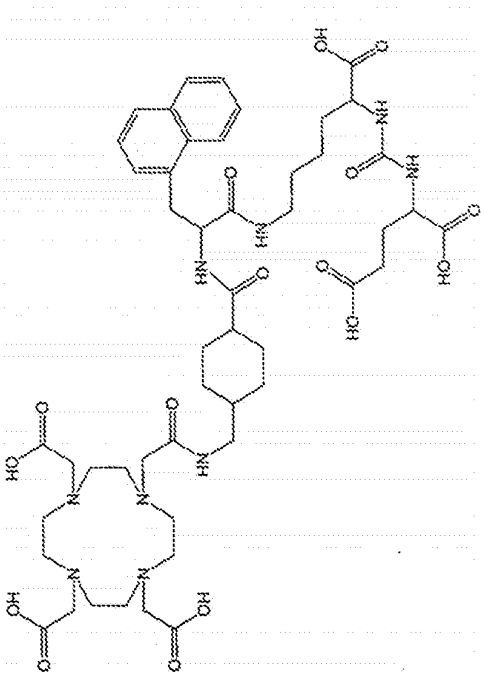
or

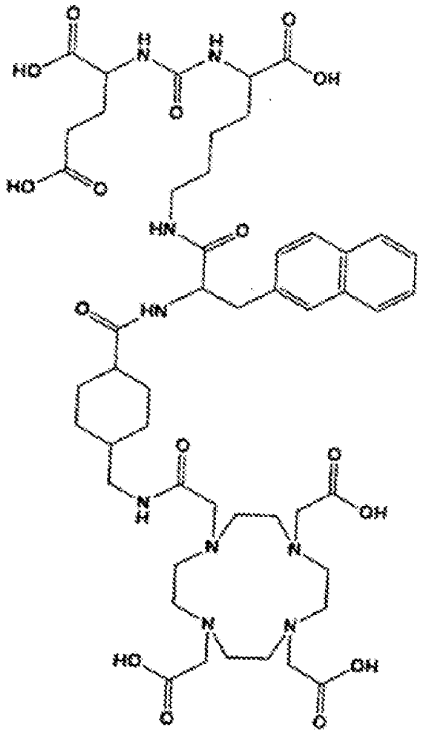
Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

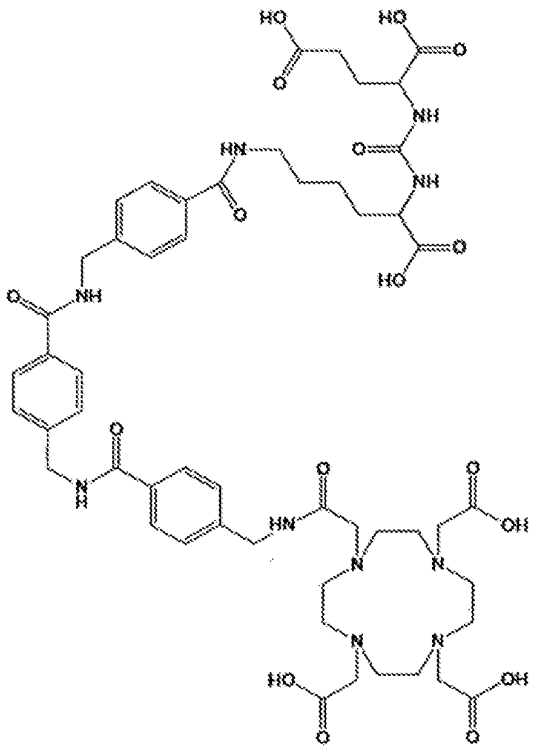
wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

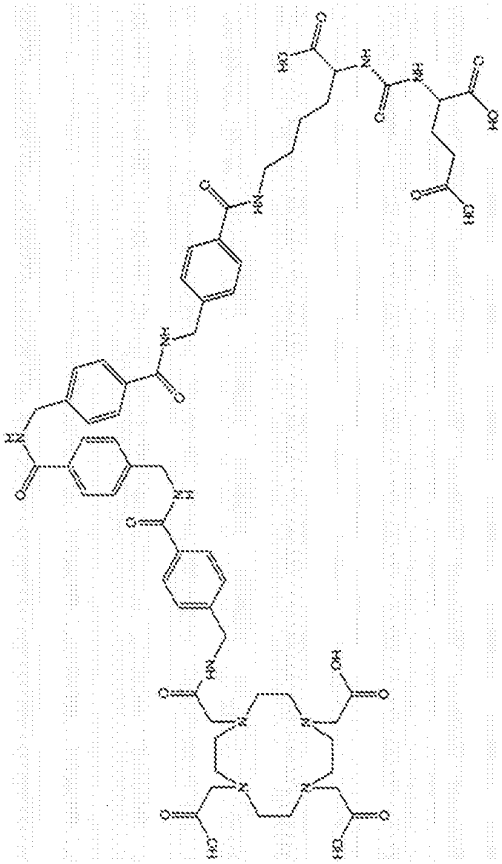
14. (Previously Presented) The method of claim 13, wherein the one or more Ac-225-radiopharmaceuticals are selected from:



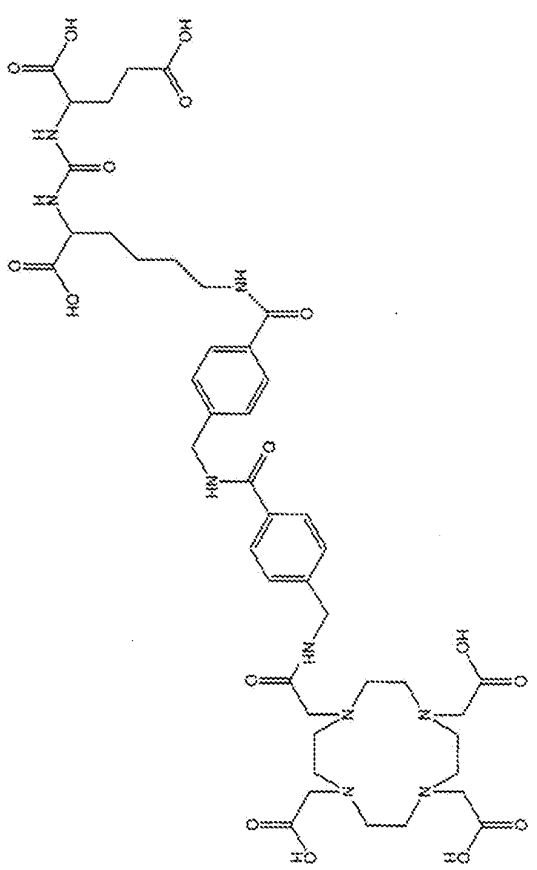


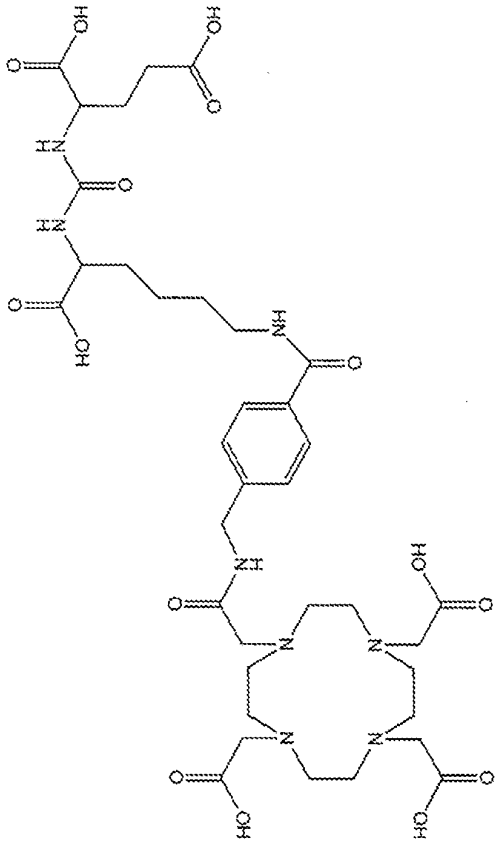
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Exhibit 1004.389



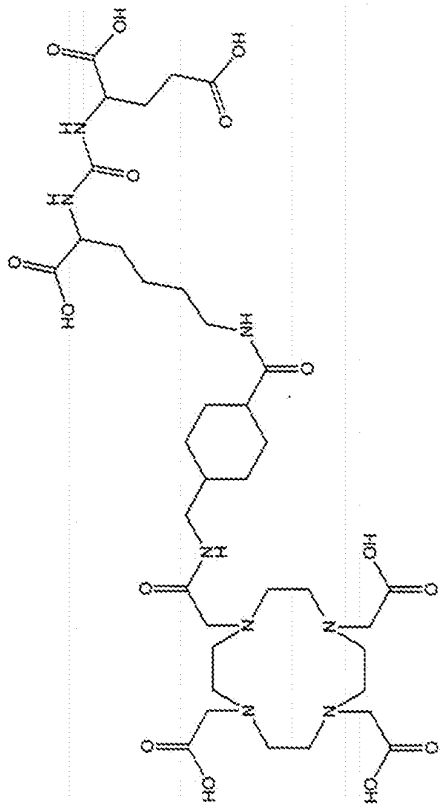


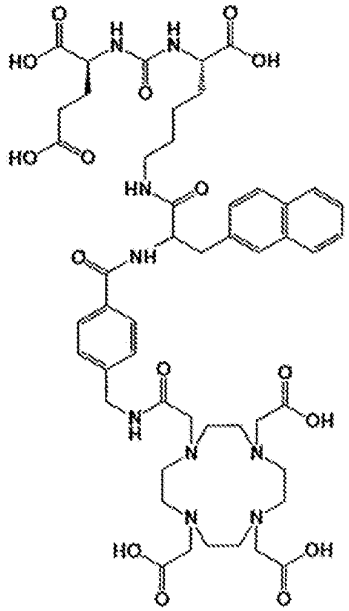
Fusion Pharmaceuticals, Inc.
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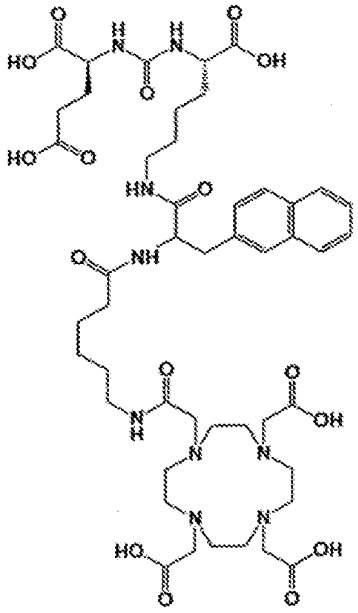


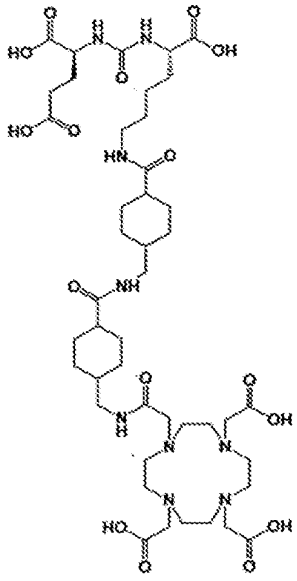


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Exhibit 1004.391

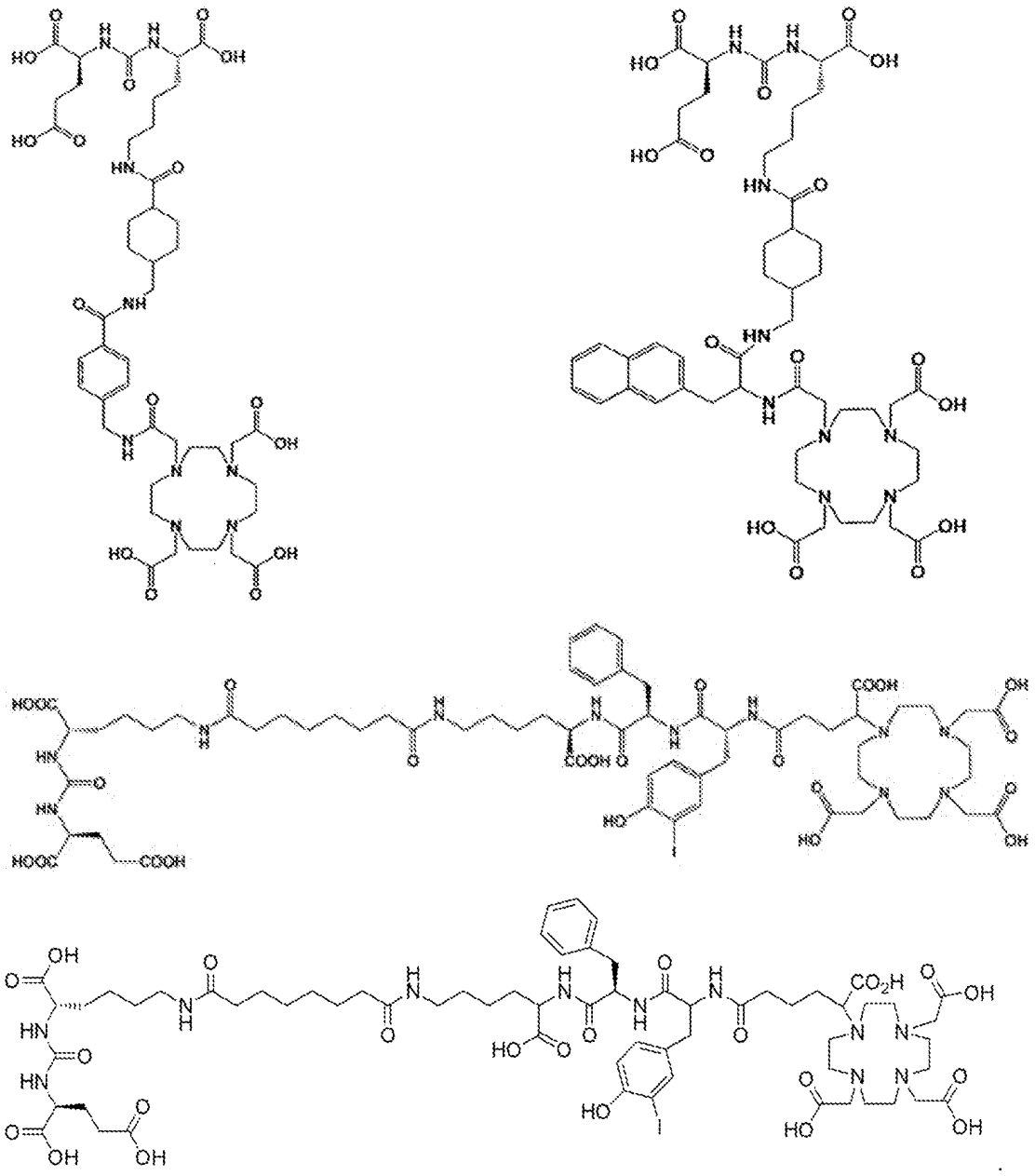








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Exhibit 1004.392



15. (Previously Presented) The method of claim 13, wherein at least one Ac-225-radiopharmaceutical is Ac-225-PSMA-617.

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Exhibit 1004.393

16. (Previously Presented) The method of claim 13, wherein said PSMA expressing cancers are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers.

17. (Previously Presented) The method of claim 13, wherein the cancer is a disseminated cancer.

18. (Previously Presented) The method of claim 16, wherein said PSMA expressing cancer is prostate cancer.

19. (Previously Presented) The method of claim 16, wherein said PSMA expressing cancer is breast cancer.

20. (Previously Presented) The method of claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

21. (Previously Presented) The method of claim 20, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

22. (Previously Presented) The method of claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

23. (Previously Presented) The method of claim 22, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

24. (Previously Presented) The method of claim 20, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

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Exhibit 1004.394

25-35. (Canceled).

36. (Previously Presented) The method of claim 22, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/470,104	Filing Date 06/14/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	10/26/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 13	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/YOLANDA CHADWICK/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

Courtesy Reminder for
Application Serial No: 16/470,104

Attorney Docket No: 173545 (304773-00005)
Customer Number: 23363
Date of Electronic Notification: 06/24/2020

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:

pto@lrrc.com
pair_cph@firsttofile.com

To view your correspondence online or update your email addresses, please visit us anytime at **https://ppair-my.uspto.gov/pair/PrivatePair.**
If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)	9416

23363 7590 06/24/2020

Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

EXAMINER	
SAMALA, JAGADISHWAR RAO	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/24/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pair_cph@firsttofile.com
pto@lrrc.com

Fusion Pharmaceuticals, Inc.
Exhibit 1004.398

Office Action Summary	**Application No.** 16/470,104	**Applicant(s)** MORGENSTERN et al.	
	Examiner JAGADISHWAR R SAMALA	**Art Unit** 1618	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 13-24 and 36 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 13-24 and 36 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 06/14/2019 & 07/30/2019.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.399

DETAILED ACTION

Notice of Pre-AIA or AIA Status

This Office action details a first action on the merits for the above referenced application No. Claims 13-24 and 36 are pending in this application. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 06/14/2019 and 07/30/2019 was noted and the submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

The drawings were received on 06/14/2019. These drawings are acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s)

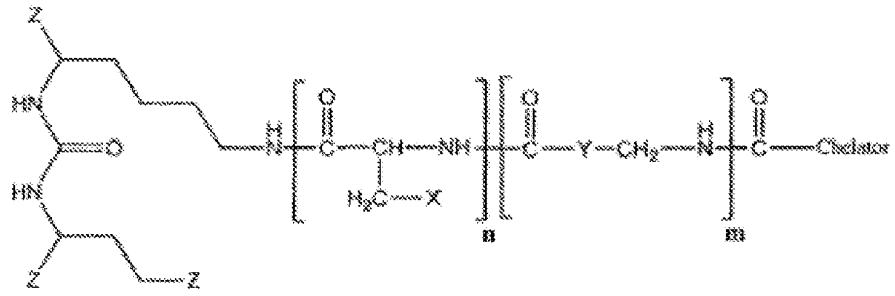
because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

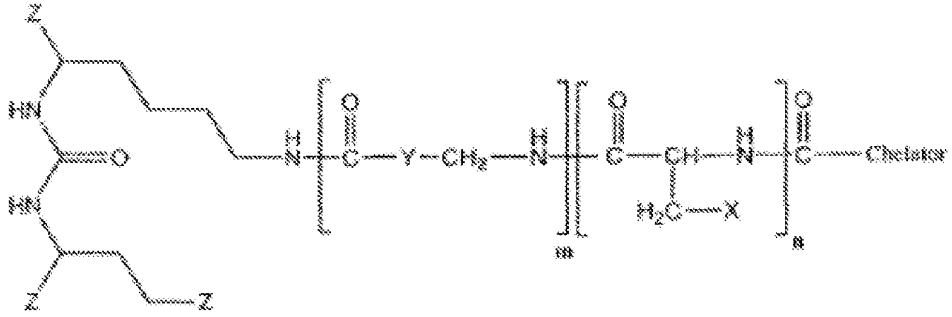
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

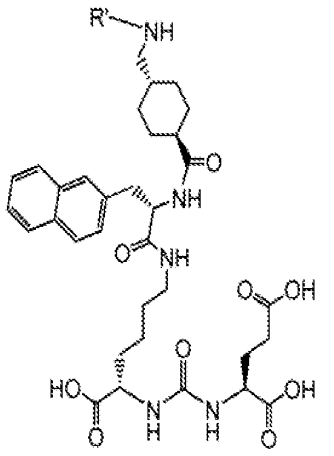
Claims 13-24 and 36 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 10,398,791. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are directed to the same art specific subject matter.

The present invention is directed to a method of treating cancer and/or a metastasis thereof, comprising administering to a patient a therapeutically effective amount of compounds of the formula:

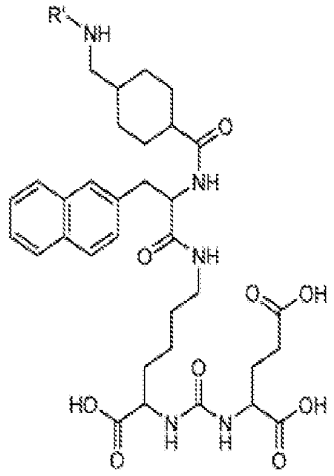




With substituents as recited in claim 13. Some of species compounds reads on claim 13:

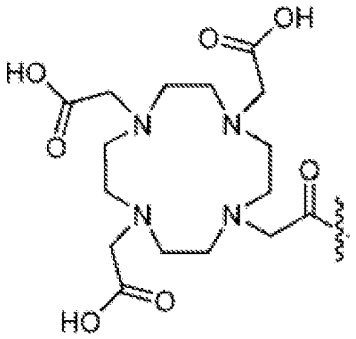


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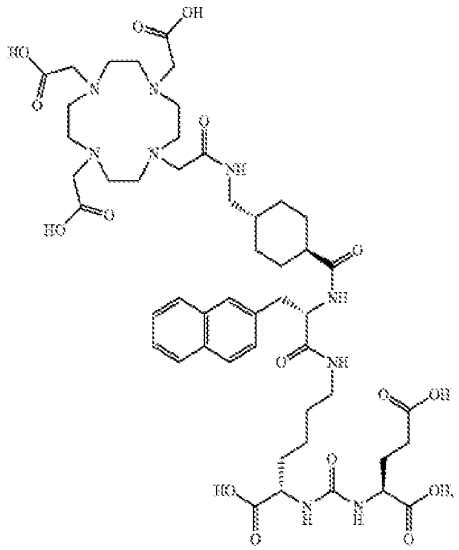
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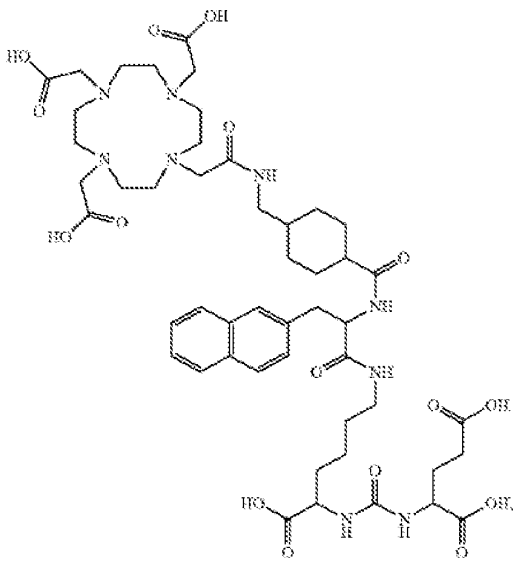
wherein R' is a chelator of the formula:



, and Wherein a radionuclide is complexed to the chelator.

The claims of U.S. Patent No. 10,398,791 are directed to compounds of formula:





,

or salts thereof and wherein 177Lu is complexed to the chelator. The difference between the instant and the issued claims is in scope only. Instant claimed compounds are used in method of treating cancer and/or a metastasis thereof.

"Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) the education level of active workers in the field." *Envtl. Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983) (*citing Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc.*, 707 F.3d 1376, 1381-82 (Fed. Cir. 1983)). The above factors are not exhaustive, but are a guide. *Id.*

In this case, the education level of the inventor and the education level of active workers in the field of organic chemistry, as well as the high degree of sophistication required to solve problems encountered in the art, a person of ordinary skill in the art would likely have at least a college degree in the field of organic chemistry, with

industry experience, i.e., a masters or doctorate level of skill and knowledge in the laboratory. Thus, the level of skill in the art is relatively high.

"Structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, create a prima facie case of obviousness." *Takeda v. Alphapharm*, 83 USPQ2d 1169 (Fed. Cir. 2007) (*quoting In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). "The 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship...to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis v. Lupin,* 84 USPQ2d 1197 (Fed. Cir. 2007) *(citing Dillion,* 919 F.2d 692). "Once such prima facie case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties." *Id.*

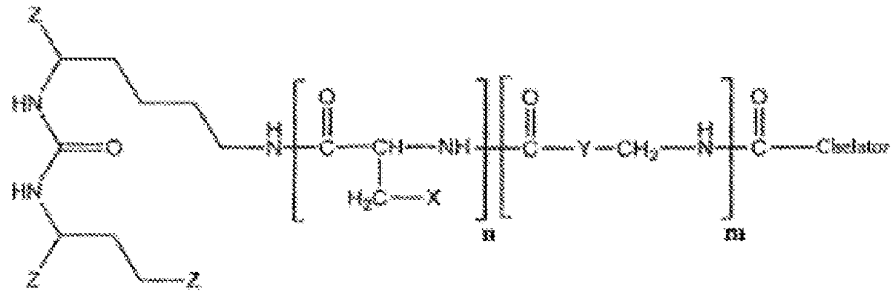
MPEP 804 states: "where the claims of an application are not the "same" as those of the first patent, but the grant of a patent with the claims in the application would unjustly extend the rights granted by the first patent, a double patenting rejection under nonstatutory grounds is proper."

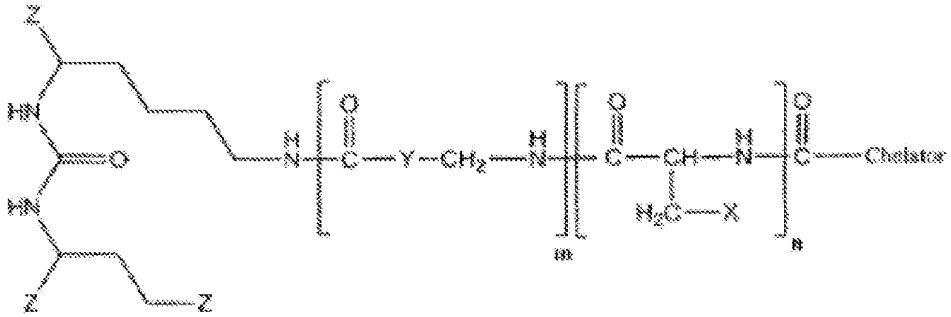
Although the conflicting claims are not identical, the Examiner finds that a person having ordinary skill in the art would recognize that the claimed invention would unjustly extend the rights granted to U.S. Patent No. 10,398,791 because a hypothetical infringer of U.S. Patent No. 10,398,791 would necessarily be an infringer of

the claimed invention. Accordingly, U.S. Patent No. 10,398,791 renders the instant claims obvious absent a showing of unpredictability or comparative evidence suggesting otherwise.

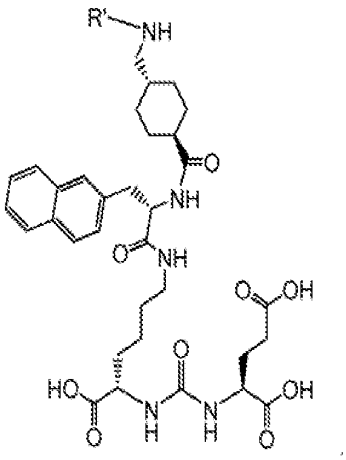
Claims 13-24 and 36 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 10,471,160. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are directed to the same art specific subject matter.

The present invention is directed to a method of treating cancer and/or a metastasis thereof, comprising administering to a patient a therapeutically effective amount of compounds of the formula:

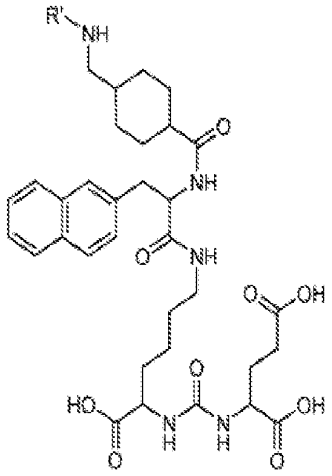




With substituents as recited in claim 13. Some of species compounds reads on claim 13:

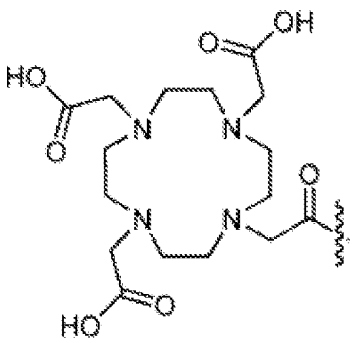


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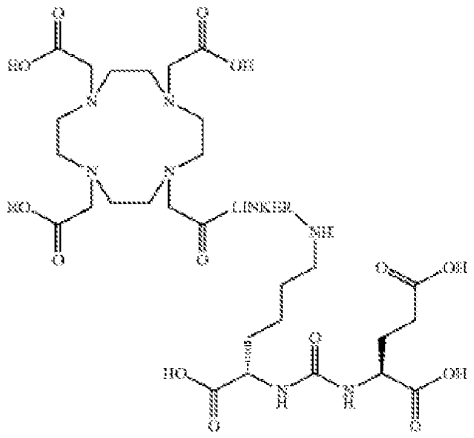
,

wherein R' is a chelator of the formula:

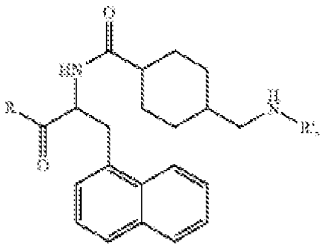


, and Wherein a radionuclide is complexed to the chelator.

The claims of U.S. Patent No. 10,471,160 are directed to compounds of formula:



wherein the R'-LINKER-R is



, a pharmaceutically acceptable salt or a carrier thereof, comprising a radionuclide and method of their use in treating prostate cancer and/or metastasis thereof. The difference between the instant and the U.S. Patent No. 10,471,160 is in scope only. In some instances, the claims are drawn to compound of claim 1, wherein chelator is a radical of.

"Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) the education level of active workers in the field." *Envtl. Designs, Ltd. V. Union Oil Co.,* 713 F.2d 693, 696 (Fed. Cir. 1983) *(citing*

Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc., 707 F.3d 1376, 1381-82 (Fed. Cir. 1983)). The above factors are not exhaustive, but are a guide. *Id.*

In this case, the education level of the inventor and the education level of active workers in the field of organic chemistry, as well as the high degree of sophistication required to solve problems encountered in the art, a person of ordinary skill in the art would likely have at least a college degree in the field of organic chemistry, with industry experience, i.e., a masters or doctorate level of skill and knowledge in the laboratory. Thus, the level of skill in the art is relatively high.

"Structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, create a prima facie case of obviousness." *Takeda v. Alphapharm*, 83 USPQ2d 1169 (Fed. Cir. 2007) (*quoting In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). "The 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship...to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis v. Lupin*, 84 USPQ2d 1197 (Fed. Cir. 2007) *(citing Dillion*, 919 F.2d 692). "Once such prima facie case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties." *Id.*

MPEP 804 states: "where the claims of an application are not the "same" as those of the first patent, but the grant of a patent with the claims in the application would unjusily

extend the rights granted by the first patent, a double patenting rejection under nonstatutory grounds is proper."

Although the conflicting claims are not identical, the Examiner finds that a person having ordinary skill in the art would recognize that the claimed invention would unjustly extend the rights granted to U.S. Patent No. 10,471,160 because a hypothetical infringer of U.S. Patent No. 10,471,160 would necessarily be an infringer of the claimed invention. Accordingly, U.S. Patent No. 10,471,160 renders the instant claims obvious absent a showing of unpredictability or comparative evidence suggesting otherwise.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR RAO SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on Monday-Friday 9am-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Hartley G Michael can be reached on 571 272 0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.R.S/
Examiner, Art Unit 1618
/JAKE M VU/
Primary Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 16/470,104	Applicant(s)/Patent Under Reexamination MORGENSTERN et al.	
	Examiner JAGADISHWAR R SAMALA	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-10398791-B2	09-2019	Eder; Matthias	A61K51/0497	1/1
*	B	US-10471160-B2	11-2019	Eder; Matthias	A61K51/0402	1/1
	C					
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	G					
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	I					
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	L					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.413

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/470,104	MORGENSTERN et al.
	Examiner	Art Unit
	JAGADISHWAR R SAMALA	1618

CPC - Searched*		
Symbol	Date	Examiner
A61K49/00; A61K51/04	07/28/2017	SJR

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST SEARCH (USPGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	06/21/2017	SJR
EAST INVENTOR NAME SEARCH	06/21/2017	SJR
PALM INVENTOR NAME SEARCH	06/21/2017	SJR
STN-SEARCH	06/23/2017	SJR
PAT CONF MICHAEL HARTLEY	06/12/2020	SJR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	49/00; 51/04	06/12/2020	SJR

Fusion Pharmaceuticals, Inc.
Exhibit 1004.414

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/470,104	MORGENSTERN et al.
	Examiner	Art Unit
	JAGADISHWAR R SAMALA	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant			☐ CPA		☐ T.D.		☐ R.1.47			
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.415

EAST Search History

EAST Search History (Prior Art)

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BIB DATA SHEET

CONFIRMATION NO. 9416

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/470,104	06/14/2019 RULE	424	1618	173545 (304773-00005)

APPLICANTS

THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION, Brussels, BELGIUM;
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Frederik GIESEL, Heidelberg, GERMANY;
Clemens KRATOCHWIL, Hirschberg a.d.B., GERMANY;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2016/081313 12/15/2016

**** FOREIGN APPLICATIONS ***************************

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10/04/2019

Foreign Priority claimed	❑ Yes ☑ No	❑ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	❑ Yes ☑ No		GERMANY	8	13	1
Verified and Acknowledged	/JAGADISHWAR RAO SAMALA/ Examiner's Signature	Initials				

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Glendale, CA 91209-9001
UNITED STATES

TITLE

TREATMENT OF PMSA EXPRESSING CANCERS

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1720	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

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Exhibit 1004.424

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		
	Attorney Docket Number	173545 (304773-00005)
	Application Number	16/470,104
	Filing Date	June 14, 2019
	Inventor(s)	Alfred Morgenstern, et al.
	Group Art Unit	To Be Determined
	Examiner Name	To Be Determined

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.[1]	DOCUMENT NUMBER Number - Kind Code[2] (If Known)	PUBLICATION DATE OR ISSUE DATE MM-DD-YYYY	NAME OF PATENTEE

FOREIGN PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (If Known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6] (✓)

OTHER DOCUMENTS

EXAMINER INITIALS	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article, title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
		APOSTOLIDIS Christos, et al., "*Production of Ac-225 from Th-229 for targeted alpha therapy*", Analytical Chemistry, 2005;77(19):6288-91
		HADASCHIK Boris, "*Re:225Ac-PSMA-617 for PSMA-Targeting Alpharadiation Therapy of Patients with Metastatic Castration-resistant Prostate Cancer*", European Urology, 21 August 2016, Volume 70, Issue 6, pp. 1080-1081
		ZIELINSKA B. et al., "*An Improved Method for the Production of Ac225/Bi-213 from Th-229 for Targeted Alpha Therapy*", Solvent Extraction and Ion Exchange, 2007;25(3):339-49

SRD 108846251.1-*-07/30/2019 2:13 PM

EXAMINER SIGNATURE	/JAGADISHWAR R SAMALA/	DATE CONSIDERED	06/17/2020

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		
	Attorney Docket Number	173545 (304773-00005)
	Application Number	To Be Determined
	Filing Date	June 14, 2019
	Inventor(s)	Alfred Morgenstern, et al.
	Group Art Unit	To Be Determined
	Examiner Name	To Be Determined

U.S. PATENT DOCUMENTS

EXAMINER INITIALS	Cite No.[1]	DOCUMENT NUMBER Number - Kind Code[2] (If Known)	PUBLICATION DATE OR ISSUE DATE MM-DD-YYYY	NAME OF PATENTEE

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		KRATOCHWIL, Clemens et al., "*225 Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer*", The Journal of Nuclear Medicine, 7 July 2016, Vol. 57, No. 12, pp. 1941–1944
		SATHEKGE, Mike et al., "*^{68}Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients*", European Journal of Nuclear Medicine and Molecular Imaging, 8 November 2016, Vol. 44, pp. 689-694
		KRATOCHWIL, Clemens et al., "*Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors*", The Journal of Nuclear Medicine, 1 May 2015, Vol. 56, No. Supplement 3, pg. 1232
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		International Search Report and Written Opinion for corresponding International Application No. PCT/EP2016/081313, dated September 7, 2017 (9 pgs.)

SRD 108416396.1-*-06/14/2019 7:29 AM

EXAMINER SIGNATURE	/JAGADISHWAR R SAMALA/	DATE CONSIDERED	06/17/2020

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/470,104	06/14/2019	1618	1720	173545 (304773-00005)	13	1

CONFIRMATION NO. 9416

UPDATED FILING RECEIPT

23363
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001



Date Mailed: 02/11/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

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UNIVERSITÄT HEIDELBERG, Heidelberg, GERMANY;

Power of Attorney: The patent practitioners associated with Customer Number 23363

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2016/081313 12/15/2016

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/470,104**
Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
Title

TREATMENT OF PMSA EXPRESSING CANCERS

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Fusion Pharmaceuticals, Inc.
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
16/470,104	Alfred MORGENSTERN	173545 (304773-00005)

23363
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

INTERNATIONAL APPLICATION NO.	
PCT/EP2016/081313	
I.A. FILING DATE	PRIORITY DATE
12/15/2016	

CONFIRMATION NO. 9416
371 ACCEPTANCE LETTER

OC000000114563114

Date Mailed: 02/11/2020

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

06/14/2019
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Copy of the International Application filed on 06/14/2019
- Copy of the International Search Report filed on 06/14/2019
- Preliminary Amendments filed on 01/28/2020
- Information Disclosure Statements filed on 07/30/2019
- Inventor's Oath or Declaration filed on 07/16/2019
- Request for Immediate Examination filed on 06/14/2019
- U.S. Basic National Fees filed on 06/14/2019
- Substitute Specification filed on 06/14/2019
- Authorize Access to Search Results filed on 06/14/2019
- Power of Attorney filed on 07/16/2019
- Authorization to Permit Access filed on 06/14/2019
- Application Data Sheet (37 CFR 1.76) filed on 06/14/2019

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Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

JACQUELINE A WHITFIELD

Telephone: (703) 756-1132

FORM PCT/DO/EO/903 (371 Acceptance Notice)

Fusion Pharmaceuticals, Inc.
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/470,104

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	520
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	13 minus 20 =	*			OR	x 100 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1580

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on January 28, 2020 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Appl No.	:	16/470,104 Confirmation No. 9416
Inventor	:	Alfred Morgenstern, et al.
Filed	:	June 14, 2019
Title	:	TREATMENT OF PMSA EXPRESSING CANCERS
TC/A.U.	:	1618
Examiner	:	To Be Determined
Docket No.	:	173545 (304773-00005)
Customer No.	:	23363

SUPPLEMENTAL PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
January 28, 2020

Commissioner:

Prior to examination, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 12 of this paper.

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Amendments to the Claims:

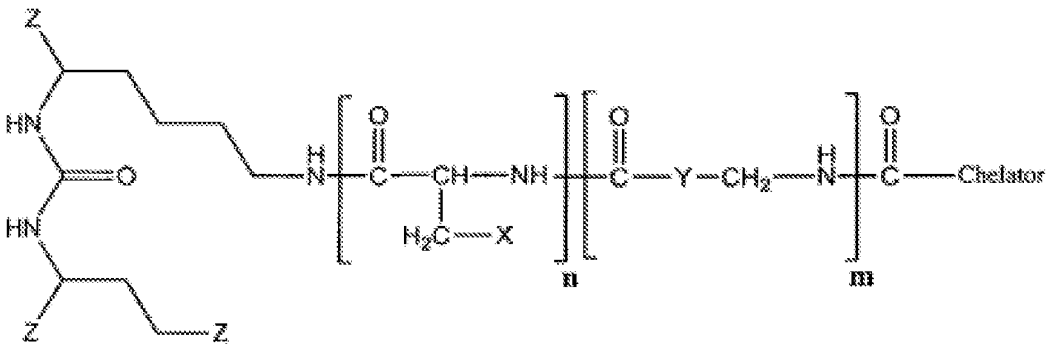
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-12. (Cancelled)

13. (Original) A method for treating PSMA expressing cancers, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

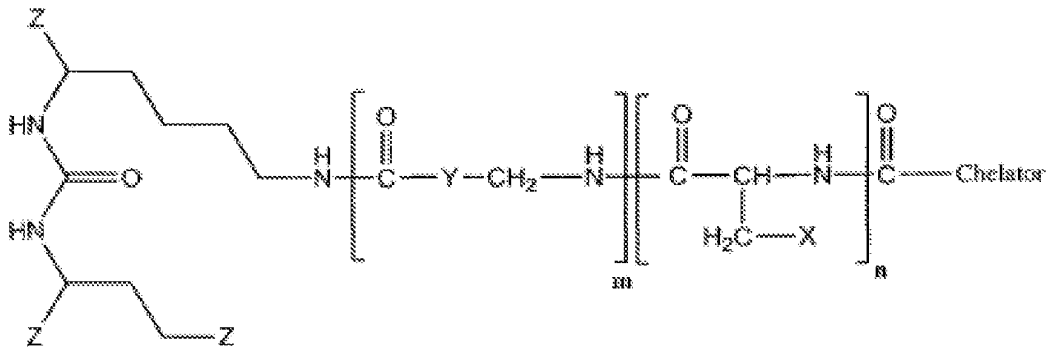
Formula (A)



or

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Formula (B)



with:

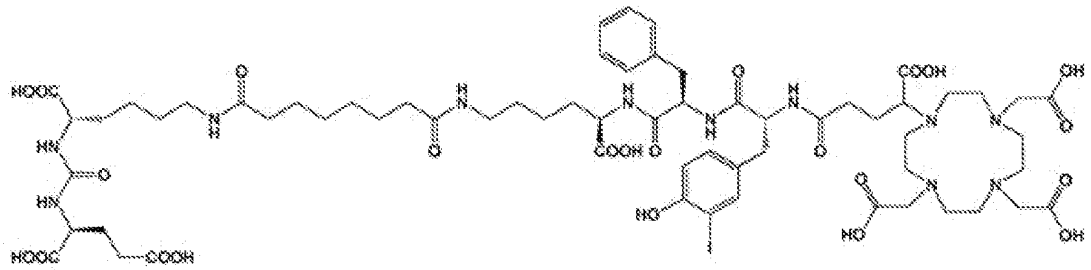
n:	0,1
m:	1,2,3,4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N''-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA), 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA), 1,4,7-triazacyclononane phosphinic acid (TRAP), 1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),

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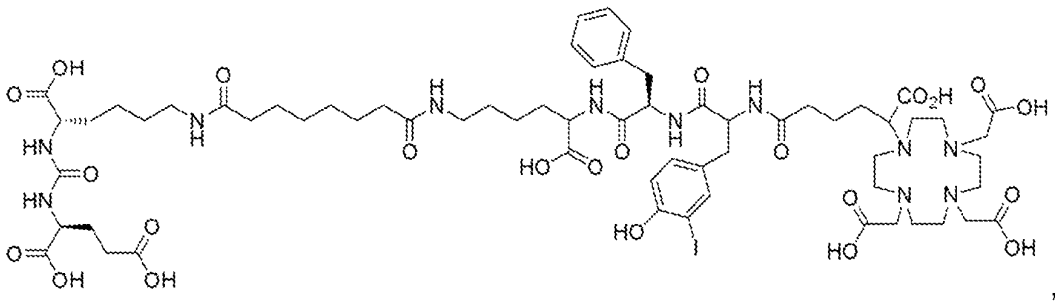
3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),
N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),
diethylenetriaminepentaacetic acid (DTPA),
Trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A)
p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA)

or

Formula (C)



Formula (D)



,

or

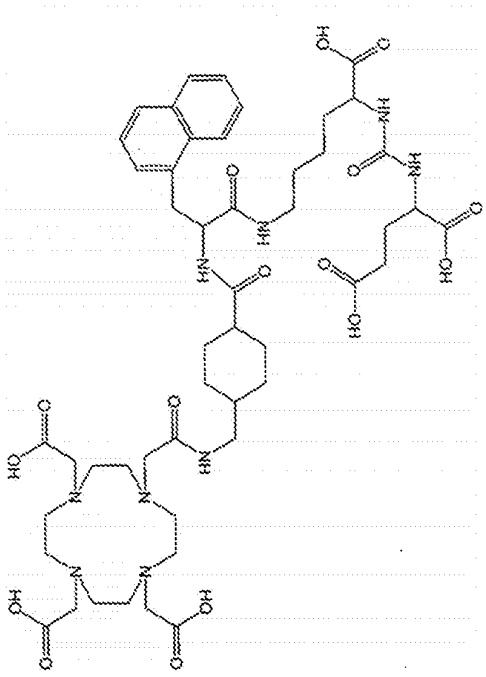
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Exhibit 1004.437

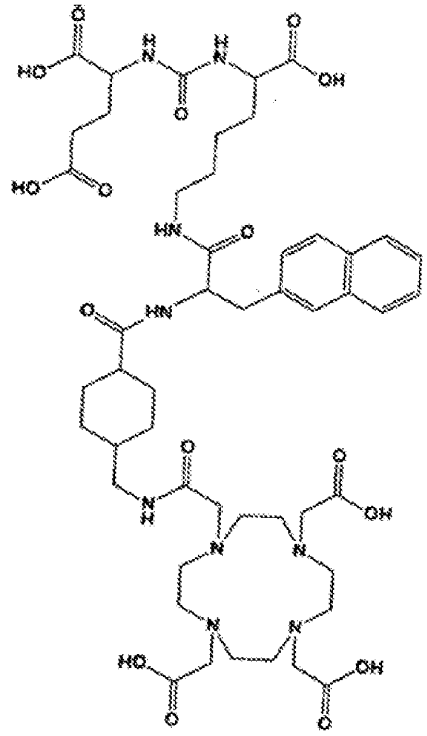
Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

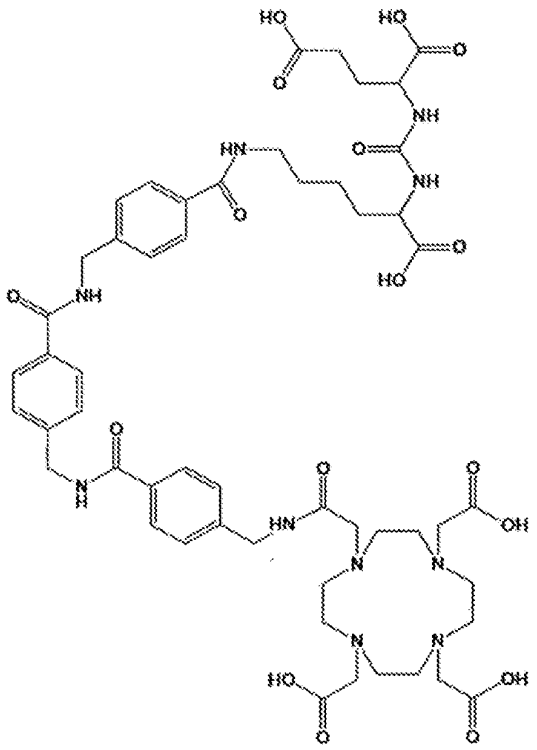
wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

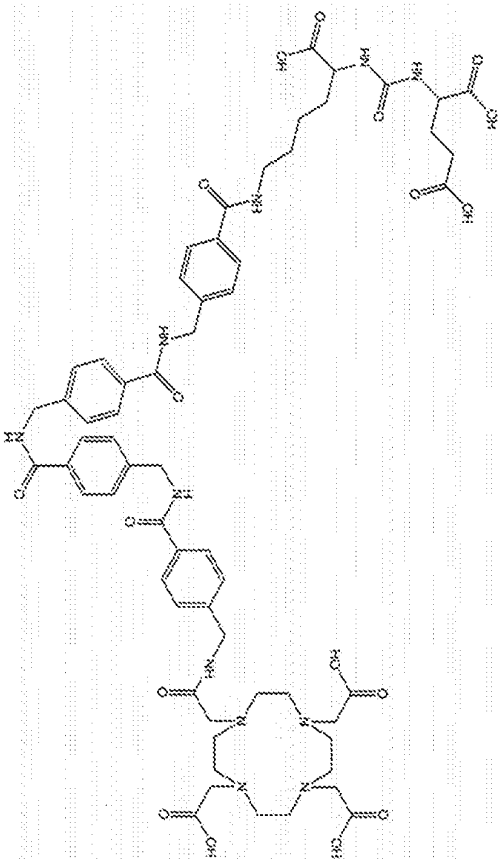
14. (Currently Amended) The method ~~as claimed in~~ of claim 13, wherein the one or more Ac-225-radiopharmaceuticals are selected from:



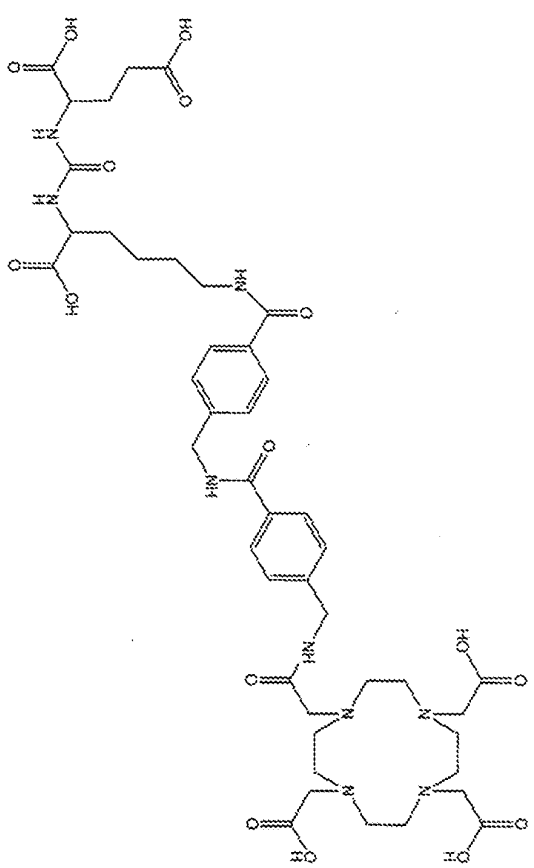


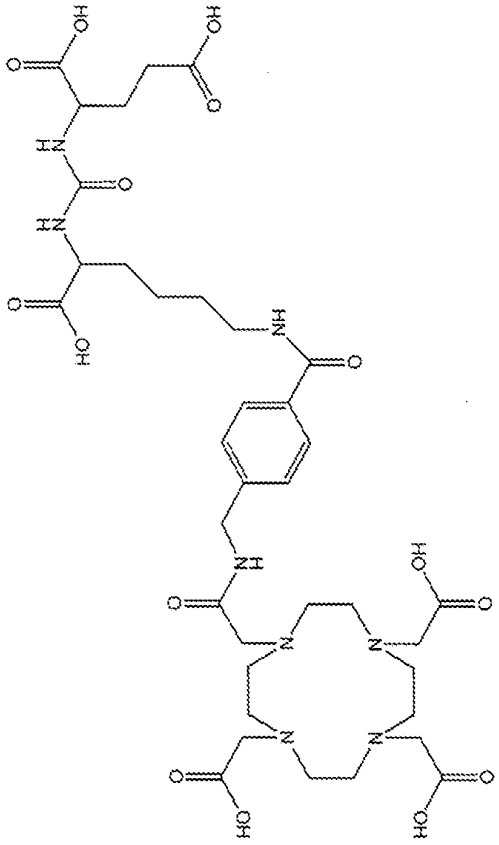
Fusion Pharmaceuticals, Inc.
Exhibit 1004.438



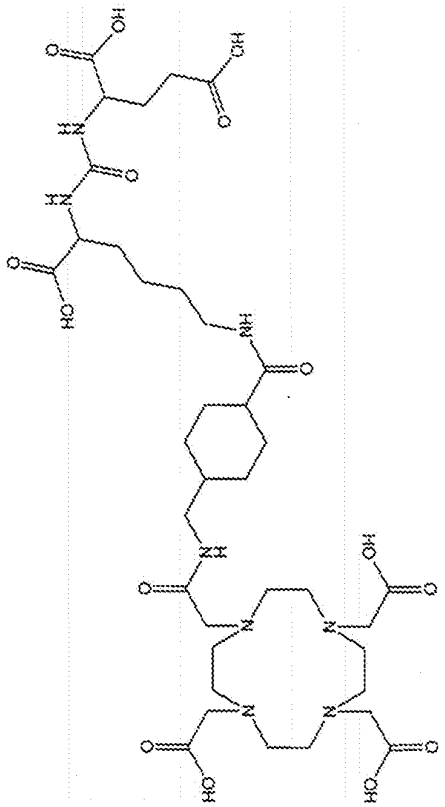


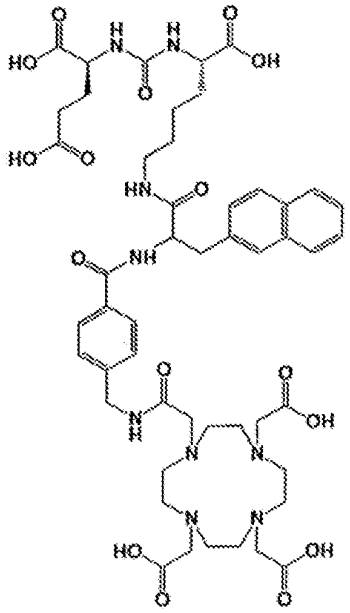
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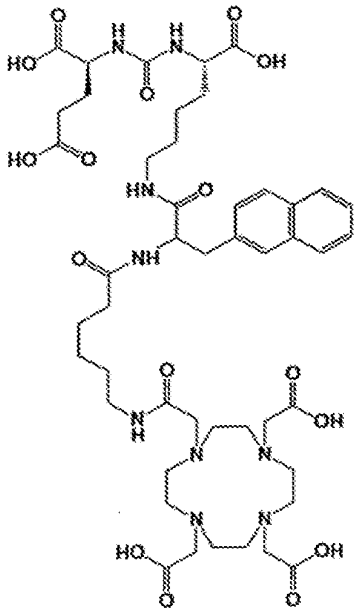


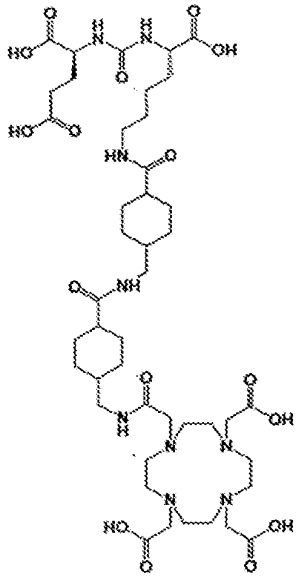


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Exhibit 1004.440

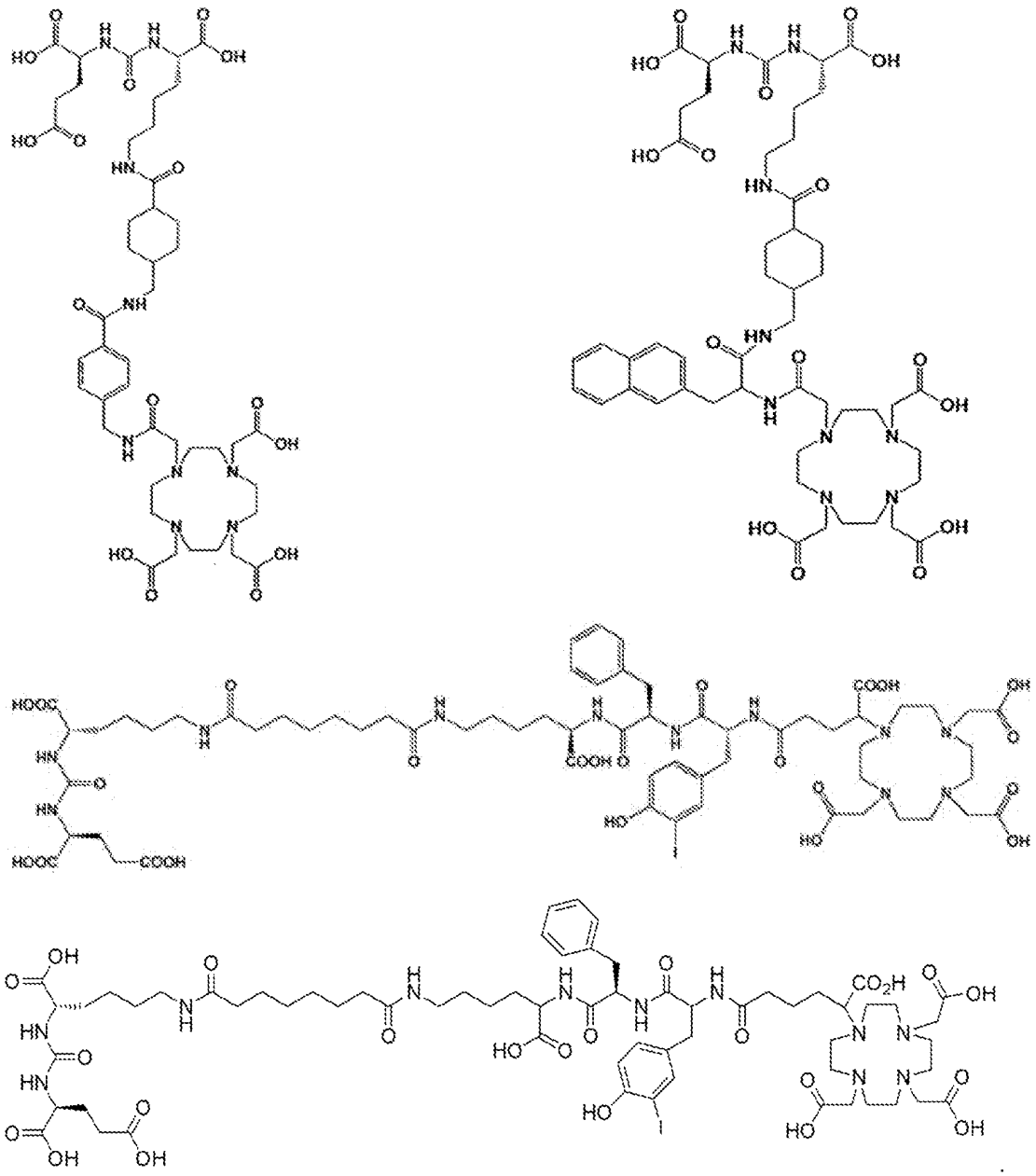








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Exhibit 1004.441



15. (Currently Amended) The method ~~as claimed in~~ of claim 13 [[or 14]], wherein at least one ~~or a sole~~ Ac-225-radiopharmaceutical is Ac-225-PSMA-617.

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Exhibit 1004.442

16. (Currently Amended) The method ~~as claimed in~~ of claim 13 [[or 15]], wherein said PSMA expressing cancers are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers.

17. (Currently Amended) The method ~~as claimed in~~ of claim 13, wherein the cancer is a disseminated cancer.

18. (Currently Amended) The method ~~as claimed in~~ of claim 16, wherein said PSMA expressing cancer is prostate cancer.

19. (Currently Amended) The method ~~as claimed in~~ of claim 16, wherein said PSMA expressing cancer is breast cancer.

20. (Currently Amended) The method ~~as claimed in~~ of claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

21. (Currently Amended) The method ~~as claimed in~~ of claim 20, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

22. (Currently Amended) The method ~~as claimed in~~ of claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

23. (Currently Amended) The method ~~as claimed in~~ of claim 22, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

24. (Currently Amended) The method ~~as claimed in claim 8 or claim 22~~ of claim 20, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

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25-35. (Cancelled)

36. (Currently Amended) The ~~use as claimed in claim 32 or claim 34~~ method of claim 22, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.444

REMARKS/ARGUMENTS

Applicant has amended claims 14-24 and 36 to remove multiple dependencies. Claims 1-12 and 25-35 have been canceled. Applicant submits that the amendments are fully supported by the original specification, claims and drawings, and that no new matter is presented.

Applicant respectfully requests entry of this Supplemental Preliminary Amendment prior to examination of the present application.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.445

Electronic Patent Application Fee Transmittal

Application Number:	16470104
Filing Date:	14-Jun-2019
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Filer:	Syed A. Hasan/Stacey Dawson
Attorney Docket Number:	173545 (304773-00005)

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	600	600
Miscellaneous:				
		Total in USD ($)		**600**

Electronic Acknowledgement Receipt

EFS ID:	38422062
Application Number:	16470104
International Application Number:	
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Syed A. Hasan/Stacey Dawson
Filer Authorized By:	Syed A. Hasan
Attorney Docket Number:	173545 (304773-00005)
Receipt Date:	28-JAN-2020
Filing Date:	14-JUN-2019
Time Stamp:	15:45:47
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$600
RAM confirmation Number	E20201RF46514097
Deposit Account	031728
Authorized User	Stacey Dawson
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	173545_Response_to_Insufficiency.pdf	102919 578f101bcd41feb4f2c7eae096f3e66e36b45217	no	1
Warnings:					
Information:					
2	Extension of Time	173545_Extension.pdf	111511 f3e26e4ad063ed58eb9ea88b436c9cac7a848138	no	2
Warnings:					
Information:					
3		173545_Supp_Prelim_Amendment.pdf	1433963 1d89854f779fd62bc049a0839764e6c1a256b952	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	11
Applicant Arguments/Remarks Made in an Amendment	12	12

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30973 79710ad63d62d1255badfd39e7f5945413c5c12d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1679366		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on January 28, 2020 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor(s)	: Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	: 16/470,104	
Filed	: June 14, 2019	
Title	: TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	: 1618	
Examiner	: To Be Determined	
Docket No.	: 173545 (304773-00005)	

LETTER IN RESPONSE TO NOTIFICATION OF INSUFFICIENCY UNDER 37 CFR 1.492 AND/OR 1.495 (DO/EO/US)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
January 28, 2020

Commissioner:

In response to the Notification of Insufficiency dated October 7, 2019, enclosed are:

1. A Petition for Extension of Time with Fee;
2. Supplemental Preliminary Amendment.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the pendency of this application to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.451

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PETITION FOR EXTENSION OF TIME
FROM THE NOTIFICATION OF INSUFFICIENCY

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on January 28, 2020 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor(s) : Alfred Morgenstern, et al. Confirmation No. 9416
Application No. : 16/470,104
Filed : June 14, 2019
Title : TREATMENT OF PMSA EXPRESSING CANCERS

Grp./Div. : 1618
Examiner : To Be Determined

Docket No. : 173545 (304773-00005)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
January 28, 2020

Commissioner:

Applicant petitions the Commissioner to extend the time for response to the Notification of Insufficiency dated October 7, 2019 for two month(s) from December 7, 2019 to February 7, 2020.

The fee for extension of time required by 37 CFR § 1.17 is calculated below.

FEE CALCULATION			
LENGTH OF EXTENSION	LARGE ENTITY	SMALL ENTITY	FEE
WITHIN FIRST MONTH	$200.00	$100.00	
WITHIN SECOND MONTH	$600.00	$300.00	$600.00
WITHIN THIRD MONTH	$1,400.00	$700.00	
WITHIN FOURTH MONTH	$2,200.00	$1,100.00	
WITHIN FIFTH MONTH	$3,000.00	$1,500.00	

Submitted herewith is the fee of $600.00 to cover the cost of the extension.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.452

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account.

Respectfully submitted,

LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.453

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/470,104	06/14/2019	Alfred MORGENSTERN	173545 (304773-00005)

CONFIRMATION NO. 9416

23363
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

PUBLICATION NOTICE

OC000000114011498

Title:TREATMENT OF PMSA EXPRESSING CANCERS

Publication No.US-2020-0016281-A1
Publication Date:01/16/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
16/470,104	Alfred MORGENSTERN	173545 (304773-00005)

23363
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

INTERNATIONAL APPLICATION NO.	
PCT/EP2016/081313	
I.A. FILING DATE	PRIORITY DATE
12/15/2016	

CONFIRMATION NO. 9416
371 FORMALITIES LETTER



Date Mailed: 10/07/2019

Notification of Insufficiency Under 37 CFR 1.492 and/or 1.495 (DO/EO/US)

The following items have been submitted by the applicant or the International Bureau to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Copy of the International Application filed on 06/14/2019
- Copy of the International Search Report filed on 06/14/2019
- Preliminary Amendments filed on 06/14/2019
- Information Disclosure Statements filed on 07/30/2019
- Inventor's Oath or Declaration filed on 07/16/2019
- Request for Immediate Examination filed on 06/14/2019
- U.S. Basic National Fees filed on 06/14/2019
- Substitute Specification filed on 06/14/2019
- Authorize Access to Search Results filed on 06/14/2019
- Power of Attorney filed on 07/16/2019
- Authorization to Permit Access filed on 06/14/2019
- Application Data Sheet (37 CFR 1.76) filed on 06/14/2019

The following items **MUST** be furnished within the period set forth below:

- Additional claim fees of $**2820** as a undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fees required for this application is $**2820** for an Undiscounted Entity:

- Total additional claim fee(s) for this application is $**2820**
  - $**2000** for **20** total claims over 20.
  - $**820** for multiple dependent claim surcharge.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

FORM PCT/DO/EO/923 (371 Formalities Notice)

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Exhibit 1004.455

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

JACQUELINE A WHITFIELD

Telephone: (703) 756-1132

FORM PCT/DO/EO/923 (371 Formalities Notice)

Fusion Pharmaceuticals, Inc.
Exhibit 1004.456

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/470,104	06/14/2019		1720	173545 (304773-00005)	36	3

CONFIRMATION NO. 9416

23363
Lewis Roca Rothgerber Christie LLP
PO BOX 29001
Glendale, CA 91209-9001

FILING RECEIPT

OC000000111682467

Date Mailed: 10/07/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Alfred MORGENSTERN, Karlsruhe, GERMANY;
Frank BRUCHERTSEIFER, Stutensee, GERMANY;
Christos APOSTOLIDIS, Heidelberg, GERMANY;
Uwe HABERKORN, Schwetzingen, GERMANY;
Frederik GIESEL, Heidelberg, GERMANY;
Clemens KRATOCHWIL, Hirschberg a.d.B., GERMANY;

Applicant(s)

THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION, Brussels, BELGIUM;
UNIVERSITÄT HEIDELBERG, Heidelberg, GERMANY;

Power of Attorney: The patent practitioners associated with Customer Number 23363

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2016/081313 12/15/2016

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

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Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/04/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/470,104**

Projected Publication Date: 01/16/2020

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PMSA EXPRESSING CANCERS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

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countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Exhibit 1004.460

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/470,104

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	520
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	40 minus 20 =	* 20			OR	x 100 =	2000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							820
			TOTAL			TOTAL	4400

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
16470104	

Applicant(s) Alfred MORGENSTERN

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend		Indep	Depend	Indep	Depend	Indep	Depend
1	1						51						
2		1					52						
3		2					53						
4		(1)					54						
5		(1)					55						
6		(1)					56						
7		(1)					57						
8		(1)					58						
9		(1)					59						
10		(1)					60						
11		(1)					61						
12		(1)					62						
13	1						63						
14		1					64						
15		2					65						
16		(1)					66						
17		1					67						
18		(1)					68						
19		(1)					69						
20		1					70						
21		1					71						
22		1					72						
23		1					73						
24		(1)					74						
25	1						75						
26		1					76						
27		2					77						
28		1					78						
29		1					79						
30		1					80						
31		1					81						
32		1					82						
33		1					83						
34		1					84						
35		1					85						
36		2					86						
37							87						
38							88						
39							89						
40							90						
41							91						
42							92						
43							93						
44							94						
45							95						
46							96						
47							97						
48							98						
49							99						
50							100						
Total Indep	3		0		0								
Total Depend	37	↵	0	↵	0	↵							
Total Claims	40		0		0								

Fusion Pharmaceuticals, Inc.
Exhibit 1004.462

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		
	Attorney Docket Number	173545 (304773-00005)
	Application Number	16/470,104
	Filing Date	June 14, 2019
	Inventor(s)	Alfred Morgenstern, et al.
	Group Art Unit	To Be Determined
	Examiner Name	To Be Determined

U.S. PATENT DOCUMENTS				
EXAMINER INITIALS	Cite No.[1]	DOCUMENT NUMBER Number - Kind Code[2] (If Known)	PUBLICATION DATE OR ISSUE DATE MM-DD-YYYY	NAME OF PATENTEE

FOREIGN PATENT DOCUMENTS					
EXAMINER INITIALS	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (If Known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6] (✓)

OTHER DOCUMENTS		
EXAMINER INITIALS	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article, title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
		APOSTOLIDIS Christos, et al., "*Production of Ac-225 from Th-229 for targeted alpha therapy*", Analytical Chemistry, 2005;77(19):6288-91
		HADASCHIK Boris, "*Re:225Ac-PSMA-617 for PSMA-Targeting Alpharadiation Therapy of Patients with Metastatic Castration-resistant Prostate Cancer*", European Urology, 21 August 2016, Volume 70, Issue 6, pp. 1080-1081
		ZIELINSKA B. et al., "*An Improved Method for the Production of Ac225/Bi-213 from Th-229 for Targeted Alpha Therapy*", Solvent Extraction and Ion Exchange, 2007;25(3):339-49

SRD 108846251.1-*-07/30/2019 2:13 PM

EXAMINER SIGNATURE		DATE CONSIDERED	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.pto.gov or MPEP 901.4. [3]Enter Office that issued the document, by the two-letter code (WIPO standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English Language Translation is attached.

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.463

Electronic Acknowledgement Receipt

EFS ID:	36733371
Application Number:	16470104
International Application Number:	
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Syed A. Hasan/Stacey Dawson
Filer Authorized By:	Syed A. Hasan
Attorney Docket Number:	173545 (304773-00005)
Receipt Date:	30-JUL-2019
Filing Date:	
Time Stamp:	17:32:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		173545_Supp_IDS_7-30-19.PDF	276941 e4fd04a69fcf865b16d5ab825b88e8749d02c213	yes	3

Fusion Pharmaceuticals, Inc.
Exhibit 1004.464

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	3

Warnings:					
Information:					
2	Non Patent Literature	Apostolidis.PDF	5923003 5da571591da81da8177e1f0b6825af68fa1fd866	no	4
Warnings:					
Information:					
3	Non Patent Literature	Hadaschik.PDF	2480007 041537e5f9006c1cbf969f44ab422233370a4156	no	2
Warnings:					
Information:					
4	Non Patent Literature	Zielinska.PDF	7096554 cf2f52e53519de32905faab55e23ed91d1ce8962	no	12
Warnings:					
Information:					
		Total Files Size (in bytes):	15776505		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on July 30, 2019 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor(s)	: Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	: 16/470,104	
Filed	: June 14, 2019	
Title	: TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	: To Be Determined	
Examiner	: To Be Determined	
Docket No.	: 173545 (304773-00005)	

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
37 CFR § 1.97(b)

Commissioner for Patents
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Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
July 30, 2019

Commissioner:

In compliance with the duty of disclosure under 37 CFR §§ 1.56, 1.97 and 1.98, and in accordance with the provisions in the Manual of Patent Examining Procedure §§ 609 and 707.05(b), enclosed is an information disclosure statement listing the references that are known to applicant. Copies of each of the listed Other Documents references are enclosed. This filing is timely because it is made during one of the periods described in 37 CFR § 1.97(b).

It is respectfully requested that the listed references be considered in the examination of this application and identified on the list of references cited on the patent issuing for this application. Applicant also requests that an initialed copy of the information disclosure statement be entered in the application file and returned to applicant with the next communication from the Office in accordance with MPEP § 609.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.466

The Commissioner is hereby authorized to charge any fees which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any Deposit Account transaction.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd
Enclosures: Information Disclosure Statement, w/references

Fusion Pharmaceuticals, Inc.
Exhibit 1004.467

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on July 16, 2019 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor	: Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	: 16/470,104	
Filed	: June 14, 2019	
Title	: TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	: To Be Determined	
Examiner	: To Be Determined	
Docket No.	: 173545 (304773-00005)	

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS IN ACCORDANCE WITH 37 CFR. 1.5

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
July 16, 2019

Commissioner:

Attached herewith is a General Power of Attorney for Applicant UNIVERSITÄT HEIDELBERG for the above-identified patent application.

Respectfully submitted,

LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

108709848_1

Fusion Pharmaceuticals, Inc.
Exhibit 1004.468

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

UNIVERSITÄT HEIDELBERG ("Applicant") is the Applicant by virtue of being the Assignee or Person to Whom the Inventor is Under an Obligation to Assign. Applicant hereby revokes all previous powers of attorney given in the application identified in the attached transmittal letter and appoints the Patent Practitioners associated with

CUSTOMER NUMBER 23363

of the firm LEWIS ROCA ROTHGERBER CHRISTIE LLP, telephone 626/795-9900, as attorneys or agents to transact all business in the United States Patent and Trademark Office for matters connected therewith for the application referenced in the attached transmittal letter.

The undersigned representative of Applicant, whose title is supplied below, is authorized to act on behalf of Applicant.

Please direct all correspondence to **CUSTOMER NUMBER 23363**. Direct all telephone calls to 626/795-9900, **LEWIS ROCA ROTHGERBER CHRISTIE LLP, P.O. Box 29001, Glendale, California 91209-9001.**

UNIVERSITÄT HEIDELBERG

Date June 4, 2019 By _____

Name: Irmtraut Gürtler

Title: Commercial Director

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.469

Electronic Acknowledgement Receipt

EFS ID:	36603749
Application Number:	16470104
International Application Number:	
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Syed A. Hasan/Stacey Dawson
Filer Authorized By:	Syed A. Hasan
Attorney Docket Number:	173545 (304773-00005)
Receipt Date:	16-JUL-2019
Filing Date:	
Time Stamp:	19:48:57
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		173545_Declaration_Heidelberg.PDF	1599830 1d41755c835661e031af8ac428397a69a4d65ed7	yes	4

Fusion Pharmaceuticals, Inc.
Exhibit 1004.470

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Oath or Declaration filed		2	4	
	Transmittal Letter		1	1	
Warnings:					
Information:					
2	Power of Attorney	173545_POA_Heidelberg.PDF	535257 3674cfdc859f8dd7d7391bd43dca89a9d2a8a47b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2135087		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INVENTOR'S DECLARATION AND ASSIGNMENT
FOR PATENT APPLICATION

PATENT

Title of Invention: TREATMENT OF PMSA EXPRESSING CANCERS

Docket No.: 173545 (304773-00005)
Application No. PCT/EP2016/081313

INVENTOR'S DECLARATION

As a below named inventor, I hereby declare that:

This declaration is directed to the attached application unless the following is checked:

X United States Application or PCT International Application Number PCT/EP2016/081313 filed on December 16, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the above-identified application.

I have reviewed and understand the contents of the above-identified application, including the claims.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both.

ASSIGNMENT

In consideration of good and valuable consideration, the receipt of which is hereby acknowledged, the undersigned,

(1) Uwe HABERKORN, Frederik GIESEL, and Clemens KRATOCHWIL

HEREBY SELL(S), ASSIGN(S) AND TRANSFER(S) TO

(2) UNIVERSITÄT HEIDELBERG

having a place of business at

(3) Grabengasse 1, 69117 Heidelberg, Germany

(hereinafter called "ASSIGNEE") the entire right, title and interest in and to any and all improvements which are disclosed in the application for United States Letters Patent entitled

Fusion Pharmaceuticals, Inc.
Exhibit 1004.472

INVENTOR'S DECLARATION AND ASSIGNMENT FOR PATENT APPLICATION

Docket No.: 173545 (304773-00005)
Application No.: PCT/EP2016/081313

(4) TREATMENT OF PMSA EXPRESSING CANCERS

which application was executed on even date herewith or was

(a) executed on (5a): _____;

(b) filed on (5b): _____;

Application No.: _____;

(LEWIS ROCA ROTHGERBER CHRISTIE LLP, P.O. Box 29001, Glendale, CA 91209-9001) is hereby authorized to insert in (b) the specified data, when known.

Including any and all United States Patents which may be granted on said application, and any and all extensions, divisions, reissues, substitutes, renewals or continuations of said application and patents, and the right to all benefits under all international conventions for the protection of industrial property and applications for said improvements.

It is hereby authorized and requested that the Commissioner of Patents issue any and all of said Letters Patent, when granted, to said ASSIGNEE, its assigns or its successors in interest or its designee.

Upon said consideration, it is further agreed that, when requested, without charge to but at the expense of said ASSIGNEE, the undersigned will execute all divisional, continuing, substitute, renewal, and reissue patent applications; execute all rightful other papers; and generally do everything possible which said ASSIGNEE shall consider desirable for aiding in securing and maintaining patent protection as provided herein.

Uwe HABERKORN
Legal Name of Inventor

05.06.2019
Date

Signature

Frederik GIESEL
Legal Name of Inventor

05.06.2019
Date

Signature

108201396.1

Fusion Pharmaceuticals, Inc.
Exhibit 1004.473

INVENTOR'S DECLARATION AND ASSIGNMENT FOR PATENT APPLICATION

Docket No.: 173545 (304773-00005)
Application No.: PCT/EP2016/081313

Clemens KRATOCHWIL
Legal Name of Inventor

05 Jan 2018
Date

Signature

WITNESSES:

Gerd-Jörg RAUCH

Volker CLEEVES

108201290 1

Fusion Pharmaceuticals, Inc.
Exhibit 1004.474

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on July 16, 2019 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor(s)	: Alfred Morgenstern, et al.	Confirmation No. 9416
Application No.	: 16/470,104	
Filed	: June 14, 2019	
Title	: TREATMENT OF PMSA EXPRESSING CANCERS	
Grp./Div.	: To Be Determined	
Examiner	: To Be Determined	
Docket No.	: 173545 (304773-00005)	

TRANSMITTAL OF INVENTORS' DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
July 16, 2019

Commissioner:

Attached herewith is the executed Declaration of Inventors Uwe HABERKORN, Frederik GIESEL, and Clemens KRATOCHWIL for the above-identified patent application.

Respectfully submitted,

LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

108709334_1

Fusion Pharmaceuticals, Inc.
Exhibit 1004.475

PTO-1390 (01-18)
Approved for use through 8/31/2019. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	U.S. Application No. (if known, see 37 CFR 1.5)
173545 (304773-00005)	

International Application No.	International Filing Date	Priority Date Claimed
PCT/EP2016/081313	December 15, 2016	

Title of Invention
TREATMENT OF PMSA EXPRESSING CANCERS

First Named Inventor
Alfred MORGENSTERN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ■ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. ☐ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ■ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. ■ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ■ A preliminary amendment.
11. ■ An Application Data Sheet under 37 CFR 1.76.
12. ■ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. ■ A power of attorney and/or change of address letter.
14. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825 (not required if sequence listing in text format was indicated on the PCT Request as part of the International Application and the sequence listing was published as part of the international application).
15. ☐ Assignment papers *(cover sheet and document(s))*. Name of Assignee: _____
16. ☐ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.
	PCT/EP2016/081313	173545 (304773-00005)

17. ☐ Other items or information:

The following fees have been submitted.	CALCULATIONS
18. ■ Basic national fee (37 CFR 1.492(a)) **$300**	$ 300
19. ■ Examination fee (37 CFR 1.492(c)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • All other situations **$760**	$ 760
20. ■ Search fee (37 CFR 1.492(b)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$140** • International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB..... **$520** • All other situations **$660**	520 $
TOTAL OF 18, 19, and 20 =	$ 1,580
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). Fee for each additional 50 sheets of paper or fraction thereof **$400**	

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE	
49 - 100 =	0 / 50 =		x **$400**	$

Surcharge for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h))..... **$140**	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	36 - 20 =	16	x **$100**	$
Independent claims	3 - 3 =	0	x **$460**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$820**	$

Fee for submission of Sequence Listing text file of 300 MB to 800 MB (37 CFR 1.21(o)(1))..... **$1,000**	$
Fee for submission of Sequence Listing text file of more than 800 MB (37 CFR 1.21(o)(2))..... **$10,000**	$
Processing fee for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i))..... **$140** +	$
TOTAL OF ABOVE CALCULATIONS =	$
☐ **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.	
☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.	
TOTAL NATIONAL FEE =	$ 1,580
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31)..... **$50.00** per property +	$
TOTAL FEES ENCLOSED =	$ 1,580

Fusion Pharmaceuticals, Inc.
Exhibit 1004.477

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☒ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-1728 as follows:

i. ☐ any required fee.

ii. ☒ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ☒ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended to pay fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013, and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE 1: By providing this statement under 37 CFR 1.55 or 1.78, **this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA**.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

☒ The address associated with Customer Number: 23363 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone			
Email					

Signature	/Art Hasan/	Date	June 14, 2019
Name (Print/Type)	Art Hasan	Registration No. (Attorney/Agent)	41,057

Fusion Pharmaceuticals, Inc.
Exhibit 1004.478

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Alfred		MORGENSTERN	

Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

City	Karlsruhe	Country of Residence [i]	DE

Mailing Address of Inventor:

Address 1	Hegaustrasse 1
Address 2	

City	Karlsruhe	State/Province	
Postal Code	76199	Country [i]	DE

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Frank		BRUCHERTSEIFER	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Stutensee	Country of Residence [i]	DE

Mailing Address of Inventor:

Address 1	Nibelungenring 91
Address 2	

City	Stutensee	State/Province	
Postal Code	76297	Country [i]	DE

Inventor 3 Remove

Legal Name

Fusion Pharmaceuticals, Inc.
Exhibit 1004.479

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Christos		APOSTOLIDIS	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Heidelberg	Country of Residence i	DE

Mailing Address of Inventor:

Address 1	Kaiserstrasse 16		
Address 2			
City	Heidelberg	State/Province	
Postal Code	69115	Country i	DE

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Uwe		HABERKORN	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Schwetzingen	Country of Residence i	DE

Mailing Address of Inventor:

Address 1	Königsäcker 82		
Address 2			
City	Schwetzingen	State/Province	
Postal Code	68723	Country i	DE

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Frederik		GIESEL	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Heidelberg	Country of Residence i	DE

Mailing Address of Inventor:

Address 1	Handschuhsheimer Landstrasse 103		
Address 2			
City	Heidelberg	State/Province	
Postal Code	69121	Country i	DE

Fusion Pharmaceuticals, Inc.
Exhibit 1004.480

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Clemens		KRATOCHWIL	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Hirschberg a.d.B.	Country of Residence [i]	DE

Mailing Address of Inventor:

Address 1	Gartenstr. 9		
Address 2			
City	Hirschberg a.d.B.	**State/Province**	
Postal Code	69493	**Country** [i]	DE

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23363		
Email Address	PTO@LRRC.COM	Add Email	Remove Email

Application Information:

Title of the Invention	TREATMENT OF PMSA EXPRESSING CANCERS		
Attorney Docket Number	173545 (304773-00005)	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	8	**Suggested Figure for Publication (if any)**	

Fusion Pharmaceuticals, Inc.
Exhibit 1004.481

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23363		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	a 371 of international	PCT/EP2016/081313	2016-12-15

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Fusion Pharmaceuticals, Inc.
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Fusion Pharmaceuticals, Inc.
Exhibit 1004.483

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Fusion Pharmaceuticals, Inc.
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name: THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN

Mailing Address Information For Applicant:

Address 1	Rue de la Loi 200		
Address 2			
City	Brussels	**State/Province**	
Country	BE	Postal Code	1049
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Fusion Pharmaceuticals, Inc.
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PTO/AIA/14 (02-18)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Applicant 2 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	UNIVERSITÄT HEIDELBERG		
Mailing Address Information For Applicant:			
Address 1	Grabengasse 1		
Address 2			
City	Heidelberg	**State/Province**	
Country	DE	Postal Code	69117
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	173545 (304773-00005)
	Application Number	
Title of Invention	TREATMENT OF PMSA EXPRESSING CANCERS	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Art Hasan/			Date (YYYY-MM-DD)	2019-06-14
First Name	Art	Last Name	Hasan	Registration Number	41,057

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Exhibit 1004.487

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Exhibit 1004.488

INVENTOR'S DECLARATION AND ASSIGNMENT FOR PATENT APPLICATION PATENT

Title of Invention: TREATMENT OF PMSA EXPRESSING CANCERS

Docket No.: 173545 (304773-00005)
Application No. PCT/EP2016/081313

INVENTOR'S DECLARATION

As a below named inventor, I hereby declare that:

This declaration is directed to the attached application unless the following is checked:

X United States Application or PCT International Application Number PCT/EP2016/081313 filed on December 15, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the above-identified application.

I have reviewed and understand the contents of the above-identified application, including the claims.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both.

ASSIGNMENT

In consideration of good and valuable consideration, the receipt of which is hereby acknowledged, the undersigned,

(1) Alfred MORGENSTERN, Frank BRUCHERTSEIFER and Christos APOSTOLIDIS

HEREBY SELL(S), ASSIGN(S) AND TRANSFER(S) TO

(2) THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION

having a place of business at

(3) Rue de la Loi 200, 1049 Brussels, Belgium

(hereinafter called "ASSIGNEE") the entire right, title and interest in and to any and all improvements which are disclosed in the application for United States Letters Patent entitled

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Exhibit 1004.489

INVENTOR'S DECLARATION AND ASSIGNMENT FOR PATENT APPLICATION

Docket No.: 173545 (304773-00005)
Application No.: PCT/EP2016/081313

(4) TREATMENT OF PMSA EXPRESSING CANCERS

which application was executed on even date herewith or was

(a) executed on (5a): _____;
(b) filed on (5b): _____;
Application No.: _____;

/LEWIS ROCA ROTHGERBER CHRISTIE LLP, P.O. Box 29001, Glendale, CA 91209-9001) is hereby authorized to insert in (b) the specified data, when known.

including any and all United States Patents which may be granted on said application, and any and all extensions, divisions, reissues, substitutes, renewals or continuations of said application and patents, and the right to all benefits under all international conventions for the protection of industrial property and applications for said improvements.

It is hereby authorized and requested that the Commissioner of Patents issue any and all of said Letters Patent, when granted, to said ASSIGNEE, its assigns or its successors in interest or its designee.

Upon said consideration, it is further agreed that, when requested, without charge to but at the expense of said ASSIGNEE, the undersigned will execute all divisional, continuing, substitute, renewal, and reissue patent applications; execute all rightful other papers; and generally do everything possible which said ASSIGNEE shall consider desirable for aiding in securing and maintaining patent protection as provided herein.

Alfred MORGENSTERN
Legal Name of Inventor

28.05.19
Date

Signature

Frank BRUCHERTSEIFER
Legal Name of Inventor

29.05.19
Date

Signature

Fusion Pharmaceuticals, Inc.
Exhibit 1004.490

INVENTOR'S DECLARATION AND ASSIGNMENT FOR PATENT APPLICATION

Docket No.: 173545 (304773-00005)
Application No.: PCT/EP2016/081313

Christos APOSTOLIDIS
Legal Name of Inventor

6.6.19
Date

Signature

WITNESSES:

108200818_1

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Exhibit 1004.491

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on June 14, 2019 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor : Alfred Morgenstern, et al. Confirmation No. To Be Determined
Application No. : To Be Determined
Filed : June 14, 2019
Title : TREATMENT OF PMSA EXPRESSING CANCERS

Grp./Div. : To Be Determined
Examiner : To Be Determined

Docket No. : 173545 (304773-00005)

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS IN ACCORDANCE WITH 37 CFR. 1.5

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
June 14, 2019

Commissioner:

Attached herewith is a General Power of Attorney for Applicant THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION for the above-identified patent application.

Respectfully submitted,

LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

SRD 108417966.1-*-06/14/2019 7:48 AM

Fusion Pharmaceuticals, Inc.
Exhibit 1004.492

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION ("Applicant") is the Applicant by virtue of being the Assignee or Person to Whom the Inventor is Under an Obligation to Assign. Applicant hereby revokes all previous powers of attorney given in the application identified in the attached transmittal letter and appoints the Patent Practitioners associated with

CUSTOMER NUMBER 23363

of the firm LEWIS ROCA ROTHGERBER CHRISTIE LLP, telephone 626/795-9900, as attorneys or agents to transact all business in the United States Patent and Trademark Office for matters connected therewith for the application referenced in the attached transmittal letter.

The undersigned representative of Applicant, whose title is supplied below, is authorized to act on behalf of Applicant.

Please direct all correspondence to **CUSTOMER NUMBER 23363**. Direct all telephone calls to 626/795-9900, **LEWIS ROCA ROTHGERBER CHRISTIE LLP, P.O. Box 29001, Glendale, California 91209-9001.**

THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION

Date 20/07/2018

By Giancarlo Carratti

Name: Giancarlo CARATTI
Head of Unit

Title: Industrial Property and Technology Transfer

SAH/srd

Fusion Pharmaceuticals, Inc.
Exhibit 1004.493

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on June 14, 2019 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Appl No.	:	To Be Determined	Confirmation No. To Be Determined
Inventor	:	Alfred Morgenstern, et al.	
Filed	:	June 14, 2019	
Title	:	TREATMENT OF PMSA EXPRESSING CANCERS	
TC/A.U.	:	To Be Determined	
Examiner	:	To Be Determined	
Docket No.	:	173545 (304773-00005)	
Customer No.	:	23363	

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
June 14, 2019

Commissioner:

Prior to examination, please amend the above-identified application as follows:

Amendments to the Specification begin on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

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Exhibit 1004.494

Amendments to the Specification:

In compliance with 37 CFR 1.121(b)(3) and 1.125, a Substitute Specification including a Replacement Abstract for examination, and a Compare Copy, showing the changes made between the original international specification and the substitute specification, are enclosed with this Amendment.

No new matter has been added.

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Exhibit 1004.495

REMARKS/ARGUMENTS

Applicant has added the "Cross Reference to Related Applications" section to the specification in order to identify the claim of priority. A substitute specification pursuant to 37 CFR 1.121(b)(3) and 1.125 is submitted herewith accompanied by a marked-up copy showing all changes made. Applicant submits that the amendments are fully supported by the original specification, claims and drawings, and that no new matter is presented.

Applicant respectfully requests entry of this Preliminary Amendment prior to examination of the present application.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd

SRD 108421756.1-*-06/14/2019 12:09 PM

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Exhibit 1004.496

TREATMENT OF PMSA EXPRESSING CANCERS

Cross Reference to Related Applications

[0001] This application is a National Phase Patent Application of International Patent Application Number PCT/EP2016/081313, filed on December 15, 2016, the contents of which are incorporated herein by reference.

Technical field

[0002] The invention generally relates to radiopharmaceuticals for treating cancer, i.e. molecules labelled with radionuclides able to target certain cancer cells, in particular PSMA expressing cancer cells.

Background Art

[0003] In fact, radiopharmaceuticals are particularly interesting as tracers, imaging agents and for treating various cancers. Radiopharmaceuticals generally comprise a targeting (ligand) moiety and chelating moiety, the former being specific to certain target markers (predominantly) expressed by target cells and the latter being able to chelate (bind) a radionuclide. The so-formed radiopharmaceutical is thus able to target and bind to the desired site of such cells and it may be traced, be used for imaging or may act locally by destroying the cell to which it is bound or nearby cells, such as cancerous cells.

[0004] There are many different cancers and thus even more potentially useful different targeting sites for appropriately conceived radiopharmaceuticals. So, even for a given cancer type a number of targeting sites may be considered and may (or may not) be of use for the docking of radiopharmaceuticals.

[0005] Hence, choosing an appropriate targeting site and developing an appropriate targeting moiety combined to the identification of an appropriate chelating unit with an

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Exhibit 1004.497

appropriate radionuclide to a working radiopharmaceutical is a challenging, yet promising way to be able to manage tumors.

[0006] Among cancers, PSMA (Prostate Specific Membrane Antigen) expressing cancers, notably prostate and breast cancers indubitably rank among the most frequent cancers. However, in spite of the considerable efforts spent in various medical approaches during the last decades to find efficient treatment methods, these cancers still are among those for which a reliable and efficient therapy is highly desirable.

Technical problem

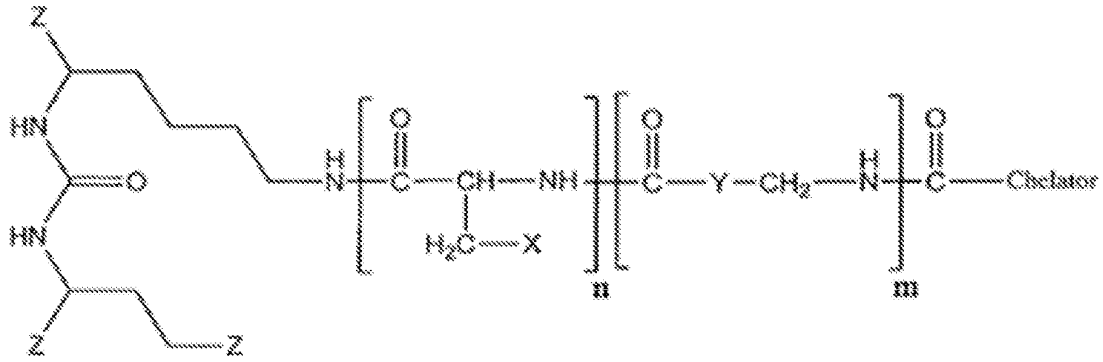
[0007] It is an object of the present invention to provide a method for treating PSMA expressing cancers. The method should allow for even treating patients refractory to established therapies. Furthermore, the devised method should allow for an efficient treatment of the cancer, while having as few side-effects as possible.

General Description of the Invention

[0008] In order to overcome the above-mentioned problems, the present invention provides in a first aspect a method for treating PSMA expressing cancers or cancer cells, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

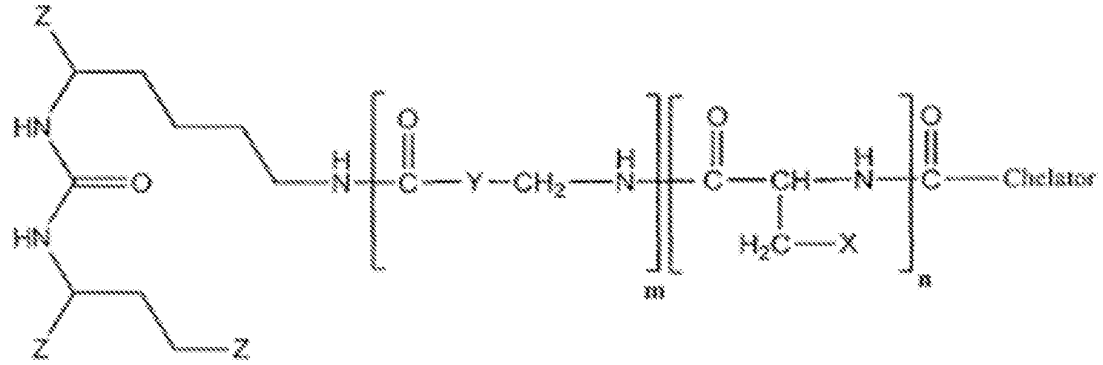
Formula (A)

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or

Formula (B)



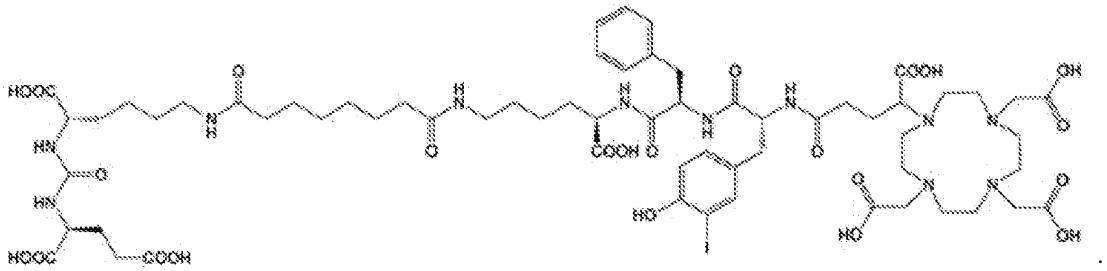
with:

n:	0, 1
m:	1, 2, 3, 4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N''-diacetic acid (HBED-CC),

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1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA),
2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA),
2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA),
1,4,7-triazacyclononane phosphinic acid (TRAP),
1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),
3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),
N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),
diethylenetriaminepentaacetic acid (DTPA),
trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A) p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA);

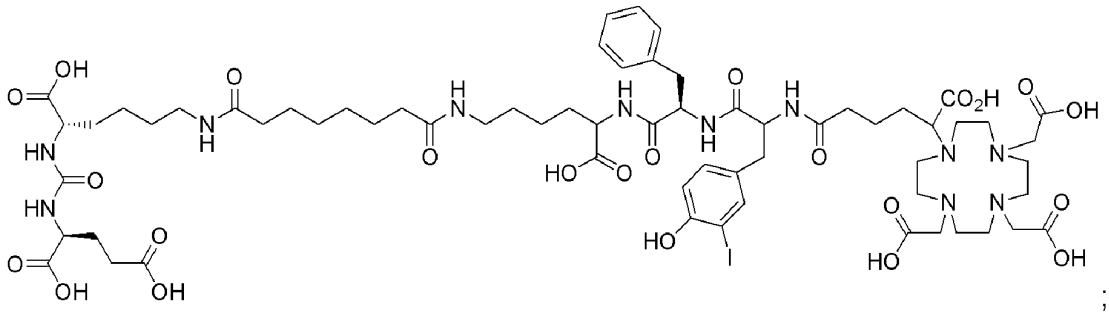
Formula (C)



;

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Formula (D)



;

or

Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator.

[0009] The "alkyl" residue preferably has 1 to 10 carbon atoms and can be linear or branched, unsubstituted or substituted. Preferred alkyl residues are methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, n-pentanyl, n-hexanyl. The same also applies to the corresponding cycloalkyl residues having preferably 3 to 10 carbon atoms.

[0010] The term "aryl" refers to an aromatic monocyclic or polycyclic ring system having 6 to 14 carbon atoms, preferably 6 to 10 carbon atoms. The aryl group can be substituted, where appropriate, with one or several ring substituents, like alkyl groups. Preferred aryl groups are phenyl, benzyl or naphthyl.

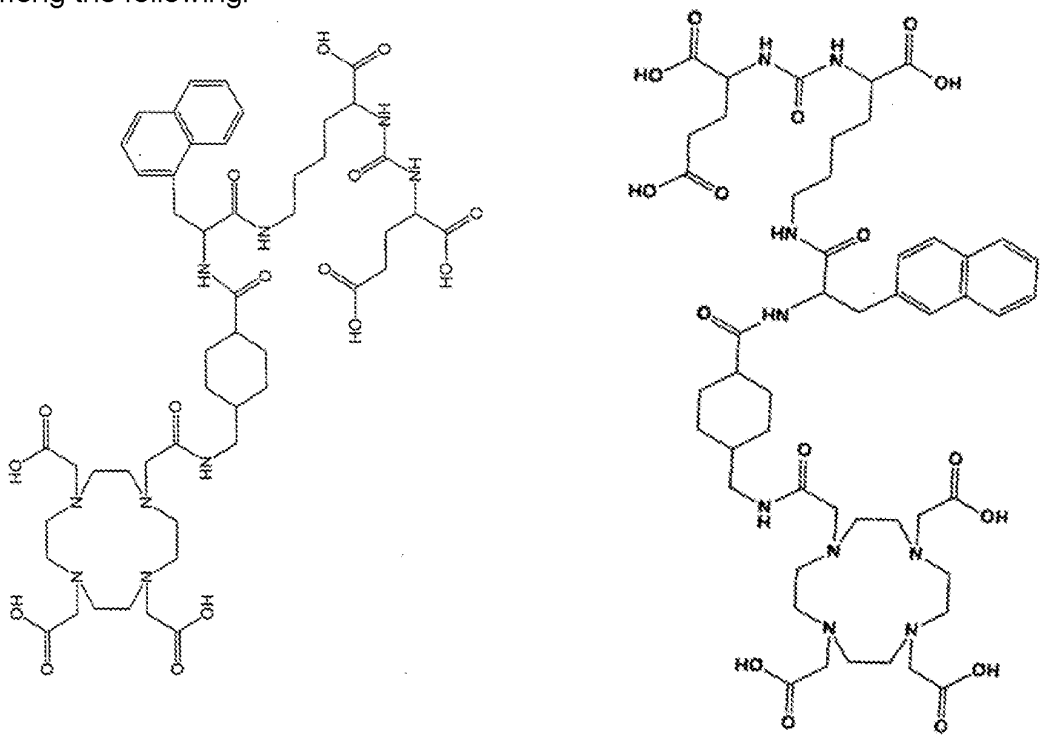
[0011] Although it is preferred that the Z group is $-CO_2H$ it may be easily replaced with biosteric replacements such as $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$.

[0012] The term “minibody” refers to an optionally engineered fragment of an (entire) antibody. Hence, a PSMA minibody (also called anti-PSMA minibody) is a fragment of a PSMA antibody (also called anti-PSMA antibody) which may be obtained in the same way as the antibody itself, i.e. by extraction from biological culture systems (cell cultures, egg, hamsters, mice, etc.) or they may be engineered. Engineered antibody fragments

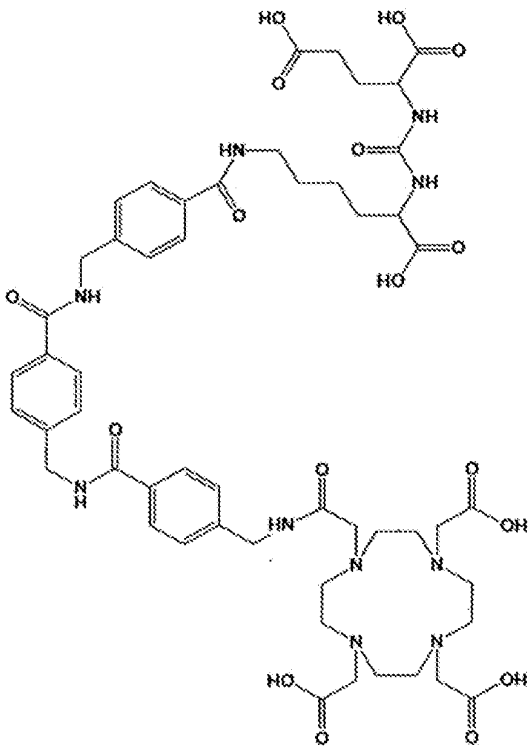
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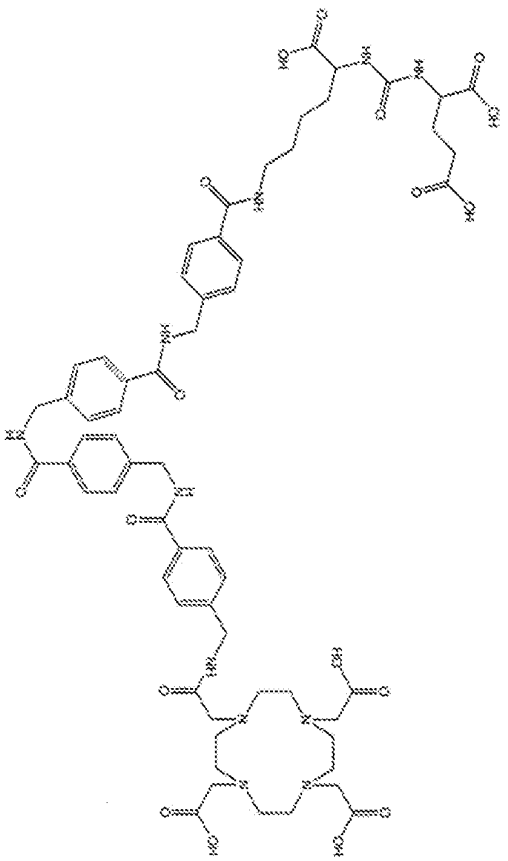
generally offer faster delivery with retained tumor specificity and rapid clearance from non-tumor tissues compared to the corresponding (entire) antibody. Appropriate PSMA antibodies and PSMA minibodies are e.g. antibody J591 and corresponding minibody IAB2M, GCP-05, 1H8H5, SP29, FOLH1, etc. Compounds of Formula (E) comprise a chelating moiety capable of chelating Ac-225. Appropriate chelating moieties are e.g. those mentioned for compounds of Formula (A) and (B), but other chelators may be used. A particularly preferred compound of Formula (E) is e.g. Df-IAB2M, Df being desferrioxamine.

[0013] Thus, preferred targeting compounds comprised within the Ac-225-radiopharmaceuticals useable according to the present invention are selected for example among the following:

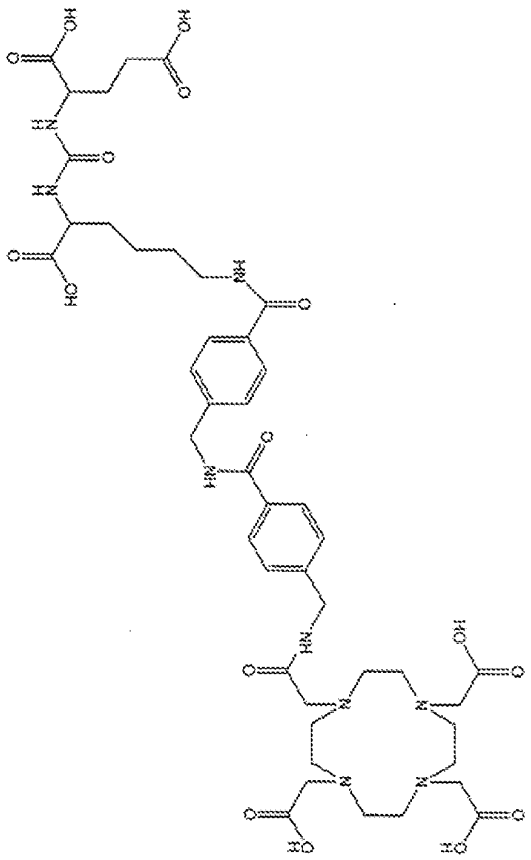


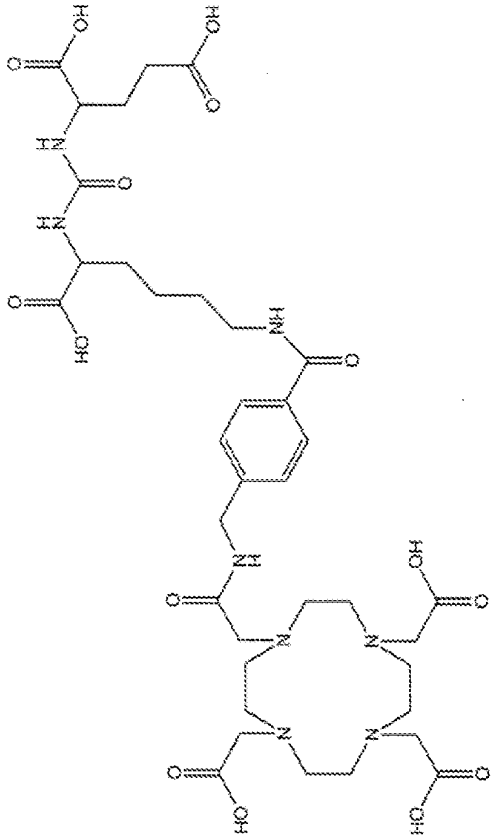
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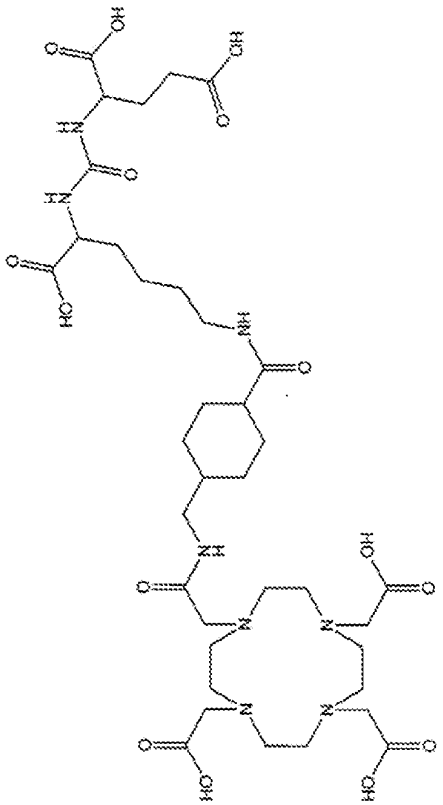


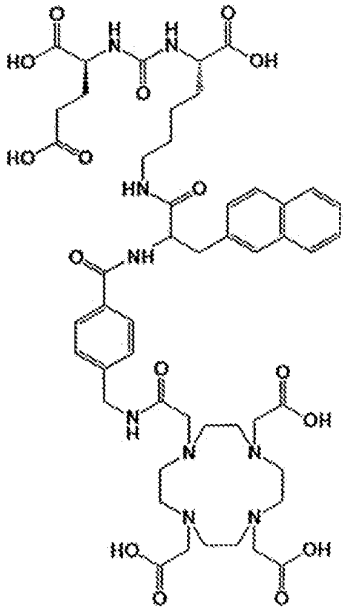
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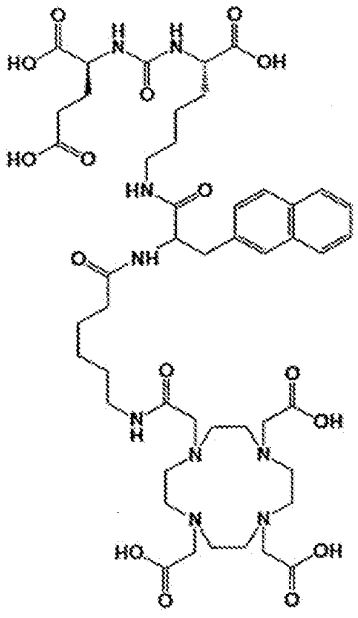


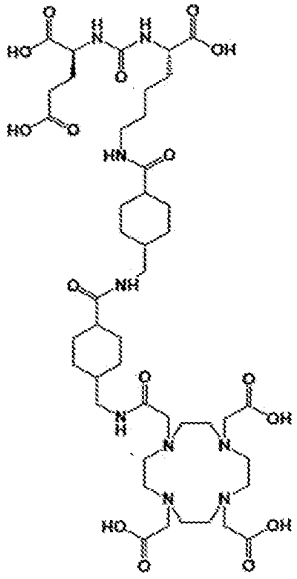


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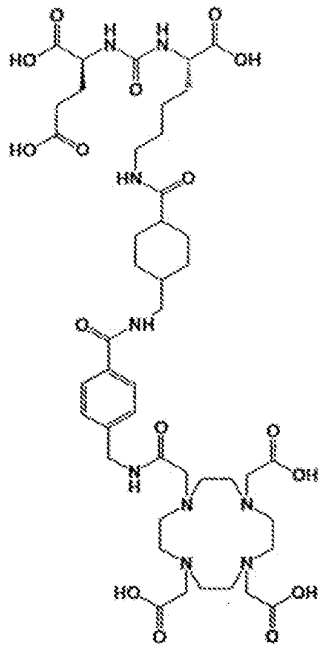


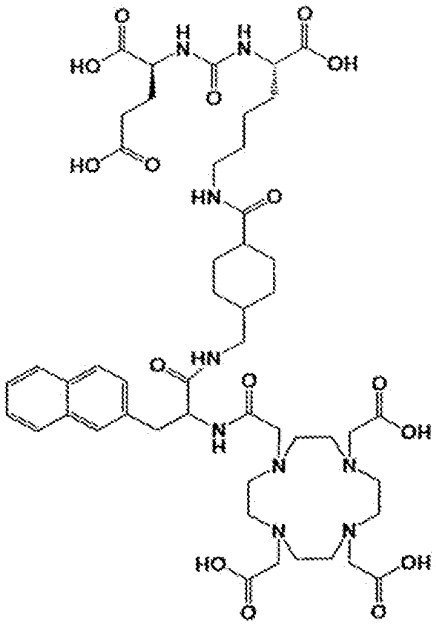


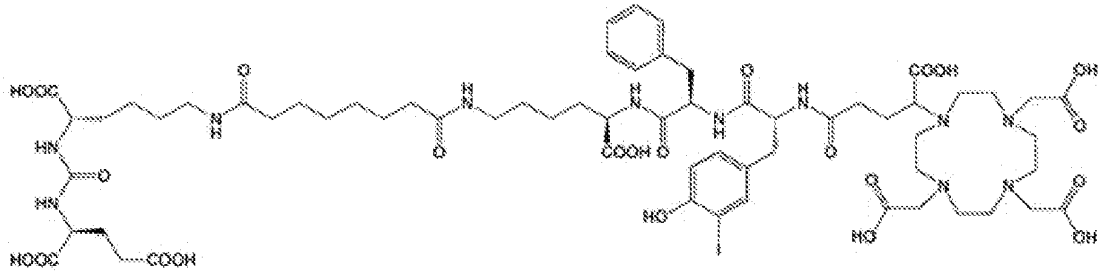


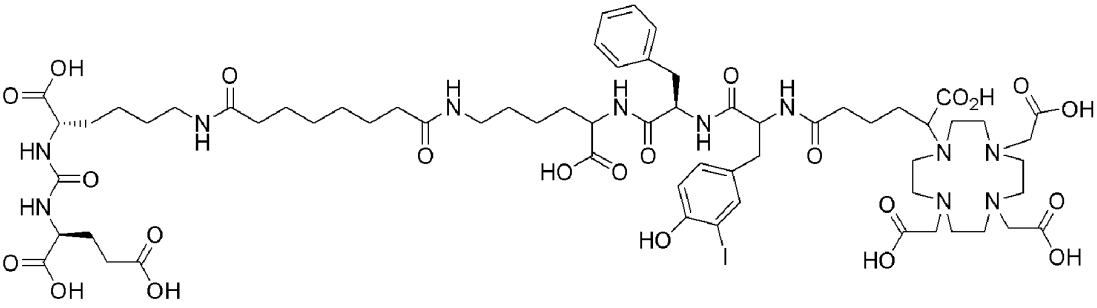


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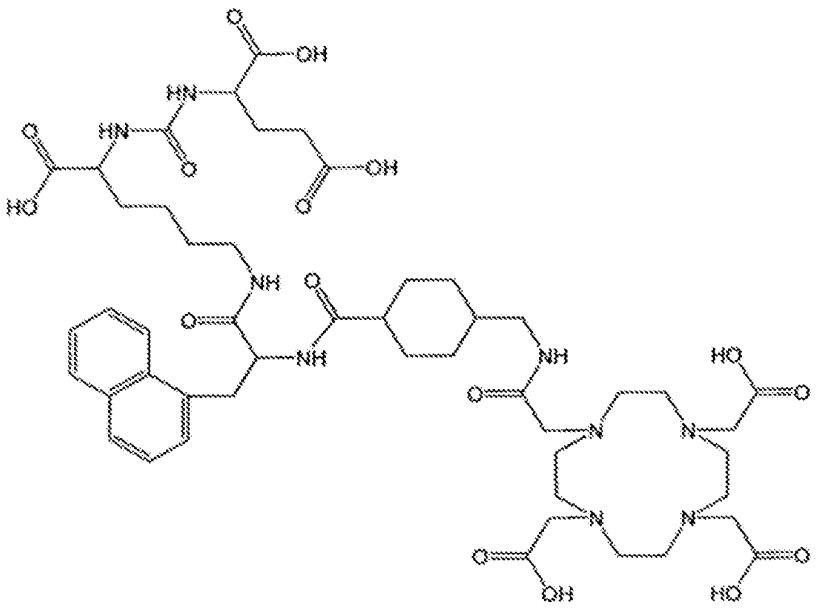






[0014] Among the particularly preferred compounds useable in the present invention is the Ac-225-radiopharmaceutical called Ac-225-PSMA-617. Ac-225-PSMA-617 is a compound according to the following formula

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chelating a Ac-225 radionuclide with its 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid moiety.

[0015] The effective amount of said one or more of Ac-225-radiopharmaceuticals is administered as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or wherein the effective amount of said Ac-225-radiopharmaceutical is administered as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0016] It has been surprisingly found that radiopharmaceuticals comprising Ac-225 as a radionuclide provide considerably and significantly better therapeutic results as corresponding radiopharmaceuticals with other radionuclides, especially with the particular administration dosages of the present invention as will become apparent from the description below.

[0017] In a second aspect, the present invention concerns the use of one or more Ac-225-radiopharmaceuticals as mentioned above for treating PSMA expressing cancers or cancer cells in a patient, wherein the use comprises administering to said patient an

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effective amount of said Ac-225-radiopharmaceutical as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0018] In a third aspect, the invention relates to one or more Ac-225-radiopharmaceuticals selected among those mentioned above for use in treating PSMA expressing cancers or cancer cells in a patient, comprising administering to said patient an effective amount of said Ac-225-radiopharmaceutical(s) as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0019] It has been surprisingly found that treating patients having PSMA expressing cancers or cancer cells with Ac-225-radiopharmaceuticals, i.e. radiopharmaceuticals comprising Ac-225 as a radionuclide, as described herein allows for a particularly strong anticancer effect with low hematotoxicity as will be shown in greater detail below.

[0020] The PSMA expressing cancers may be any cancer whose cancerous cells express Prostate Specific Membrane Antigen (PSMA). Preferably cancers (or cancer cells) that may be treated according to the invention are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers. In particularly preferred aspects of the invention, said PSMA expressing cancer is prostate cancer or breast cancer.

[0021] The cells of said PSMA expressing cancers or cancer cells may be treated not only within a solid tumor, but also after dissemination. Hence, in a particularly preferred aspect, the invention relates to the treatment of a disseminated cancer or cancer cells. Indeed, the very efficient and specific targeting of the Ac-225-radiopharmaceuticals to PSMA combined to the short range (< 100 micrometers) action of the Ac-225 alpha

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emitter allows for very good results of destruction of cancer cells without notable damage to non-target tissues, as further described below.

[0022] The effective amount of said one or more Ac-225-radiopharmaceuticals to be administered to a patient generally is determined in light of the patient's case. However, the effective amount thereof will represent a dosage within a range from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient. More particularly, the dosage may preferably range from about 30 kBq/kg to about 250 kBq/kg of body weight, for example about 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 , 210, 220, 230, 240 or 250 kBq/kg, or any range between any two of the above values.

[0023] Alternatively, the effective amount may be administered as a unitary dosage or constant activities, such as from about 3 MBq to about 30 MBq for one administration to the patient. Preferably the unitary dosage or constant activities range from about 4 MBq to about 25 MBq per administration, in particular about 5 MBq to about 20 MBq, such as for example about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 MBq, or any range between any two of the above values.

[0024] If necessary or desirable, the treatment may comprise more than one administration of an effective amount of one or more Ac-225-radiopharmaceuticals as described above. Indeed it is generally beneficial to repeat, one or more times, the administration of an effective amount of said one or more Ac-225-radiopharmaceuticals to the patient after 15 to 90 days, such as at a one- or two-month intervals. Neither the effective amount of such repeated administration, nor the intervals between multiple consecutive administrations need to be the same as those of previous administrations or repetitions.

[0025] Bq, kBq and MBq represent the SI unit becquerel, as well as its multiples kilobecquerel (10^3 Bq) and megabecquerel (10^6 Bq) respectively, wherein 1 Bq

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corresponds to the activity of a quantity of radioactive material in which one nucleus decays per second.

[0026] An "effective amount" in the context of the invention is an amount of Ac-225-radiopharmaceutical(s) that produces at least some measurable therapeutic response or desired effect in some fraction of the patient to whom it is administered. The effective amount may be expressed as dosage per weight unit of the patient (and per administration), such as kBq/kg body weight of the patient or as a unitary dosage (also called "constant activity"), meaning a dosage for one administration to one patient independently of the patient's weight, such as MBq.

[0027] The terms "administer", "administering" and "administration" refer to the giving of the Ac-225-radiopharmaceutical(s) to a patient by any appropriate route. In particular, the Ac-225-radiopharmaceutical(s) may be administered by oral or parenteral route, preferably parenteral route, such as by injection or infusion, wherein the injection or infusion may be made intravenously, intramuscularly, intra-arterially, subcutaneously, intra-dermally, intraperitoneally, etc. Depending on the administration route, the Ac-225-radiopharmaceutical(s) may comprise further appropriate constituents, such as carriers, solvents and excipients generally known in the art.

[0028] All approximate values given herein as indicated by the presence of the word "about" include a range of +/- 10 % centered on said value.

Brief Description of the Drawings

[0029] Preferred embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings in which:

[0030] Fig. 1 is a graph of experimental data showing the decrease in PSA (Prostate-Specific Antigen) (%) after first treatment with Ac-225-PSMA-617;

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[0031] Fig. 2 is a graph of experimental data illustrating the decrease in PSA (%) after a second treatment with Ac-225-PSMA-617;

[0032] Fig. 3 is a graph of experimental data representing the decrease in PSA (%) after third treatment with Ac-225-PSMA-617;

[0033] Fig. 4 to 6 show Gallium-68-PSMA11 PET/CT imaging of three patients before (Fig. 4A, 5A and 6A) and after (Fig. 4B, 5B and 6B) therapy as described herein below;

[0034] Fig. 7 illustrates the development of thrombocyte count during Ac-225-PSMA-617 therapy as described herein below;

[0035] Fig. 8 shows the development of leukocyte count during Ac-225-PSMA-617 therapy as described herein below.

[0036] Fig. 9 is a graph of experimental data showing the decrease in PSA (%) after first treatment and after third treatment with Lu-177-PSMA-617;

[0037] Fig. 10 shows the development of thrombocyte count during Lu-177-PSMA-617 comparative experiments as described herein below;

[0038] Fig. 11 illustrates the development of leukocyte count during Lu-177-PSMA-617 comparative experiments as described herein below;

[0039] Fig. 12 shows Ga-68-PSMA-11 PET/CT scans of a patient: pretherapeutic tumor spread (A), restaging 2 months after third cycle of Ac-225-PSMA-617(B), and restaging 2 months after one additional consolidation therapy (C);

[0040] Fig. 13 illustrates laboratory test follow-up of a patient; arrows indicate administration of treatment cycles; (A) blood cell count demonstrates moderate hematologic toxicity; (B) decline of tumor markers to none measurable or reference range correlates with imaging response;

[0041] Fig. 14 show 68-Ga-PSMA-11 PET/CT scans of another patient; in comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting Lu-177-PSMA-617

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Exhibit 1004.511

presented progression (B); in contrast, restaging after second (C) and third (D) cycles of α-emitting Ac-225-PSMA-617 presented impressive response; and

[0042] Fig. 15 illustrates laboratory test follow-up of a patient; arrows indicate administration of treatment cycles; blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

[0043] Further details and advantages of the present invention will be apparent from the following detailed description of the not limiting embodiments with reference to the attached drawings below.

Description of Preferred Embodiments

[0044] A1. Peptide, radionuclides and radiolabeling:

[0045] PSMA-617 was obtained from ABX, Germany.

Ac-225 (also noted ^{225}Ac) was produced by radiochemical extraction from Th-229 as described in Apostolidis C, Molinet R, Rasmussen G, Morgenstern A., Production of Ac-225 from Th-229 for targeted alpha therapy. Analytical Chemistry, 2005;77(19):6288-91 and Zielinska B, Apostolidis C, Bruchertseifer F, Morgenstern A., An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy, Solvent Extraction and Ion Exchange, 2007;25(3):339-49.

[0046] For radiolabeling an aliquot of Ac-225 stock solution (6-39 MBq Ac-225) in 0.1 M hydrochloric acid was added into a microwave vial containing 0.5 ml of 0.1 M Tris buffer (pH 9) and an appropriate amount of 10 mM PSMA-617 stock solution (35 - 160 nMol peptide). The reaction mixture was heated to 95° C for 5 min using a microwave synthesizer (Biotage® Initiator) and subsequently cooled to < 50 °C using pressurized air.

[0047] Quality control was performed by instant thin layer chromatography (ITLC-SG, Pall Life Sciences) with 0.05 M citric acid (pH 5) as solvent. Under these conditions, unbound Ac-225 moves with the solvent front (Rf = 1), while Ac-225-PSMA-617 remains

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on the bottom of the strip (Rf = 0). After development the ITLC strip was stored for at least 1 hour until radiochemical equilibrium between Ac-225 and its daughter nuclide Fr-221 ($T_{1/2}$ = 4.8 min) was obtained. Subsequently radiochemical purity was determined by measuring the activity of the 218 keV gamma emission of Fr-221 on the upper and lower part of the ITLC strip using high resolution gamma spectrometry (Ortec).

[0048] After synthesis 0.5 ml of 18% ascorbic acid solution (pH 5.8) was added to the reaction mixture to minimize radiolytic degradation of Ac-225-PSMA-617. The final pH of the formulation was 7.4. Before injection, sterility of the final formulation was assured via sterile filtration (Millex-GV, 0.20 µm, Millipore).

[0049] Gallium-68-PSMA11 PET/CT imaging was performed using a radiotracer labeled with Ga-68.

[0050] A2. Results

[0051] Radiochemical purity was 98.6 ± 1.4 % (*n=67*), specific activity was 0.23 ± 0.1 MBq per nmol of peptide.

[0052] A3. Patient treatment

[0053] 20 Patients were treated 3 times with activities of 100 kBq/kg body weight of Ac-225-PSMA-617 in two month intervals.

[0054] Treatment response was monitored by PSA values in blood and with PET/CT (positron emission tomography-computed tomography) with Ga-68-PSMA-HBED-CC (also called Gallium-68-PSMA11) before therapy and after the third therapy.

[0055] Toxicity was monitored by blood sampling.

[0056] A4. Results

[0057] A4.1 Treatment efficacy

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[0058] Eight weeks after the first treatment cycle 19/20 patients presented a decrease in PSA, in 17 patients the decrease was > 25 %, in 12 patients the decrease was even > 50 %.

[0059] The graph of Fig. 1 shows the decrease in PSA (%) after a first treatment with Ac-225-PSMA-617.

[0060] Sixteen weeks after the first treatment cycle 15/20 patients presented a decrease in PSA, in 14 patients the decrease was > 50 %.

[0061] As illustrated by the graph of Fig. 2 the decrease in PSA (%) after a second treatment with Ac-225-PSMA-617.

[0062] Twenty-four weeks after the first treatment cycle 15/20 patients presented with a decrease in PSA, in 12 patients the decrease was even > 50 %.

[0063] Fig. 3 shows the decrease in PSA (%) after third treatment with Ac-225-PSMA-617.

[0064] The exceptional results obtainable by the present invention are illustrated in Fig. 4 to 6. These figures show PET/CT images of three different patients before and after the treatment as described above. The PET/CT imaging combines both a positron emission tomography (PET) scanner and an x-ray computed tomography (CT) scanner, so that images acquired from both devices can be taken sequentially, in the same session, and combined into a single superposed image. As can be seen the betterment of the patients' condition is most remarkable.

[0065] A4.2 Toxicity

[0066] Hematologic response was evaluated every 4 weeks per lab tests and clinical side effects were monitored every 8 weeks. The treatment was well tolerated. There was no significant change in thrombocyte or white blood cell count (Fig. 7 and 8). Several patients reported dysfunction of salivary glands.

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[0067] Fig. 7 shows the development of thrombocyte count during Ac-225-PSMA-617 therapy, whereas Fig. 8 displays the development of leukocyte count during Ac-225-PSMA-617 therapy.

[0068] A5. Conclusions of the above experiments

[0069] The inventors found that treatment response with said Ac-225-radiopharmaceutical(s) is very good and hematologic toxicity is moderate to low at dosages of about 100 kBq/kg body weight (i.e. about 7 MBq for a patient of 70 kg). The treatment may be done using a unitary dosage or constant activities, e.g. about 6 MBq per treatment. Furthermore, the patients may be treated in eight week or two month intervals for practical reasons. Shorter intervals (e.g. four weeks or one month) with correspondingly lower dosing are also possible.

[0070] A6. Comparative Examples

[0071] Experiments have been conducted to compare the efficiency of the Ac-225-radiopharmaceuticals as used in the present invention, such as Ac-225-PSMA-617, with that of non-Ac-225-radiopharmaceuticals comprising the same targeting compound, but chelated e.g. with Lu-177, such as a radionuclide Lu-177-PSMA-617.

[0072] A6.1 Treatment efficacy

[0073] Eight weeks after the first treatment cycle 21/30 patients presented a decrease in PSA, In 16 patients the decrease was > 50 %.

[0074] Twenty-four weeks after the first treatment cycle some patients were dropped out from the therapy because some physical conditions were considered a contraindication for treatment with β-emitters. 9/30 patients presented a decreased in PSA. For all of them the decrease was > 50 %.

[0075] The graph of Fig. 9 shows the decrease in PSA (%) after a first and a third treatment with Lu-177-PSMA-617.

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Exhibit 1004.515

[0076] A6.2 Toxicity

[0077] The treatment was well tolerated. There was no significant change in thrombocyte or white blood cells count (Fig. 10 and 11). Mild moderate dysfunction of salivary glands was reported.

[0078] Fig. 10 shows the development of thrombocyte count during Lu-117-PSMA-617 therapy, whereas Fig. 11 displays the development of leukocyte count during Lu-117-PSMA-617 therapy.

[0079] A6.3 Conclusions of the above comparative experiments

[0080] The group treated with Lu-117-PSMA-617 had a lower response rate in comparison to the one treated with Ac-225-PSMA-617. Indeed, the treatment analysis revealed that 15/28 patients (54%) treated with Ac-225-PSMA-617 were in PSA response but only 9/30 patients (30%) treated with Lu-177-PSMA-617 were in PSA response at week-24. This is a remarkable difference taking into account similar hematological toxicity and the more advanced patients selected for Ac-225-radiopharmaceutical therapy.

[0081] B1. Treatment of metastatic castration-resistant prostate cancer (mCRPC) with Ac-225-radiopharmaceutical:

[0082] FIG. 12: Ga-68-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 months after third cycle of Ac-225-PSMA-617(B), and restaging 2 months after one additional consolidation therapy (C).

[0083] Clinical Course of Patient A presented with diffuse red marrow infiltration of mCRPC (this physical condition was considered a contraindication for treatment with β-emitters).Patient A was treated with 3 cycles of 9–10 MBq (100 kBq per kilogram of body weight) of Ac-225-PSMA-617 at bimonthly intervals. Posttherapeutic emission scans validated sufficient tumor targeting Two months later, all previously PSMA-positive lesions had visually disappeared on PSMA PET/CT (Fig. 12B) and, accordingly, the PSA level

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had dropped from more than 3,000 ng/ml to 0.26 ng/ml. The patient received an additional 6 MBq of Ac-225-PSMA-617 as consolidation therapy, resulting in a further PSA decline to less than 0.1 ng/ml along with a complete imaging response (Fig. 1C).

[0084] FIG. 13: Laboratory test follow-up of patient A. Arrows indicate administration of treatment cycles. (A) Blood cell count demonstrates moderate hematologic toxicity. (B) Decline of tumor markers to none measurable or reference range correlates with imaging response. AP = alkalinephosphatase; Hb= 5 hemoglobin; PLT = platelets; WBC = white blood cells.

[0085] After each cycle, the blood cell count and alkaline phosphatase level were checked every 2 week. The platelet level never dropped below 100/nl (grade 1 according to the Common Terminology Criteria for Adverse Events, version 4.0), the total white blood cell count never dropped below 2.5/nl (grade 1), and the hemoglobin level never dropped below 9.5 g/dl (grade 2) (Fig. 13A). Moderate but enduring dysfunction of salivary glands was the only clinically reported side effect. A concordant decline in PSA level and alkaline phosphatase level (Fig. 13B) further underlined the excellent treatment response.

[0086] B2 Treatment with Lu-177 then Ac-225:

[0087] FIG. 14: 68-Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting Lu-177-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting Ac-225-PSMA-617 presented impressive response.

[0088] Clinical Course of Patient B presented with peritoneal carcinomatosis and liver metastases.

[0089] Patient B was initially treated with Lu-177-PSMA-617 (7.4 GBq per cycle), which was offered as salvage therapy. The initial PSA level was 294 ng/ml. After cycle 2 the PSA level increased to 419 ng/ml and most lesions demonstrated tumor progression on

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PSMA PET/CT (Fig. 14B). Therapy was changed to Ac-225-PSMA-617, and the patient received 3 cycles of 6.4 MBq (100 kBq per kilogram of body weight) at bimonthly intervals. Restaging based on the PSMA PET/CT results finally indicated a partial response after 2 cycles (Fig. 14C) and a complete remission after 3 cycles (Fig. 14D). Laboratory tests revealed no relevant hematologic toxicity; PSA dropped to below the measurable level (0.1 ng/ml) (Fig. 15). However, the patient reported severe dysfunction of salivary glands.

[0090] FIG. 15: Laboratory test follow-up of patient B. Arrows indicate administration of treatment cycles. Blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

[0091] B3. Conclusion:

[0092] The early results already indicate that Ac-225-targeted α-therapy has high potential for the epidemiologically important tumor entity prostate cancer, which presumably will further accelerate the routine availability of Ac-225 for systematic clinical trials, for example.

[0093] The two impressive responses reported here demonstrate the high potential of Ac-225-radiopharmaceuticals, such as Ac-225-PSMA-617 to significantly benefit mCRPC patients who are in a clinically critical situation, that is, patients with diffuse red marrow infiltration and resistance to other therapies. Investigation of this therapeutic modality in larger patient cohorts is warranted.

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Abstract

The invention relates to a method for treating PSMA expressing cancers, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

TREATMENT OF PMSA EXPRESSING CANCERS

Cross Reference to Related Applications

[0001] This application is a National Phase Patent Application of International Patent Application Number PCT/EP2016/081313, filed on December 15, 2016, the contents of which are incorporated herein by reference.

Technical field

[0002] [0001] The invention generally relates to radiopharmaceuticals for treating cancer, i.e. molecules labelled with radionuclides able to target certain cancer cells, in particular PSMA expressing cancer cells.

Background Art

[0003] [0002] In fact, radiopharmaceuticals are particularly interesting as tracers, imaging agents and for treating various cancers. Radiopharmaceuticals generally comprise a targeting (ligand) moiety and chelating moiety, the former being specific to certain target markers (predominantly) expressed by target cells and the latter being able to chelate (bind) a radionuclide. The so-formed radiopharmaceutical is thus able to target and bind to the desired site of such cells and it may be traced, be used for imaging or may act locally by destroying the cell to which it is bound or nearby cells, such as cancerous cells.

[0004] [0003] There are many different cancers and thus even more potentially useful different targeting sites for appropriately conceived radiopharmaceuticals. So, even for a given cancer type a number of targeting sites may be considered and may (or may not) be of use for the docking of radiopharmaceuticals.

[0005] [0004] Hence, choosing an appropriate targeting site and developing an appropriate targeting moiety combined to the identification of an appropriate chelating

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unit with an appropriate radionuclide to a working radiopharmaceutical is a challenging, yet promising way to be able to manage tumors.

[0006] [0005] Among cancers, PSMA (Prostate Specific Membrane Antigen) expressing cancers, notably prostate and breast cancers indubitably rank among the most frequent cancers. However, in spite of the considerable efforts spent in various medical approaches during the last decades to find efficient treatment methods, these cancers still are among those for which a reliable and efficient therapy is highly desirable.

Technical problem

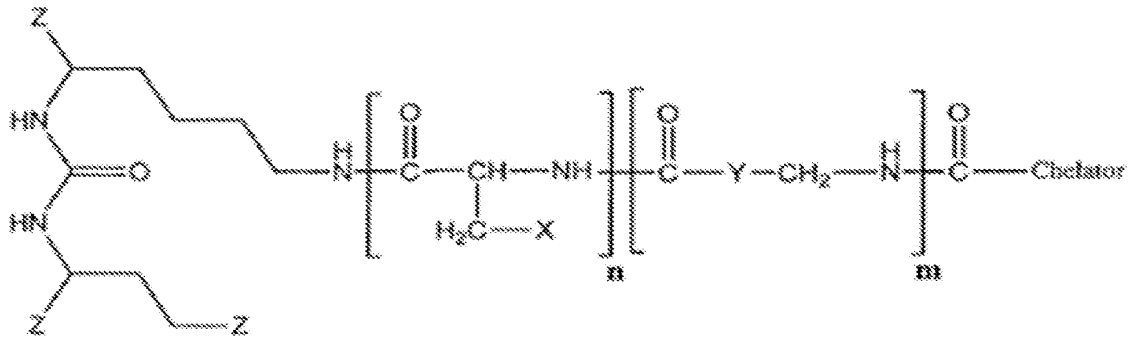
[0007] [0006] It is an object of the present invention to provide a method for treating PSMA expressing cancers. The method should allow for even treating patients refractory to established therapies. Furthermore, the devised method should allow for an efficient treatment of the cancer, while having as few side-effects as possible.

General Description of the Invention

[0008] [0007] In order to overcome the above-mentioned problems, the present invention provides in a first aspect a method for treating PSMA expressing cancers or cancer cells, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

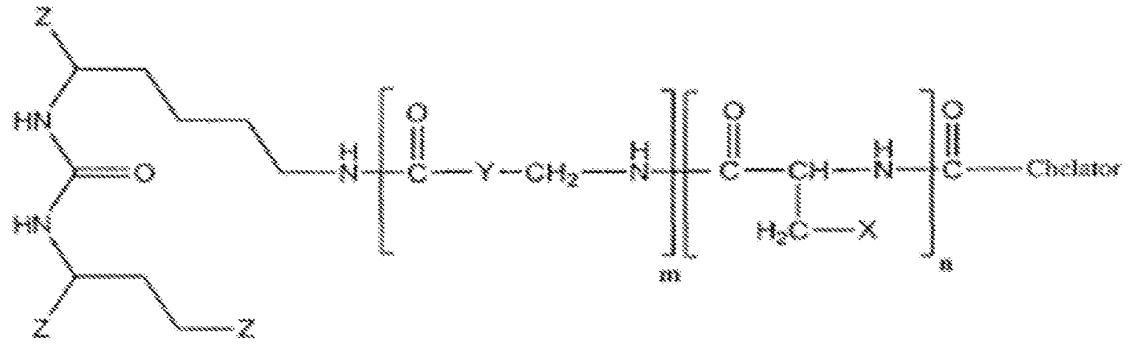
Formula (A)

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or

Formula (B)



with:

n:	0, 1
m:	1, 2, 3, 4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N''-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA),

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2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA),

1,4,7-triazacyclononane phosphinic acid (TRAP),

1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),

3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),

N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),

diethylenetriaminepentaacetic acid (DTPA),

trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),

1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A)

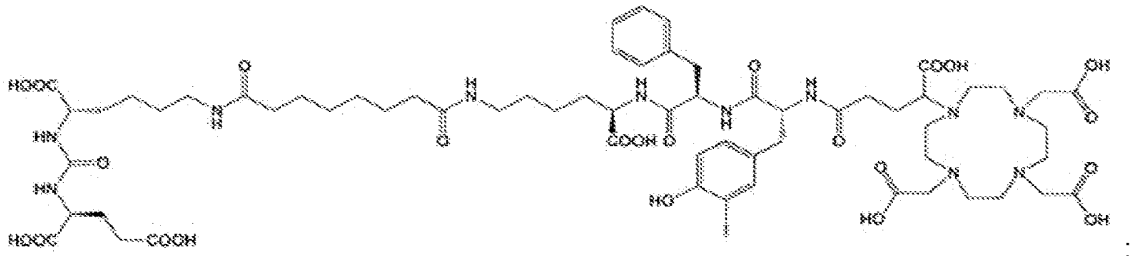
p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),

1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),

2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or

1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA);

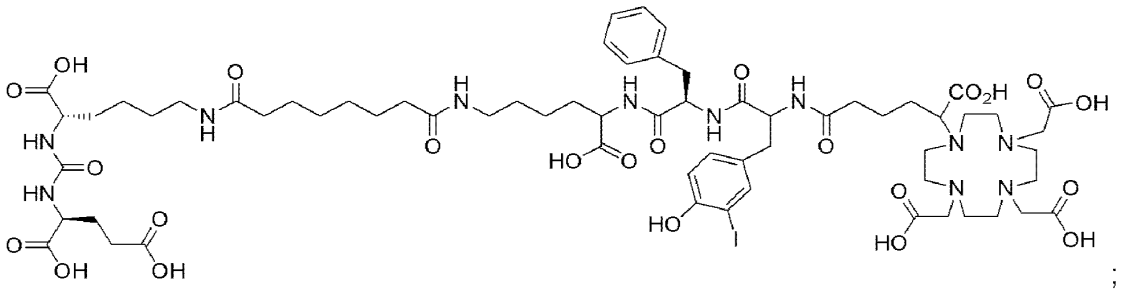
Formula (C)



;

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Formula (D)



;

or

Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator.

[0009] [0008] The "alkyl" residue preferably has 1 to 10 carbon atoms and can be linear or branched, unsubstituted or substituted. Preferred alkyl residues are methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, n-pentanyl, n-hexanyl. The same also applies to the corresponding cycloalkyl residues having preferably 3 to 10 carbon atoms.

[0010] [0009] The term "aryl" refers to an aromatic monocyclic or polycyclic ring system having 6 to 14 carbon atoms, preferably 6 to 10 carbon atoms. The aryl group can be substituted, where appropriate, with one or several ring substituents, like alkyl groups. Preferred aryl groups are phenyl, benzyl or naphthyl.

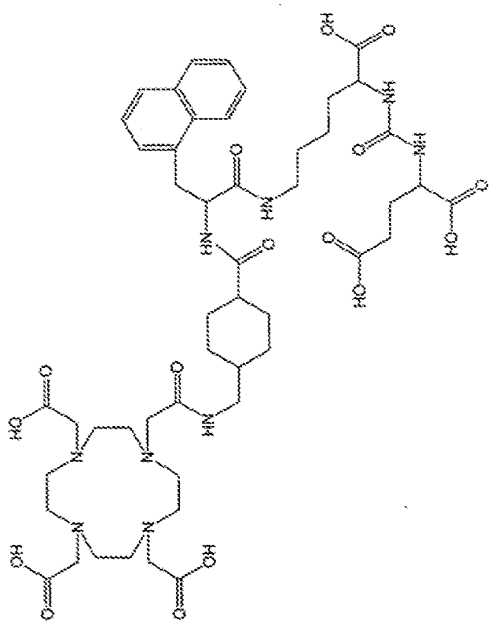
[0011] [0010] Although it is preferred that the Z group is $-CO_2H$ it may be easily replaced with biosteric replacements such as $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$.

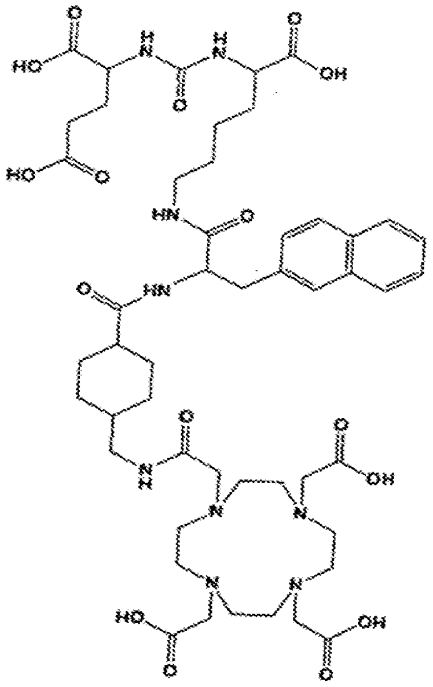
[0012] [0011] The term “minibody” refers to an optionally engineered fragment of an (entire) antibody. Hence, a PSMA minibody (also called anti-PSMA minibody) is a fragment of a PSMA antibody (also called anti-PSMA antibody) which may be obtained in the same way as the antibody itself, i.e. by extraction from biological culture systems (cell cultures, egg, hamsters, mice, etc.) or they may be engineered. Engineered

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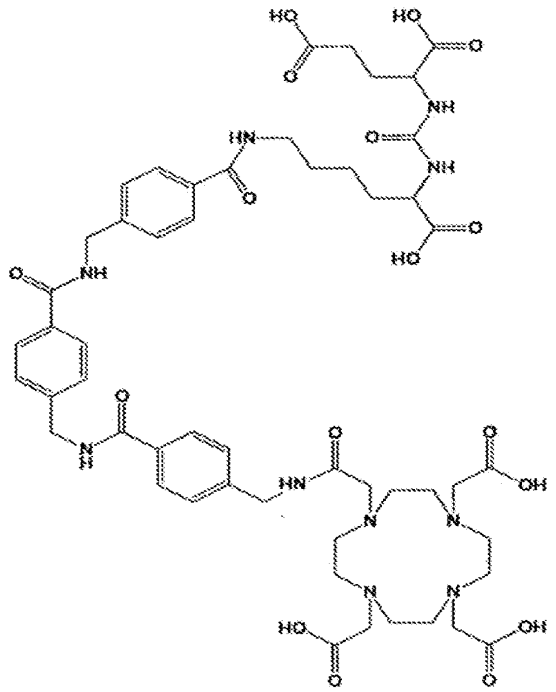
antibody fragments generally offer faster delivery with retained tumor specificity and rapid clearance from non-tumor tissues compared to the corresponding (entire) antibody. Appropriate PSMA antibodies and PSMA minibodies are e.g. antibody J591 and corresponding minibody IAB2M, GCP-05, 1H8H5, SP29, FOLH1, etc. Compounds of Formula (E) comprise a chelating moiety capable of chelating Ac-225. Appropriate chelating moieties are e.g. those mentioned for compounds of Formula (A) and (B), but other chelators may be used. A particularly preferred compound of Formula (E) is e.g. Df-IAB2M, Df being desferrioxamine.

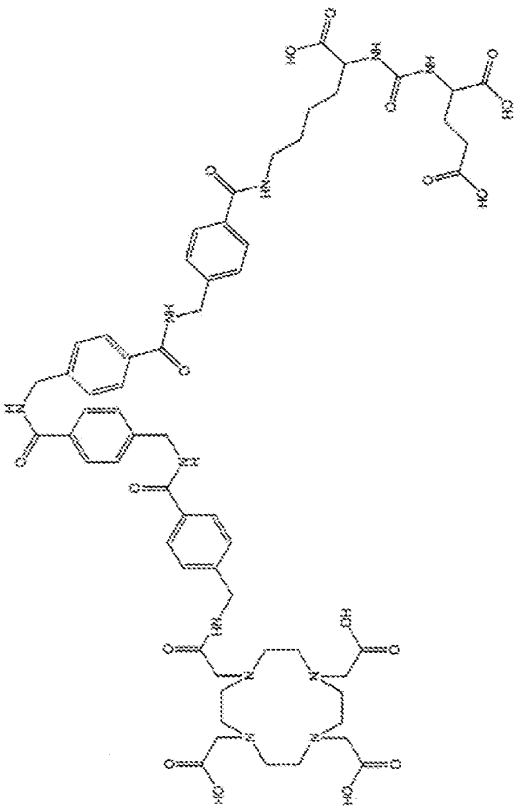
[0013] ~~[0012]~~ Thus, preferred targeting compounds comprised within the Ac-225-radiopharmaceuticals useable according to the present invention are selected for example among the following:



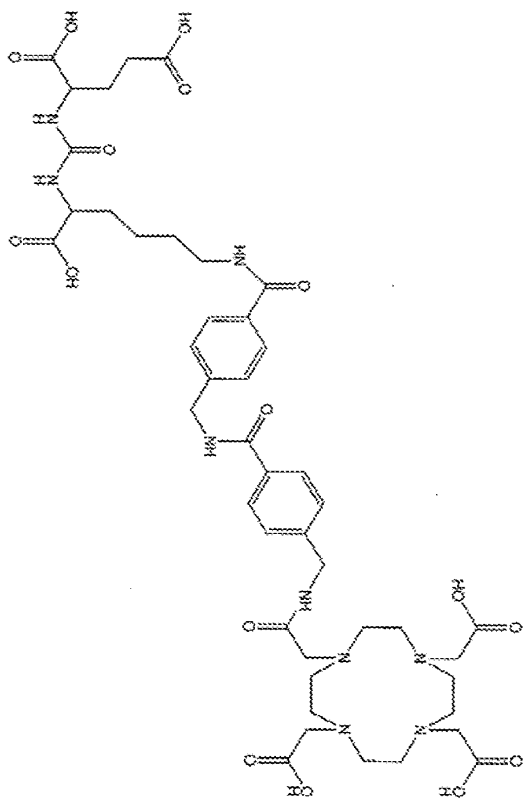


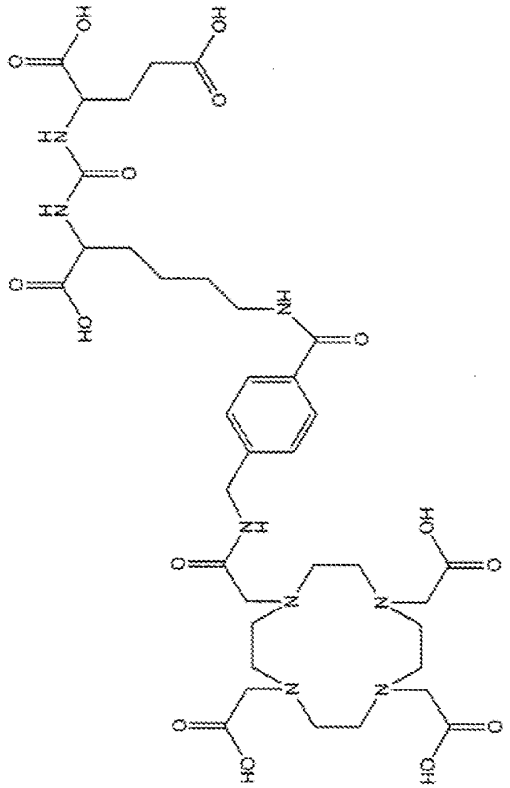
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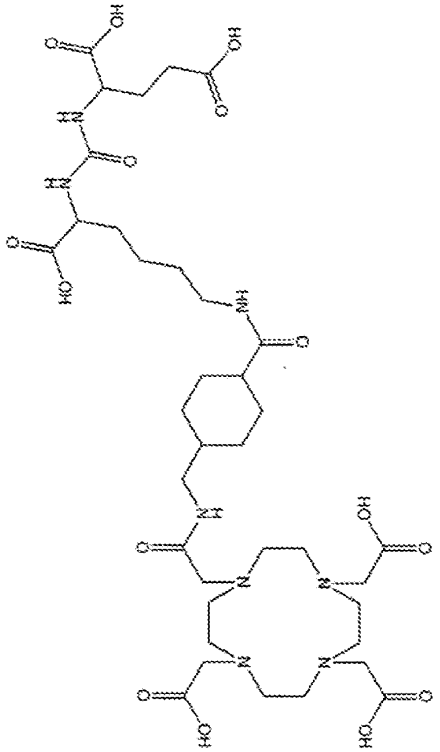


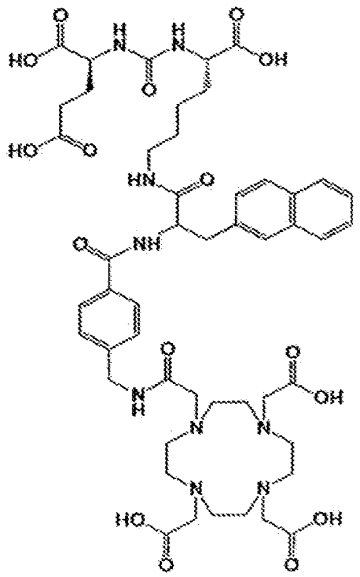


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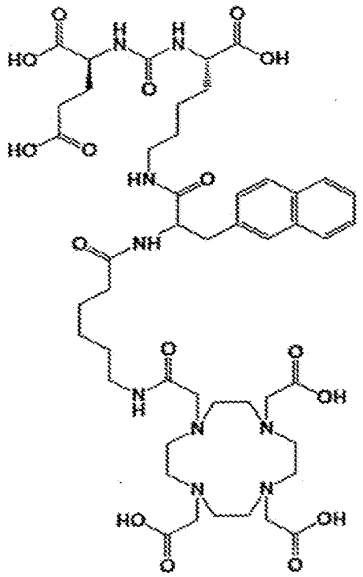


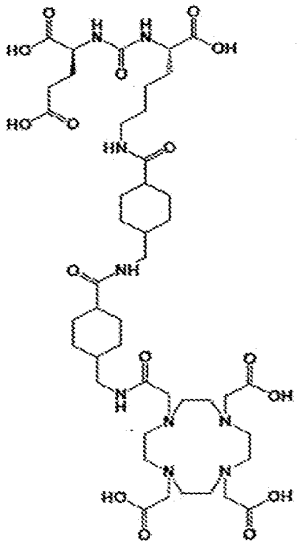


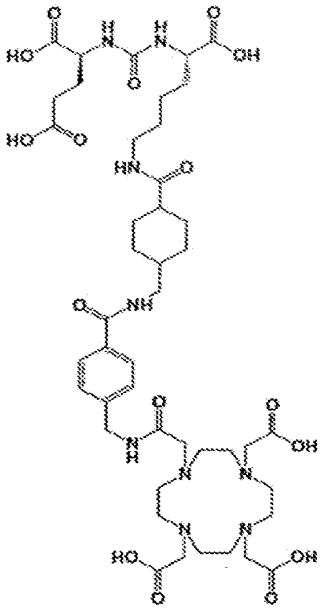


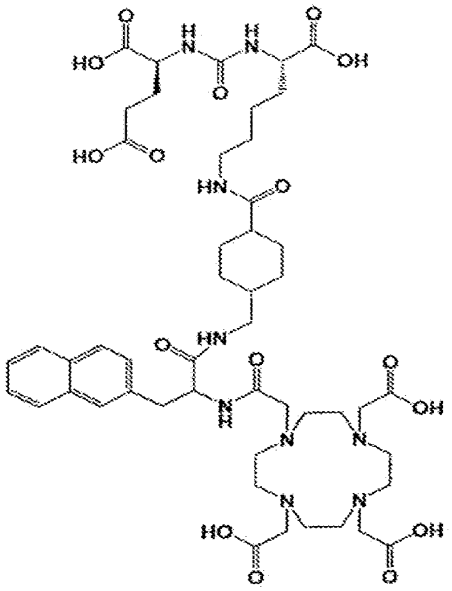


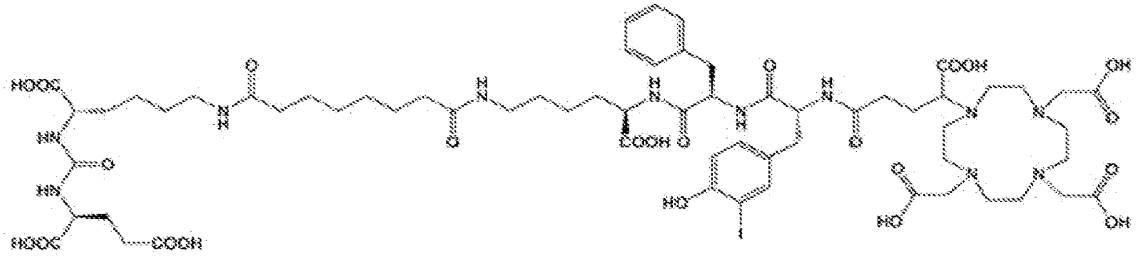
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Exhibit 1004.527



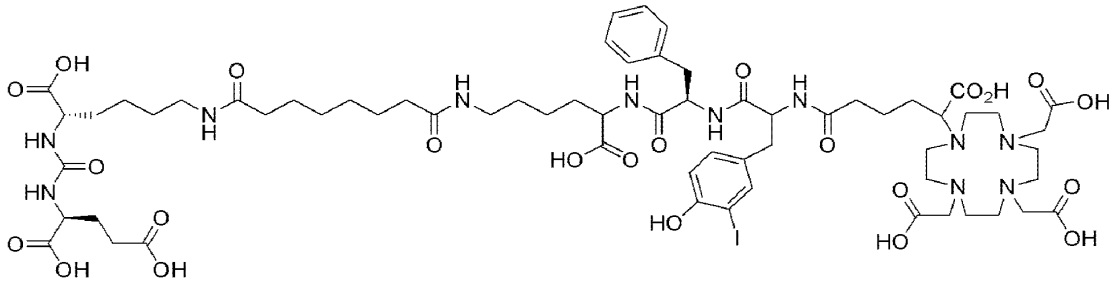




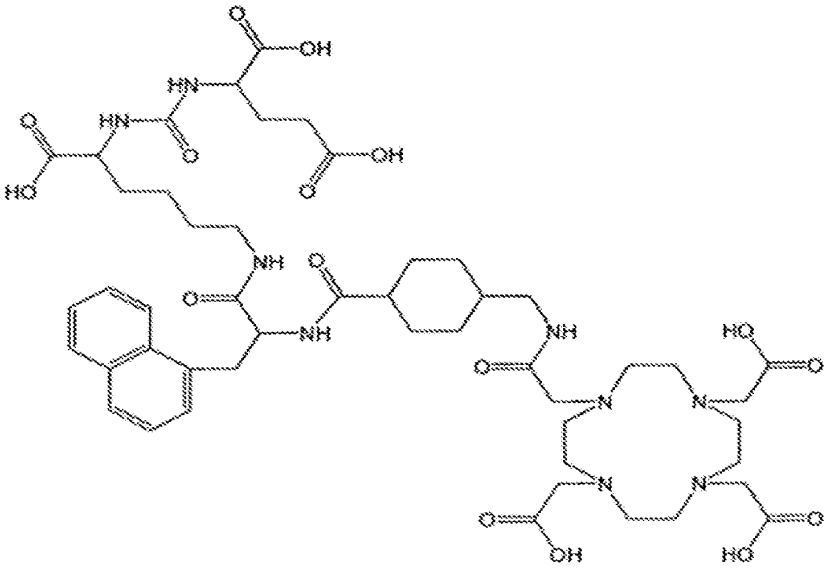




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[0014] [0013] Among the particularly preferred compounds useable in the present invention is the Ac-225-radiopharmaceutical called Ac-225-PSMA-617. Ac-225-PSMA-617 is a compound according to the following formula



chelating a Ac-225 radionuclide with its 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid moiety.

[0015] [0014] The effective amount of said one or more of Ac-225-radiopharmaceuticals is administered as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or wherein the effective amount of said Ac-225-radiopharmaceutical is administered as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

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[0016] [0015] It has been surprisingly found that radiopharmaceuticals comprising Ac-225 as a radionuclide provide considerably and significantly better therapeutic results as corresponding radiopharmaceuticals with other radionuclides, especially with the particular administration dosages of the present invention as will become apparent from the description below.

[0017] [0016] In a second aspect, the present invention concerns the use of one or more Ac-225-radiopharmaceuticals as mentioned above for treating PSMA expressing cancers or cancer cells in a patient, wherein the use comprises administering to said patient an effective amount of said Ac-225-radiopharmaceutical as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0018] [0017] In a third aspect, the invention relates to one or more Ac-225-radiopharmaceuticals selected among those mentioned above for use in treating PSMA expressing cancers or cancer cells in a patient, comprising administering to said patient an effective amount of said Ac-225-radiopharmaceutical(s) as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0019] [0018] It has been surprisingly found that treating patients having PSMA expressing cancers or cancer cells with Ac-225-radiopharmaceuticals, i.e. radiopharmaceuticals comprising Ac-225 as a radionuclide, as described herein allows for a particularly strong anticancer effect with low hematotoxicity as will be shown in greater detail below.

[0020] [0019] The PSMA expressing cancers may be any cancer whose cancerous cells express Prostate Specific Membrane Antigen (PSMA). Preferably cancers (or cancer cells) that may be treated according to the invention are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the

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bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers. In particularly preferred aspects of the invention, said PSMA expressing cancer is prostate cancer or breast cancer.

[0021] [0020] The cells of said PSMA expressing cancers or cancer cells may be treated not only within a solid tumor, but also after dissemination. Hence, in a particularly preferred aspect, the invention relates to the treatment of a disseminated cancer or cancer cells. Indeed, the very efficient and specific targeting of the Ac-225-radiopharmaceuticals to PSMA combined to the short range (< 100 micrometers) action of the Ac-225 alpha emitter allows for very good results of destruction of cancer cells without notable damage to non-target tissues, as further described below.

[0022] [0021] The effective amount of said one or more Ac-225-radiopharmaceuticals to be administered to a patient generally is determined in light of the patient's case. However, the effective amount thereof will represent a dosage within a range from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient. More particularly, the dosage may preferably range from about 30 kBq/kg to about 250 kBq/kg of body weight, for example about 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 , 210, 220, 230, 240 or 250 kBq/kg, or any range between any two of the above values.

[0023] [0022] Alternatively, the effective amount may be administered as a unitary dosage or constant activities, such as from about 3 MBq to about 30 MBq for one administration to the patient. Preferably the unitary dosage or constant activities range from about 4 MBq to about 25 MBq per administration, in particular about 5 MBq to about 20 MBq, such as for example about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 MBq, or any range between any two of the above values.

[0024] [0023] If necessary or desirable, the treatment may comprise more than one administration of an effective amount of one or more Ac-225-radiopharmaceuticals as

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described above. Indeed it is generally beneficial to repeat, one or more times, the administration of an effective amount of said one or more Ac-225-radiopharmaceuticals to the patient after 15 to 90 days, such as at a one- or two-month intervals. Neither the effective amount of such repeated administration, nor the intervals between multiple consecutive administrations need to be the same as those of previous administrations or repetitions.

[0025] [0024] Bq, kBq and MBq represent the SI unit becquerel, as well as its multiples kilobecquerel (10^3 Bq) and megabecquerel (10^6 Bq) respectively, wherein 1 Bq corresponds to the activity of a quantity of radioactive material in which one nucleus decays per second.

[0026] [0025] An "effective amount" in the context of the invention is an amount of Ac-225-radiopharmaceutical(s) that produces at least some measurable therapeutic response or desired effect in some fraction of the patient to whom it is administered. The effective amount may be expressed as dosage per weight unit of the patient (and per administration), such as kBq/kg body weight of the patient or as a unitary dosage (also called "constant activity"), meaning a dosage for one administration to one patient independently of the patient's weight, such as MBq.

[0027] [0026] The terms "administer", "administering" and "administration" refer to the giving of the Ac-225-radiopharmaceutical(s) to a patient by any appropriate route. In particular, the Ac-225-radiopharmaceutical(s) may be administered by oral or parenteral route, preferably parenteral route, such as by injection or infusion, wherein the injection or infusion may be made intravenously, intramuscularly, intra-arterially, subcutaneously, intra-dermally, intraperitoneally, etc. Depending on the administration route, the Ac-225-radiopharmaceutical(s) may comprise further appropriate constituents, such as carriers, solvents and excipients generally known in the art.

[0028] [0027] All approximate values given herein as indicated by the presence of the word "about" include a range of +/- 10 % centered on said value.

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Brief Description of the Drawings

[0029] [0028] Preferred embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings in which:

[0030] Fig. 1 is a graph of experimental data showing the decrease in PSA (Prostate-Specific Antigen) (%) after first treatment with Ac-225-PSMA-617;

[0031] Fig. 2 is a graph of experimental data illustrating the decrease in PSA (%) after a second treatment with Ac-225-PSMA-617;

[0032] Fig. 3 is a graph of experimental data representing the decrease in PSA (%) after third treatment with Ac-225-PSMA-617;

[0033] Fig. 4 to 6 show Gallium-68-PSMA11 PET/CT imaging of three patients before (Fig. 4A, 5A and 6A) and after (Fig. 4B, 5B and 6B) therapy as described herein below;

[0034] Fig. 7 illustrates the development of thrombocyte count during Ac-225-PSMA-617 therapy as described herein below;

[0035] Fig. 8 shows the development of leukocyte count during Ac-225-PSMA-617 therapy as described herein below.

[0036] Fig. 9 is a graph of experimental data showing the decrease in PSA (%) after first treatment and after third treatment with Lu-177-PSMA-617;

[0037] Fig. 10 shows the development of thrombocyte count during Lu-177-PSMA-617 comparative experiments as described herein below;

[0038] Fig. 11 illustrates the development of leukocyte count during Lu-177-PSMA-617 comparative experiments as described herein below;

[0039] Fig. 12 shows Ga-68-PSMA-11 PET/CT scans of a patient: pretherapeutic tumor spread (A), restaging 2 months after third cycle of Ac-225-PSMA-617(B), and restaging 2 months after one additional consolidation therapy (C);

[0040] Fig. 13 illustrates laboratory test follow-up of a patient; arrows indicate administration of treatment cycles; (A) blood cell count demonstrates moderate

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hematologic toxicity; (B) decline of tumor markers to none measurable or reference range correlates with imaging response;

[0041] Fig. 14 show 68-Ga-PSMA-11 PET/CT scans of another patient; in comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting Lu-177-PSMA-617 presented progression (B); in contrast, restaging after second (C) and third (D) cycles of α-emitting Ac-225-PSMA-617 presented impressive response; and

[0042] Fig. 15 illustrates laboratory test follow-up of a patient; arrows indicate administration of treatment cycles; blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

[0043] [0029] Further details and advantages of the present invention will be apparent from the following detailed description of the not limiting embodiments with reference to the attached drawings below.

Description of Preferred Embodiments

[0044] [0030] A1. Peptide, radionuclides and radiolabeling:

[0045] [0031] PSMA-617 was obtained from ABX, Germany.

Ac-225 (also noted ^{225}Ac) was produced by radiochemical extraction from Th-229 as described in Apostolidis C, Molinet R, Rasmussen G, Morgenstern A., Production of Ac-225 from Th-229 for targeted alpha therapy. Analytical Chemistry, 2005;77(19):6288-91 and Zielinska B, Apostolidis C, Bruchertseifer F, Morgenstern A., An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy, Solvent Extraction and Ion Exchange, 2007;25(3):339-49.

[0046] [0032] For radiolabeling an aliquot of Ac-225 stock solution (6-39 MBq Ac-225) in 0.1 M hydrochloric acid was added into a microwave vial containing 0.5 ml of 0.1 M Tris buffer (pH 9) and an appropriate amount of 10 mM PSMA-617 stock solution (35 - 160 nMol peptide). The reaction mixture was heated to 95° C for 5 min

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Exhibit 1004.534

using a microwave synthesizer (Biotage® Initiator) and subsequently cooled to < 50 °C using pressurized air.

[0047] [0033] Quality control was performed by instant thin layer chromatography (ITLC-SG, Pall Life Sciences) with 0.05 M citric acid (pH 5) as solvent. Under these conditions, unbound Ac-225 moves with the solvent front (Rf = 1), while Ac-225-PSMA-617 remains on the bottom of the strip (Rf = 0). After development the ITLC strip was stored for at least 1 hour until radiochemical equilibrium between Ac-225 and its daughter nuclide Fr-221 ($T_{1/2}$ = 4.8 min) was obtained. Subsequently radiochemical purity was determined by measuring the activity of the 218 keV gamma emission of Fr-221 on the upper and lower part of the ITLC strip using high resolution gamma spectrometry (Ortec).

[0048] [0034] After synthesis 0.5 ml of 18% ascorbic acid solution (pH 5.8) was added to the reaction mixture to minimize radiolytic degradation of Ac-225-PSMA-617. The final pH of the formulation was 7.4. Before injection, sterility of the final formulation was assured via sterile filtration (Millex-GV, 0.20 µm, Millipore).

[0049] [0035] Gallium-68-PSMA11 PET/CT imaging was performed using a radiotracer labeled with Ga-68.

[0050] [0036] A2. Results

[0051] [0037] Radiochemical purity was 98.6 ± 1.4 % (*n=67*), specific activity was 0.23 ± 0.1 MBq per nmol of peptide.

[0052] [0038] A3. Patient treatment

[0053] [0039] 20 Patients were treated 3 times with activities of 100 kBq/kg body weight of Ac-225-PSMA-617 in two month intervals.

[0054] [0040] Treatment response was monitored by PSA values in blood and with PET/CT (positron emission tomography-computed tomography) with Ga-68-PSMA-HBED-CC (also called Gallium-68-PSMA11) before therapy and after the third therapy.

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[0055] [0044] Toxicity was monitored by blood sampling.

[0056] [0042] A4. Results

[0057] [0043] A4.1 Treatment efficacy

[0058] [0044] Eight weeks after the first treatment cycle 19/20 patients presented a decrease in PSA, in 17 patients the decrease was > 25 %, in 12 patients the decrease was even > 50 %.

[0059] [0046] The graph of Fig. 1 shows the decrease in PSA (%) after a first treatment with Ac-225-PSMA-617.

[0060] [0046] Sixteen weeks after the first treatment cycle 15/20 patients presented a decrease in PSA, in 14 patients the decrease was > 50 %.

[0061] [0047] As illustrated by the graph of Fig. 2 the decrease in PSA (%) after a second treatment with Ac-225-PSMA-617.

[0062] [0048] Twenty-four weeks after the first treatment cycle 15/20 patients presented with a decrease in PSA, in 12 patients the decrease was even > 50 %.

[0063] [0049] Fig. 3 shows the decrease in PSA (%) after third treatment with Ac-225-PSMA-617.

[0064] [0050] The exceptional results obtainable by the present invention are illustrated in Fig. 4 to 6. These figures show PET/CT images of three different patients before and after the treatment as described above. The PET/CT imaging combines both a positron emission tomography (PET) scanner and an x-ray computed tomography (CT) scanner, so that images acquired from both devices can be taken sequentially, in the same session, and combined into a single superposed image. As can be seen the betterment of the patients' condition is most remarkable.

[0065] [0051] A4.2 Toxicity

[0066] [0052] Hematologic response was evaluated every 4 weeks per lab tests and clinical side effects were monitored every 8 weeks. The treatment was well

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tolerated. There was no significant change in thrombocyte or white blood cell count (Fig. 7 and 8). Several patients reported dysfunction of salivary glands.

[0067] [0053] Fig. 7 shows the development of thrombocyte count during Ac-225-PSMA-617 therapy, whereas Fig. 8 displays the development of leukocyte count during Ac-225-PSMA-617 therapy.

[0068] [0054] A5. Conclusions of the above experiments

[0069] [0055] The inventors found that treatment response with said Ac-225-radiopharmaceutical(s) is very good and hematologic toxicity is moderate to low at dosages of about 100 kBq/kg body weight (i.e. about 7 MBq for a patient of 70 kg). The treatment may be done using a unitary dosage or constant activities, e.g. about 6 MBq per treatment. Furthermore, the patients may be treated in eight week or two month intervals for practical reasons. Shorter intervals (e.g. four weeks or one month) with correspondingly lower dosing are also possible.

[0070] [0056] A6. Comparative Examples

[0071] [0057] Experiments have been conducted to compare the efficiency of the Ac-225-radiopharmaceuticals as used in the present invention, such as Ac-225-PSMA-617, with that of non-Ac-225-radiopharmaceuticals comprising the same targeting compound, but chelated e.g. with Lu-177, such as a radionuclide Lu-177-PSMA-617.

[0072] [0058] A6.1 Treatment efficacy

[0073] [0059] Eight weeks after the first treatment cycle 21/30 patients presented a decrease in PSA, In 16 patients the decrease was > 50 %.

[0074] [0060] Twenty-four weeks after the first treatment cycle some patients were dropped out from the therapy because some physical conditions were considered a contraindication for treatment with β-emitters. 9/30 patients presented a decreased in PSA. For all of them the decrease was > 50 %.

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[0075] [0064] The graph of Fig. 9 shows the decrease in PSA (%) after a first and a third treatment with Lu-177-PSMA-617.

[0076] [0062] A6.2 Toxicity

[0077] [0063] The treatment was well tolerated. There was no significant change in thrombocyte or white blood cells count (Fig. 10 and 11). Mild moderate dysfunction of salivary glands was reported.

[0078] [0064] Fig. 10 shows the development of thrombocyte count during Lu-117-PSMA-617 therapy, whereas Fig. 11 displays the development of leukocyte count during Lu-117-PSMA-617 therapy.

[0079] [0065] A6.3 Conclusions of the above comparative experiments

[0080] The group treated with Lu-117-PSMA-617 had a lower response rate in comparison to the one treated with Ac-225-PSMA-617. Indeed, the treatment analysis revealed that 15/28 patients (54%) treated with Ac-225-PSMA-617 were in PSA response but only 9/30 patients (30%) treated with Lu-177-PSMA-617 were in PSA response at week-24. This is a remarkable difference taking into account similar hematological toxicity and the more advanced patients selected for Ac-225-radiopharmaceutical therapy.

[0081] [0066] B1. Treatment of metastatic castration-resistant prostate cancer (mCRPC) with Ac-225-radiopharmaceutical:

[0082] [0067] FIG. 12: Ga-68-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 months after third cycle of Ac-225-PSMA-617(B), and restaging 2 months after one additional consolidation therapy (C).

[0083] [0068] Clinical Course of Patient A presented with diffuse red marrow infiltration of mCRPC (this physical condition was considered a contraindication for treatment with β-emitters).Patient A was treated with 3 cycles of 9–10 MBq (100 kBq per kilogram of body weight) of Ac-225-PSMA-617 at bimonthly intervals. Posttherapeutic emission scans validated sufficient tumor targeting Two months later,

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all previously PSMA-positive lesions had visually disappeared on PSMA PET/CT (Fig. 12B) and, accordingly, the PSA level had dropped from more than 3,000 ng/ml to 0.26 ng/ml. The patient received an additional 6 MBq of Ac-225-PSMA-617 as consolidation therapy, resulting in a further PSA decline to less than 0.1 ng/ml along with a complete imaging response (Fig. 1C).

[0084] [0069] FIG. 13: Laboratory test follow-up of patient A. Arrows indicate administration of treatment cycles. (A) Blood cell count demonstrates moderate hematologic toxicity. (B) Decline of tumor markers to none measurable or reference range correlates with imaging response. AP = alkalinephosphatase; Hb= 5 hemoglobin; PLT = platelets; WBC = white blood cells.

[0085] [0070] After each cycle, the blood cell count and alkaline phosphatase level were checked every 2 week. The platelet level never dropped below 100/nl (grade 1 according to the Common Terminology Criteria for Adverse Events, version 4.0), the total white blood cell count never dropped below 2.5/nl (grade 1), and the hemoglobin level never dropped below 9.5 g/dl (grade 2) (Fig. 13A). Moderate but enduring dysfunction of salivary glands was the only clinically reported side effect. A concordant decline in PSA level and alkaline phosphatase level (Fig. 13B) further underlined the excellent treatment response.

[0086] [0074] B2 Treatment with Lu-177 then Ac-225:

[0087] [0072] FIG. 14: 68-Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting Lu-177-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting Ac-225-PSMA-617 presented impressive response.

[0088] [0073] Clinical Course of Patient B presented with peritoneal carcinomatosis and liver metastases.

[0089] [0074] Patient B was initially treated with Lu-177-PSMA-617 (7.4 GBq per cycle), which was offered as salvage therapy. The initial PSA level was 294 ng/ml.

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After cycle 2 the PSA level increased to 419 ng/ml and most lesions demonstrated tumor progression on PSMA PET/CT (Fig. 14B). Therapy was changed to Ac-225-PSMA-617, and the patient received 3 cycles of 6.4 MBq (100 kBq per kilogram of body weight) at bimonthly intervals. Restaging based on the PSMA PET/CT results finally indicated a partial response after 2 cycles (Fig. 14C) and a complete remission after 3 cycles (Fig. 14D). Laboratory tests revealed no relevant hematologic toxicity; PSA dropped to below the measurable level (0.1 ng/ml) (Fig. 15). However, the patient reported severe dysfunction of salivary glands.

[0090] [0076] FIG. 15: Laboratory test follow-up of patient B. Arrows indicate administration of treatment cycles. Blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

[0091] [0076] B3. Conclusion:

[0092] [0077] The early results already indicate that Ac-225-targeted α-therapy has high potential for the epidemiologically important tumor entity prostate cancer, which presumably will further accelerate the routine availability of Ac-225 for systematic clinical trials, for example.

[0093] [0078] The two impressive responses reported here demonstrate the high potential of Ac-225-radiopharmaceuticals, such as Ac-225-PSMA-617 to significantly benefit mCRPC patients who are in a clinically critical situation, that is, patients with diffuse red marrow infiltration and resistance to other therapies. Investigation of this therapeutic modality in larger patient cohorts is warranted.

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Exhibit 1004.540

Abstract

The invention relates to a method for treating PSMA expressing cancers, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

(Fig. 4)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office on June 14, 2019 at or before 11:59 p.m. Pacific Time under the Rules of 37 CFR § 1.8.

/Stacey Dawson/
Stacey Dawson

Inventor(s) : Alfred Morgenstern, et al. Confirmation No. To Be Determined
Application No. : To Be Determined
Filed : June 14, 2019
Title : TREATMENT OF PMSA EXPRESSING CANCERS

Grp./Div. : To Be Determined
Examiner : To Be Determined

Docket No. : 173545 (304773-00005)

INFORMATION DISCLOSURE STATEMENT
37 CFR § 1.97(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 29001
Glendale, CA 91209-9001
June 14, 2019

Commissioner:

In compliance with the duty of disclosure under 37 CFR §§ 1.56, 1.97 and 1.98, and in accordance with the provisions in the Manual of Patent Examining Procedure §§ 609 and 707.05(b), enclosed is an information disclosure statement listing the references that are known to applicant. Copies of each of the listed Foreign Patent Documents and Other Documents references are enclosed. This filing is timely because it is made during one of the periods described in 37 CFR § 1.97(b).

It is respectfully requested that the listed references be considered in the examination of this application and identified on the list of references cited on the patent issuing for this application. Applicant also requests that an initialed copy of the information disclosure statement be entered in the application file and returned to applicant with the next communication from the Office in accordance with MPEP § 609.

Docket No.: 173545 (304773-00005)

The Commissioner is hereby authorized to charge any fees which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any Deposit Account transaction.

Respectfully submitted,
LEWIS ROCA ROTHGERBER CHRISTIE LLP

By /Art Hasan/
Art Hasan
Reg. No. 41,057
626/795-9900

SAH/srd
Enclosures: Information Disclosure Statement, w/references

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		
	Attorney Docket Number	173545 (304773-00005)
	Application Number	To Be Determined
	Filing Date	June 14, 2019
	Inventor(s)	Alfred Morgenstern, et al.
	Group Art Unit	To Be Determined
	Examiner Name	To Be Determined

U.S. PATENT DOCUMENTS				
EXAMINER INITIALS	Cite No.[1]	DOCUMENT NUMBER Number - Kind Code[2] (If Known)	PUBLICATION DATE OR ISSUE DATE MM-DD-YYYY	NAME OF PATENTEE

FOREIGN PATENT DOCUMENTS					
EXAMINER INITIALS	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (If Known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6] (✓)

OTHER DOCUMENTS		
EXAMINER INITIALS	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article, title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
		KRATOCHWIL, Clemens et al., "*225 Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer*", The Journal of Nuclear Medicine, 7 July 2016, Vol. 57, No. 12, pp. 1941–1944
		SATHEKGE, Mike et al., "*^{68}Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients*", European Journal of Nuclear Medicine and Molecular Imaging, 8 November 2016, Vol. 44, pp. 689-694
		KRATOCHWIL, Clemens et al., "*Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors*", The Journal of Nuclear Medicine, 1 May 2015, Vol. 56, No. Supplement 3, pg. 1232
		AFSHAR-OROMIEH, Ali et al., "*The Rise of PSMA Ligands for Diagnosis and Therapy of Prostate Cancer*", The Journal of Nuclear Medicine, October 2016, Vol. 57, No. Suppl. 3, pp. 79S-89S
		International Search Report and Written Opinion for corresponding International Application No. PCT/EP2016/081313, dated September 7, 2017 (9 pgs.)

SRD 108416396.1-*-06/14/2019 7:29 AM

EXAMINER SIGNATURE		DATE CONSIDERED	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.pto.gov or MPEP 901.4. [3]Enter Office that issued the document, by the two-letter code (WIPO standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English Language Translation is attached.

SAH/srd

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Exhibit 1004.544

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PAT2526911PC00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2016/081313	15 December 2016 (15-12-2016)	

Applicant

THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM ..

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. 4

[X] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

b. [ ] none of the figures is to be published with the abstract

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081313

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K51/04 A61P35/00
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)
A61K

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, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C. KRATOCHWIL ET AL: "225Ac-PSMA-617 for PSMA-Targeted -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer", THE JOURNAL OF NUCLEAR MEDICINE, vol. 57, no. 12, 7 July 2016 (2016-07-07), pages 1941-1944, XP055401535, US ISSN: 0161-5505, DOI: 10.2967/jnumed.116.178673	1-6, 8-18, 20-25, 27-30, 32-36
Y	page 1942, column 2, paragraph 5	1-36

-/--

[X] Further documents are listed in the continuation of Box C. [ ] 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
31 August 2017	07/09/2017

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	Langer, Miren

3

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

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Exhibit 1004.546

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SATHEKGE MIKE ET AL: "68Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients", EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING, SPRINGER VERLAG, HEIDELBERG, DE, vol. 44, no. 4, 8 November 2016 (2016-11-08), pages 689-694, XP036183546, ISSN: 1619-7070, DOI: 10.1007/S00259-016-3563-6 [retrieved on 2016-11-08] page 693, column 1, paragraph 2 -----	1-36
A	HADASCHIK BORIS: "Re:225Ac-PSMA-617 for PSMA-Targeting Alpha-radiation Therapy of Patients with Metastatic Castration-resistant Prostate Cancer", EUROPEAN UROLOGY, ELSEVIER, AMSTERDAM, NL, vol. 70, no. 6, 21 August 2016 (2016-08-21), pages 1080-1081, XP029779996, ISSN: 0302-2838, DOI: 10.1016/J.EURURO.2016.08.028 -----	1-36
A	KRATOCHWIL CLEMENS ET AL: "Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors", THE JOURNAL OF NUCLEAR MEDICINE, SOCIETY OF NUCLEAR MEDICINE, US , vol. 56, no. 3, Supplement 3 1 May 2015 (2015-05-01), page 1, XP008185796, ISSN: 0161-5505 Retrieved from the Internet: URL:http://jnm.snmjournals.org/content/56/supplement_3/1232 -----	1-36
A	AFSHAR-OROMIEH A ET AL: "The rise of PSMA ligands for diagnosis and therapy of prostate cancer", THE JOURNAL OF NUCLEAR MEDICINE, SOCIETY OF NUCLEAR MEDICINE, US, vol. 57, no. Supplement 1, 1 October 2016 (2016-10-01), pages 79S-89S, XP008185794, ISSN: 0161-5505, DOI: 10.2967/JNUMED.115.170720 -----	1-36

3

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Exhibit 1004.547

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2016/081313	15.12.2016	

International Patent Classification (IPC) or both national classification and IPC
INV. A61K51/04 A61P35/00

Applicant
THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Langer, Miren Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

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Exhibit 1004.548

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☑ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7, 19, 26, 31
	No:	Claims	1-6, 8-18, 20-25, 27-30, 32-36
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Exhibit 1004.550

Re Item V.

Reasoned statement with due regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The patentability can be dependent upon the formulation of the claims. The EPO for example does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Reference is made to the following documents:

D1 C. KRATOCHWIL ET AL: "225Ac-PSMA-617 for PSMA-Targeted - Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer", THE JOURNAL OF NUCLEAR MEDICINE, vol. 57, no. 12, 7 July 2016 (2016-07-07), pages 1941-1944, XP055401535, US ISSN: 0161-5505, DOI: 10.2967/jnumed.116.178673

D2 SATHEKGE MIKE ET AL: "68Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients", EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING, SPRINGER VERLAG, HEIDELBERG, DE, vol. 44, no. 4, 8 November 2016 (2016-11-08), pages 689-694, XP036183546, ISSN: 1619-7070, DOI: 10.1007/S00259-016-3563-6 [retrieved on 2016-11-08]

1. Article 33(2) PCT

The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-6, 8-18, 20-25, 27-30, 32-36 is not novel in view of the cited prior art documents.

D1, was published online on 7.7.2016 and teaches the use of the only exemplified radiolabelled compound, namely 225 Ac-PSMA-617 in two patients with prostate cancer. The radiopharmaceutical was administered at a dose of 100 kBq/kg of body

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Exhibit 1004.551

weight (page 1942, col. 2, par. 5), which falls in the claimed range of claim 1. Patient A was treated with 3 cycles of 9-10 MBq (100 kBq per kg of bodyweight) of 225 Ac-PSMA-617 at a bimonthly interval (p. 1942, col. 2, par. 5), which falls under the range of claim 12. It appears that exactly the same experimental data has been presented in the present application par. 66-78. Thus D1 takes away the novelty of present claims 1-6, 8-18, 20-25, 27-30, 32-36.

2. Article 33(3) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-36, as far as novel, does not involve an inventive step in the sense of Article 33(3) PCT.

Document D1 is considered to represent the closes prior art.

The subject-matter of present claims 1-36, as far as novel, differs herefrom in that the claimed radiopharmaceutical is used for other PSMA expressing cancers such as breast cancer.

There is no technical effect relating to said difference. Experimental data has been provided only for treating prostate cancer.

Therefore the objective technical problem in view of D1 can be formulated as the provision of alternative PSMA expressing cancers.

The provision of alternative PSMA expressing cancers is obvious to the skilled person. D2 discloses the use of PSMA-ligands for imaging of breast cancer. Based on the result the therapeutic use of PSMA-ligands in treating breast cancer is suggested (page 693, col. 1, par. 2). It would be obvious to the skilled person to use the claimed radiopharmaceuticals in other PSMA expressing tumors such as breast cancer based on D2.

Therefore the subject-matter of claims 1-36, as far as novel, does not involve an inventive step in the sense of Article 33(3) PCT

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Exhibit 1004.552

Re item VIII

The term "disseminated cancer" in claims 5 and 17 is unclear is vague and unclear and lacks clarity within the meaning of Article 6 PCT. The claims cover all compounds having this characteristic or property, whereas the application provides support and/or disclosure within the meaning of Article 6 and 5 PCT for only a very limited number of such cancer types.

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Exhibit 1004.553

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Filer:	Syed A. Hasan/Stacey Dawson
Attorney Docket Number:	173545 (304773-00005)

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
NATIONAL STAGE FEE	1631	1	300	300
NATL STAGE SEARCH FEE - REPORT PROVIDED	1642	1	520	520
NATIONAL STAGE EXAM - ALL OTHER CASES	1633	1	760	760
Pages:				
Claims:				
Miscellaneous-Filing:				
OATH/DECL > 30 MOS FROM 371 COMMENCEMENT	1617	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1720**

Electronic Acknowledgement Receipt

EFS ID:	36308494
Application Number:	16470104
International Application Number:	PCT/EP2016/081313
Confirmation Number:	9416
Title of Invention:	TREATMENT OF PMSA EXPRESSING CANCERS
First Named Inventor/Applicant Name:	Alfred MORGENSTERN
Customer Number:	23363
Filer:	Syed A. Hasan/Stacey Dawson
Filer Authorized By:	Syed A. Hasan
Attorney Docket Number:	173545 (304773-00005)
Receipt Date:	14-JUN-2019
Filing Date:	
Time Stamp:	17:20:30
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1720
RAM confirmation Number	061719INTEFSW17231500
Deposit Account	031728
Authorized User	Stacey Dawson
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.492 (National application filing, search, and examination fees) 37 CFR 1.492(a) (Basic national fee only)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	173545_Transmittal.PDF	2965039 17975e92e743cb066affdc2522539efe189a3020	no	3
Warnings:					
Information:					
2	Application Data Sheet	173545_ADS.PDF	1344213 8f9f6862a13cb0563ba97b4b02dcb304f2b0c5d7	no	10
Warnings:					
Information:					
3	Oath or Declaration filed	173545_Declaration_EURATOM.PDF	1276952 9d9b1d057c922b50b5e0432c9a83a082378523e4	no	3
Warnings:					
Information:					
4	Power of Attorney	173545_POA_EURATOM.PDF	644291 bbed4d8b32fb7cc1f5af9d85121a6be604131232	no	2
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Information:					
5		173545_Preliminary_Amendment.PDF	109137 ca68e08ffa52e39817042bb8f7ea30f59283201e	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Applicant Arguments/Remarks Made in an Amendment	3	3

Fusion Pharmaceuticals, Inc.
Exhibit 1004.557

Warnings:					
Information:					
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	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	22
	Abstract	23	23

Warnings:					
Information:					
7	Applicant Arguments/Remarks Made in an Amendment	173545_Compare_Copy.PDF	1881185 a03c8ba9c142a766bca30e1e4e600f48387cdddd	no	22
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Information:					
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	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	3

Warnings:					
Information:					
9	Non Patent Literature	Kratochwil.PDF	5688524 41caee8ce835a1adc72945563ec0402b0462bc22	no	5
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Information:					
10	Non Patent Literature	Sathekge.PDF	6754902 cd63af74907dbce69599ef1c9d8de4b70e6f6e1e	no	6

Warnings:					
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11	Non Patent Literature	Kratochwil_Ac-225.PDF	163862 4997e7f8a47f5c2abd3cde311cbb7af01c79aa3a	no	1
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13	Other Reference-Patent/App/Search documents	ISRandWO.PDF	4458012 ad0b956b8b0e4f05d46cf2ee2c99aeb34599f8b6	no	9
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Warnings:					
Information:					
		Total Files Size (in bytes):	44620971		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

TREATMENT OF PMSA EXPRESSING CANCERS

Technical field

[0001] The invention generally relates to radiopharmaceuticals for treating cancer, i.e. molecules labelled with radionuclides able to target certain cancer cells, in particular PSMA expressing cancer cells.

Background Art

[0002] In fact, radiopharmaceuticals are particularly interesting as tracers, imaging agents and for treating various cancers. Radiopharmaceuticals generally comprise a targeting (ligand) moiety and chelating moiety, the former being specific to certain target markers (predominantly) expressed by target cells and the latter being able to chelate (bind) a radionuclide. The so-formed radiopharmaceutical is thus able to target and bind to the desired site of such cells and it may be traced, be used for imaging or may act locally by destroying the cell to which it is bound or nearby cells, such as cancerous cells.

[0003] There are many different cancers and thus even more potentially useful different targeting sites for appropriately conceived radiopharmaceuticals. So, even for a given cancer type a number of targeting sites may be considered and may (or may not) be of use for the docking of radiopharmaceuticals.

[0004] Hence, choosing an appropriate targeting site and developing an appropriate targeting moiety combined to the identification of an appropriate chelating unit with an appropriate radionuclide to a working radiopharmaceutical is a challenging, yet promising way to be able to manage tumors.

[0005] Among cancers, PSMA (Prostate Specific Membrane Antigen) expressing cancers, notably prostate and breast cancers indubitably rank among the most frequent cancers. However, in spite of the considerable efforts spent in various medical approaches during the last decades to find efficient treatment methods, these cancers still are among those for which a reliable and efficient therapy is highly desirable.

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Exhibit 1004.560

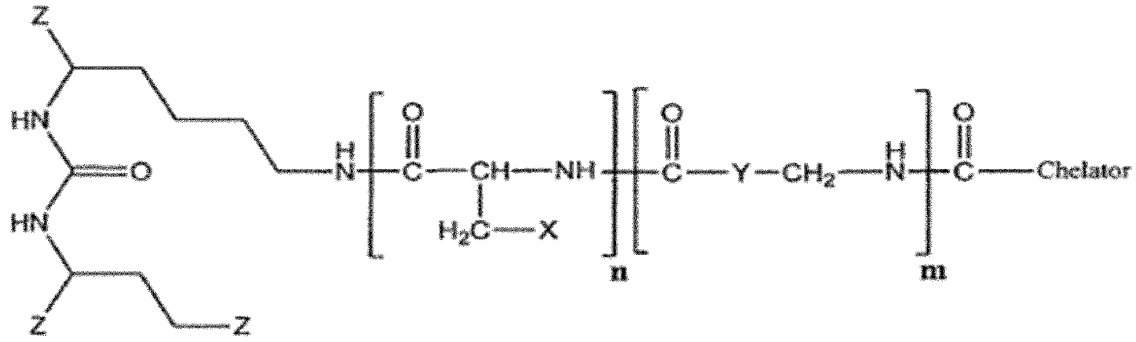
Technical problem

[0006] It is an object of the present invention to provide a method for treating PSMA expressing cancers. The method should allow for even treating patients refractory to established therapies. Furthermore, the devised method should allow for an efficient treatment of the cancer, while having as few side-effects as possible.

General Description of the Invention

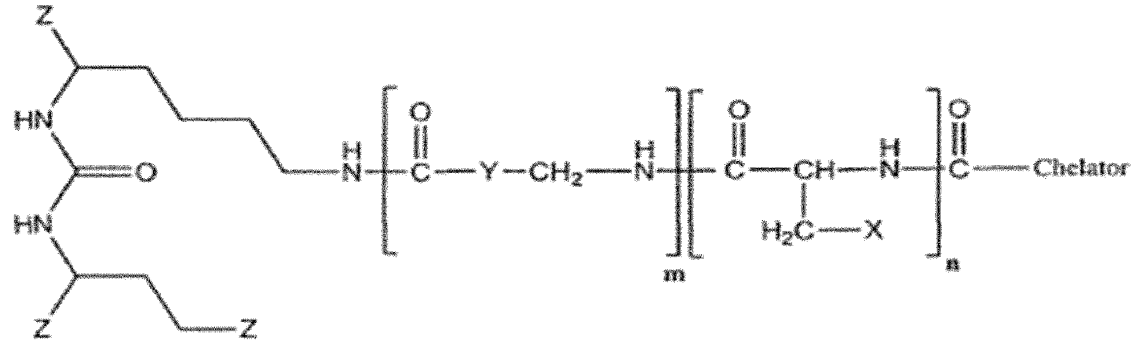
[0007] In order to overcome the above-mentioned problems, the present invention provides in a first aspect a method for treating PSMA expressing cancers or cancer cells, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

Formula (A)



or

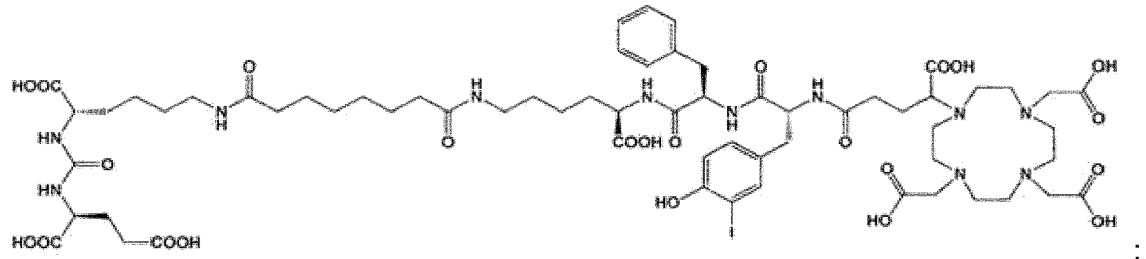
Formula (B)



with:

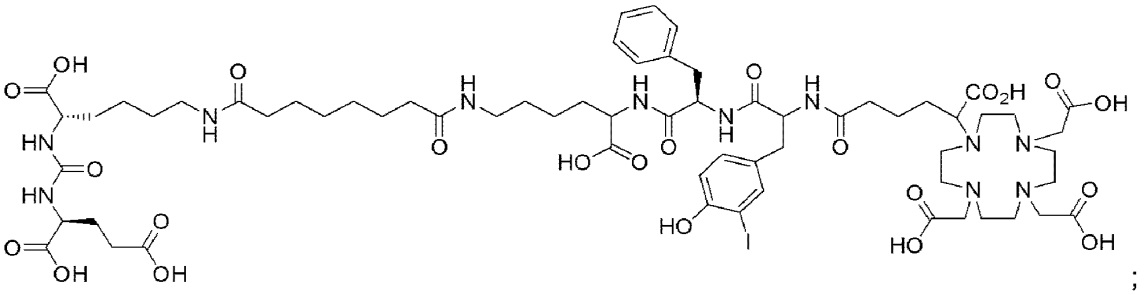
n:	0, 1
m:	1, 2, 3, 4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N"-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA), 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA), 1,4,7-triazacyclononane phosphinic acid (TRAP), 1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO), 3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA), N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO), diethylenetriaminepentaacetic acid (DTPA), trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA), 1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A) p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA), 1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M), 2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or 1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA);

Formula (C)



;

Formula (D)



;

or

Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator.

[0008] The "alkyl" residue preferably has 1 to10 carbon atoms and can be linear or branched, unsubstituted or substituted. Preferred alkyl residues are methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, n-pentanyl, n-hexanyl. The same also applies to the corresponding cycloalkyl residues having preferably 3 to 10 carbon atoms.

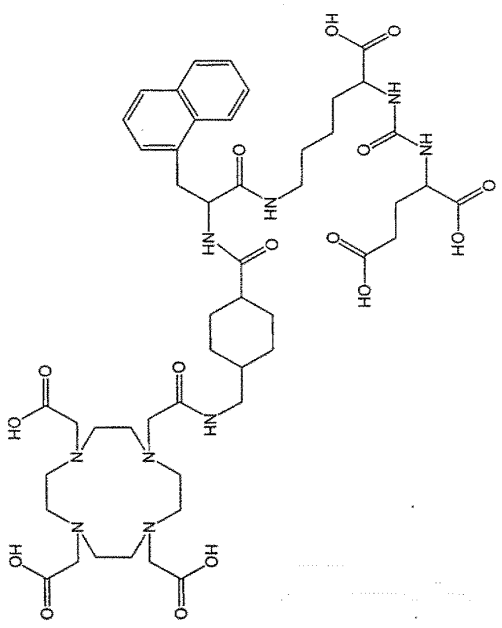
[0009] The term "aryl" refers to an aromatic monocyclic or polycyclic ring system having 6 to 14 carbon atoms, preferably 6 to 10 carbon atoms. The aryl group can be substituted, where appropriate, with one or several ring substituents, like alkyl groups. Preferred aryl groups are phenyl, benzyl or naphthyl.

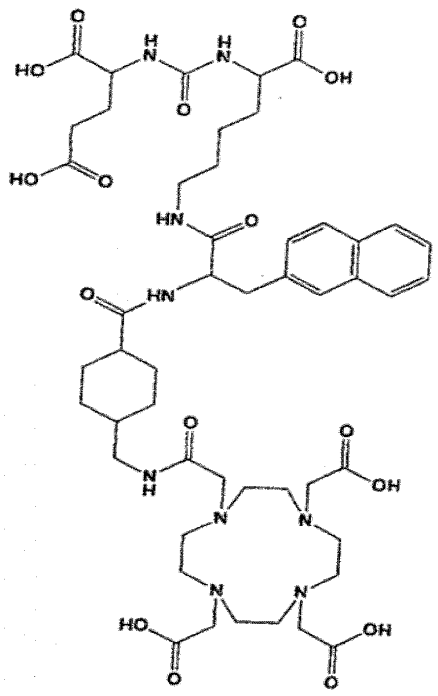
[0010] Although it is preferred that the Z group is $-CO_2H$ it may be easily replaced with biosteric replacements such as $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$.

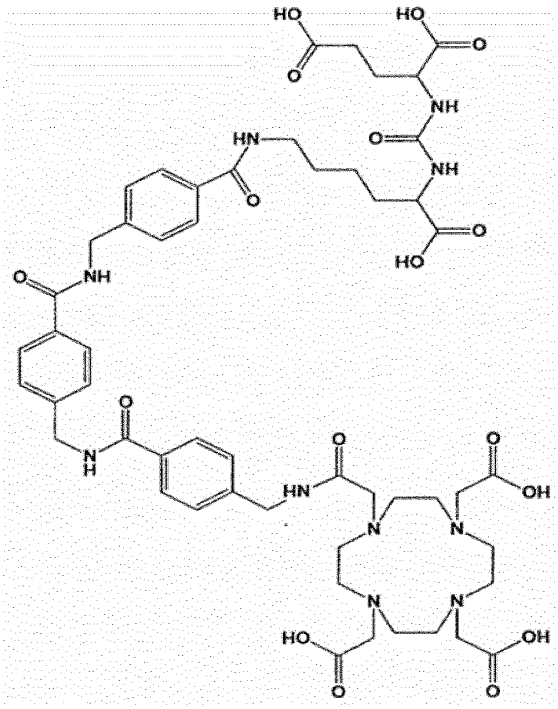
[0011] The term “minibody” refers to an optionally engineered fragment of an (entire) antibody. Hence, a PSMA minibody (also called anti-PSMA minibody) is a

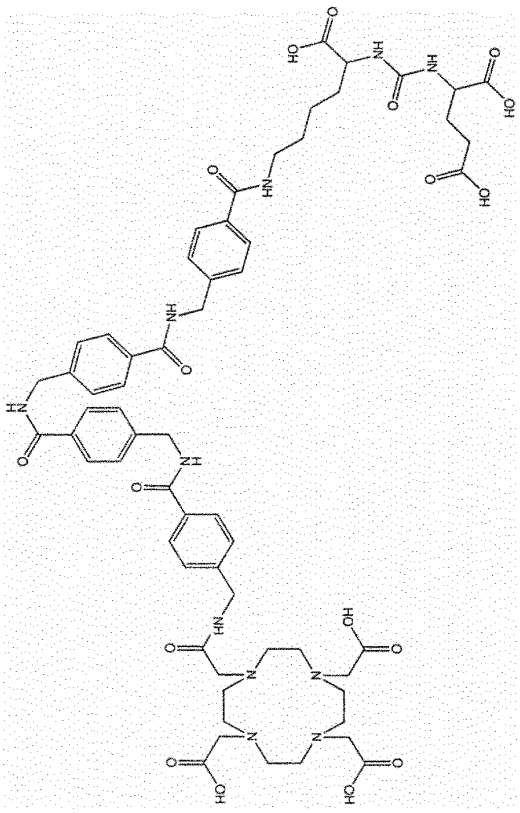
fragment of a PSMA antibody (also called anti-PSMA antibody) which may be obtained in the same way as the antibody itself, i.e. by extraction from biological culture systems (cell cultures, egg, hamsters, mice, etc.) or they may be engineered. Engineered antibody fragments generally offer faster delivery with retained tumor specificity and rapid clearance from non-tumor tissues compared to the corresponding (entire) antibody. Appropriate PSMA antibodies and PSMA minibodies are e.g. antibody J591 and corresponding minibody IAB2M, GCP-05, 1H8H5, SP29, FOLH1, etc. Compounds of Formula (E) comprise a chelating moiety capable of chelating Ac-225. Appropriate chelating moieties are e.g. those mentioned for compounds of Formula (A) and (B), but other chelators may be used. A particularly preferred compound of Formula (E) is e.g. Df-IAB2M, Df being desferrioxamine.

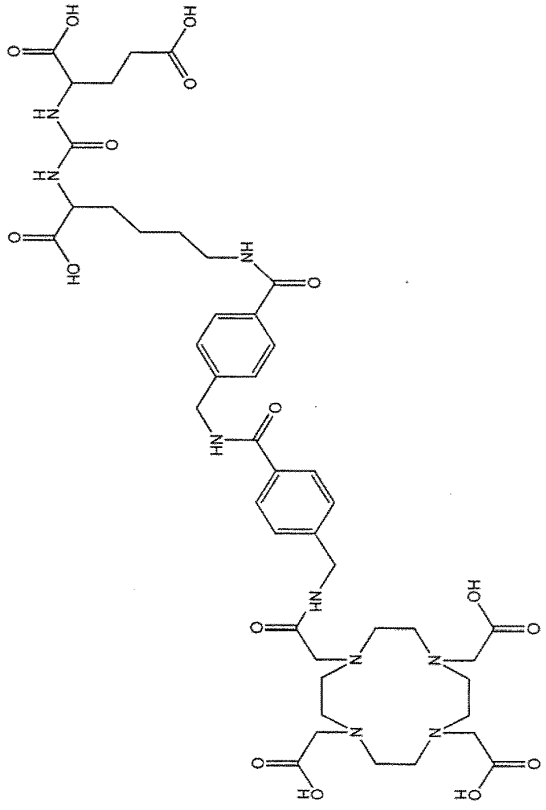
[0012] Thus, preferred targeting compounds comprised within the Ac-225-radiopharmaceuticals useable according to the present invention are selected for example among the following:

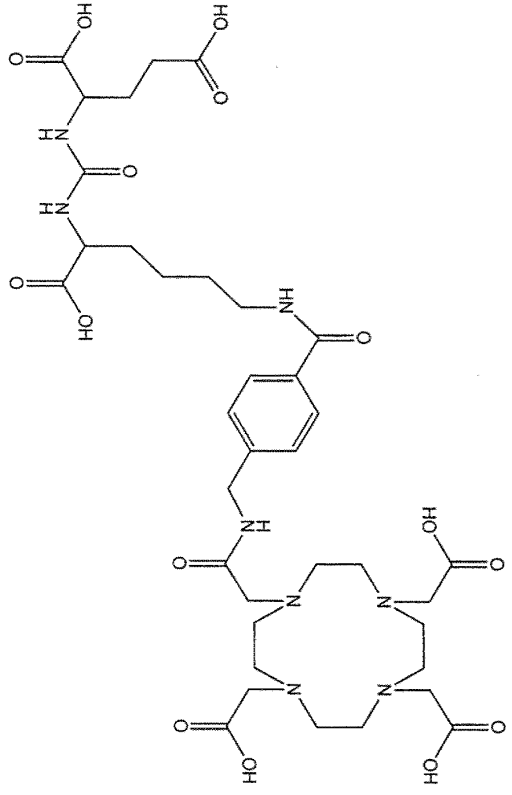


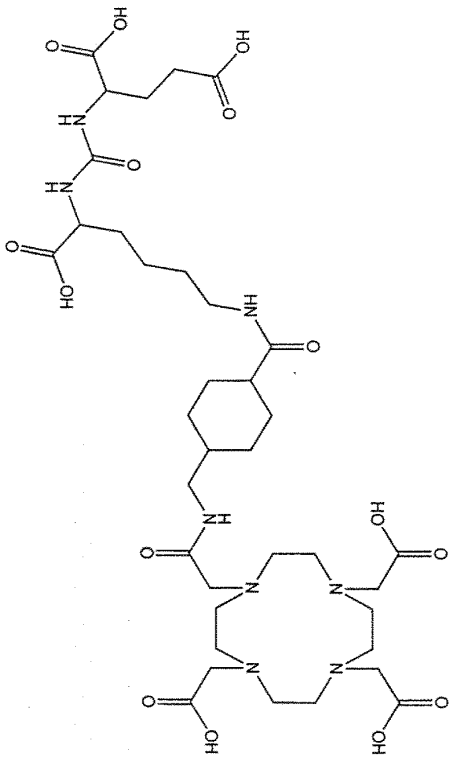


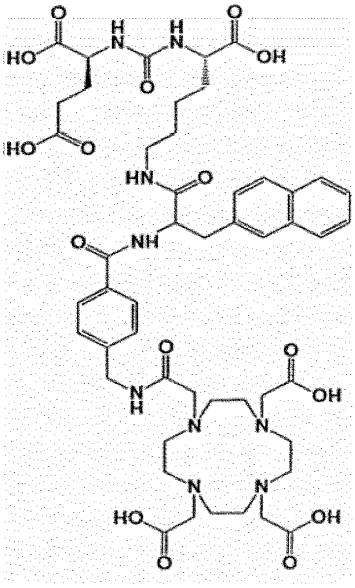


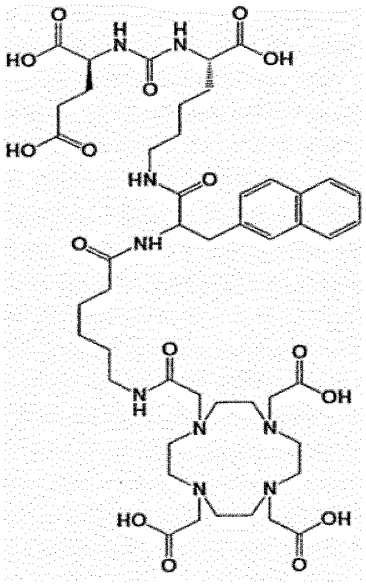


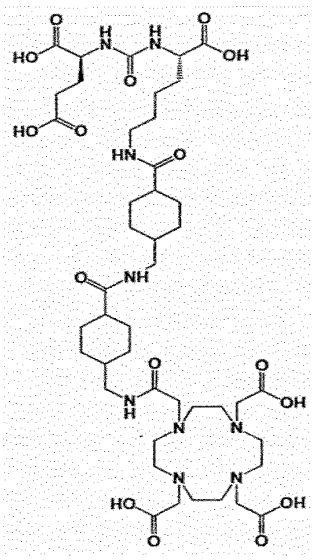


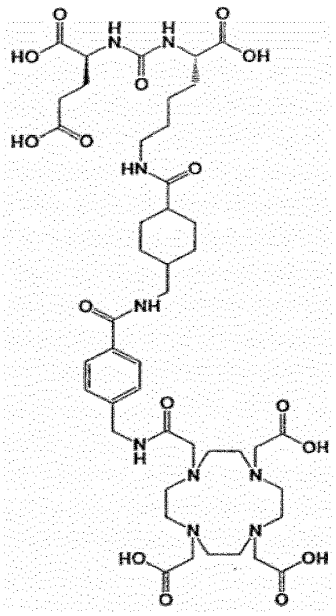


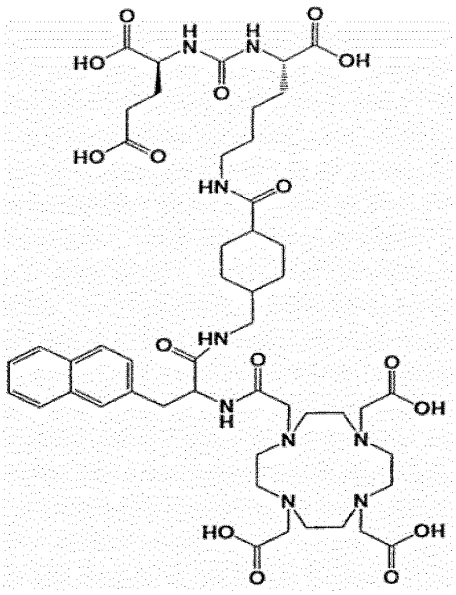


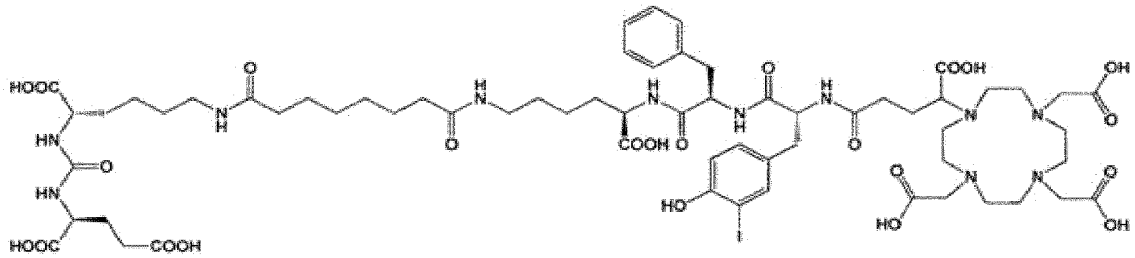


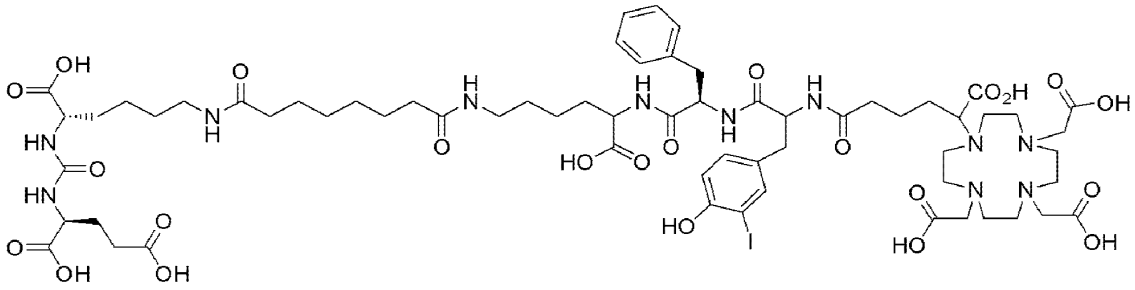




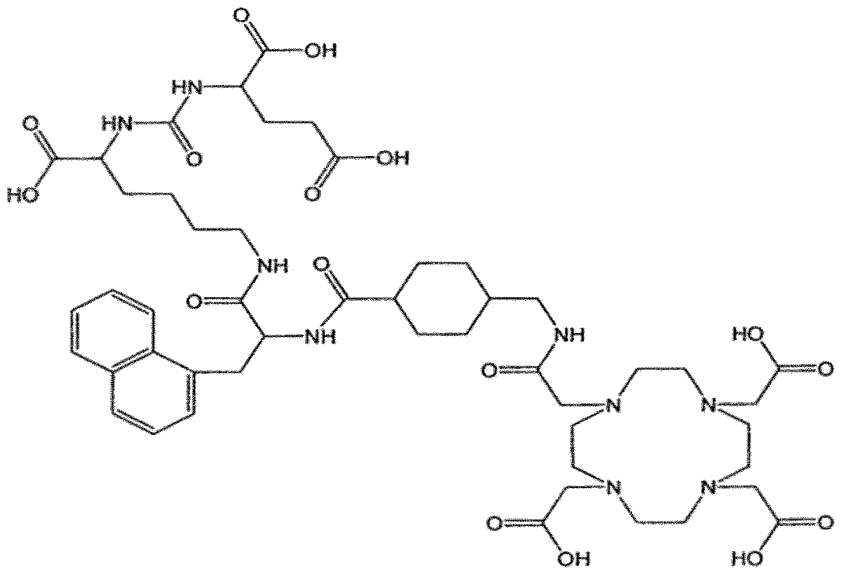








[0013] Among the particularly preferred compounds useable in the present invention is the Ac-225-radiopharmaceutical called Ac-225-PSMA-617. Ac-225-PSMA-617 is a compound according to the following formula



chelating a Ac-225 radionuclide with its 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid moiety.

[0014] The effective amount of said one or more of Ac-225-radiopharmaceuticals is administered as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or wherein the effective amount of said Ac-225-radiopharmaceutical is administered as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0015] It has been surprisingly found that radiopharmaceuticals comprising Ac-225 as a radionuclide provide considerably and significantly better therapeutic results as corresponding radiopharmaceuticals with other radionuclides, especially with the particular administration dosages of the present invention as will become apparent from the description below.

[0016] In a second aspect, the present invention concerns the use of one or more Ac-225-radiopharmaceuticals as mentioned above for treating PSMA expressing cancers or cancer cells in a patient, wherein the use comprises administering to said patient an effective amount of said Ac-225-radiopharmaceutical as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0017] In a third aspect, the invention relates to one or more Ac-225-radiopharmaceuticals selected among those mentioned above for use in treating PSMA expressing cancers or cancer cells in a patient, comprising administering to said patient an effective amount of said Ac-225-radiopharmaceutical(s) as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

[0018] It has been surprisingly found that treating patients having PSMA expressing cancers or cancer cells with Ac-225-radiopharmaceuticals, i.e. radiopharmaceuticals comprising Ac-225 as a radionuclide, as described herein allows for a particularly strong anticancer effect with low hematotoxicity as will be shown in greater detail below.

[0019] The PSMA expressing cancers may be any cancer whose cancerous cells express Prostate Specific Membrane Antigen (PSMA). Preferably cancers (or cancer cells) that may be treated according to the invention are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers. In particularly preferred aspects of the invention, said PSMA expressing cancer is prostate cancer or breast cancer.

[0020] The cells of said PSMA expressing cancers or cancer cells may be treated not only within a solid tumor, but also after dissemination. Hence, in a particularly preferred aspect, the invention relates to the treatment of a disseminated cancer or cancer cells. Indeed, the very efficient and specific targeting of the Ac-225-radiopharmaceuticals to PSMA combined to the short range (< 100 micrometers) action of the Ac-225 alpha emitter allows for very good results of destruction of cancer cells without notable damage to non-target tissues, as further described below.

[0021] The effective amount of said one or more Ac-225-radiopharmaceuticals to be administered to a patient generally is determined in light of the patient's case. However, the effective amount thereof will represent a dosage within a range from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient. More particularly, the dosage may preferably range from about 30 kBq/kg to about 250 kBq/kg of body weight, for example about 30, 40, 50, 60, 70, 80, 90, 100, 110,

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Exhibit 1004.569

120, 130, 140, 150, 160, 170, 180, 190, 200 , 210, 220, 230, 240 or 250 kBq/kg, or any range between any two of the above values.

[0022] Alternatively, the effective amount may be administered as a unitary dosage or constant activities, such as from about 3 MBq to about 30 MBq for one administration to the patient. Preferably the unitary dosage or constant activities range from about 4 MBq to about 25 MBq per administration, in particular about 5 MBq to about 20 MBq, such as for example about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 MBq, or any range between any two of the above values.

[0023] If necessary or desirable, the treatment may comprise more than one administration of an effective amount of one or more Ac-225-radiopharmaceuticals as described above. Indeed it is generally beneficial to repeat, one or more times, the administration of an effective amount of said one or more Ac-225-radiopharmaceuticals to the patient after 15 to 90 days, such as at a one- or two-month intervals. Neither the effective amount of such repeated administration, nor the intervals between multiple consecutive administrations need to be the same as those of previous administrations or repetitions.

[0024] Bq, kBq and MBq represent the SI unit becquerel, as well as its multiples kilobecquerel (10^3 Bq) and megabecquerel (10^6 Bq) respectively, wherein 1 Bq corresponds to the activity of a quantity of radioactive material in which one nucleus decays per second.

[0025] An "effective amount" in the context of the invention is an amount of Ac-225-radiopharmaceutical(s) that produces at least some measurable therapeutic response or desired effect in some fraction of the patient to whom it is administered. The effective amount may be expressed as dosage per weight unit of the patient (and per administration), such as kBq/kg body weight of the patient or as a unitary dosage (also called "constant activity"), meaning a dosage for one administration to one patient independently of the patient's weight, such as MBq.

[0026] The terms "administer", "administering" and "administration" refer to the giving of the Ac-225-radiopharmaceutical(s) to a patient by any appropriate route. In particular, the Ac-225-radiopharmaceutical(s) may be administered by oral or parenteral route, preferably parenteral route, such as by injection or infusion,

wherein the injection or infusion may be made intravenously, intramuscularly, intra-arterially, subcutaneously, intra-dermally, intraperitoneally, etc. Depending on the administration route, the Ac-225-radiopharmaceutical(s) may comprise further appropriate constituents, such as carriers, solvents and excipients generally known in the art.

[0027] All approximate values given herein as indicated by the presence of the word "about" include a range of +/- 10 % centered on said value.

Brief Description of the Drawings

[0028] Preferred embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings in which:

Fig. 1 is a graph of experimental data showing the decrease in PSA (Prostate-Specific Antigen) (%) after first treatment with Ac-225-PSMA-617;

Fig. 2 is a graph of experimental data illustrating the decrease in PSA (%) after a second treatment with Ac-225-PSMA-617;

Fig. 3 is a graph of experimental data representing the decrease in PSA (%) after third treatment with Ac-225-PSMA-617;

Fig. 4 to 6 show Gallium-68-PSMA11 PET/CT imaging of three patients before (Fig. 4A, 5A and 6A) and after (Fig. 4B, 5B and 6B) therapy as described herein below;

Fig. 7 illustrates the development of thrombocyte count during Ac-225-PSMA-617 therapy as described herein below;

Fig. 8 shows the development of leukocyte count during Ac-225-PSMA-617 therapy as described herein below.

Fig. 9 is a graph of experimental data showing the decrease in PSA (%) after first treatment and after third treatment with Lu-177-PSMA-617;

Fig. 10 shows the development of thrombocyte count during Lu-177-PSMA-617 comparative experiments as described herein below;

Fig. 11 illustrates the development of leukocyte count during Lu-177-PSMA-617 comparative experiments as described herein below;

Fig. 12 shows Ga-68-PSMA-11 PET/CT scans of a patient: pretherapeutic tumor spread (A), restaging 2 months after third cycle of Ac-225-PSMA-617(B), and restaging 2 months after one additional consolidation therapy (C);

Fig. 13 illustrates laboratory test follow-up of a patient; arrows indicate administration of treatment cycles; (A) blood cell count demonstrates moderate hematologic toxicity; (B) decline of tumor markers to none measurable or reference range correlates with imaging response;

Fig. 14 show 68-Ga-PSMA-11 PET/CT scans of another patient; in comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting Lu-177-PSMA-617 presented progression (B); in contrast, restaging after second (C) and third (D) cycles of α-emitting Ac-225-PSMA-617 presented impressive response; and

Fig. 15 illustrates laboratory test follow-up of a patient; arrows indicate administration of treatment cycles; blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

[0029] Further details and advantages of the present invention will be apparent from the following detailed description of the not limiting embodiments with reference to the attached drawings below.

Description of Preferred Embodiments

[0030] A1. Peptide, radionuclides and radiolabeling:

[0031] PSMA-617 was obtained from ABX, Germany.

Ac-225 (also noted ^{225}Ac) was produced by radiochemical extraction from Th-229 as described in Apostolidis C, Molinet R, Rasmussen G, Morgenstern A., Production of Ac-225 from Th-229 for targeted alpha therapy. Analytical Chemistry, 2005;77(19):6288-91 and Zielinska B, Apostolidis C, Bruchertseifer F, Morgenstern A., An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy, Solvent Extraction and Ion Exchange, 2007;25(3):339-49.

[0032] For radiolabeling an aliquot of Ac-225 stock solution (6-39 MBq Ac-225) in 0.1 M hydrochloric acid was added into a microwave vial containing 0.5 ml of 0.1 M Tris buffer (pH 9) and an appropriate amount of 10 mM PSMA-617 stock solution (35 - 160 nMol peptide). The reaction mixture was heated to 95° C for

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Exhibit 1004.572

5 min using a microwave synthesizer (Biotage® Initiator) and subsequently cooled to < 50 °C using pressurized air.

[0033] Quality control was performed by instant thin layer chromatography (ITLC-SG, Pall Life Sciences) with 0.05 M citric acid (pH 5) as solvent. Under these conditions, unbound Ac-225 moves with the solvent front (Rf = 1), while Ac-225-PSMA-617 remains on the bottom of the strip (Rf = 0). After development the ITLC strip was stored for at least 1 hour until radiochemical equilibrium between Ac-225 and its daughter nuclide Fr-221 ($T_{1/2}$ = 4.8 min) was obtained. Subsequently radiochemical purity was determined by measuring the activity of the 218 keV gamma emission of Fr-221 on the upper and lower part of the ITLC strip using high resolution gamma spectrometry (Ortec).

[0034] After synthesis 0.5 ml of 18% ascorbic acid solution (pH 5.8) was added to the reaction mixture to minimize radiolytic degradation of Ac-225-PSMA-617. The final pH of the formulation was 7.4. Before injection, sterility of the final formulation was assured via sterile filtration (Millex-GV, 0.20 µm, Millipore).

[0035] Gallium-68-PSMA11 PET/CT imaging was performed using a radiotracer labeled with Ga-68.

[0036] A2. Results

[0037] Radiochemical purity was 98.6 ± 1.4 % (*n=67*), specific activity was 0.23 ± 0.1 MBq per nmol of peptide.

[0038] A3. Patient treatment

[0039] 20 Patients were treated 3 times with activities of 100 kBq/kg body weight of Ac-225-PSMA-617 in two month intervals.

[0040] Treatment response was monitored by PSA values in blood and with PET/CT (positron emission tomography-computed tomography) with Ga-68-PSMA-HBED-CC (also called Gallium-68-PSMA11) before therapy and after the third therapy.

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[0041] Toxicity was monitored by blood sampling.

[0042] A4. Results

[0043] A4.1 Treatment efficacy

[0044] Eight weeks after the first treatment cycle 19/20 patients presented a decrease in PSA, in 17 patients the decrease was > 25 %, in 12 patients the decrease was even > 50 %.

[0045] The graph of Fig. 1 shows the decrease in PSA (%) after a first treatment with Ac-225-PSMA-617.

[0046] Sixteen weeks after the first treatment cycle 15/20 patients presented a decrease in PSA, in 14 patients the decrease was > 50 %.

[0047] As illustrated by the graph of Fig. 2 the decrease in PSA (%) after a second treatment with Ac-225-PSMA-617.

[0048] Twenty-four weeks after the first treatment cycle 15/20 patients presented with a decrease in PSA, in 12 patients the decrease was even > 50 %.

[0049] Fig. 3 shows the decrease in PSA (%) after third treatment with Ac-225-PSMA-617.

[0050] The exceptional results obtainable by the present invention are illustrated in Fig. 4 to 6. These figures show PET/CT images of three different patients before and after the treatment as described above. The PET/CT imaging combines both a positron emission tomography (PET) scanner and an x-ray computed tomography (CT) scanner, so that images acquired from both devices can be taken sequentially, in the same session, and combined into a single superposed image. As can be seen the betterment of the patients' condition is most remarkable.

[0051] A4.2 Toxicity

[0052] Hematologic response was evaluated every 4 weeks per lab tests and clinical side effects were monitored every 8 weeks. The treatment was well tolerated. There was no significant change in thrombocyte or white blood cell count (Fig. 7 and 8). Several patients reported dysfunction of salivary glands.

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Exhibit 1004.574

[0053] Fig. 7 shows the development of thrombocyte count during Ac-225-PSMA-617 therapy, whereas Fig. 8 displays the development of leukocyte count during Ac-225-PSMA-617 therapy.

[0054] A5. Conclusions of the above experiments

[0055] The inventors found that treatment response with said Ac-225-radiopharmaceutical(s) is very good and hematologic toxicity is moderate to low at dosages of about 100 kBq/kg body weight (i.e. about 7 MBq for a patient of 70 kg). The treatment may be done using a unitary dosage or constant activities, e.g. about 6 MBq per treatment. Furthermore, the patients may be treated in eight week or two month intervals for practical reasons. Shorter intervals (e.g. four weeks or one month) with correspondingly lower dosing are also possible.

[0056] A6. Comparative Examples

[0057] Experiments have been conducted to compare the efficiency of the Ac-225-radiopharmaceuticals as used in the present invention, such as Ac-225-PSMA-617, with that of non-Ac-225-radiopharmaceuticals comprising the same targeting compound, but chelated e.g. with Lu-177, such as a radionuclide Lu-177-PSMA-617.

[0058] A6.1 Treatment efficacy

[0059] Eight weeks after the first treatment cycle 21/30 patients presented a decrease in PSA, In 16 patients the decrease was > 50 %.

[0060] Twenty-four weeks after the first treatment cycle some patients were dropped out from the therapy because some physical conditions were considered a contraindication for treatment with β-emitters. 9/30 patients presented a decreased in PSA. For all of them the decrease was > 50 %.

[0061] The graph of Fig. 9 shows the decrease in PSA (%) after a first and a third treatment with Lu-177-PSMA-617.

[0062] A6.2 Toxicity

[0063] The treatment was well tolerated. There was no significant change in thrombocyte or white blood cells count (Fig. 10 and 11). Mild moderate dysfunction of salivary glands was reported.

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Exhibit 1004.575

[0064] Fig. 10 shows the development of thrombocyte count during Lu-117-PSMA-617 therapy, whereas Fig. 11 displays the development of leukocyte count during Lu-117-PSMA-617 therapy.

[0065] A6.3 Conclusions of the above comparative experiments

The group treated with Lu-117-PSMA-617 had a lower response rate in comparison to the one treated with Ac-225-PSMA-617. Indeed, the treatment analysis revealed that 15/28 patients (54%) treated with Ac-225-PSMA-617 were in PSA response but only 9/30 patients (30%) treated with Lu-177-PSMA-617 were in PSA response at week-24. This is a remarkable difference taking into account similar hematological toxicity and the more advanced patients selected for Ac-225-radiopharmaceutical therapy.

[0066] B1. Treatment of metastatic castration-resistant prostate cancer (mCRPC) with Ac-225-radiopharmaceutical:

[0067] FIG. 12: Ga-68-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 months after third cycle of Ac-225-PSMA-617(B), and restaging 2 months after one additional consolidation therapy (C).

[0068] Clinical Course of Patient A presented with diffuse red marrow infiltration of mCRPC (this physical condition was considered a contraindication for treatment with β-emitters).Patient A was treated with 3 cycles of 9–10 MBq (100 kBq per kilogram of body weight) of Ac-225-PSMA-617 at bimonthly intervals. Post-therapeutic emission scans validated sufficient tumor targeting Two months later, all previously PSMA-positive lesions had visually disappeared on PSMA PET/CT (Fig. 12B) and, accordingly, the PSA level had dropped from more than 3,000 ng/ml to 0.26 ng/ml. The patient received an additional 6 MBq of Ac-225-PSMA-617 as consolidation therapy, resulting in a further PSA decline to less than 0.1 ng/ml along with a complete imaging response (Fig. 1C).

[0069] FIG. 13: Laboratory test follow-up of patient A. Arrows indicate administration of treatment cycles. (A) Blood cell count demonstrates moderate hematologic toxicity. (B) Decline of tumor markers to none measurable or reference range correlates with imaging response. AP = alkalinephosphatase; Hb= 5 hemoglobin; PLT = platelets; WBC = white blood cells.

[0070] After each cycle, the blood cell count and alkaline phosphatase level were checked every 2 week. The platelet level never dropped below 100/nl (grade 1 according to the Common Terminology Criteria for Adverse Events, version 4.0), the total white blood cell count never dropped below 2.5/nl (grade 1), and the hemoglobin level never dropped below 9.5 g/dl (grade 2) (Fig. 13A). Moderate but enduring dysfunction of salivary glands was the only clinically reported side effect. A concordant decline in PSA level and alkaline phosphatase level (Fig. 13B) further underlined the excellent treatment response.

[0071] B2 Treatment with Lu-177 then Ac-225:

[0072] FIG. 14: 68-Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting Lu-177-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting Ac-225-PSMA-617 presented impressive response.

[0073] Clinical Course of Patient B presented with peritoneal carcinomatosis and liver metastases.

[0074] Patient B was initially treated with Lu-177-PSMA-617 (7.4 GBq per cycle), which was offered as salvage therapy. The initial PSA level was 294 ng/ml. After cycle 2 the PSA level increased to 419 ng/ml and most lesions demonstrated tumor progression on PSMA PET/CT (Fig. 14B). Therapy was changed to Ac-225-PSMA-617, and the patient received 3 cycles of 6.4 MBq (100 kBq per kilogram of body weight) at bimonthly intervals. Restaging based on the PSMA PET/CT results finally indicated a partial response after 2 cycles (Fig. 14C) and a complete remission after 3 cycles (Fig. 14D). Laboratory tests revealed no relevant hematologic toxicity; PSA dropped to below the measurable level (0.1 ng/ml) (Fig. 15). However, the patient reported severe dysfunction of salivary glands.

[0075] FIG. 15: Laboratory test follow-up of patient B. Arrows indicate administration of treatment cycles. Blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

[0076] B3. Conclusion:

[0077] The early results already indicate that Ac-225-targeted α-therapy has high potential for the epidemiologically important tumor entity prostate cancer,

which presumably will further accelerate the routine availability of Ac-225 for systematic clinical trials, for example.

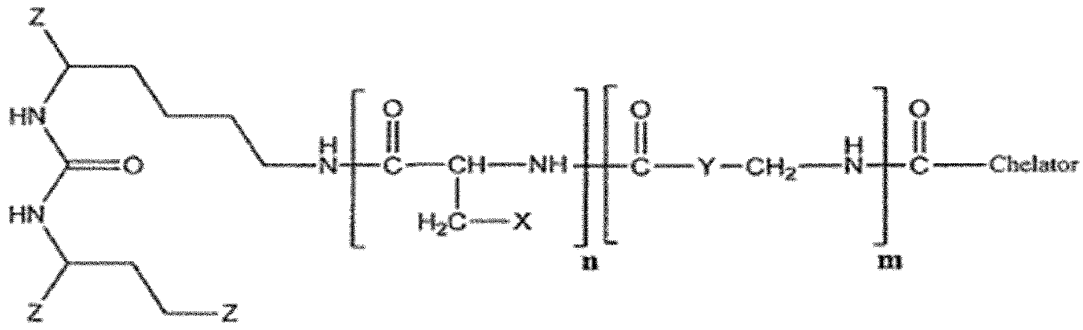
[0078] The two impressive responses reported here demonstrate the high potential of Ac-225-radiopharmaceuticals, such as Ac-225-PSMA-617 to significantly benefit mCRPC patients who are in a clinically critical situation, that is, patients with diffuse red marrow infiltration and resistance to other therapies. Investigation of this therapeutic modality in larger patient cohorts is warranted.

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Exhibit 1004.578

Claims

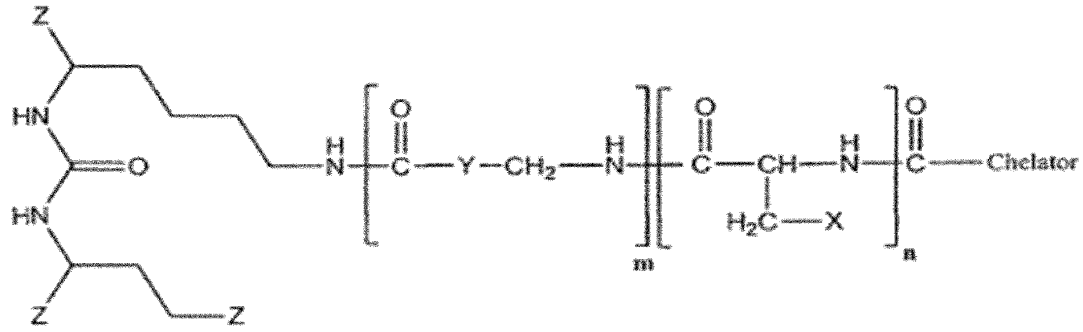
1. One or more Ac-225-radiopharmaceuticals selected among comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

Formula (A)



or

Formula (B)



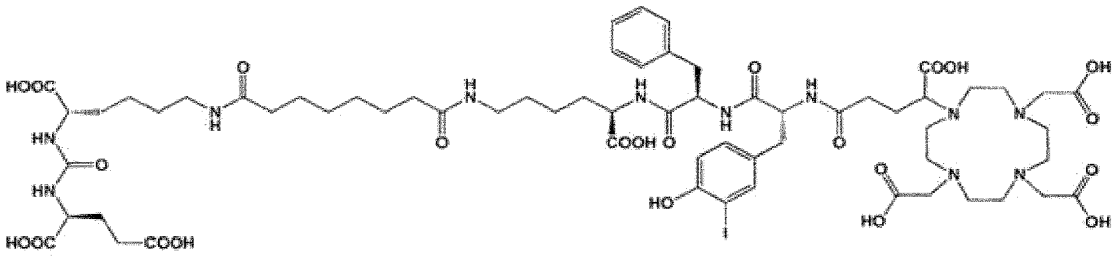
with:

n:	0,1
m:	1,2,3,4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N"-diacetic acid (HBED-CC),

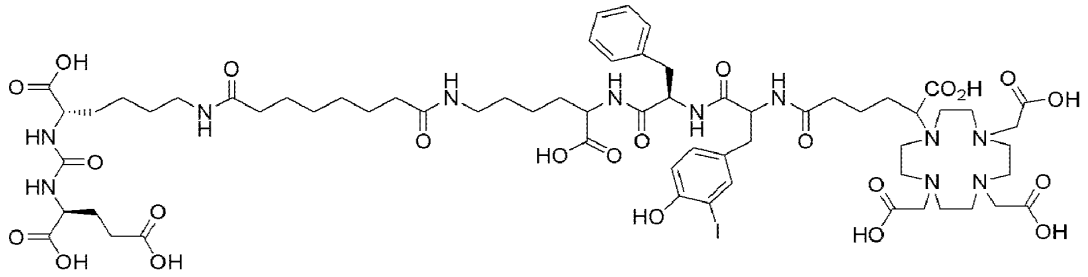
1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA),
2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA),
2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA),
1,4,7-triazacyclononane phosphinic acid (TRAP),
1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),
3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),
N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),
diethylenetriaminepentaacetic acid (DTPA),
trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A)
p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA)

or

Formula (C)



Formula (D)



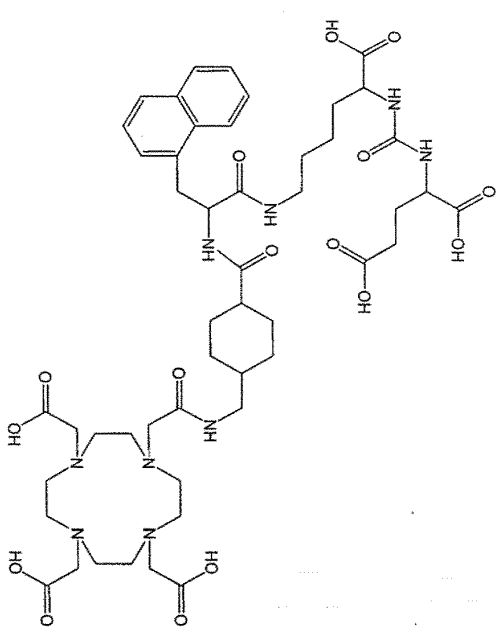
or

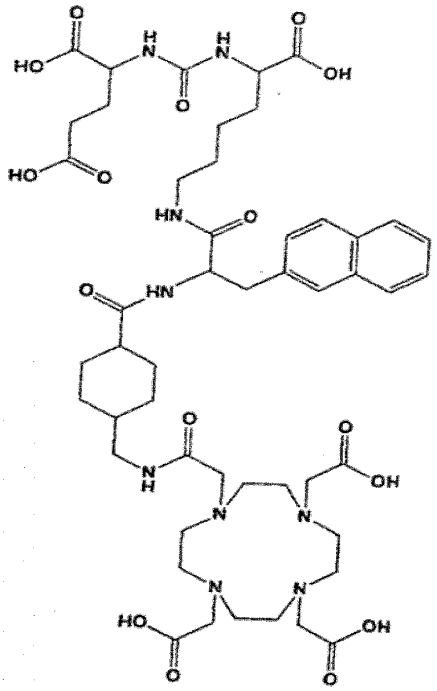
Formula (E)

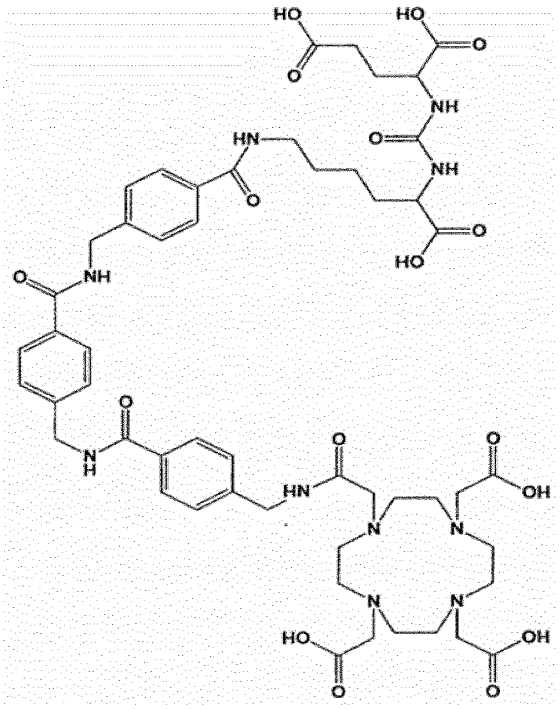
(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

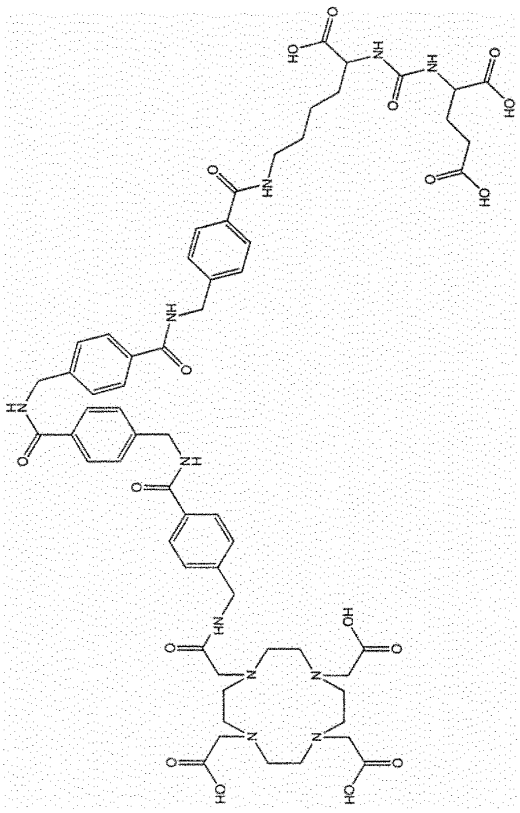
for use in treating PSMA expressing cancers or cancer cells in a patient, comprising administering to said patient an effective amount of said Ac-225-radiopharmaceutical(s) as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

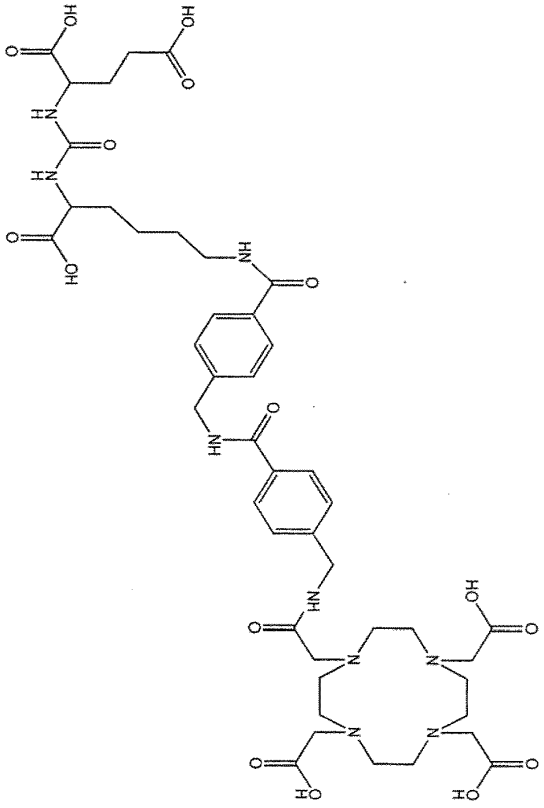
2. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 1, being selected from:

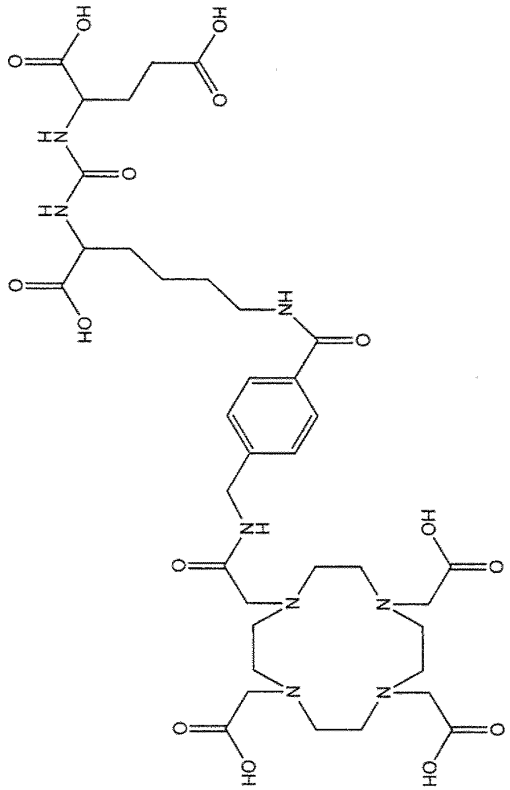


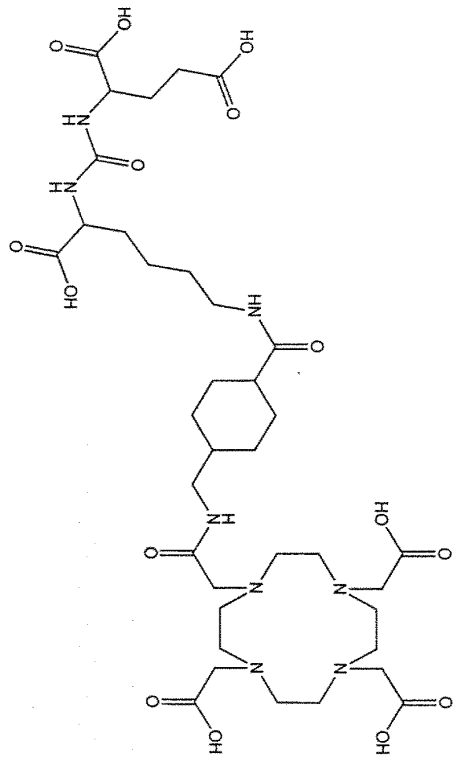


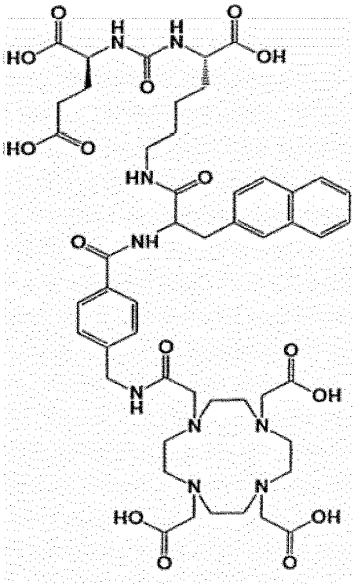


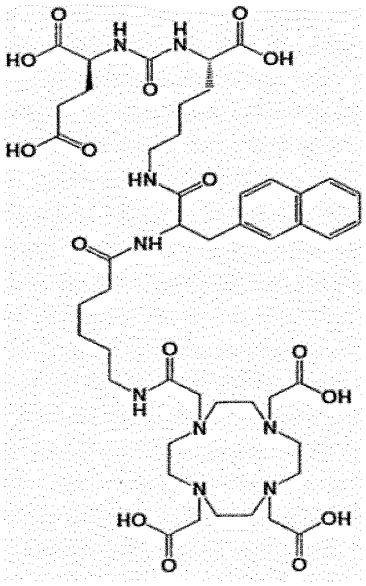


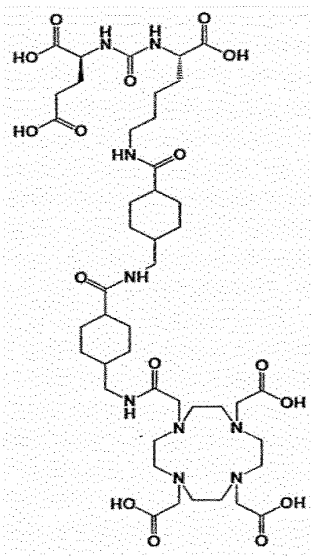


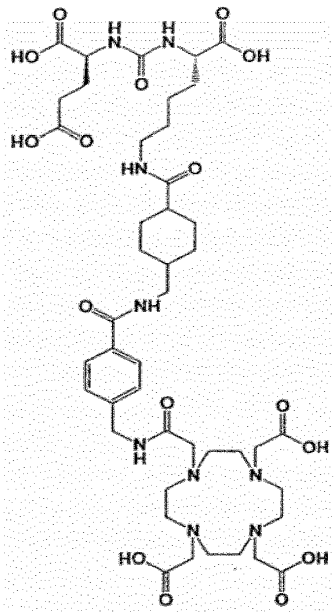


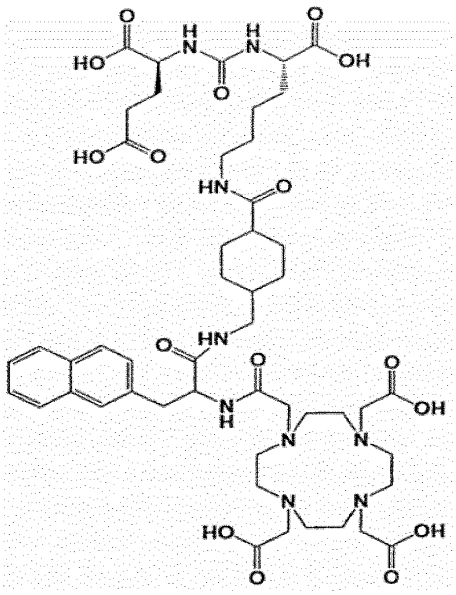


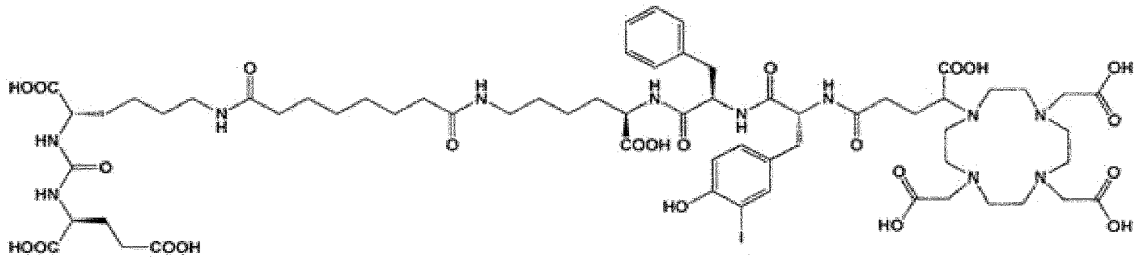


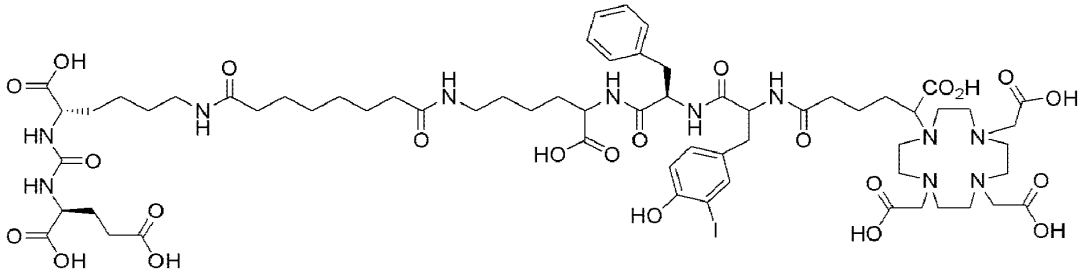












3. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 1 or 2, wherein one or a sole Ac-225-radiopharmaceutical is Ac-225-PSMA-617.

4. The one or more Ac-225-radiopharmaceuticals for use as claimed in any of claims 1 to 3, wherein said PSMA expressing cancers are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers.

5. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 4, wherein the cancer is a disseminated cancer.

6. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 4, wherein said PSMA expressing cancer is prostate cancer.

7. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 4, wherein said PSMA expressing cancer is breast cancer.

8. The one or more Ac-225-radiopharmaceuticals for use as claimed in any of claims 1 to 7, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

9. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 8, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

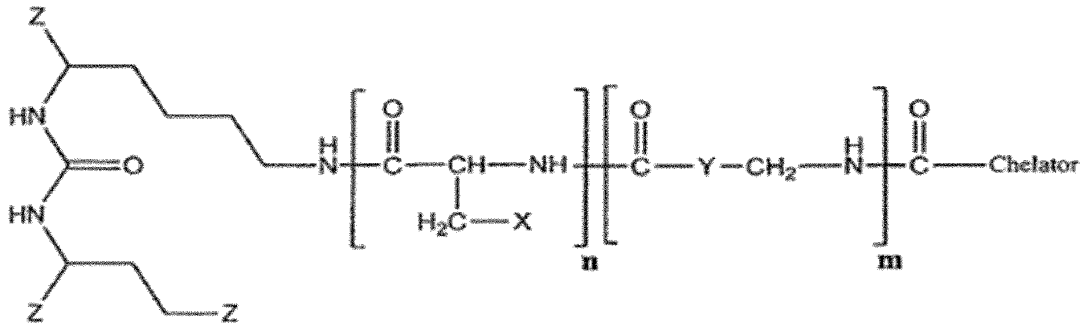
10. The one or more Ac-225-radiopharmaceuticals for use as claimed in any of claims 1 to 9, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

11. The one or more Ac-225-radiopharmaceuticals for use as claimed in claim 10, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

12. The one or more Ac-225-radiopharmaceuticals for use as claimed in any of claims 1 to 11, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

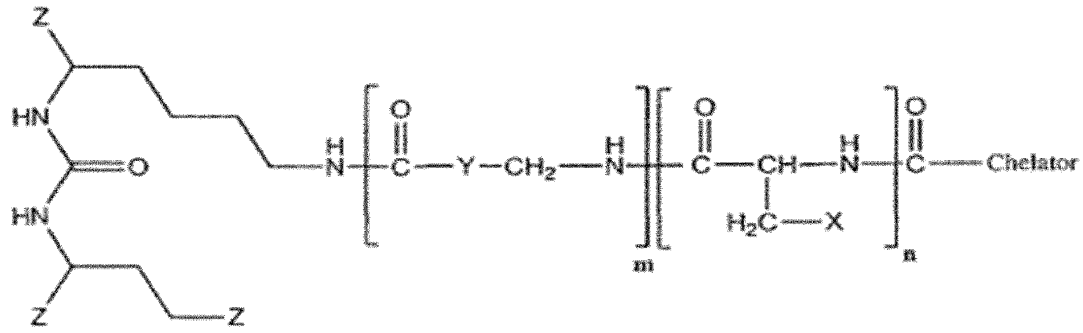
13. A method for treating PSMA expressing cancers, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

Formula (A)



or

Formula (B)



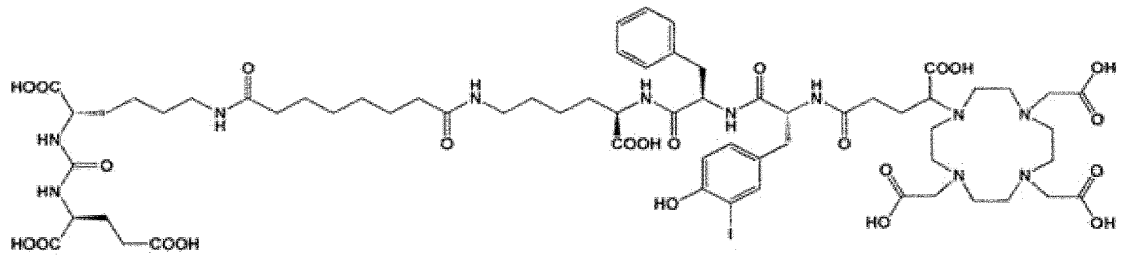
with:

n:	0,1
m:	1,2,3,4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N"-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA),

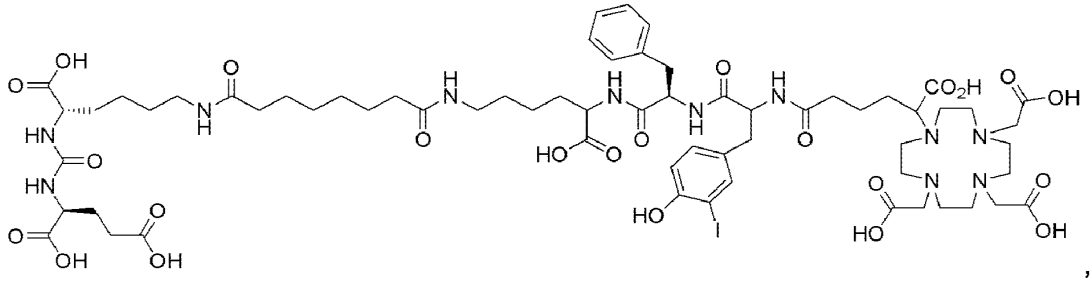
2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA),
1,4,7-triazacyclononane phosphinic acid (TRAP),
1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO),
3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA),
N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),
diethylenetriaminepentaacetic acid (DTPA),
Trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A)
p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA)

or

Formula (C)



Formula (D)



,

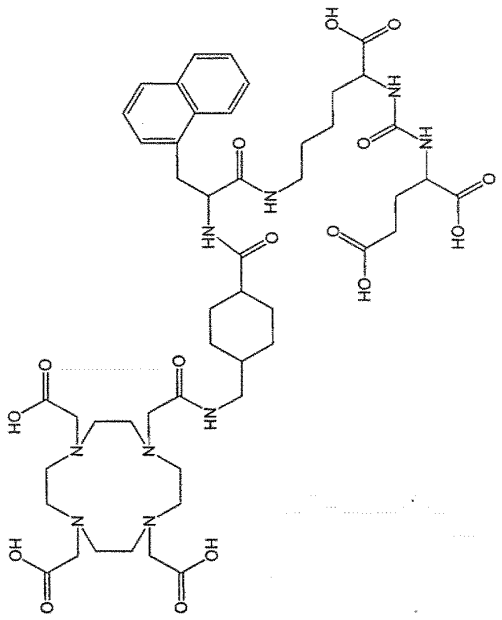
or

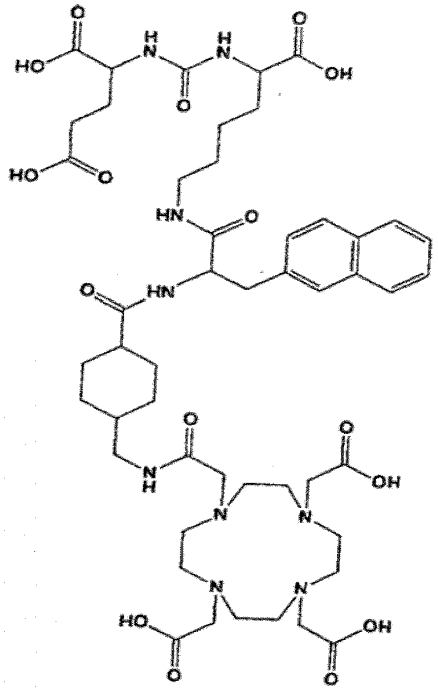
Formula (E)

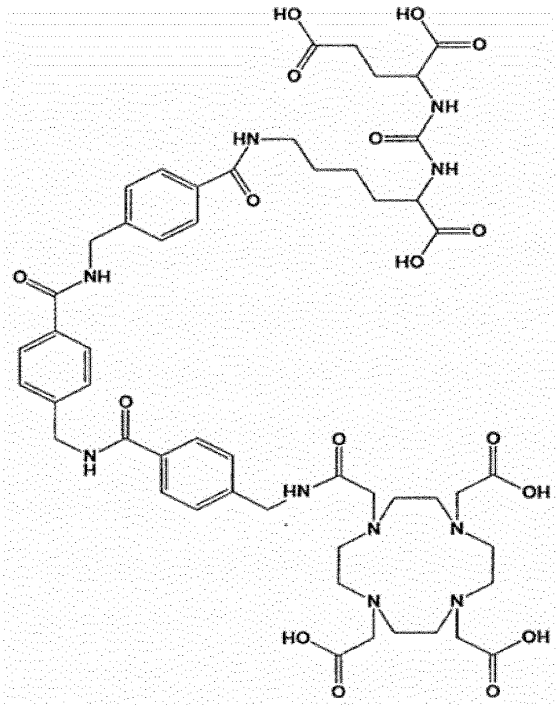
(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

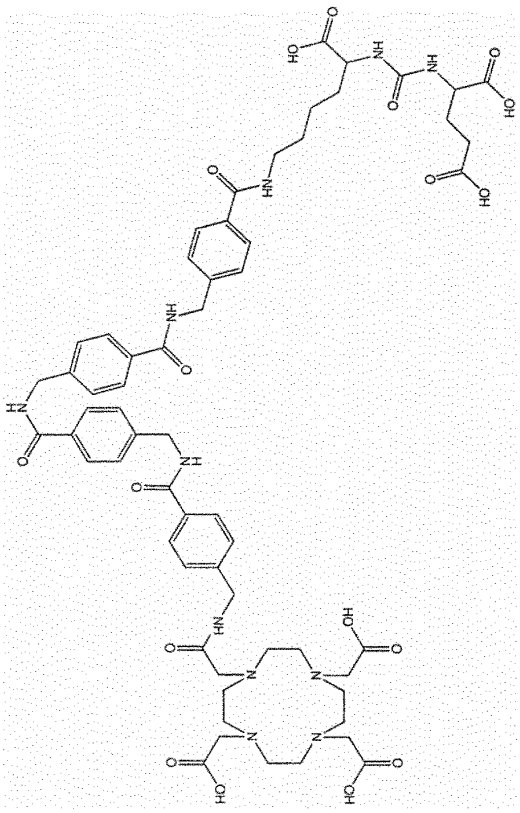
wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

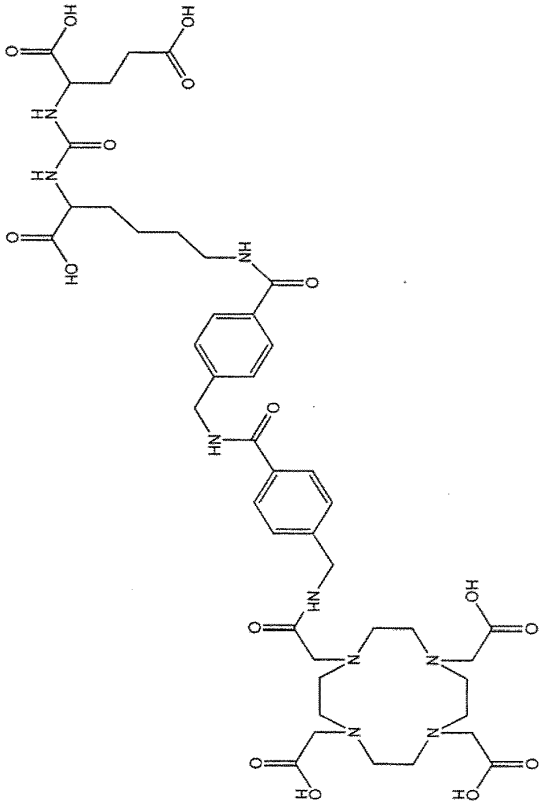
14. The method as claimed in claim 13, wherein the one or more Ac-225-radiopharmaceuticals are selected from:

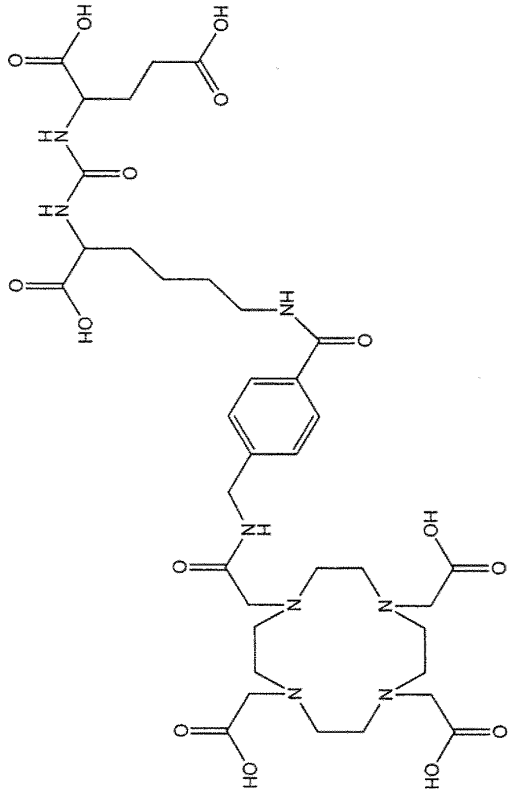


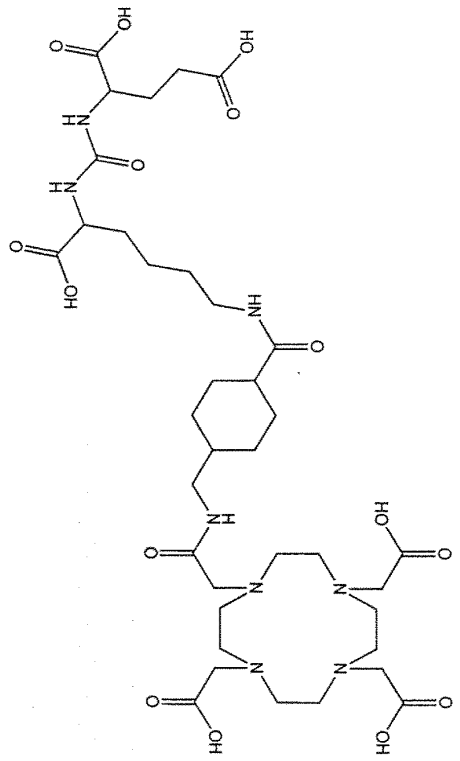


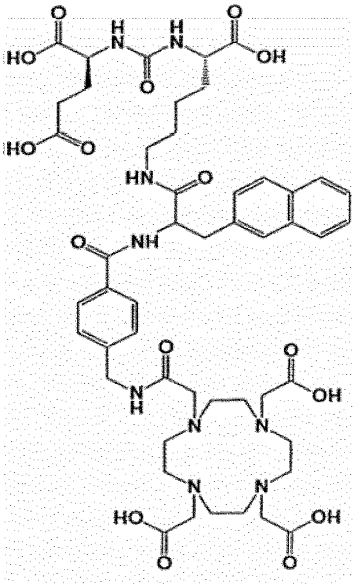


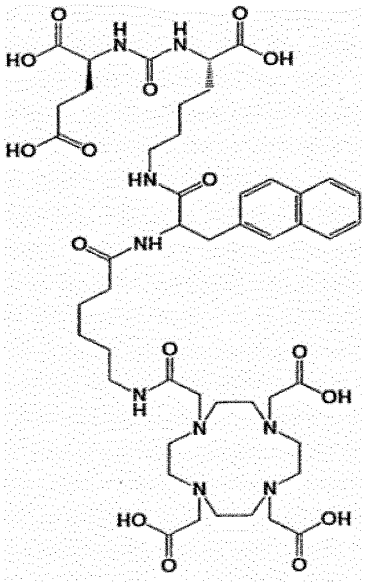


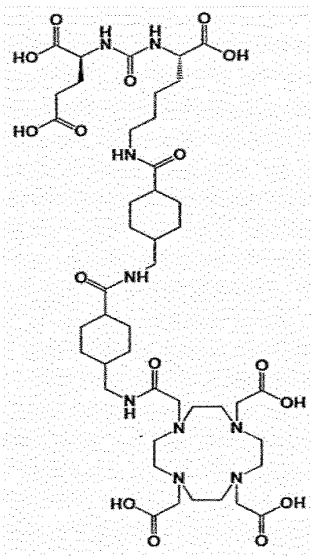


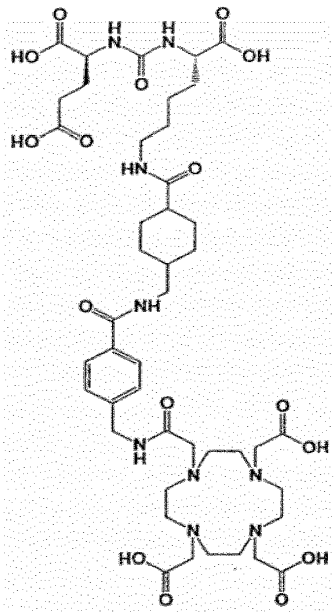


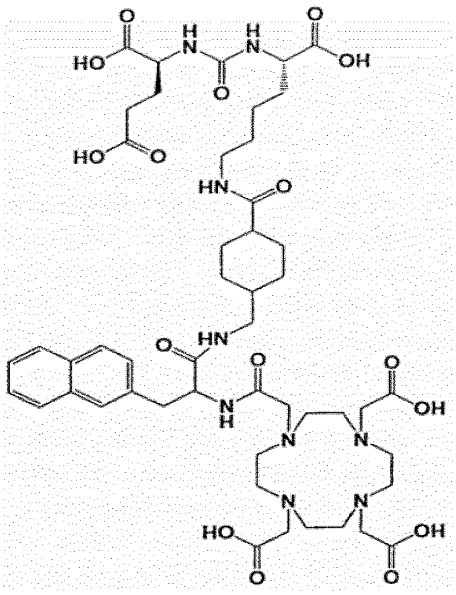


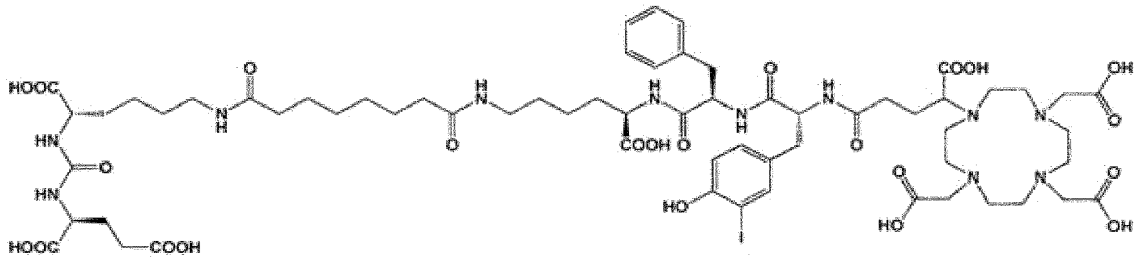


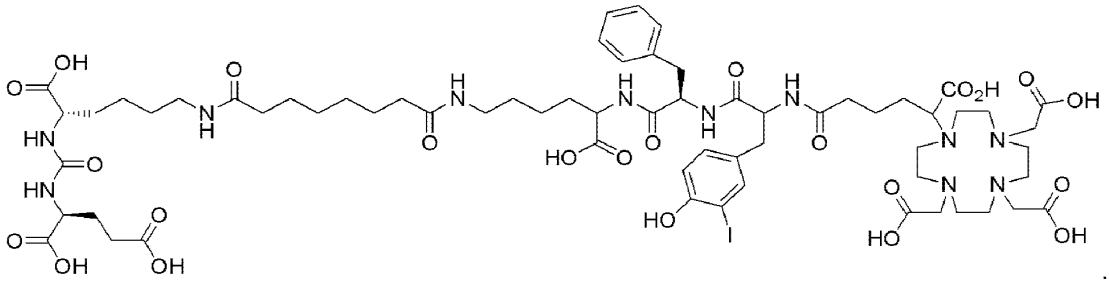












15. The method as claimed in claim 13 or 14, wherein one or a sole Ac-225-radiopharmaceutical is Ac-225-PSMA-617.

16. The method as claimed in claim 13 or 15, wherein said PSMA expressing cancers are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers.

17. The method as claimed in claim 13, wherein the cancer is a disseminated cancer.

18. The method as claimed in claim 16, wherein said PSMA expressing cancer is prostate cancer.

19. The method as claimed in claim 16, wherein said PSMA expressing cancer is breast cancer.

20. The method as claimed in claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

21. The method as claimed in claim 20, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

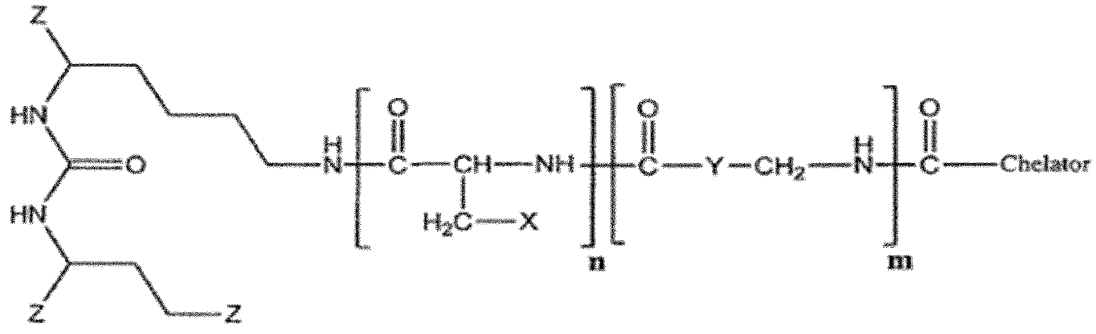
22. The method as claimed in claim 13, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

23. The method as claimed in claim 22, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

24. The method as claimed in claim 8 or claim 22, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

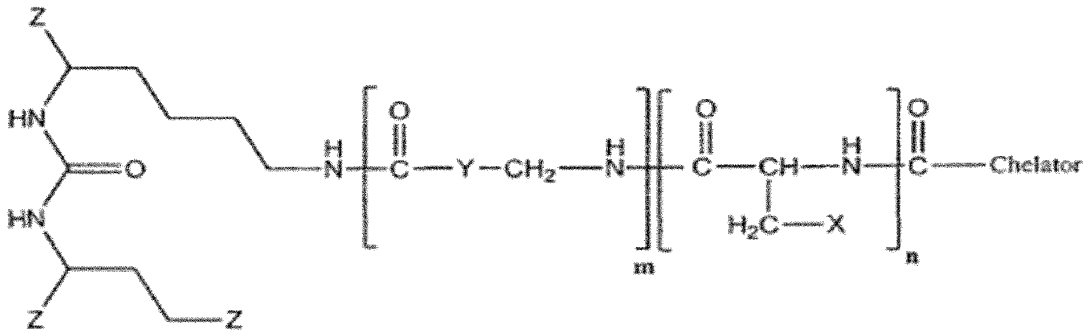
25. Use of one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

Formula (A)



or

Formula (B)



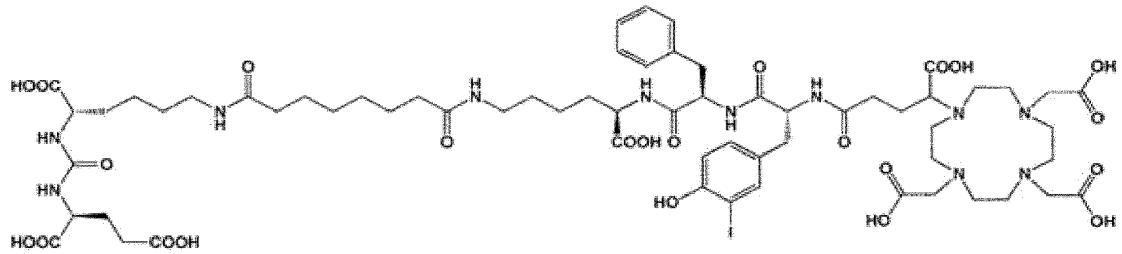
with:

n:	0,1
m:	1,2,3,4
Z:	$-CO_2H$, $-SO_2H$, $-SO_3H$, $-SO_4H$, $-PO_2H$, $-PO_3H$, $-PO_4H_2$
X:	naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
Y:	aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
Chelator:	1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), N,N"-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N"-diacetic acid (HBED-CC), 1,4,7-triazacyclononane-1,4,7-triacetic acid (= NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl)pentanedioic acid (NODAGA), 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA), 1,4,7-triazacyclononane phosphinic acid (TRAP), 1,4,7-triazacyclononane-1 -[methyl(2-carboxyethyl)phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl)phosphinic acid] (NOPO), 3,6,9,15-tetraazabicyclo[9.3.1.]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA), N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxobutanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO),

diethylenetriaminepentaacetic acid (DTPA),
Trans-cyclohexyl-diethylenetriaminepentaacetic acid (CHX-DTPA),
1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A) p-isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA),
1-(p-isothiocyanatobenzyl)-3-methyl-DTPA (1B3M),
2-(p-isothiocyanatobenzyl)-4-methyl-DTPA (1M3B), or
1-(2)-methyl-4-isocyanatobenzyl-DTPA (MX-DTPA)

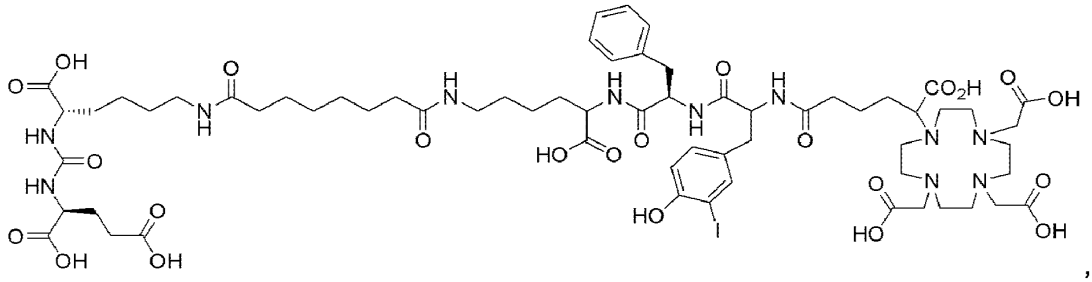
or

Formula (C)



;

Formula (D)



,

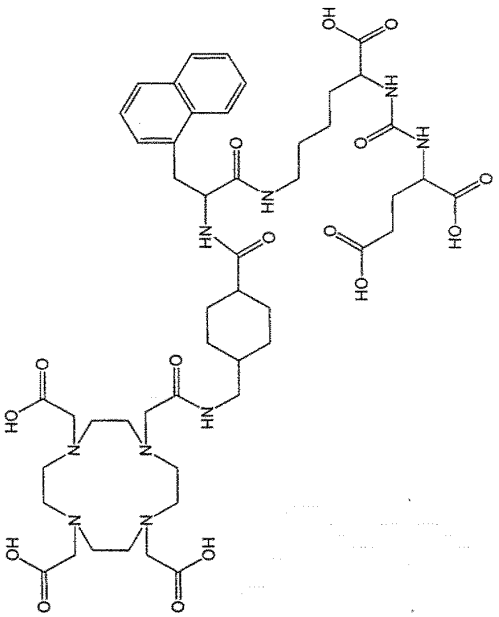
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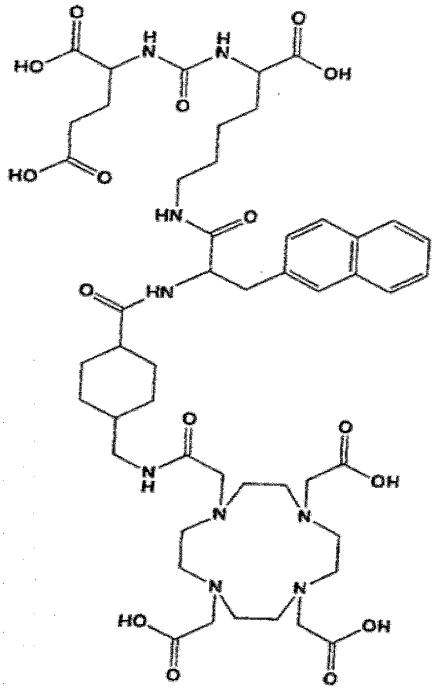
Formula (E)

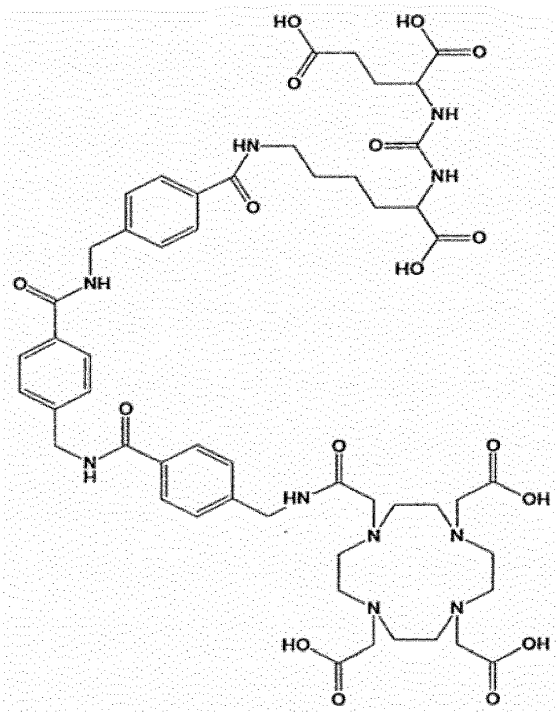
(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

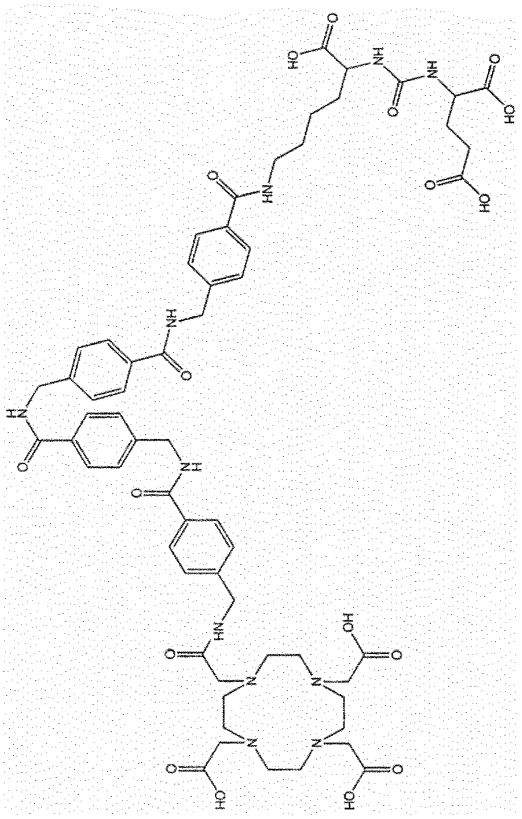
for treating PSMA expressing cancers or cancer cells in a patient, wherein the use comprises administering to said patient an effective amount of said one or more Ac-225-radiopharmaceuticals as a dosage of from about 25 kBq/kg to about 400 kBq/kg of body weight of said patient or as a unitary dosage or constant activities of from about 3 MBq to about 30 MBq to said patient.

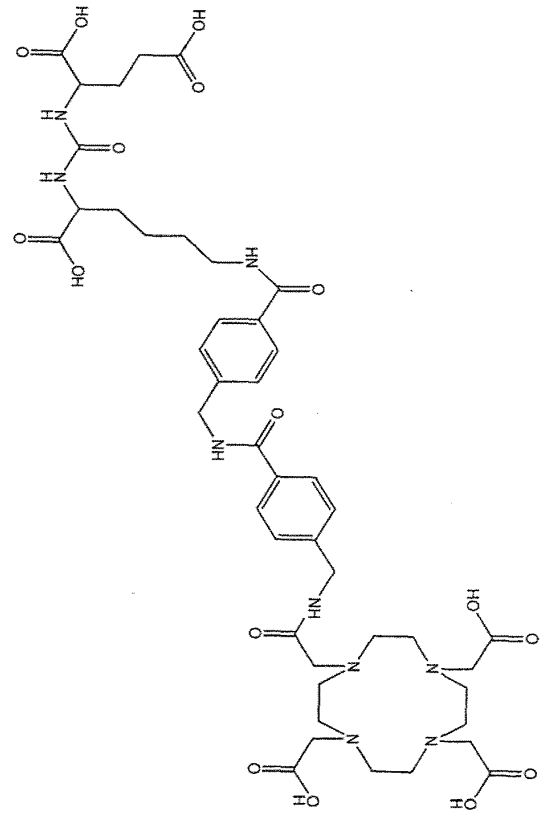
26. The use as claimed in claim 25, wherein the one or more Ac-225-radiopharmaceuticals are selected from:

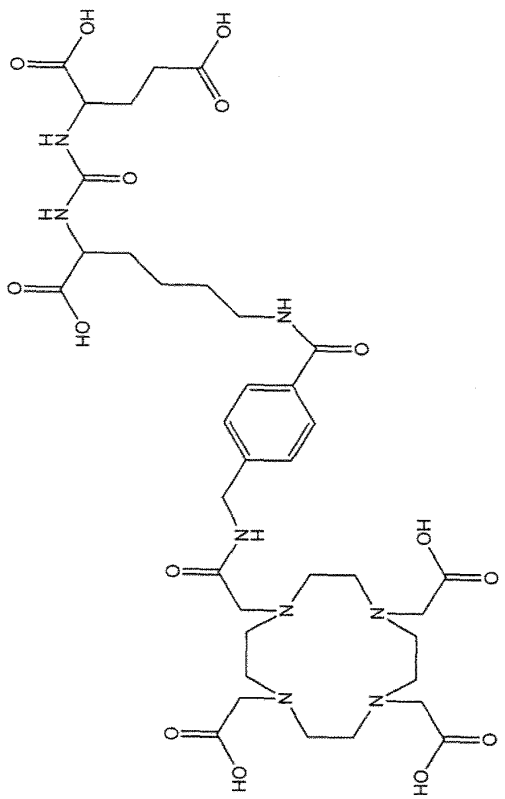


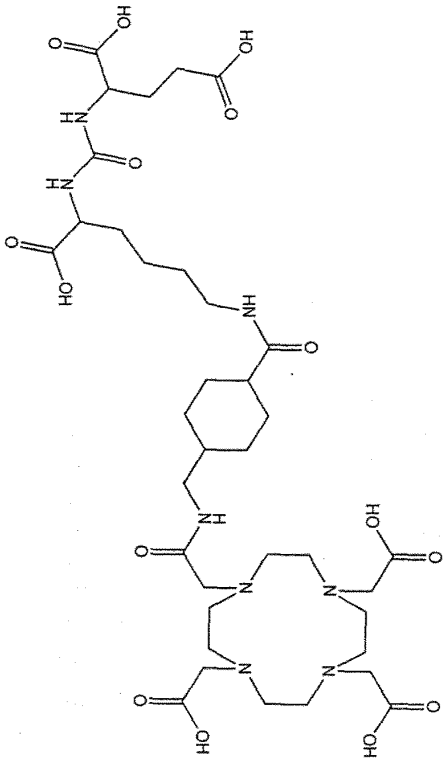


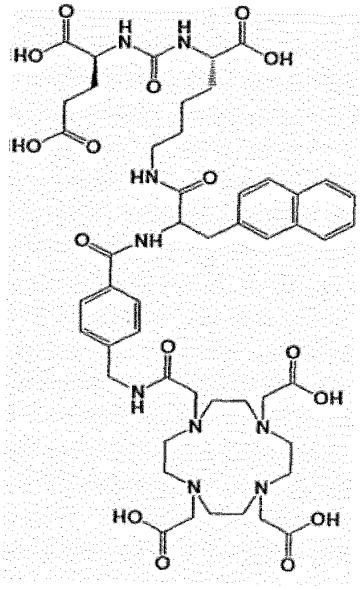


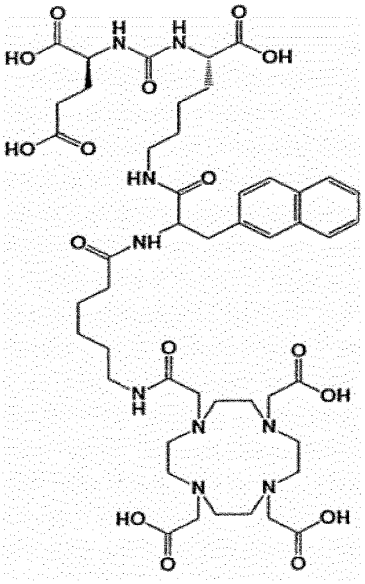


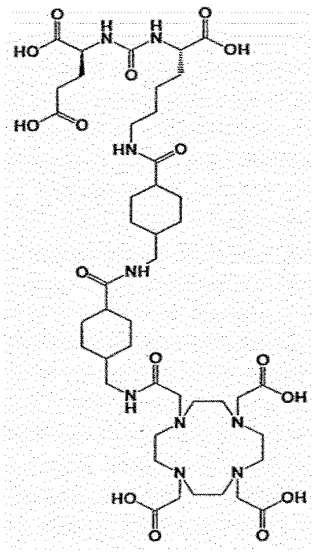


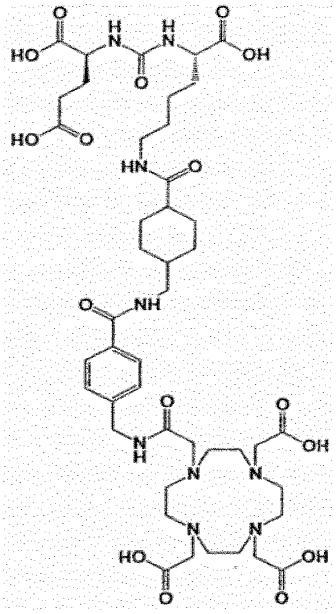


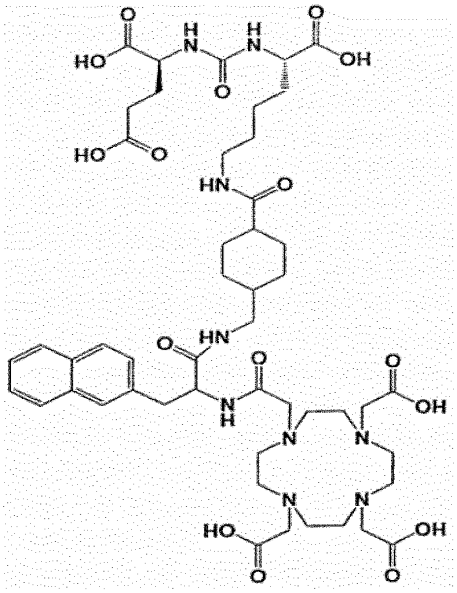


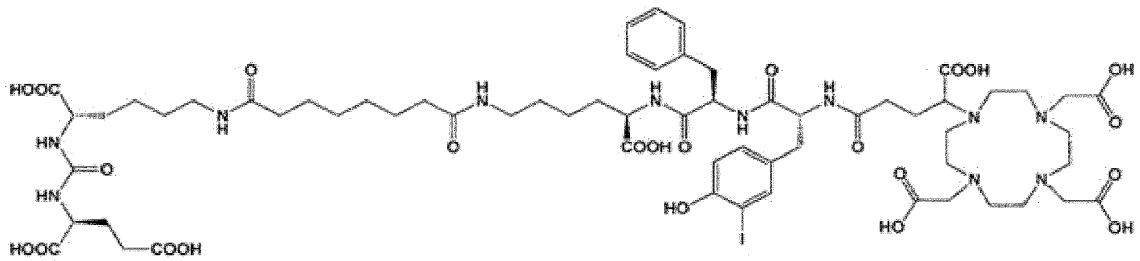


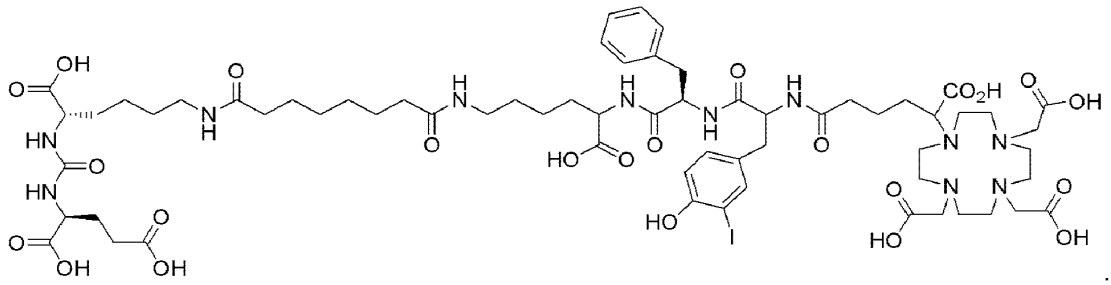












27. The use as claimed in claim 25 or 26, wherein one or a sole Ac-225-radiopharmaceutical is Ac-225-PSMA-617.

28. The use as claimed in claim 25, wherein said PSMA expressing cancers are selected among conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers and breast cancers.

29. The use as claimed in claim 25, wherein the cancer is a disseminated cancer.

30. The use as claimed in claim 28, wherein said PSMA expressing cancer is prostate cancer.

31. The use as claimed in claim 28, wherein said PSMA expressing cancer is breast cancer.

32. The use as claimed in claim 25, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

33. The use as claimed in claim 32, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

34. The use as claimed in claim 25, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

35. The use as claimed in claim 34, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

36. The use as claimed in claim 32 or claim 34, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

PCT REQUEST

Print Out (Original in Electronic Form)

0	**For receiving Office use only**	
0-1	International Application No.	**PCT/EP2016/081313**
0-2	International Filing Date	**15 DEC 2016 (15.12.2016)**
0-3	Name of receiving Office and "PCT International Application"	**RO/EP**

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT Online Filing Version 3.5.000.251e MT/FOP 20141031/0.20.5.20
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	European Patent Office (EPO) (RO/EP)
0-7	**Applicant's or agent's file reference**	P-2963-WO
I	**Title of Invention**	TREATMENT OF PMSA EXPRESSING CANCERS
II	**Applicant**	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States
II-4	Name	THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION
II-5	Address	200, rue de la Loi, 1049 Brussels Belgium
II-6	State of nationality	BE* *RO/EP
II-7	State of residence	BE
III-1	**Applicant and/or inventor**	
III-1-1	This person is	Applicant only
III-1-2	Applicant for	All designated States
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III-1-5	Address	Grabengasse 1 69117 Heidelberg Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

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III-2	**Applicant and/or inventor**	
III-2-1	This person is	Inventor only
III-2-3	Inventor for	All designated States
III-2-4	Name (LAST, First)	MORGENSTERN, Alfred
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III-6	**Applicant and/or inventor**	
III-6-1	This person is	Inventor only
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III-7	**Applicant and/or inventor**	
III-7-1	This person is	Inventor only
III-7-3	Inventor for	All designated States
III-7-4	Name (LAST, First)	KRATOCHWIL, Clemens
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.600

PCT REQUEST

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IV-1	**Agent or common representative; or address for correspondence**		
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent	
IV-1-1	Name (LAST, First)	KIHN, Henri	
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IV-1-4	Facsimile No.	+352-31 38 33	
IV-1-5	e-mail	office@freylinger.com	
IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent	
IV-2-1	Name(s)	BEISSEL, Jean; KIHN, Pierre; LAMBERT, Romain; OCVIRK, Philippe	
V	**DESIGNATIONS**		
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**		
VI-1	**Priority Claim**	NONE	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

PCT REQUEST

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IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	4	✓
IX-2	Description	19	✓
IX-3	Claims	20	✓
IX-4	Abstract	1	✓
IX-5	Drawings	8	✓
IX-7	TOTAL	52	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	–	✓
IX-20	**Figure of the drawings which should accompany the abstract**	4	
IX-21	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**	(PKCS7 Digital Signature)	
X-1-1	Name (LAST, First)	KIHN, Henri	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	(Representative)	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	**15 DEC 2016 (15.12.2016)**
10-2	**Drawings:**	X
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

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11-1	**Date of receipt of the record copy by the International Bureau**	

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

GEVERS PATENTS
Intellectual Property House
Holidaystraat 5
1831 Diegem
BELGIQUE

Date of mailing *(day/month/year)*
10 August 2017 (10.08.2017)

Applicant's or agent's file reference
PAT2526911PC00

IMPORTANT NOTIFICATION

International application No.
PCT/EP2016/081313

International filing date *(day/month/year)*
15 December 2016 (15.12.2016)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

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Intellectual Property House
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Belgium

State of Nationality

State of Residence

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+32 3 206 99 92

Facsimile No.
+32 3 206 99 51

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
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4. A copy of this notification has been sent to:

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☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
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Fusion Pharmaceuticals, Inc.
Exhibit 1004.603

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WIPO | PCT

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(71) Applicants: **THE EUROPEAN ATOMIC ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN COMMISSION** [BE/BE]; 200, rue de la Loi, 1049 Brussels (BE). **UNIVERSITÄT HEIDELBERG** [DE/DE]; Grabengasse 1, 69117 Heidelberg (DE).

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(74) Agent: **GEVERS PATENTS** et al.; Intellectual Property House, Holidaystraat 5, 1831 Diegem (BE).

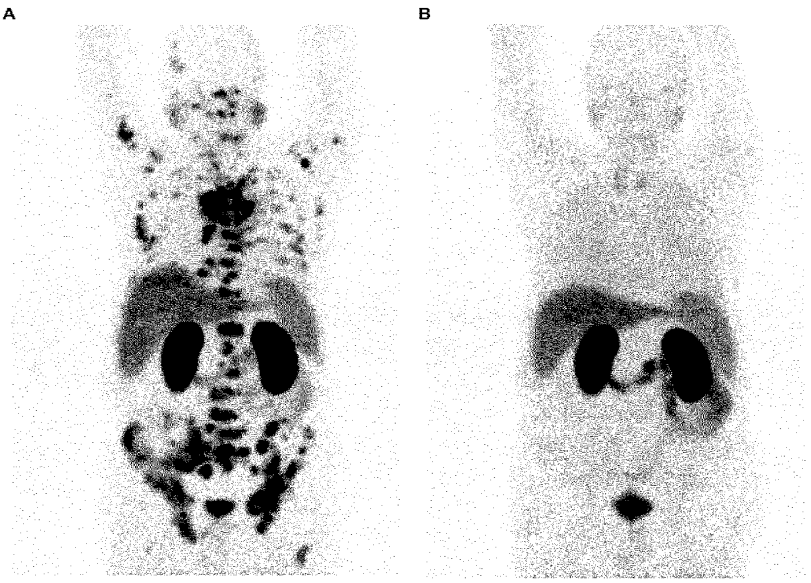
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

WO 2018/108287 A1

(54) Title: TREATMENT OF PMSA EXPRESSING CANCERS

Fig. 4



(57) Abstract: The invention relates to a method for treating PSMA expressing cancers, wherein the method comprises administering to patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25kBq to 400kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3MBq to 30MBq to said patient.

[Continued on next page]

Fusion Pharmaceuticals, Inc.
Exhibit 1004.604

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, KM, ML, MR, NE, SN, TD, TG).

Published:

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

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Exhibit 1004.605

Fig. 1

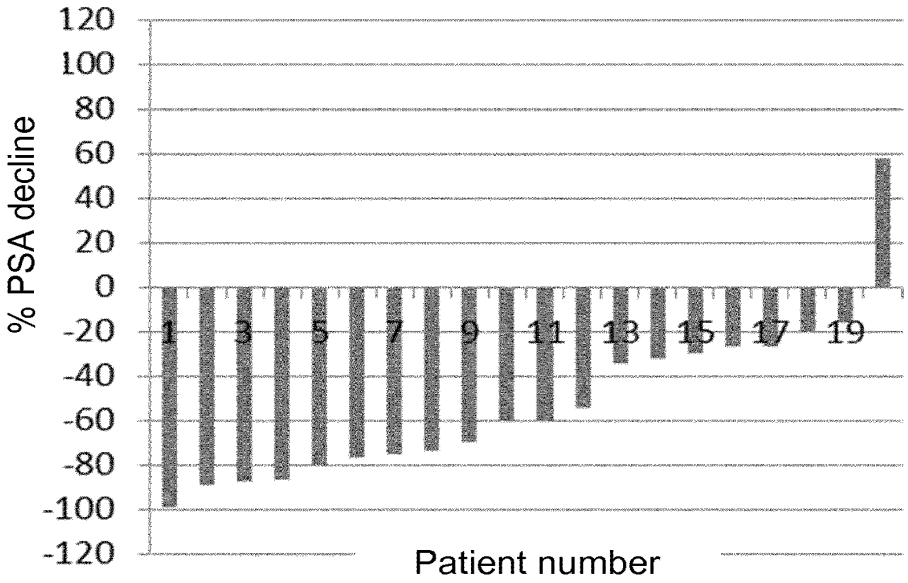

120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
% PSA decline
1
3
5
7
9
11
13
15
17
19
Patient number

Fig. 2

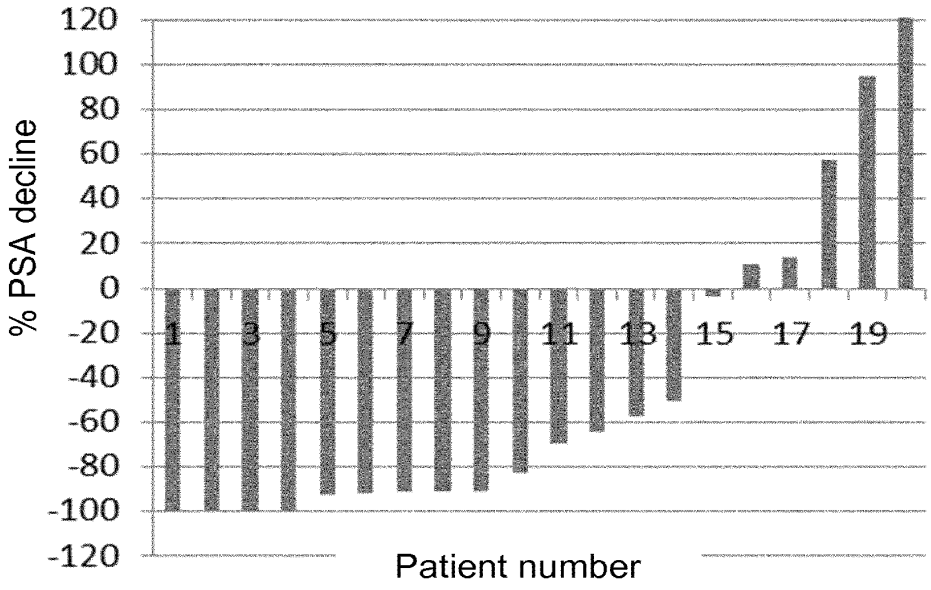

120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
% PSA decline
1
3
5
7
9
11
13
15
17
19
Patient number

Fig. 3

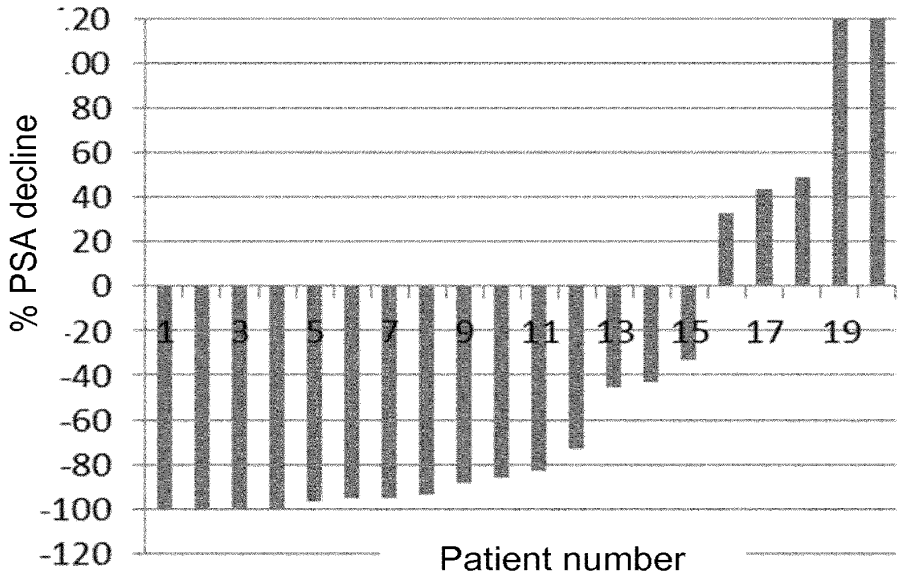

% PSA decline
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
1
3
5
7
9
11
13
15
17
19
Patient number

Fig. 4

A



B

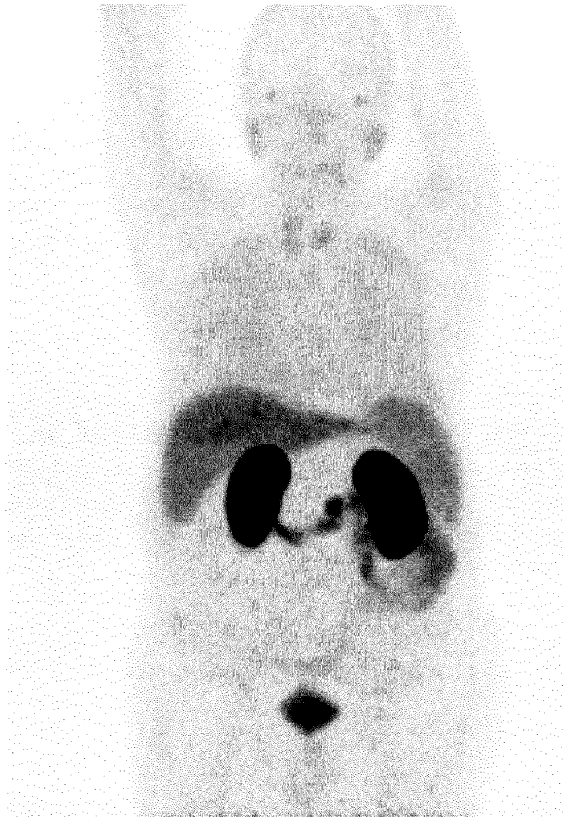


Fig. 5

A



B



Fig. 6

A



B



Fig. 7

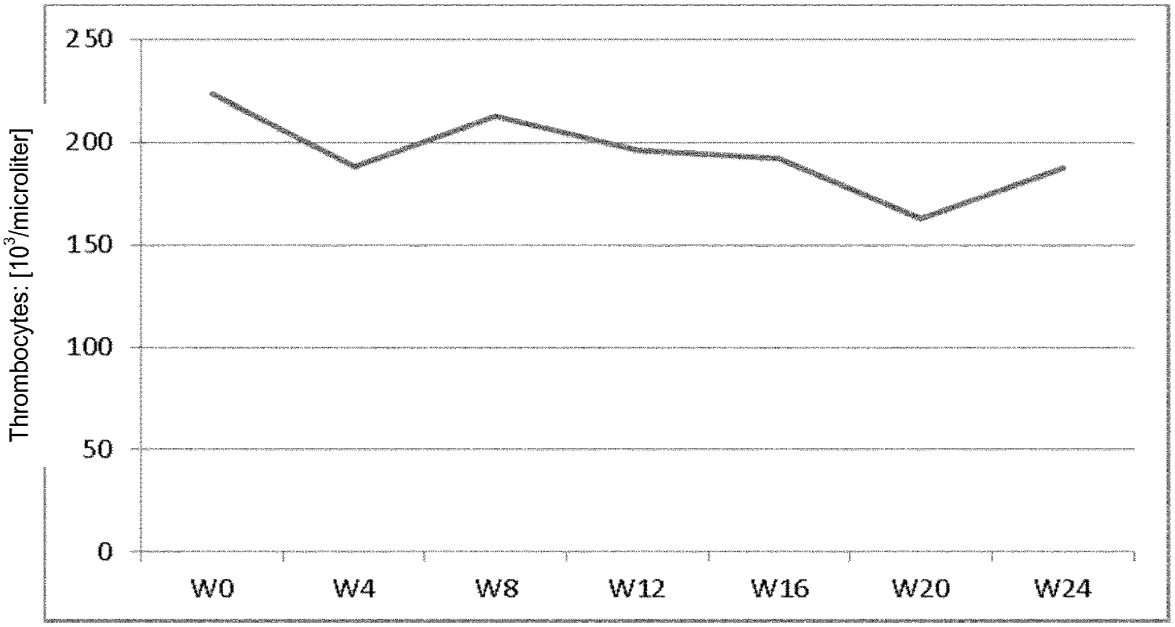

Thrombocytes: [10³/microliter]
250
200
150
100
50
0
W0
W4
W8
W12
W16
W20
W24

Fig. 8

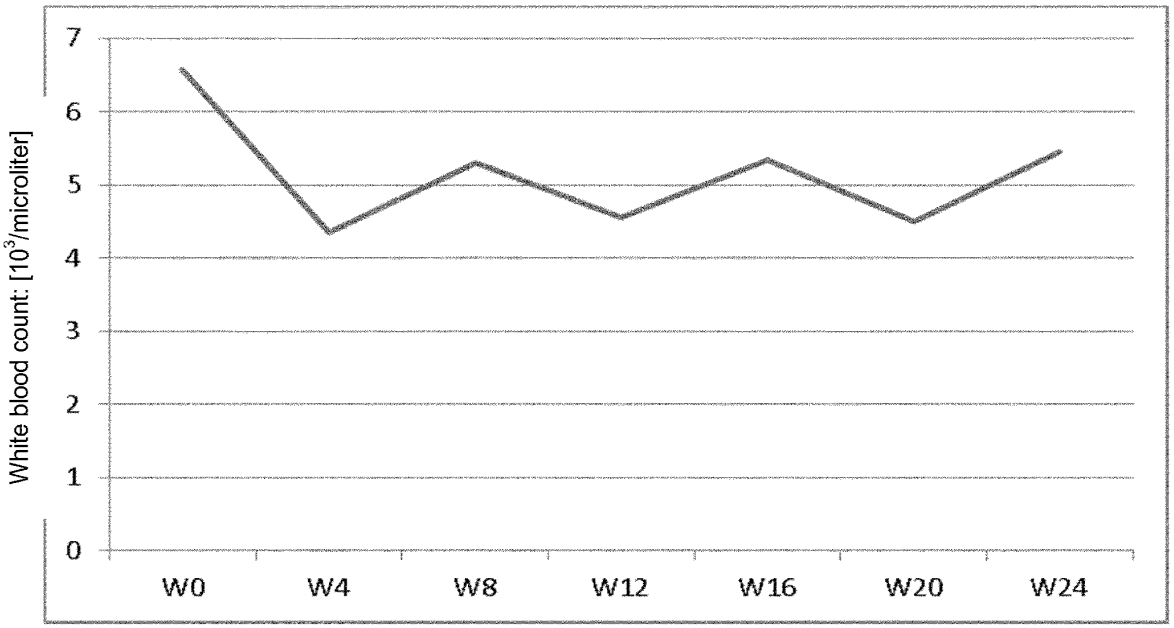

White blood count: [10³/microliter]
7
6
5
4
3
2
1
0
W0
W4
W8
W12
W16
W20
W24

Fig. 9

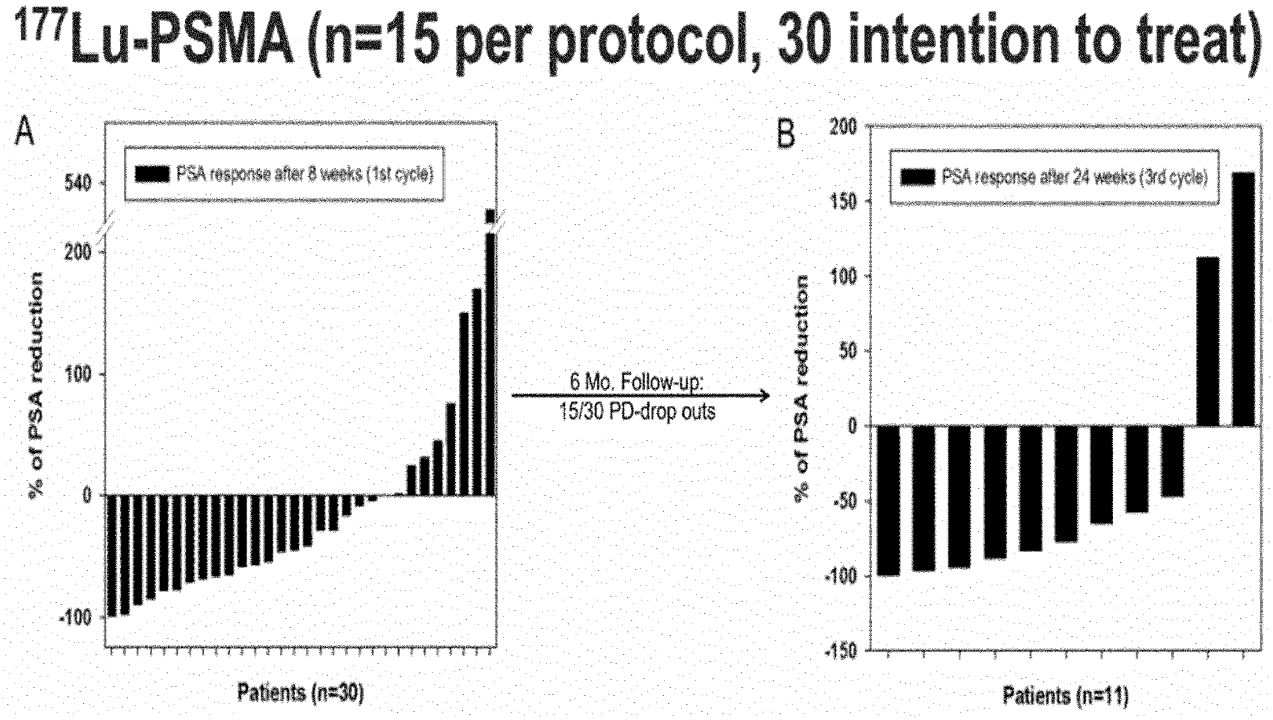

177Lu-PSMA (n=15 per protocol, 30 intention to treat)
A
PSA response after 8 weeks (1st cycle)
% of PSA reduction
540
200
100
0
-100
Patients (n=30)
6 Mo. Follow-up:
15/30 PD-drop outs
B
PSA response after 24 weeks (3rd cycle)
% of PSA reduction
200
150
100
50
0
-50
-100
-150
Patients (n=11)

Fig. 10

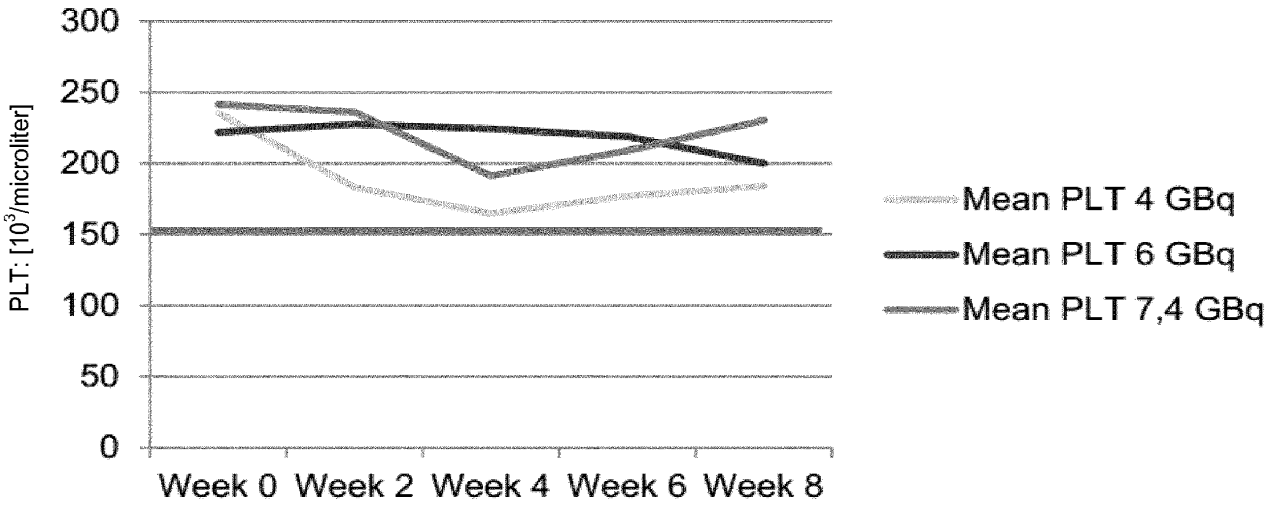

PLT: [10^3/microliter]
300
250
200
150
100
50
0
Week 0
Week 2
Week 4
Week 6
Week 8
Mean PLT 4 GBq
Mean PLT 6 GBq
Mean PLT 7,4 GBq

Fig. 11

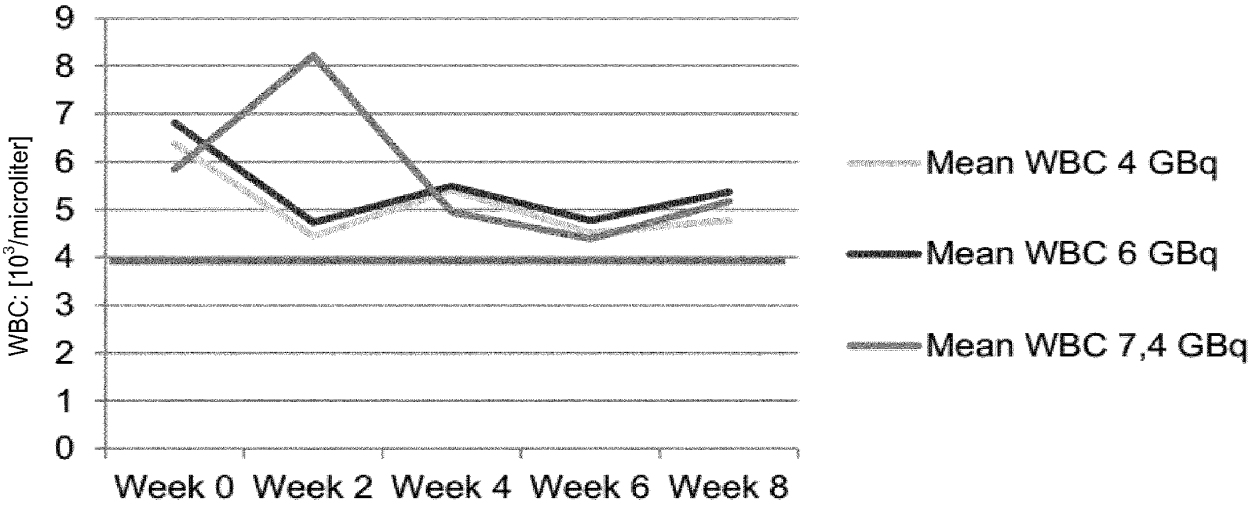

9
8
7
6
5
4
3
2
1
0
WBC: [10³/microliter]
Week 0
Week 2
Week 4
Week 6
Week 8
Mean WBC 4 GBq
Mean WBC 6 GBq
Mean WBC 7,4 GBq

Fig. 12

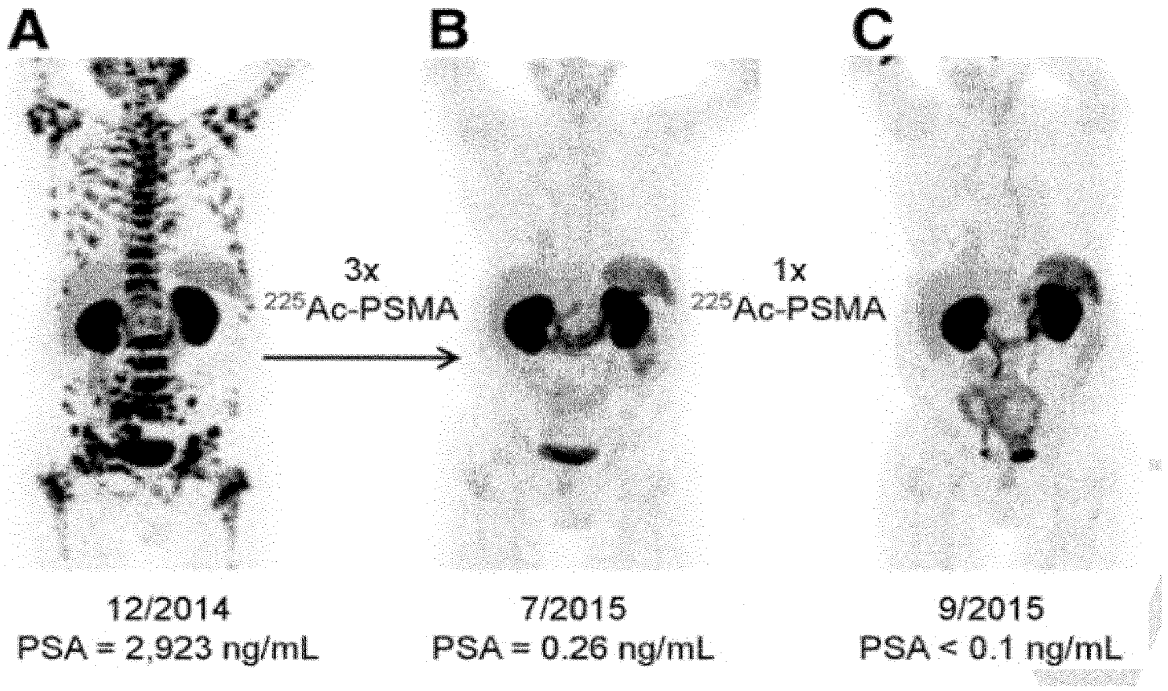

A
B
C
3x
225Ac-PSMA
1x
225Ac-PSMA
12/2014
PSA = 2,923 ng/mL
7/2015
PSA = 0.26 ng/mL
9/2015
PSA < 0.1 ng/mL

Fig. 13

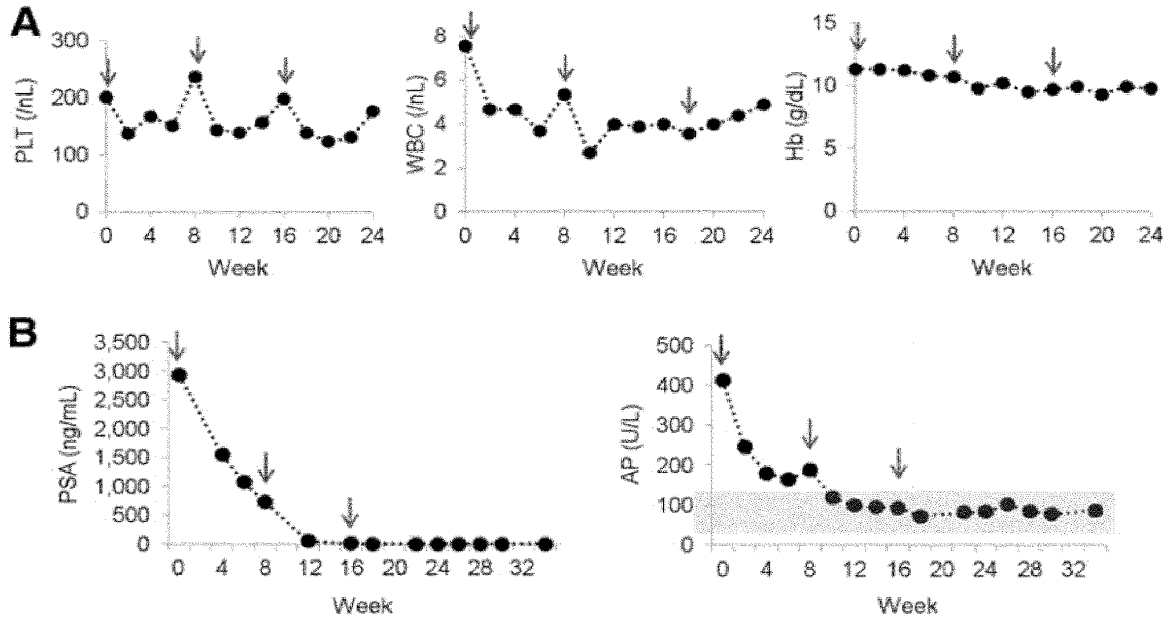

A
PLT (/nL)
300
200
100
0
0 4 8 12 16 20 24
Week
WBC (/nL)
8
6
4
2
0
0 4 8 12 16 20 24
Week
Hb (g/dL)
15
10
5
0
0 4 8 12 16 20 24
Week
B
PSA (ng/mL)
3,500
3,000
2,500
2,000
1,500
1,000
500
0
0 4 8 12 16 20 24 28 32
Week
AP (U/L)
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32
Week

Fig. 14

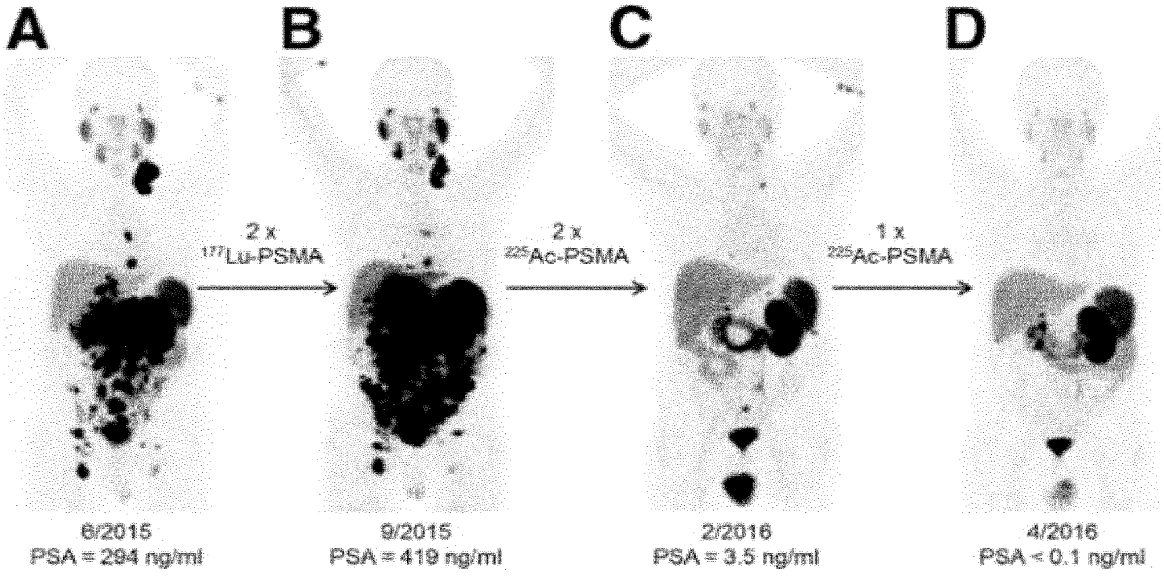
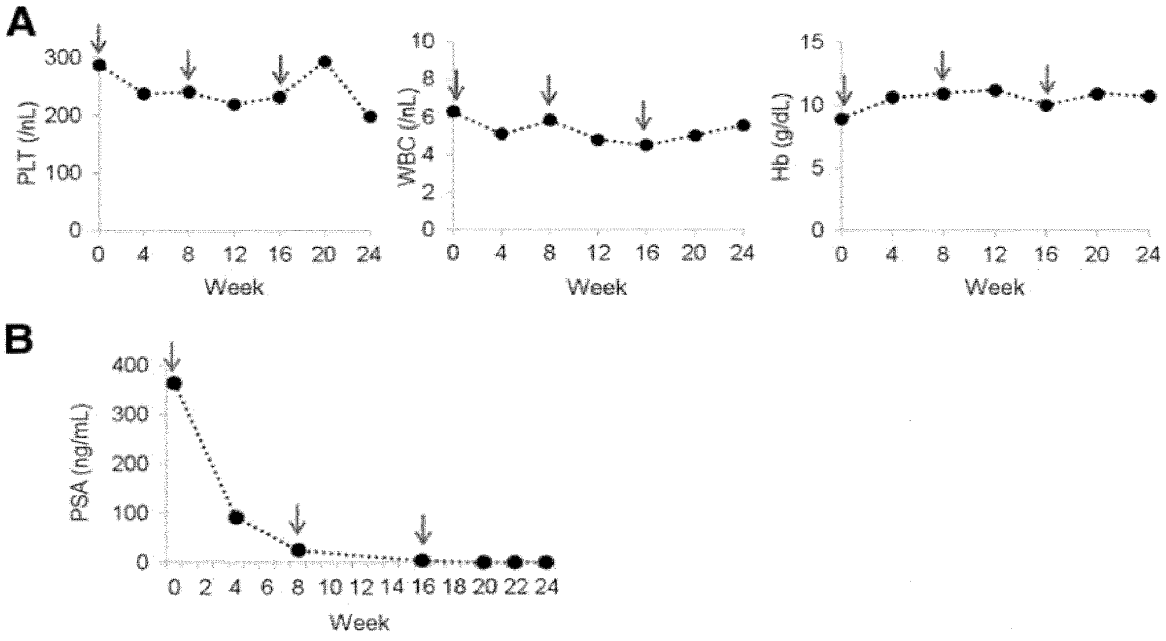

A
B
C
D
2 x
177Lu-PSMA
2 x
225Ac-PSMA
1 x
225Ac-PSMA
6/2015
PSA = 294 ng/ml
9/2015
PSA = 419 ng/ml
2/2016
PSA = 3.5 ng/ml
4/2016
PSA < 0.1 ng/ml

Fig. 15


A
PLT (/nL)
300
200
100
0
0 4 8 12 16 20 24
Week
WBC (/nL)
10
8
6
4
2
0
0 4 8 12 16 20 24
Week
Hb (g/dL)
15
10
5
0
0 4 8 12 16 20 24
Week
B
PSA (ng/mL)
400
300
200
100
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Week