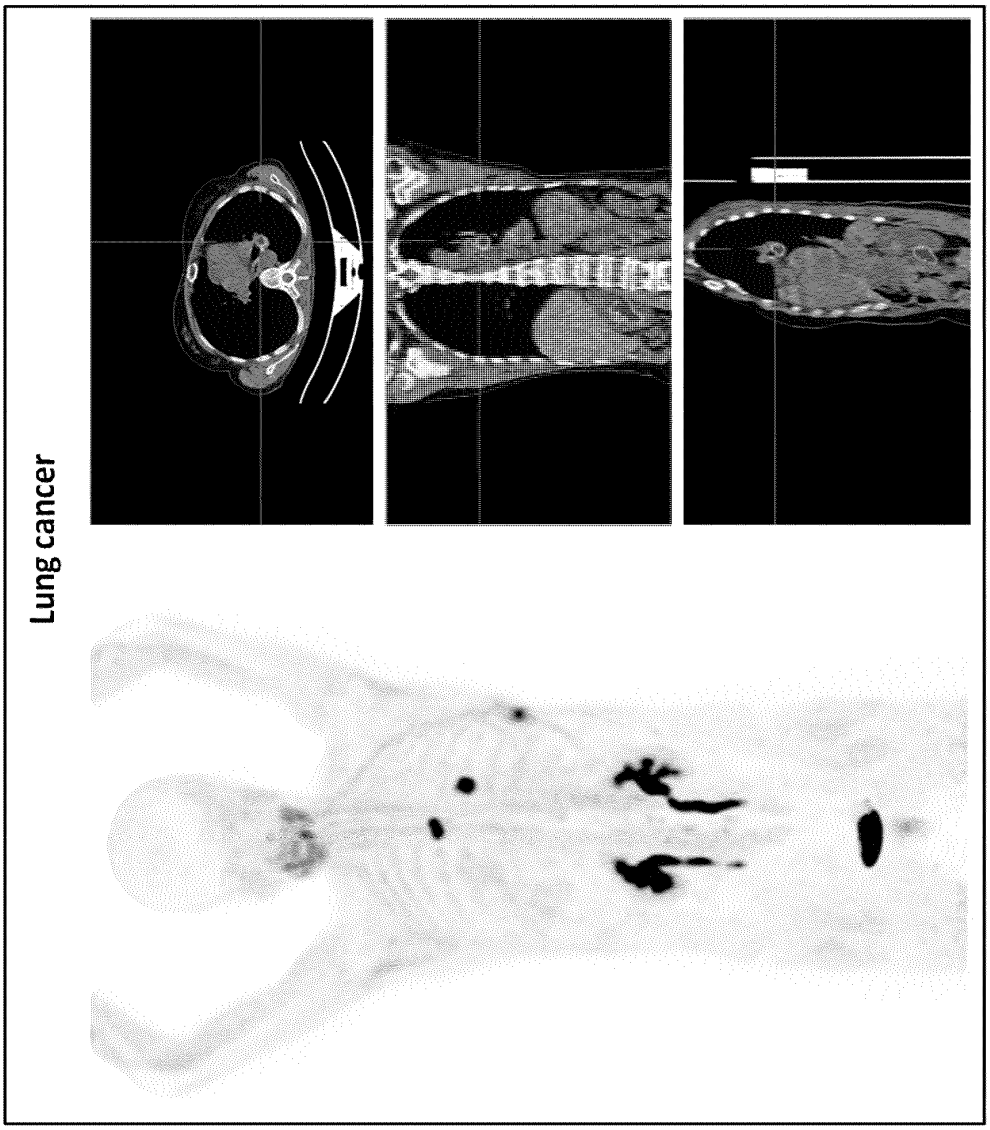


Figure 12

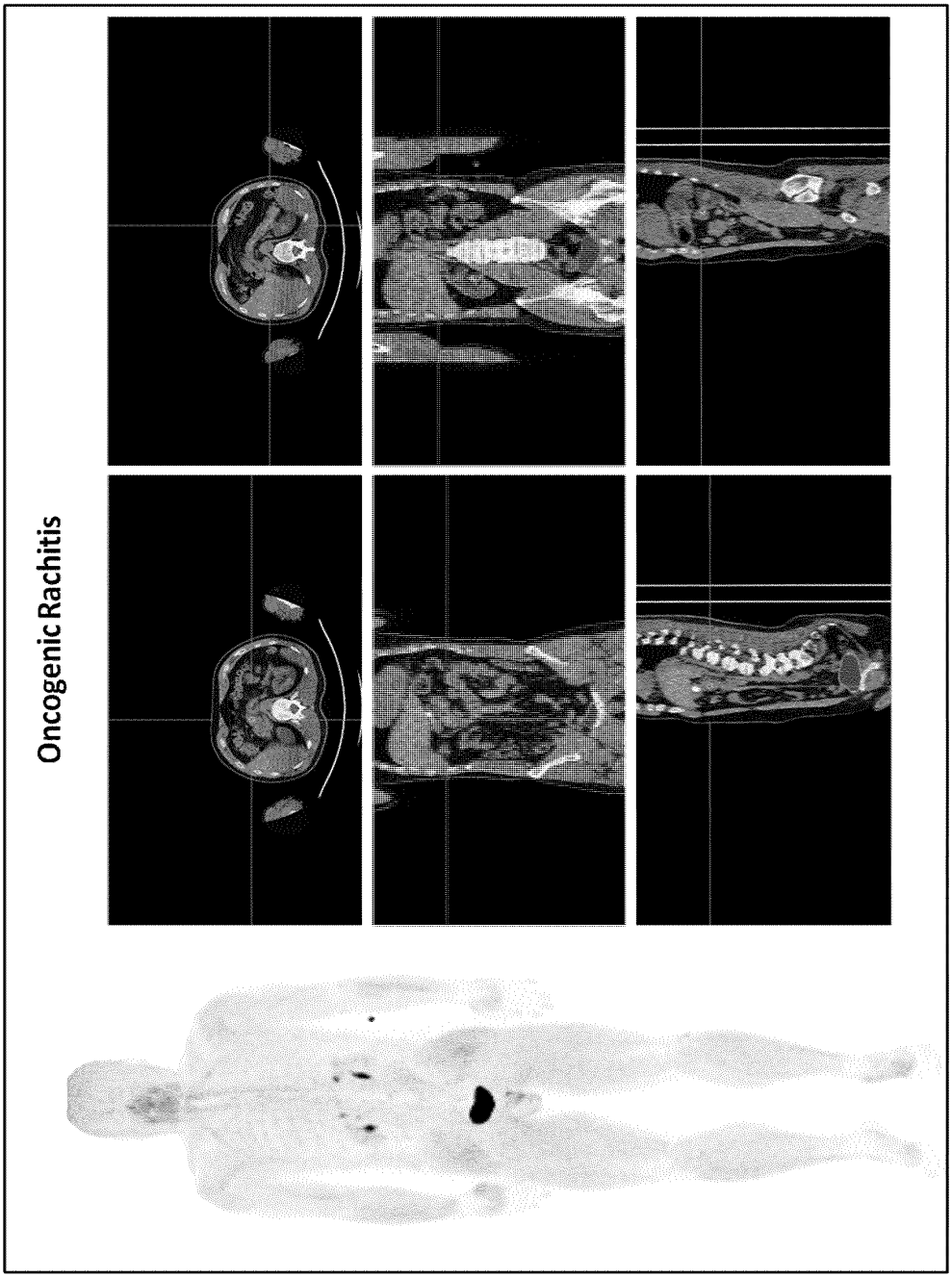


Figure 13

Figure 14

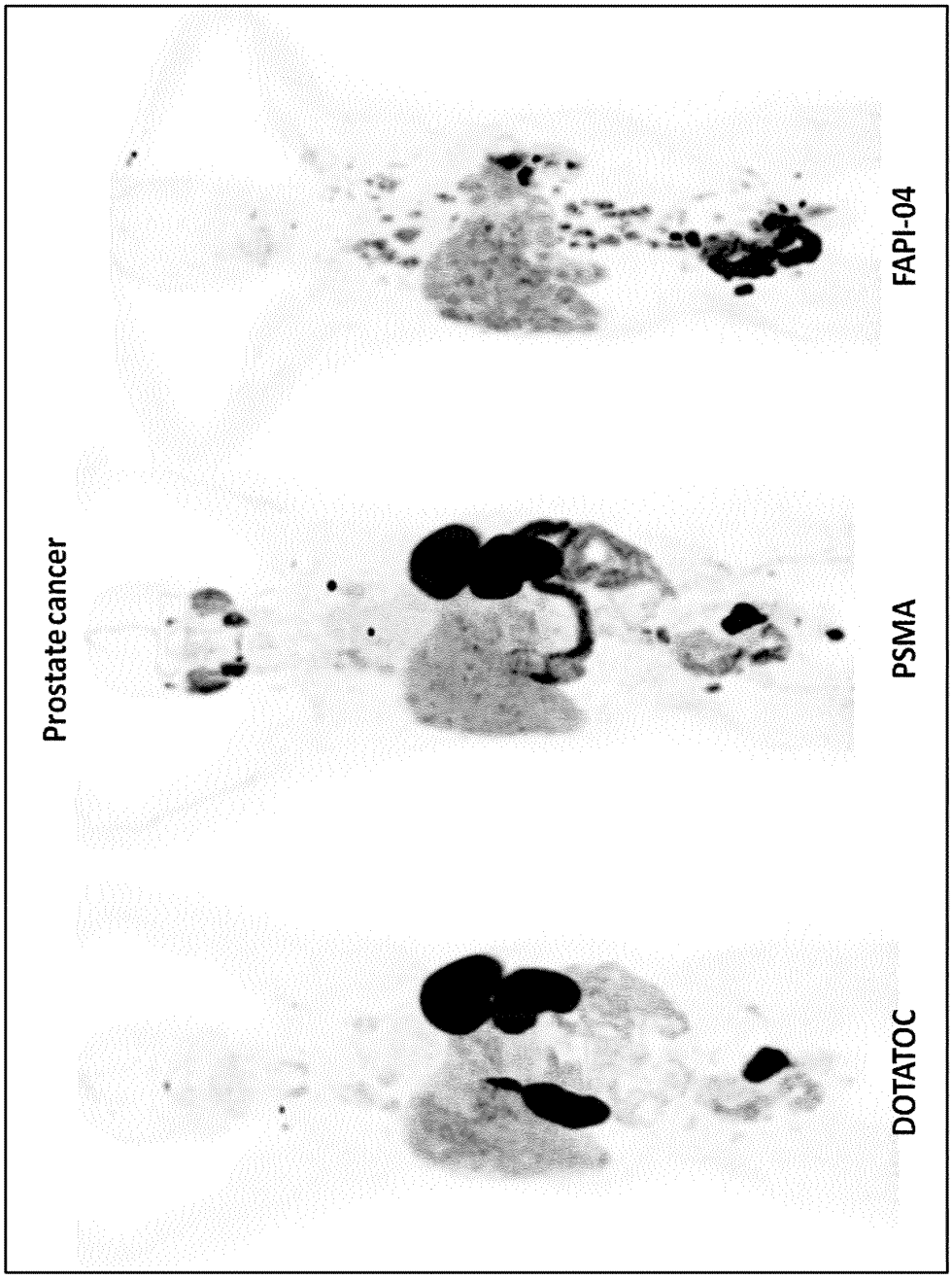


Figure 15

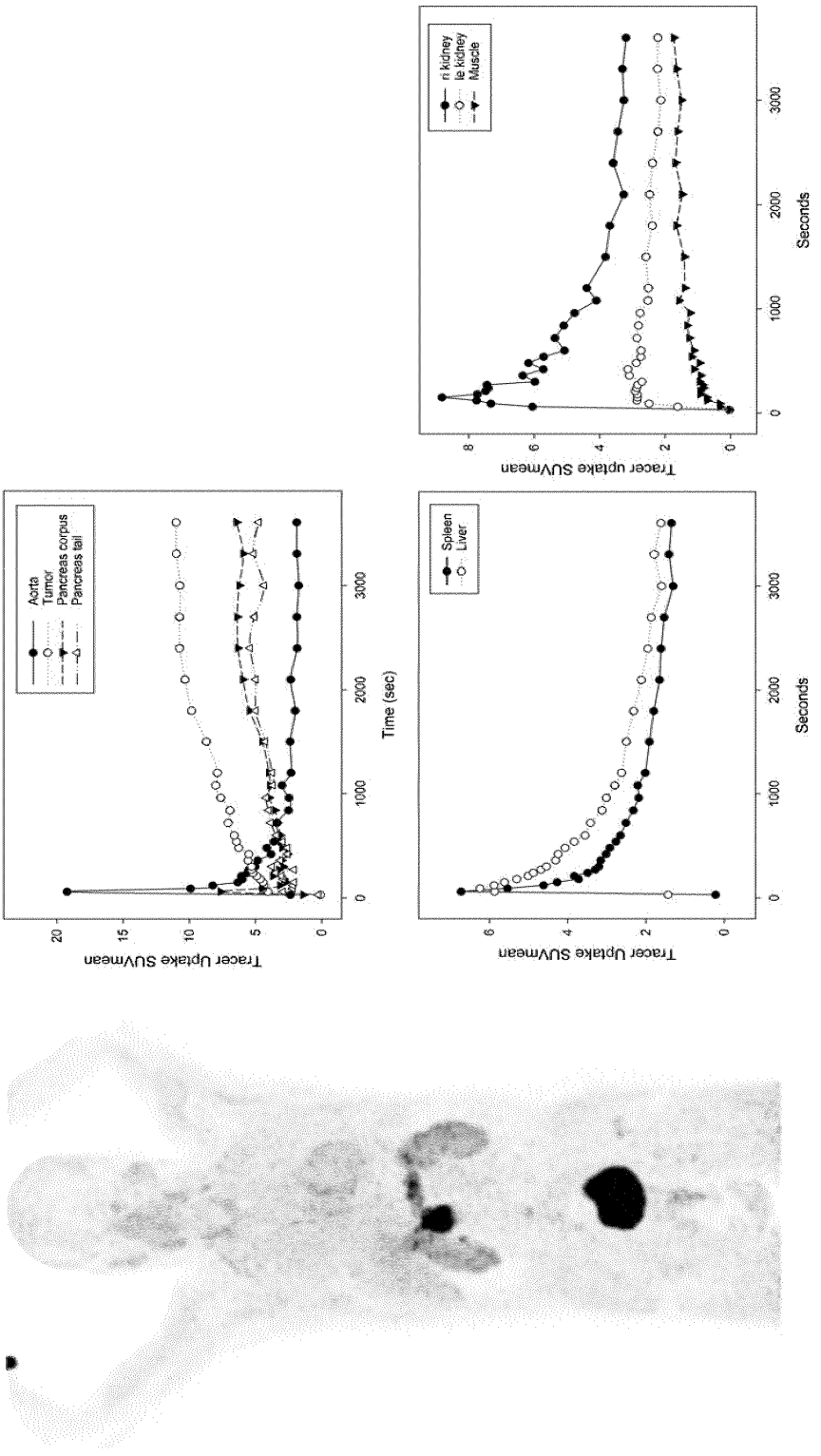

Aorta
Tumor
Pancreas corpus
Pancreas tail
Tracer Uptake SUVmean
Time (sec)
Spleen
Liver
Tracer Uptake SUVmean
Seconds
ri kidney
le kidney
Muscle
Tracer uptake SUVmean
Seconds

Figure 16

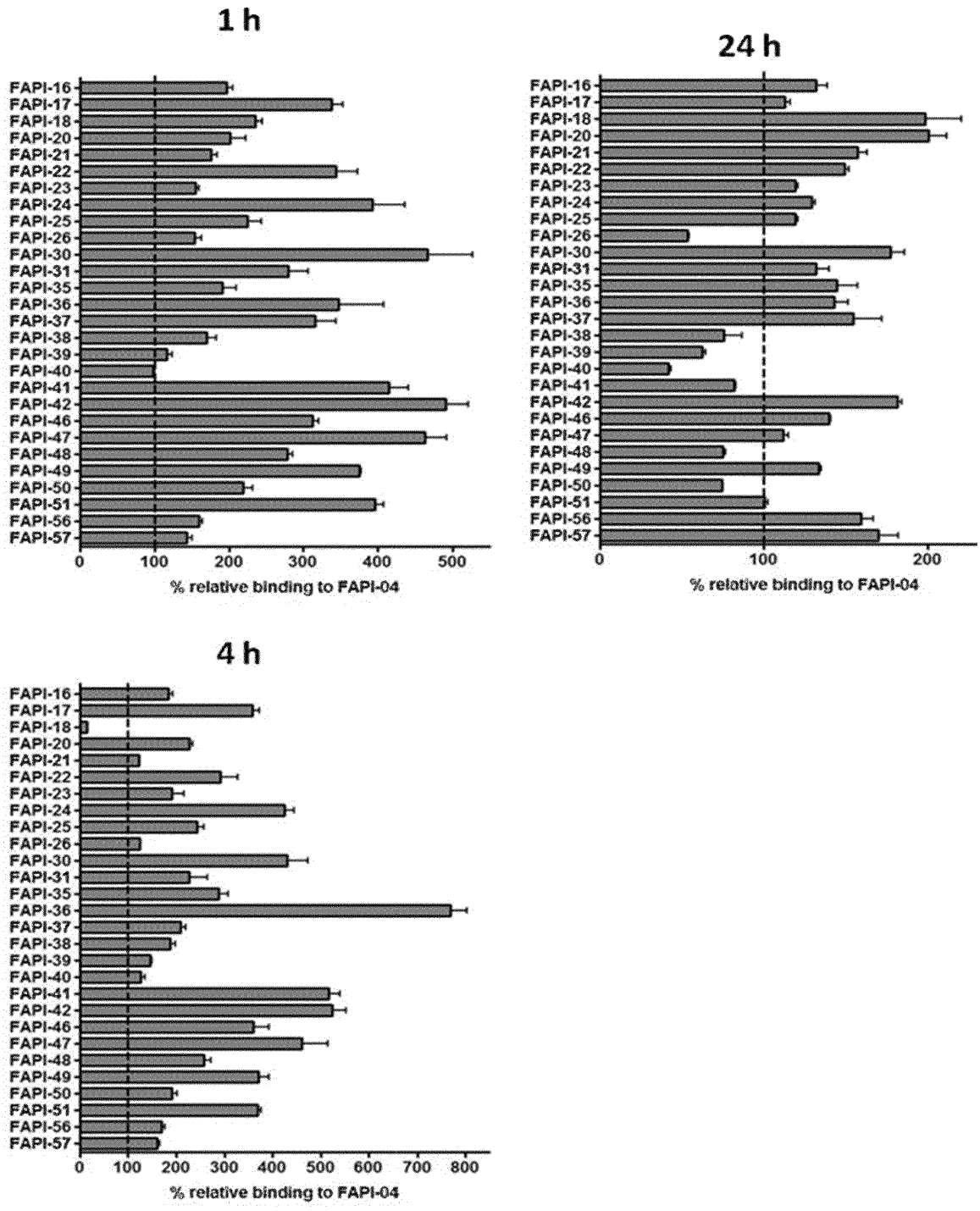

1 h
FAPI-16
FAPI-17
FAPI-18
FAPI-20
FAPI-21
FAPI-22
FAPI-23
FAPI-24
FAPI-25
FAPI-26
FAPI-30
FAPI-31
FAPI-35
FAPI-36
FAPI-37
FAPI-38
FAPI-39
FAPI-40
FAPI-41
FAPI-42
FAPI-46
FAPI-47
FAPI-48
FAPI-49
FAPI-50
FAPI-51
FAPI-56
FAPI-57
0 100 200 300 400 500
% relative binding to FAPI-04
24 h
FAPI-16
FAPI-17
FAPI-18
FAPI-20
FAPI-21
FAPI-22
FAPI-23
FAPI-24
FAPI-25
FAPI-26
FAPI-30
FAPI-31
FAPI-35
FAPI-36
FAPI-37
FAPI-38
FAPI-39
FAPI-40
FAPI-41
FAPI-42
FAPI-46
FAPI-47
FAPI-48
FAPI-49
FAPI-50
FAPI-51
FAPI-56
FAPI-57
0 100 200
% relative binding to FAPI-04
4 h
FAPI-16
FAPI-17
FAPI-18
FAPI-20
FAPI-21
FAPI-22
FAPI-23
FAPI-24
FAPI-25
FAPI-26
FAPI-30
FAPI-31
FAPI-35
FAPI-36
FAPI-37
FAPI-38
FAPI-39
FAPI-40
FAPI-41
FAPI-42
FAPI-46
FAPI-47
FAPI-48
FAPI-49
FAPI-50
FAPI-51
FAPI-56
FAPI-57
0 100 200 300 400 500 600 700 800
% relative binding to FAPI-04

Figure 17

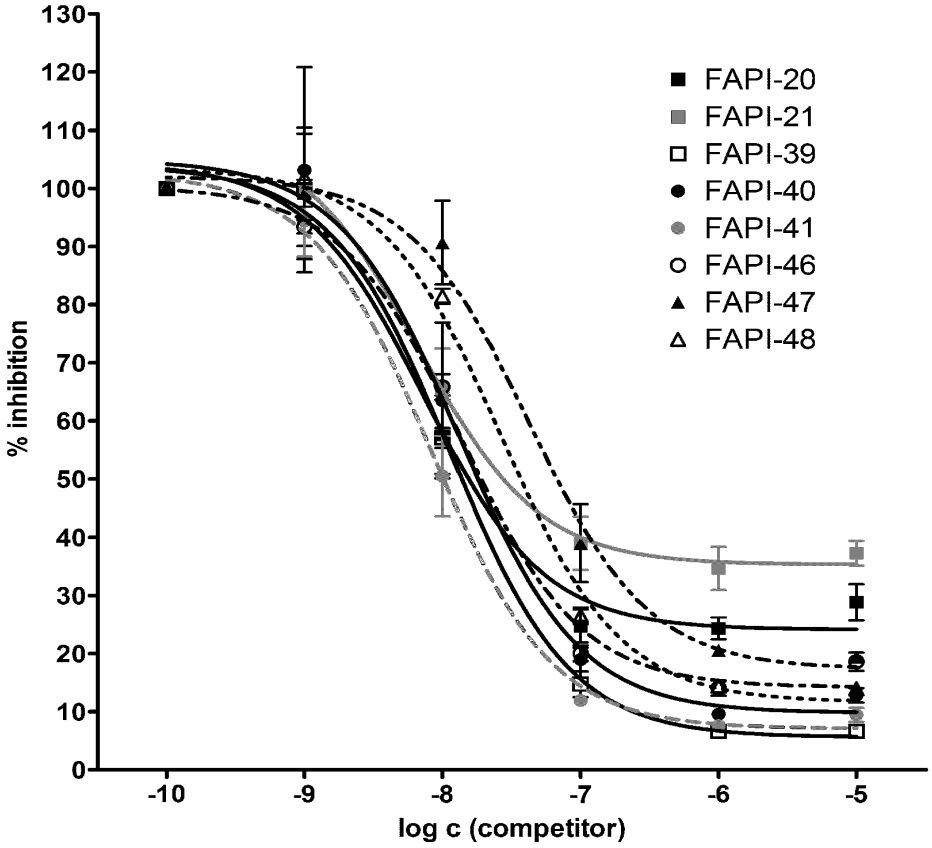

130
120
110
100
90
80
70
60
50
40
30
20
10
0
% inhibition
-10
-9
-8
-7
-6
-5
log c (competitor)
FAPI-20
FAPI-21
FAPI-39
FAPI-40
FAPI-41
FAPI-46
FAPI-47
FAPI-48

Figure 18

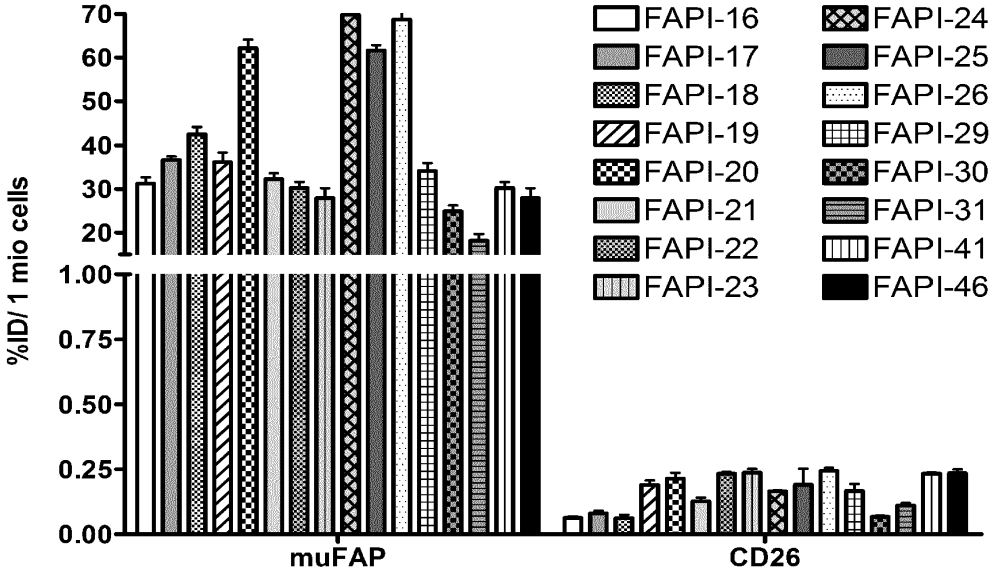

%ID/ 1 mio cells
70
60
50
40
30
20
1.00
0.75
0.50
0.25
0.00
muFAP
CD26
FAPI-16
FAPI-17
FAPI-18
FAPI-19
FAPI-20
FAPI-21
FAPI-22
FAPI-23
FAPI-24
FAPI-25
FAPI-26
FAPI-29
FAPI-30
FAPI-31
FAPI-41
FAPI-46

Figure 19

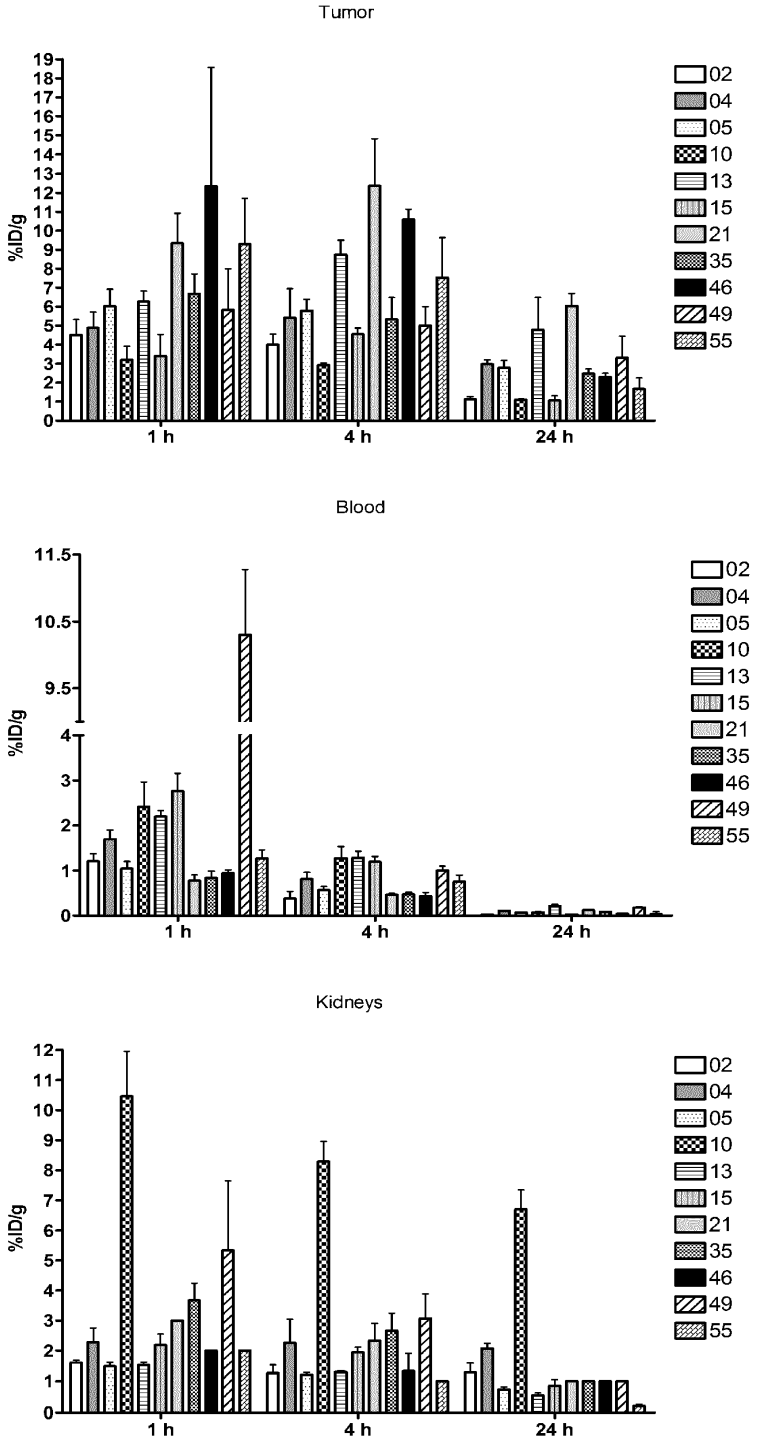

Tumor
%ID/g
1 h
4 h
24 h
02
04
05
10
13
15
21
35
46
49
55
Blood
%ID/g
1 h
4 h
24 h
02
04
05
10
13
15
21
35
46
49
55
Kidneys
%ID/g
1 h
4 h
24 h
02
04
05
10
13
15
21
35
46
49
55

Figure 20

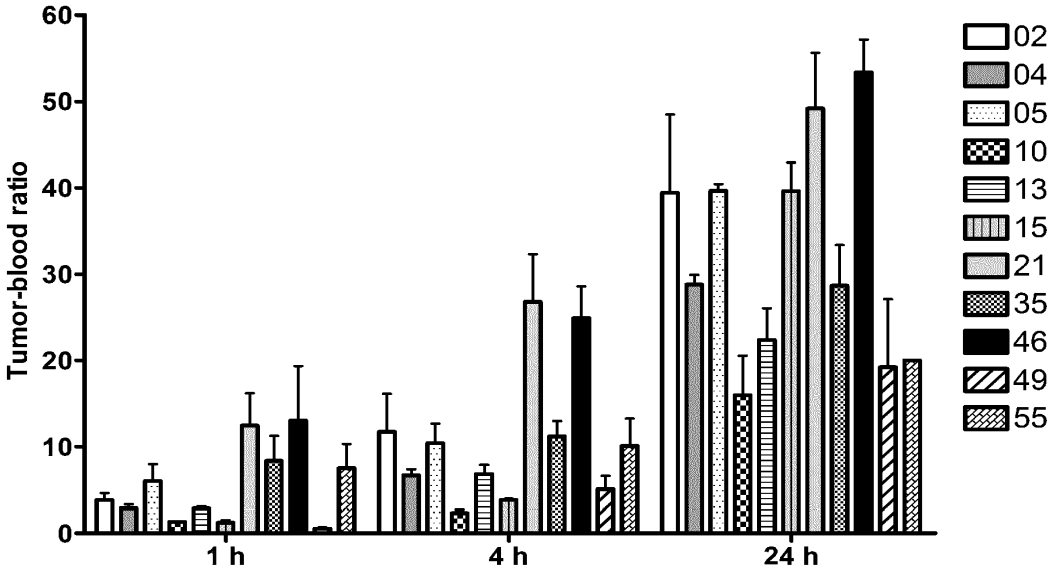


Figure 21

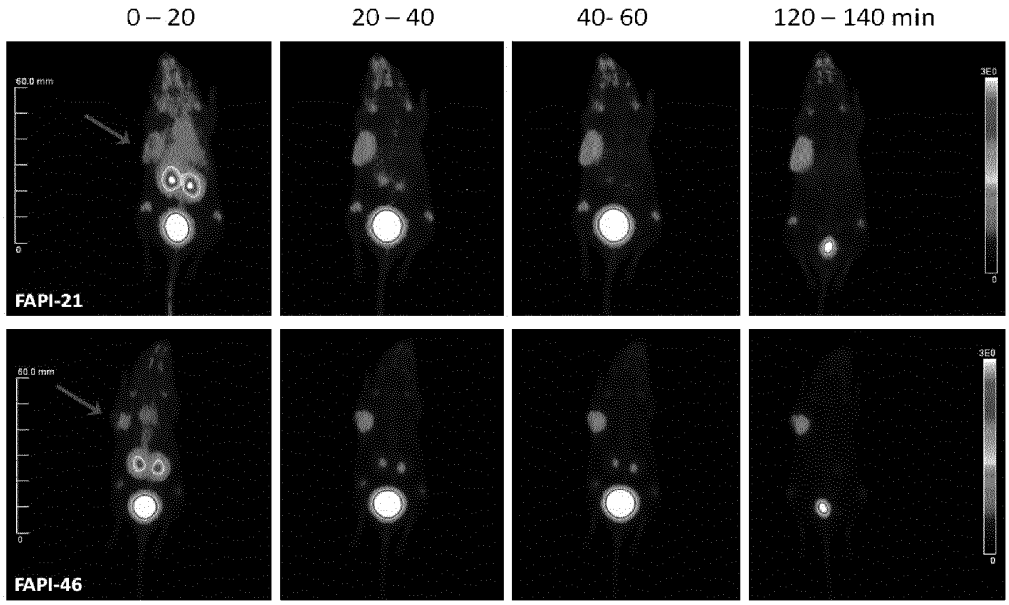
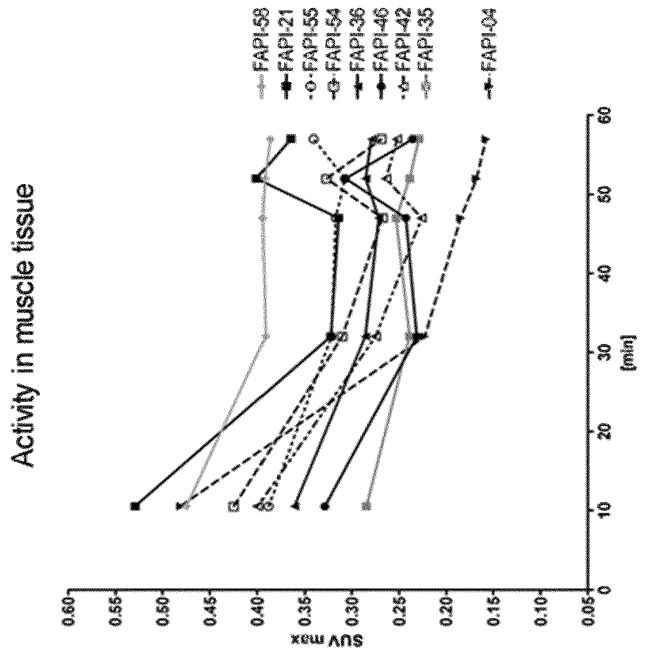


Figure 22


Activity in muscle tissue
FAPI-58
FAPI-21
FAPI-55
FAPI-54
FAPI-36
FAPI-46
FAPI-42
FAPI-35
FAPI-04
SUV max
[min]

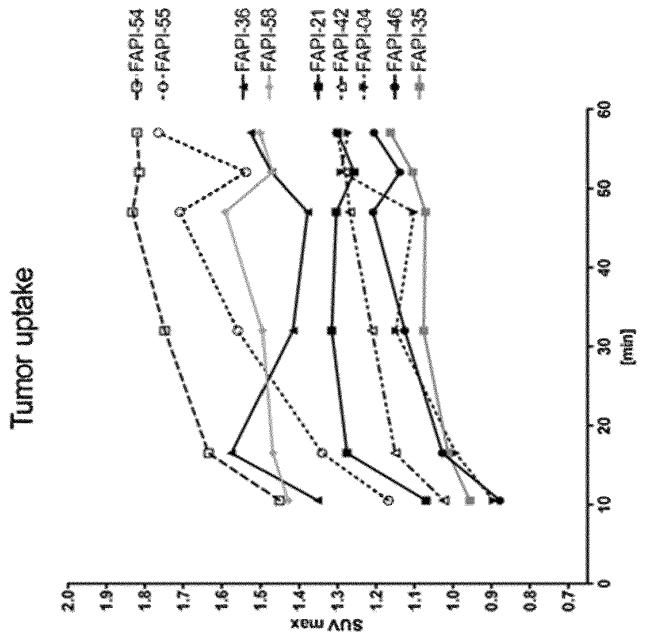
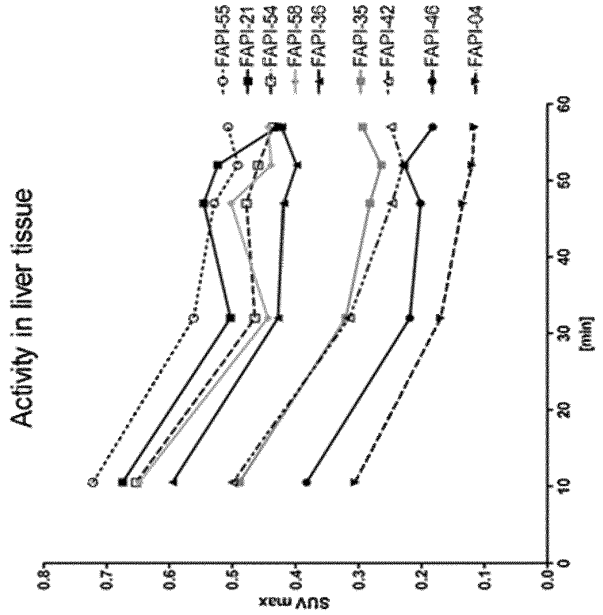

Tumor uptake
FAPI-54
FAPI-55
FAPI-36
FAPI-58
FAPI-21
FAPI-42
FAPI-04
FAPI-46
FAPI-35
SUV max
[min]

Figure 22 continued



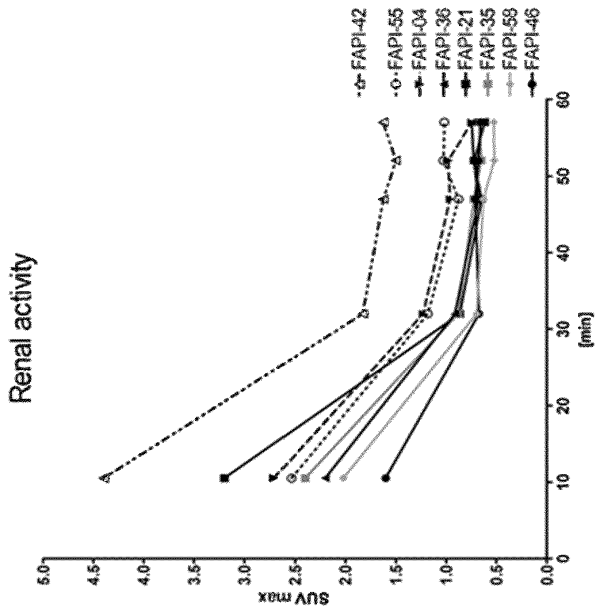
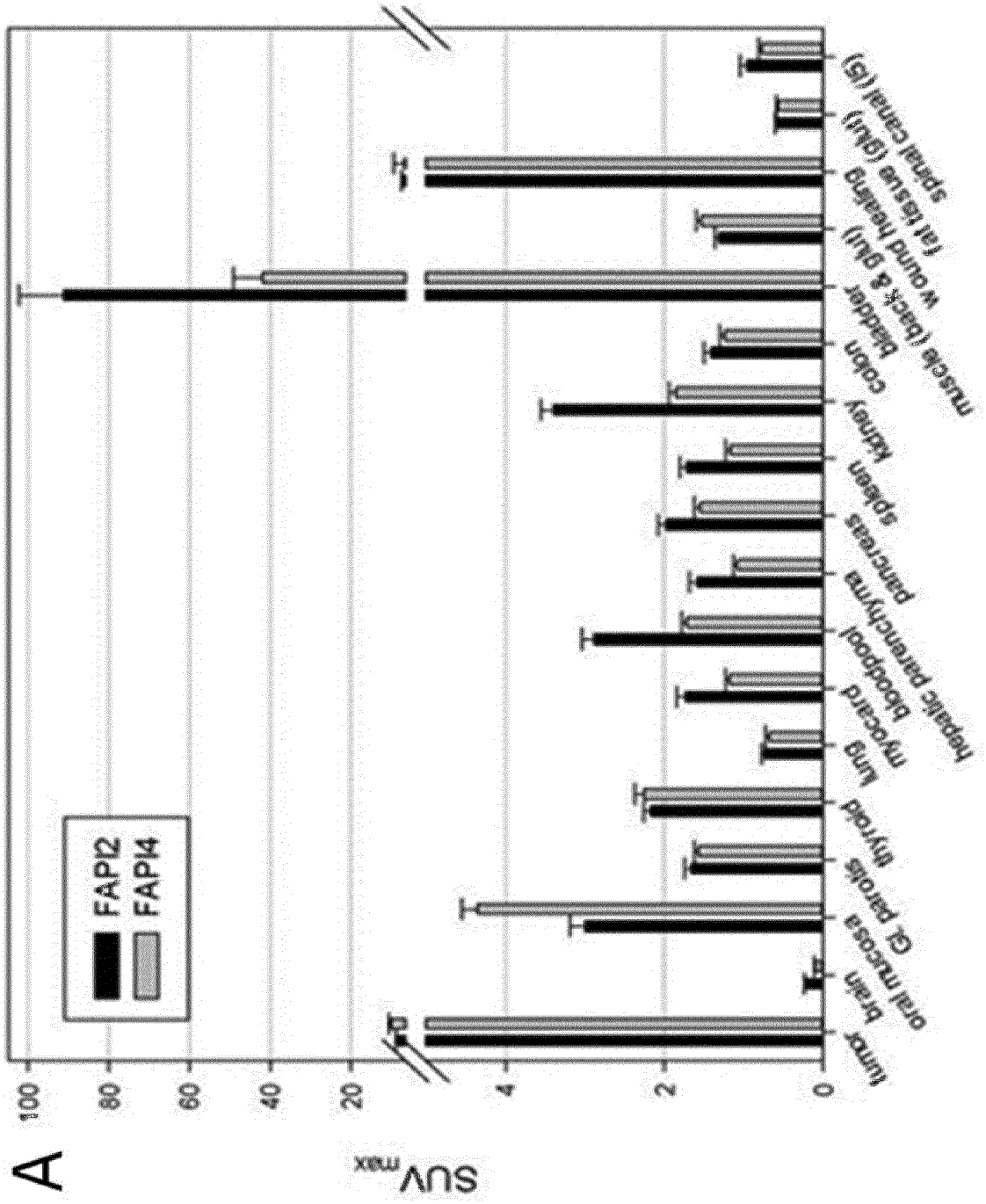


Figure 23



ITM Exhibit 1004, Page 1099 of 1652

Figure 23 continued

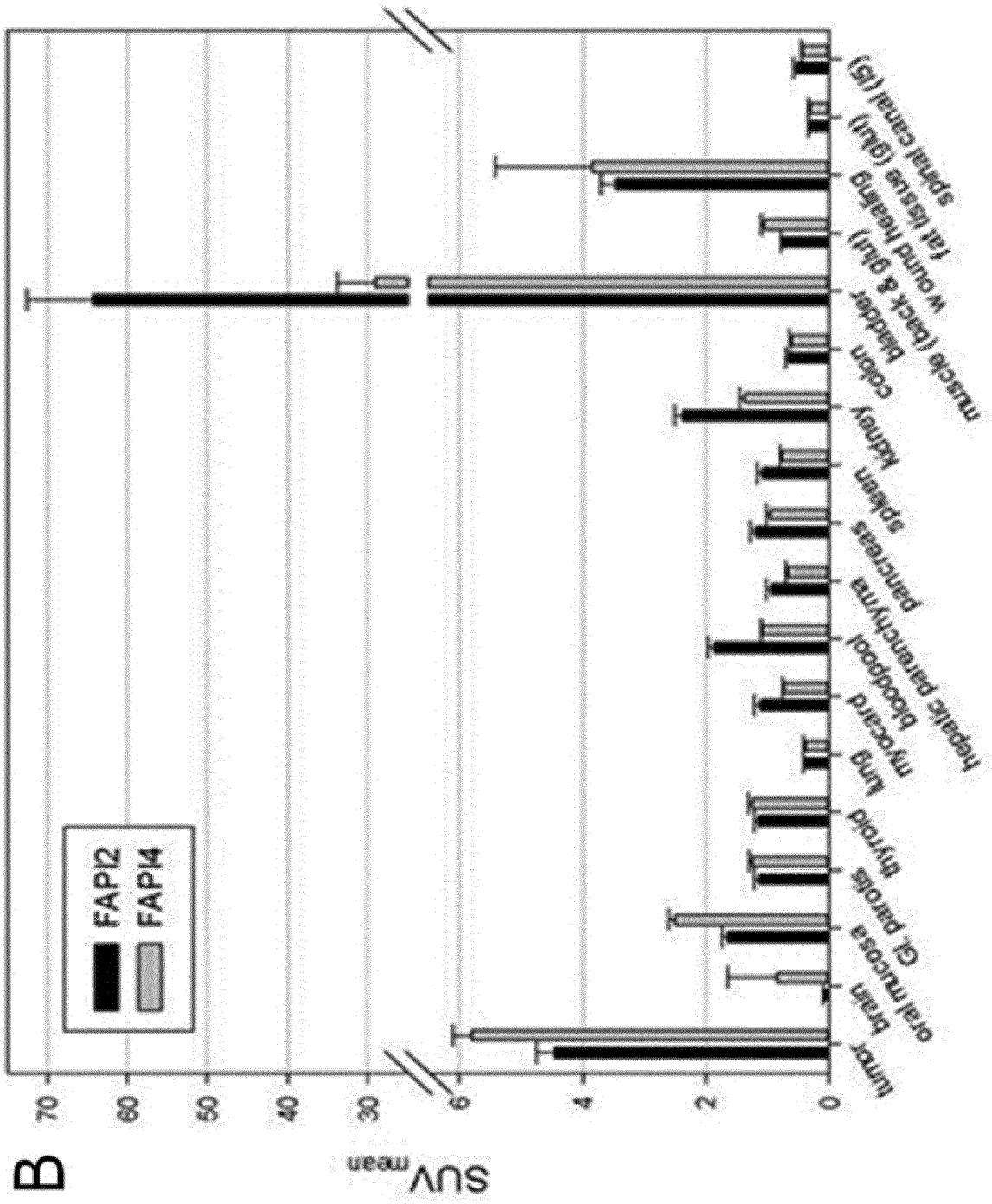


Figure 24

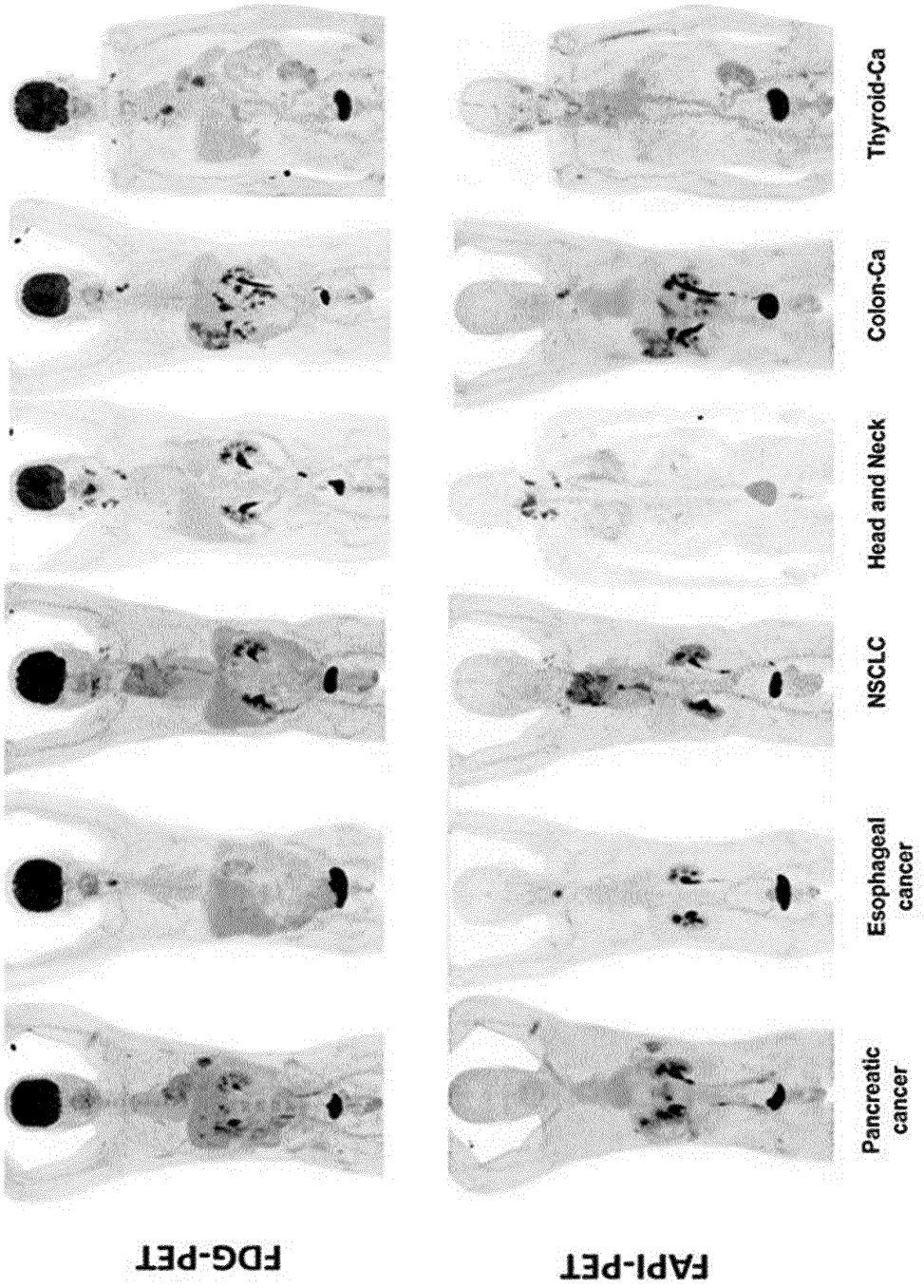

Thyroid-Ca
Colon-Ca
Head and Neck
NSCLC
Esophageal cancer
Pancreatic cancer
FAPI-PET
FDG-PET

Figure 24 continued

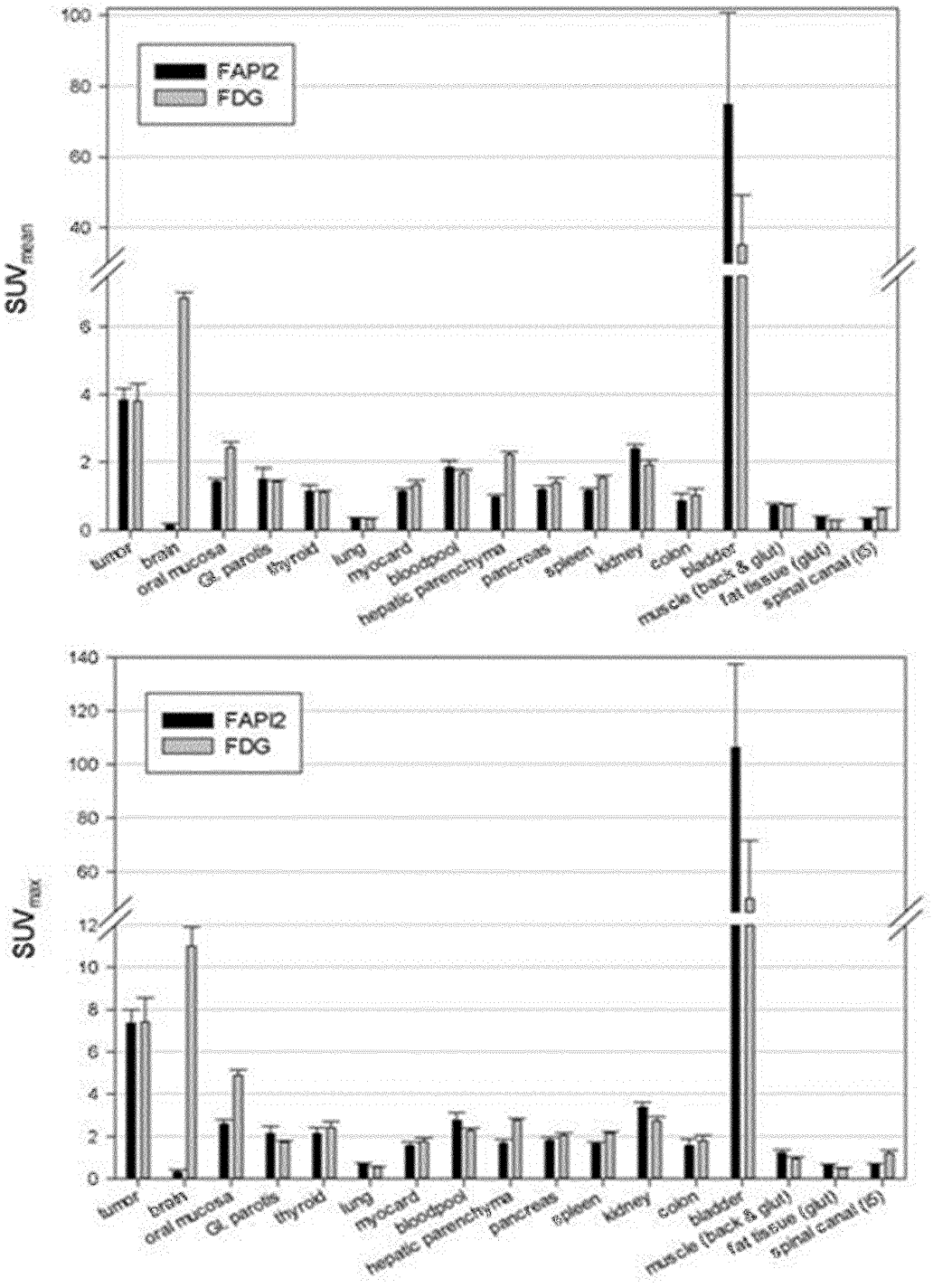


Figure 25

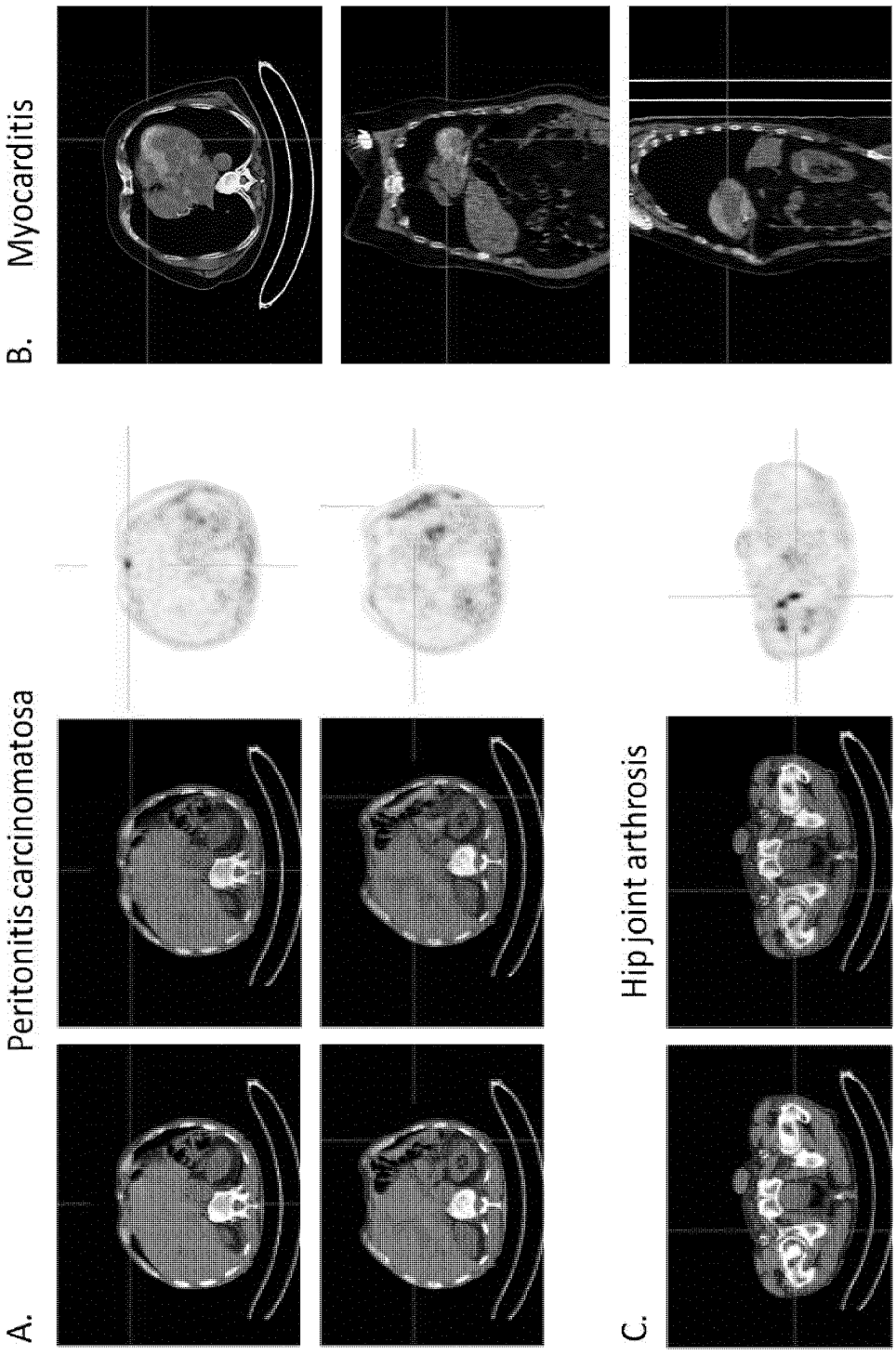

B. Myocarditis
Peritonitis carcinomatosa
Hip joint arthrosis
A.
C.

Figure 26

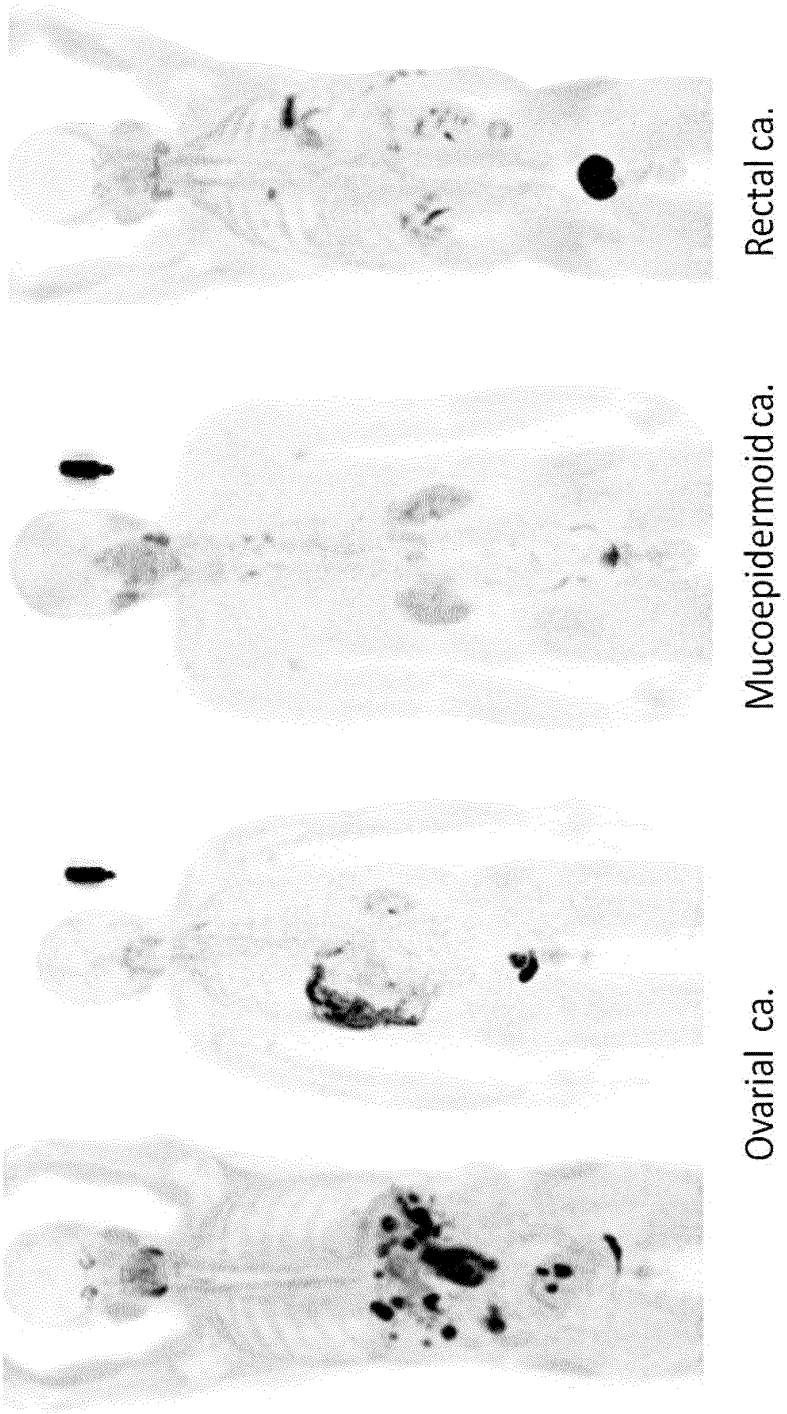


Figure 27

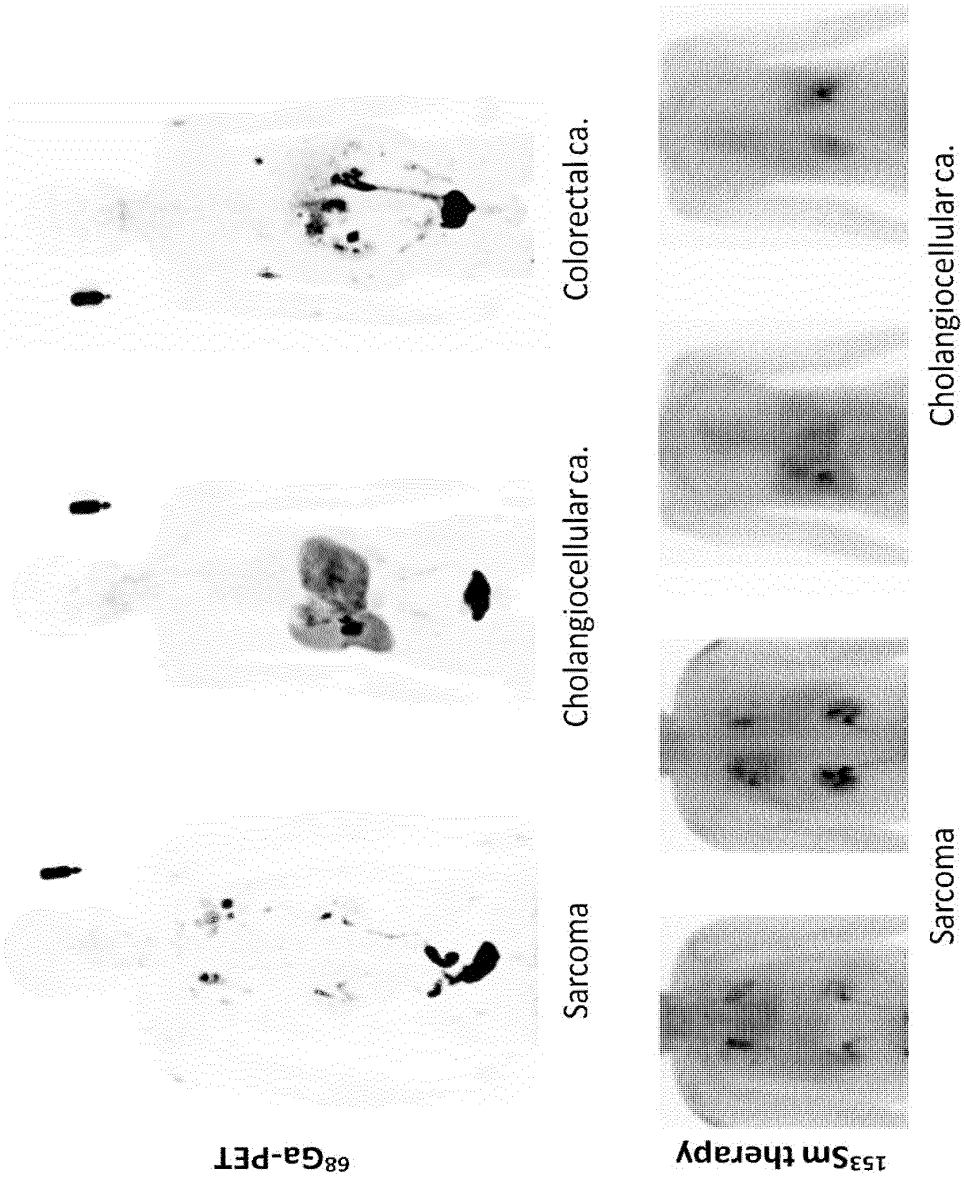

Colorectal ca.
Cholangiocellular ca.
Sarcoma
^{68}Ga-PET
Cholangiocellular ca.
Sarcoma
^{153}Sm therapy

Figure 28

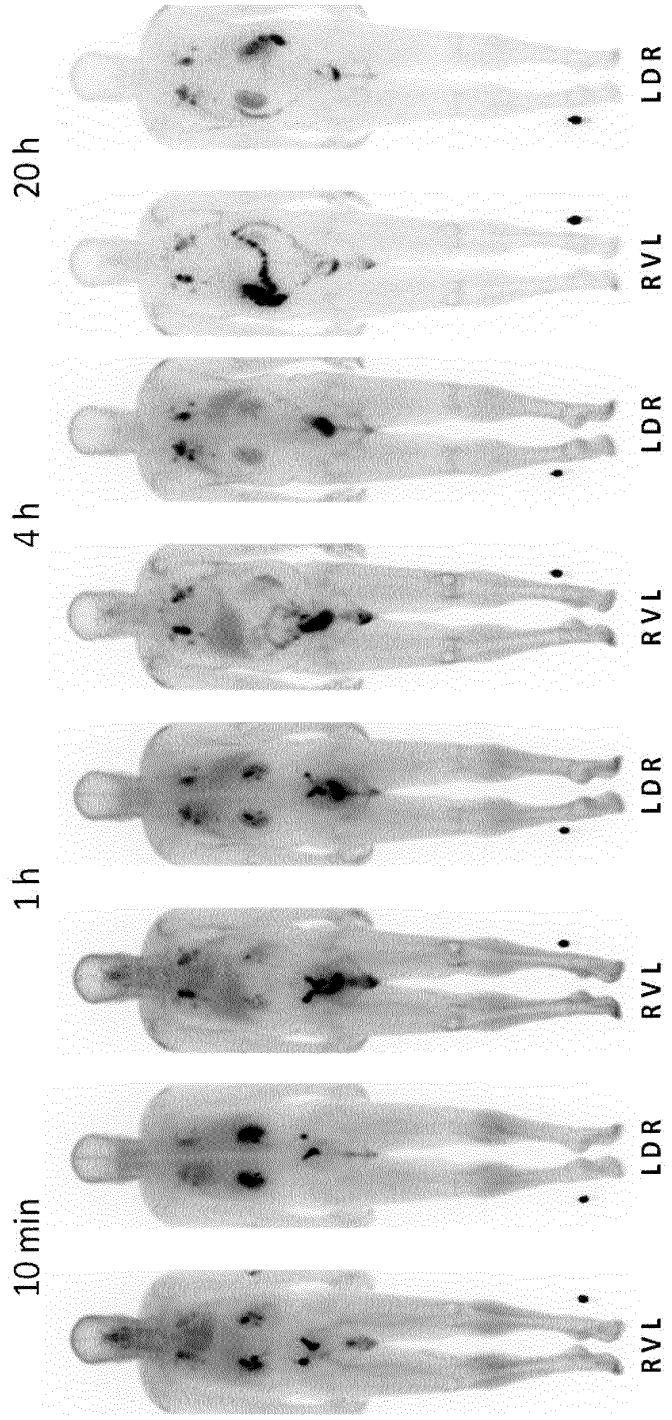


Figure 29

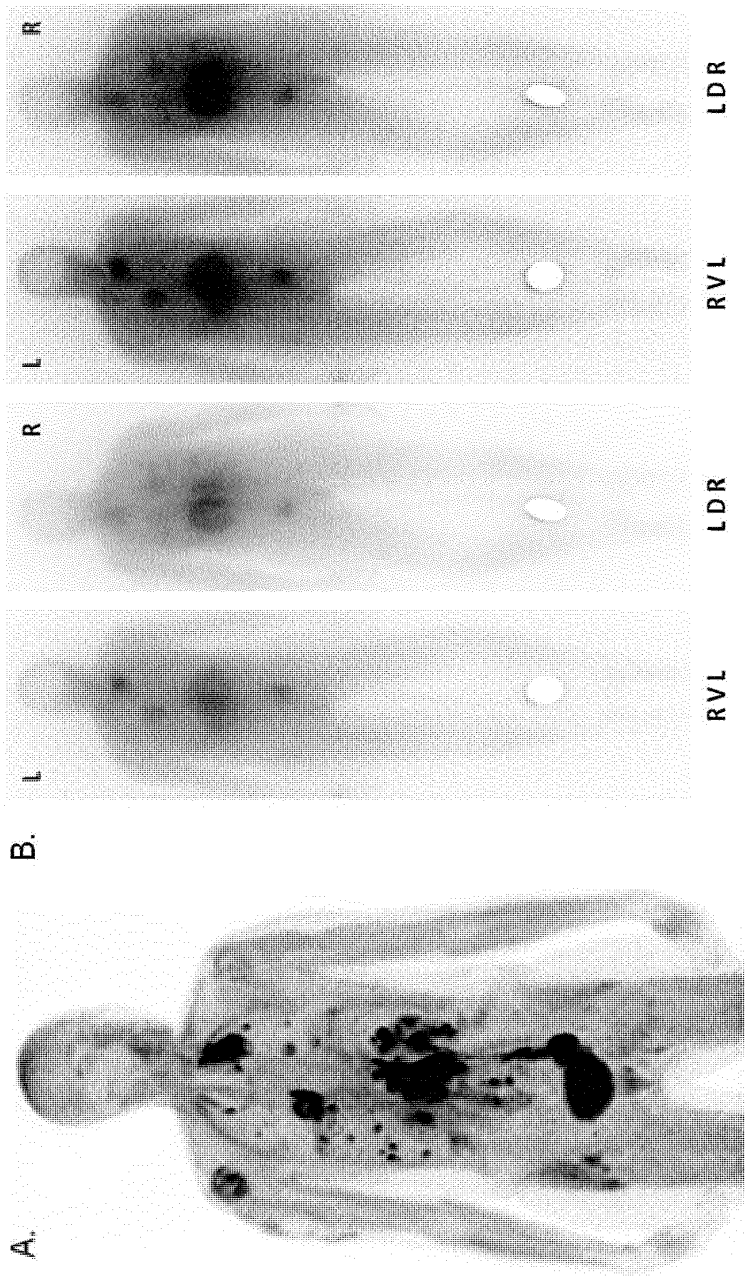
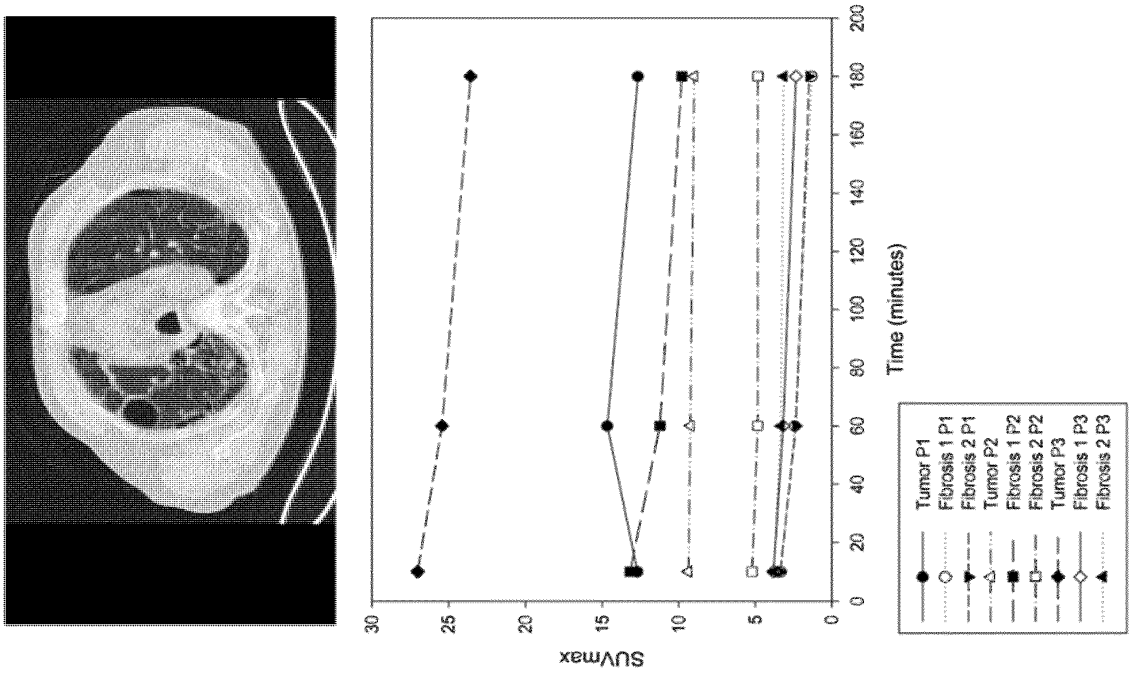


Figure 30


SUVmax
Time (minutes)
Tumor P1
Fibrosis 1 P1
Fibrosis 2 P1
Tumor P2
Fibrosis 1 P2
Fibrosis 2 P2
Tumor P3
Fibrosis 1 P3
Fibrosis 2 P3

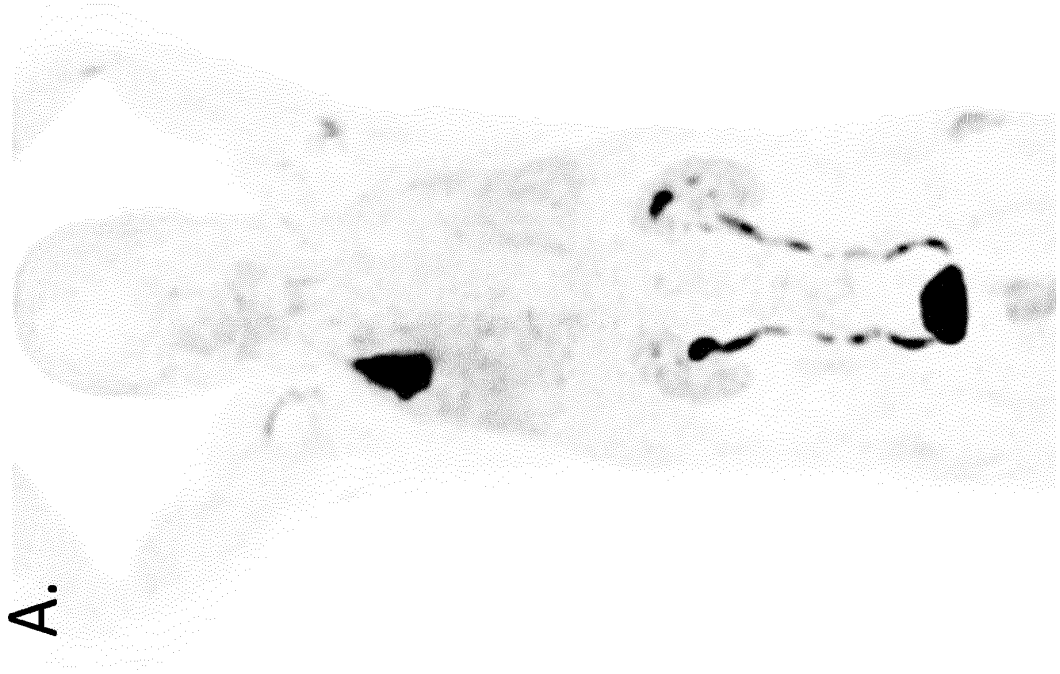
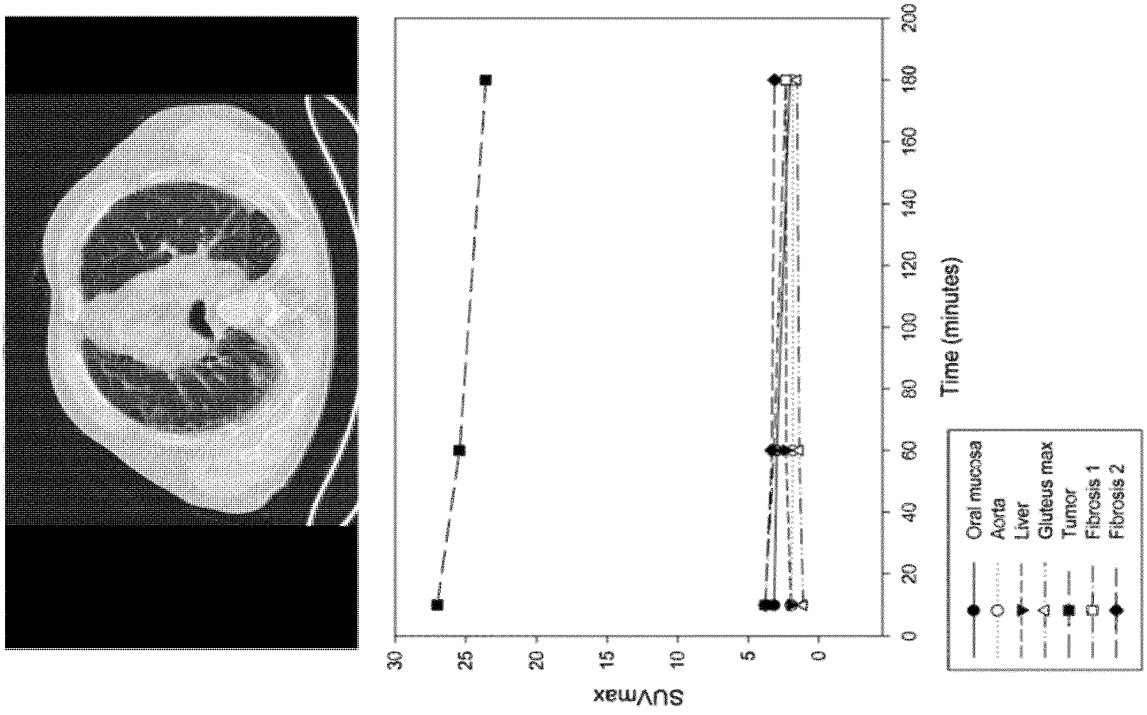

A.

Figure 30 continued



B.

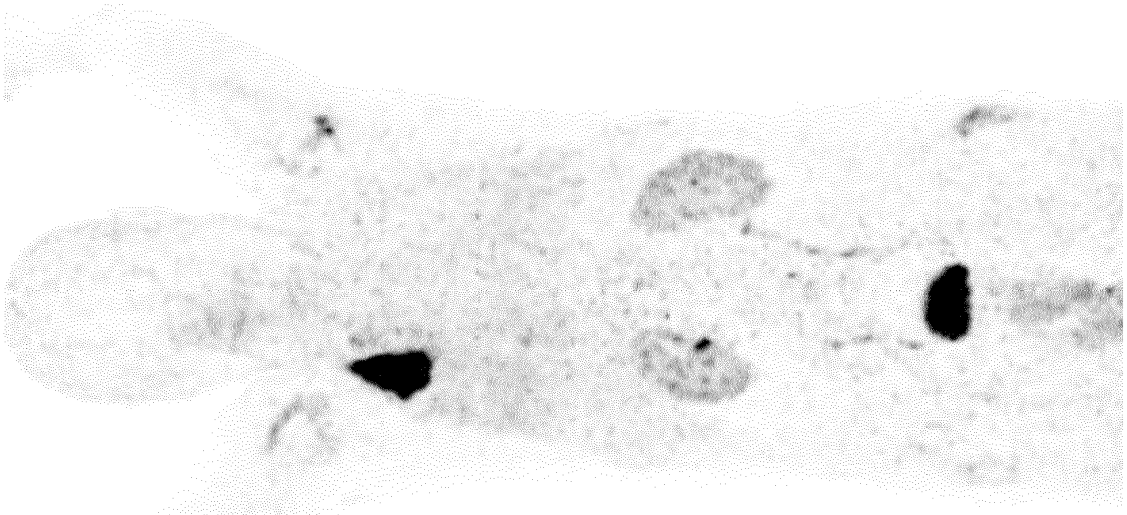
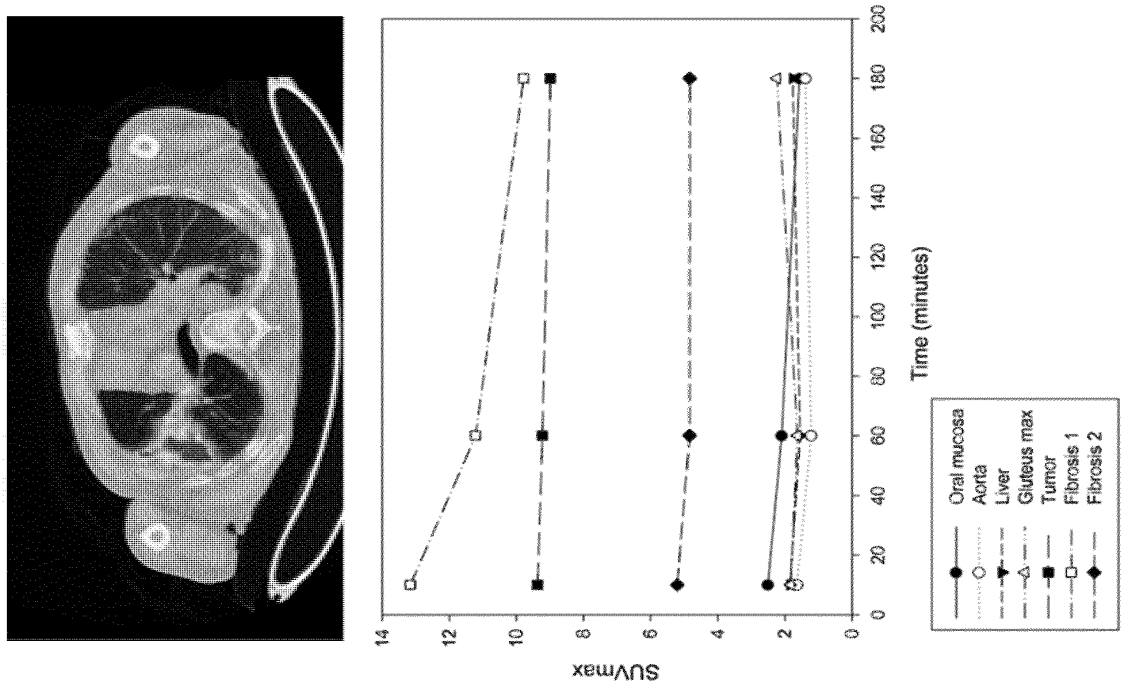
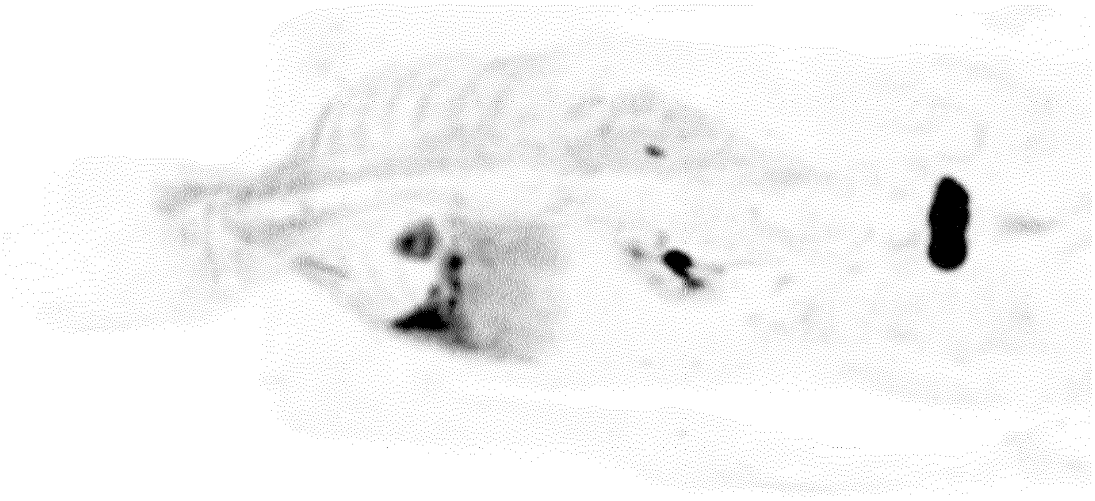


Figure 30 continued





c

Figure 31

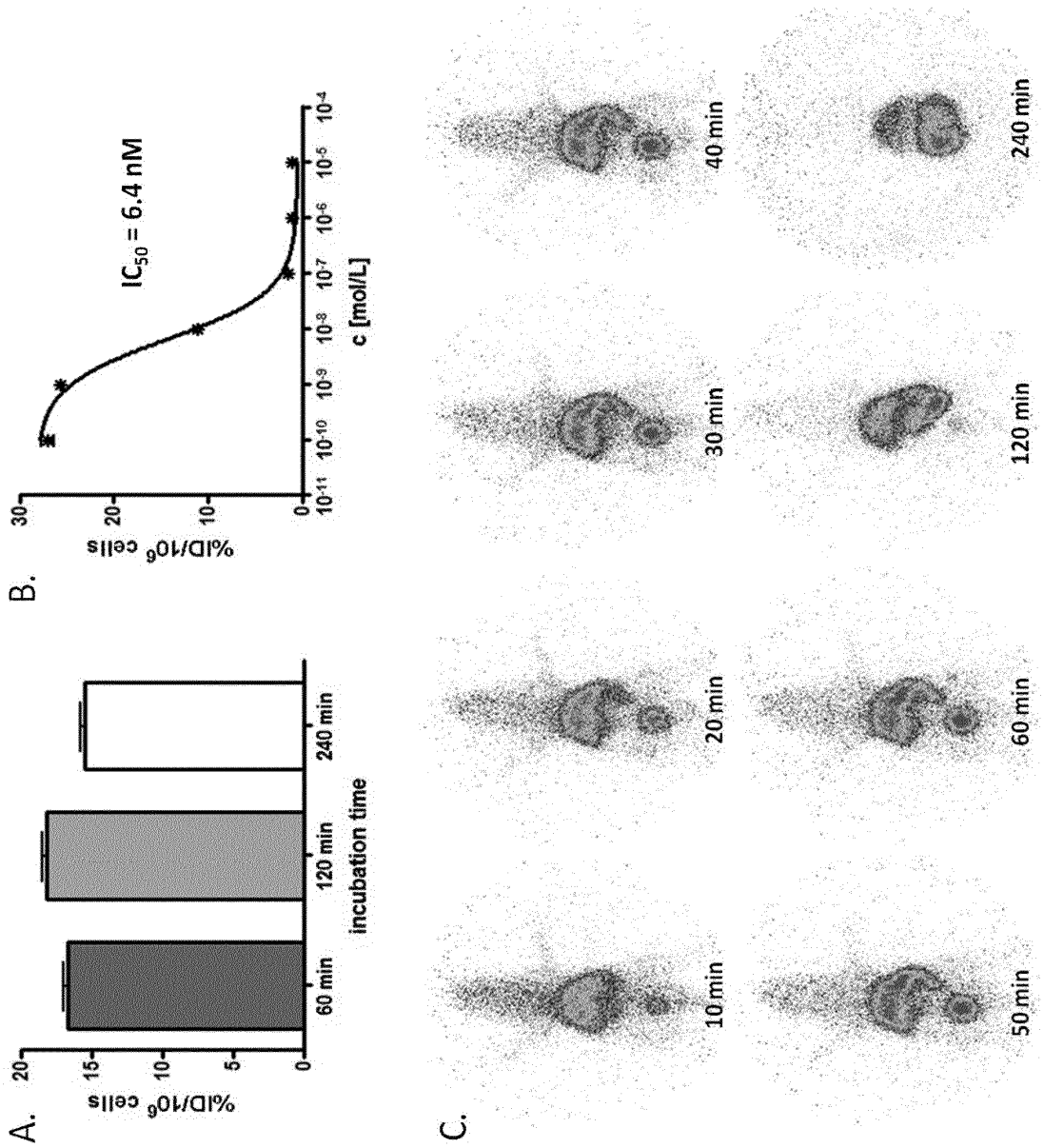

A.
%ID/10^6 cells
incubation time
60 min
120 min
240 min
B.
IC50 = 6.4 nM
%ID/10^6 cells
c [mol/L]
C.
10 min
20 min
30 min
40 min
50 min
60 min
120 min
240 min

Figure 32

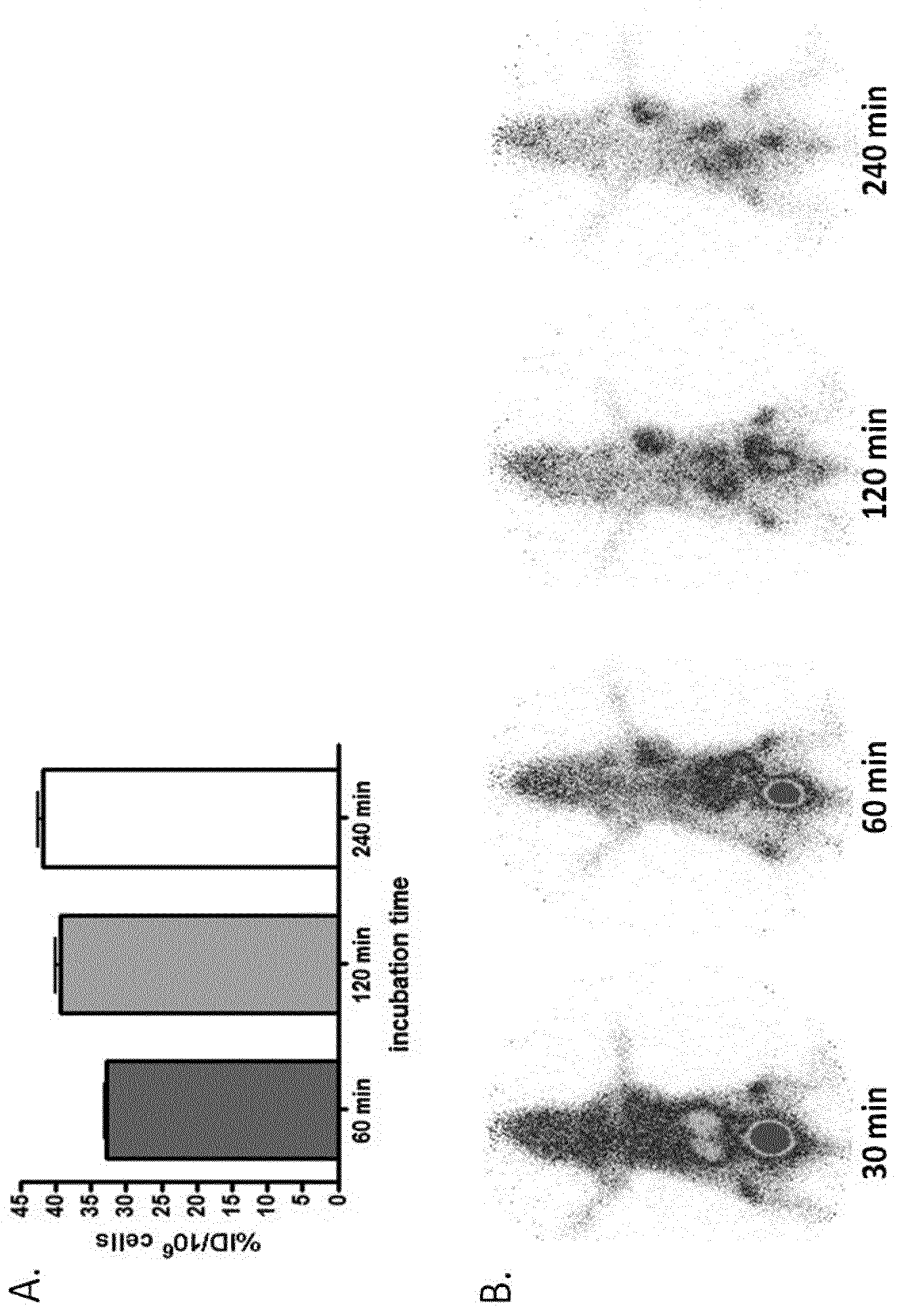

A.
%ID/10^6 cells
45
40
35
30
25
20
15
10
5
0
60 min
120 min
240 min
incubation time
B.
30 min
60 min
120 min
240 min

Figure 33

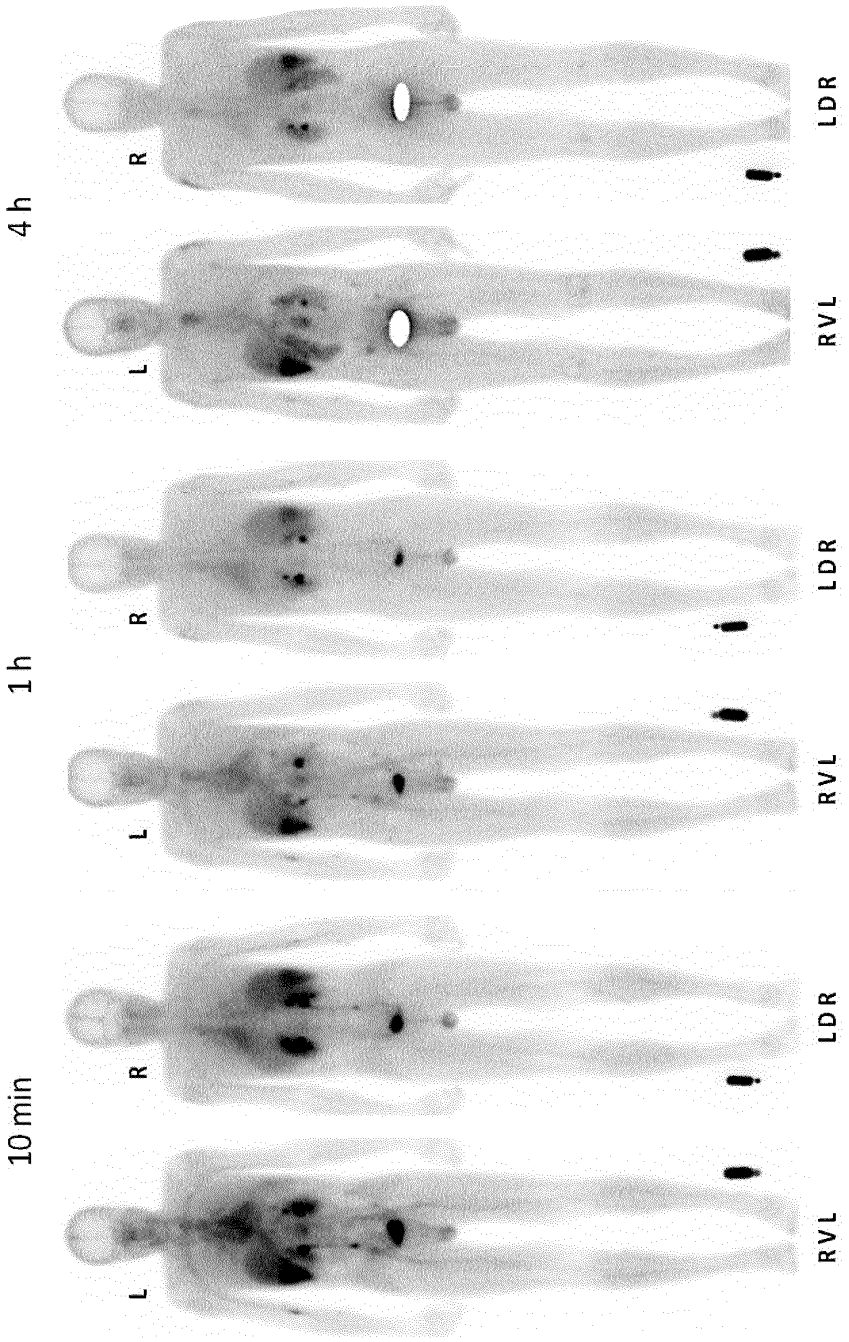


Figure 34

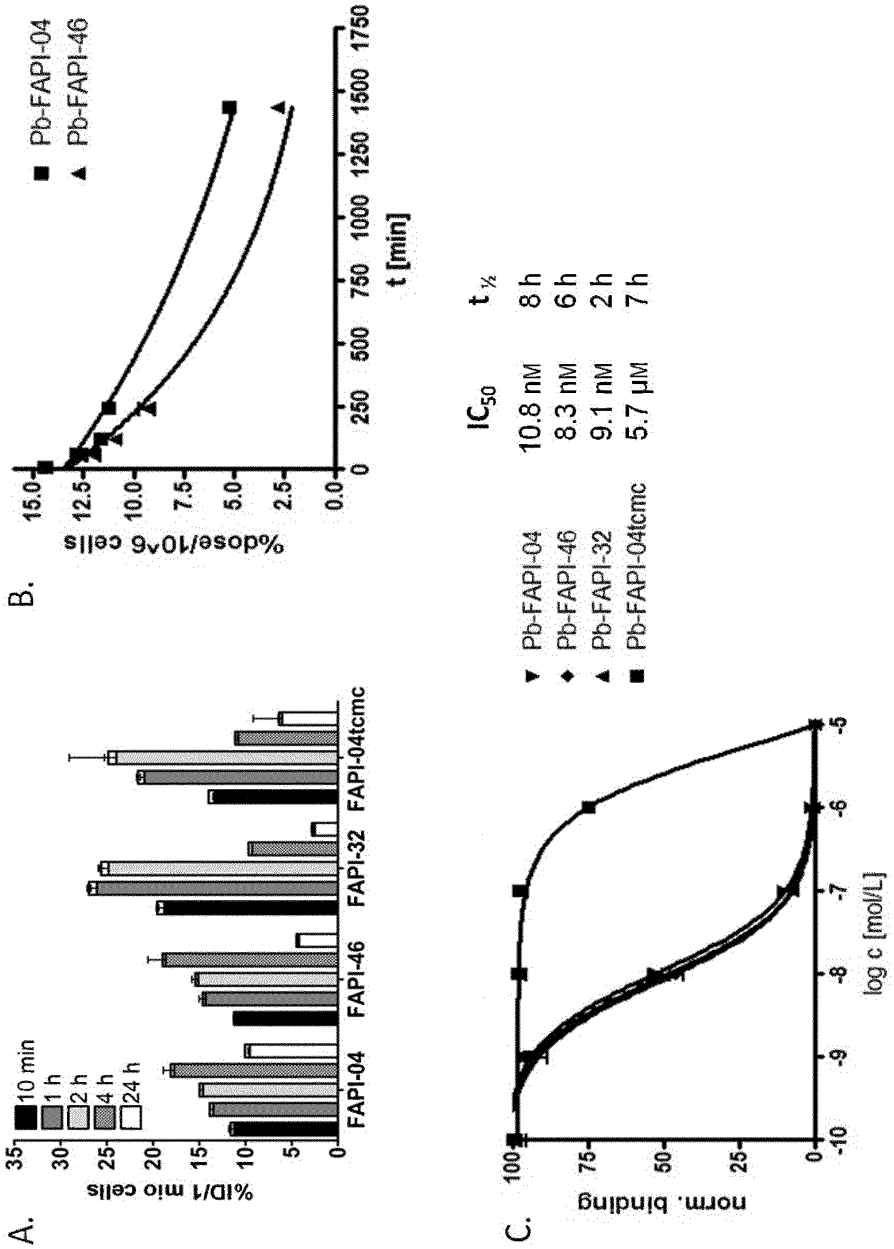

A.
%ID/1 mio cells
10 min
1 h
2 h
4 h
24 h
FAPI-04
FAPI-46
FAPI-32
FAPI-04tcmc
B.
%dose/10^6 cells
t [min]
Pb-FAPI-04
Pb-FAPI-46
C.
norm. binding
log c [mol/L]
IC50
t ½
Pb-FAPI-04 10.8 nM 8 h
Pb-FAPI-46 8.3 nM 6 h
Pb-FAPI-32 9.1 nM 2 h
Pb-FAPI-04tcmc 5.7 µM 7 h

Figure 35

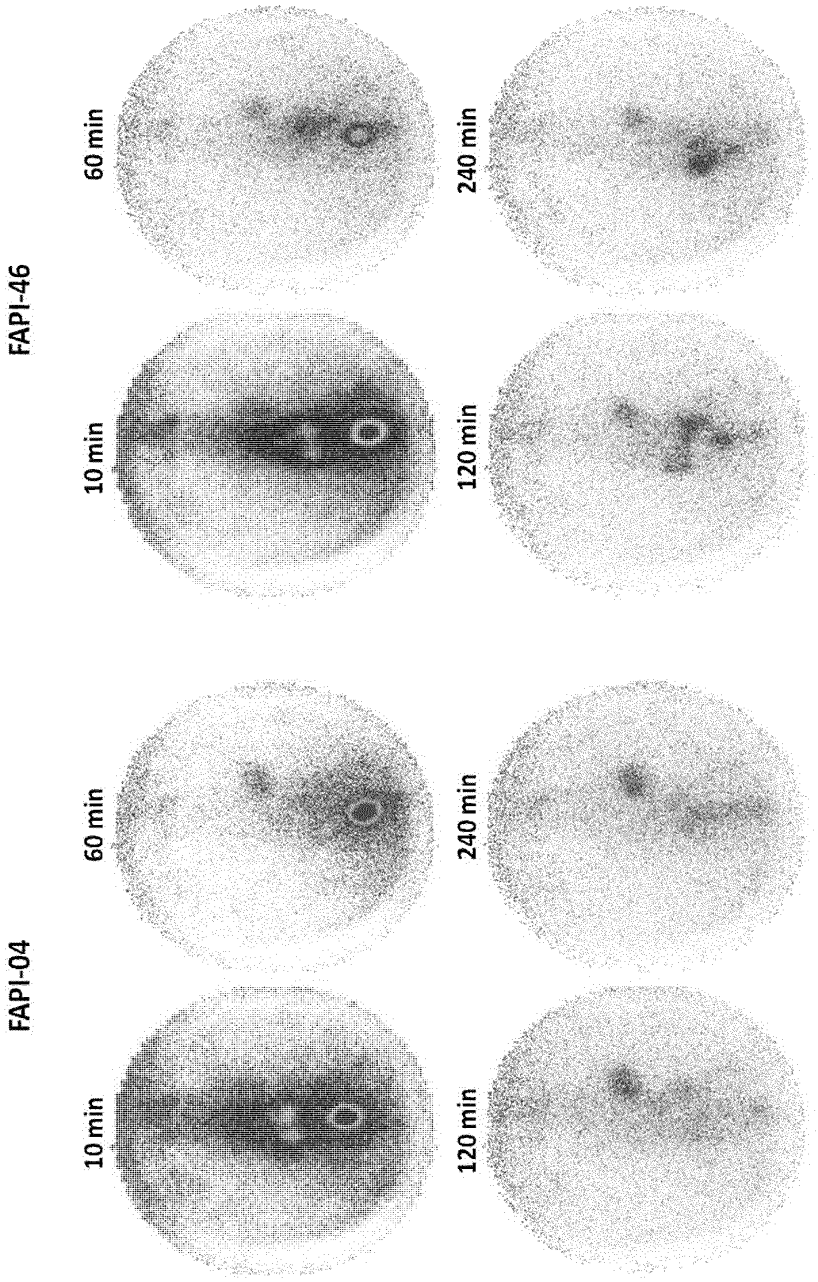

FAPI-46
60 min
240 min
10 min
120 min
FAPI-04
60 min
240 min
10 min
120 min

Figure 36

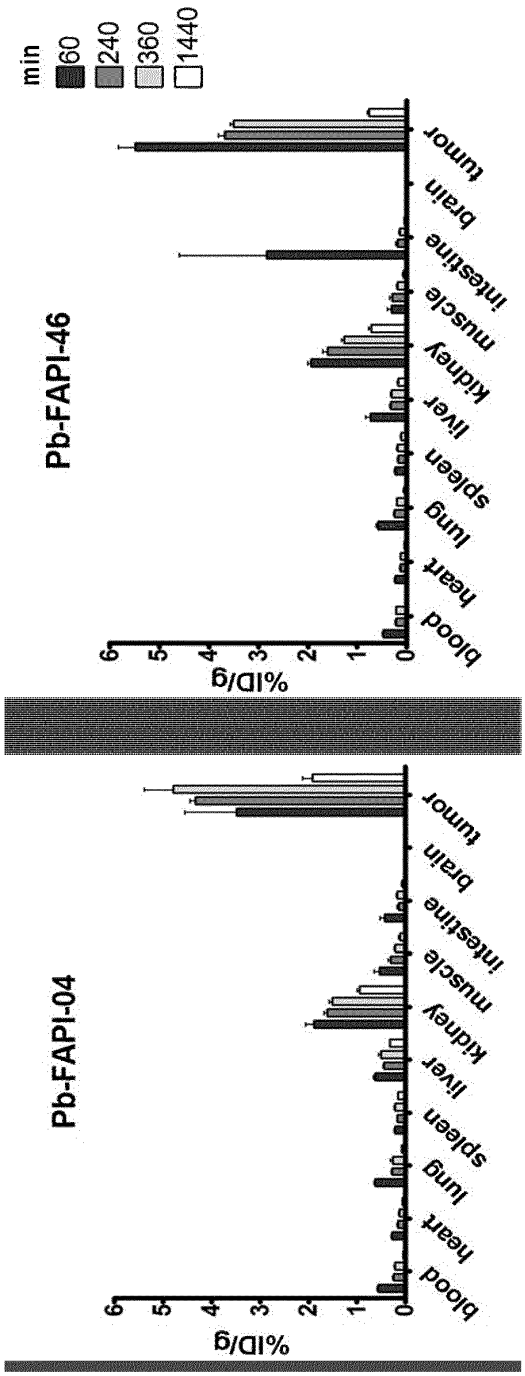

min
60
240
360
1440
Pb-FAPI-46
%ID/g
0
1
2
3
4
5
6
blood
heart
lung
spleen
liver
kidney
muscle
intestine
brain
tumor
Pb-FAPI-04
%ID/g
0
1
2
3
4
5
6
blood
heart
lung
spleen
liver
kidney
muscle
intestine
brain
tumor

Figure 37

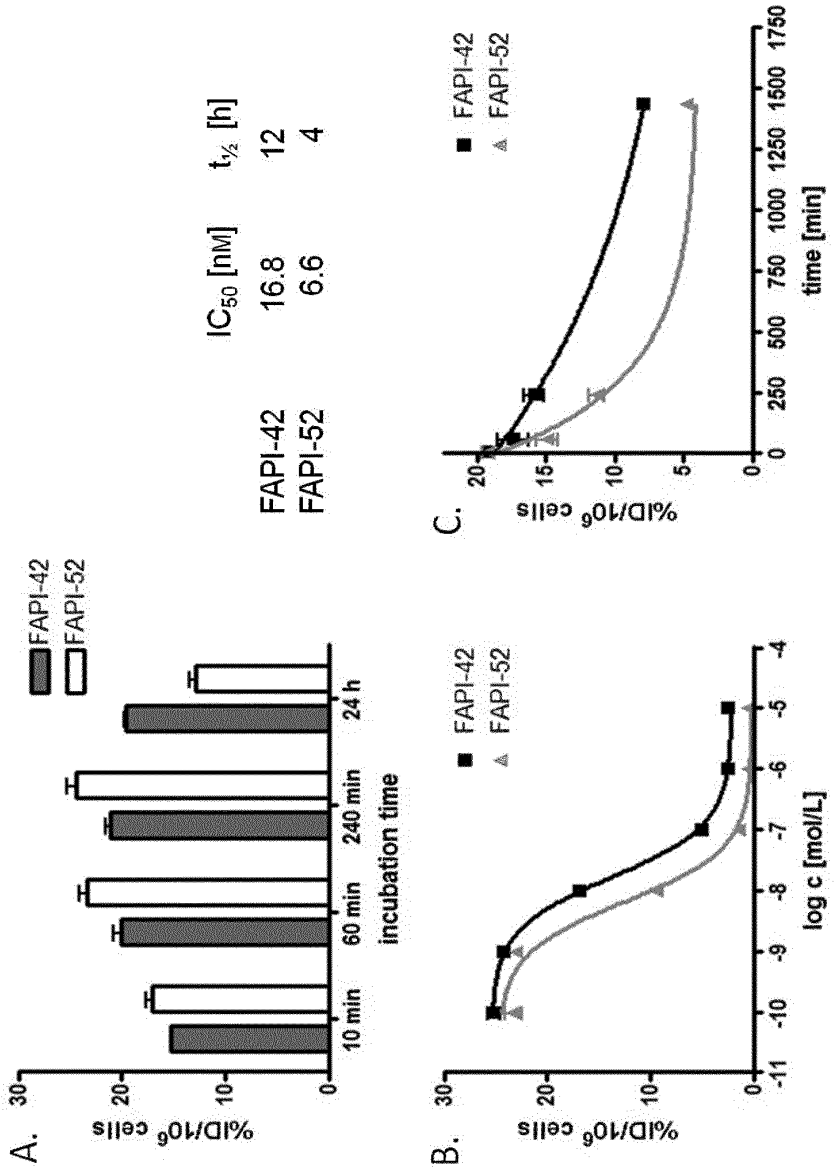

A.
FAPI-42
FAPI-52
%ID/10^6 cells
incubation time
10 min
60 min
240 min
24 h
IC50 [nM] t½ [h]
FAPI-42 16.8 12
FAPI-52 6.6 4
B.
log c [mol/L]
C.
time [min]

Figure 38

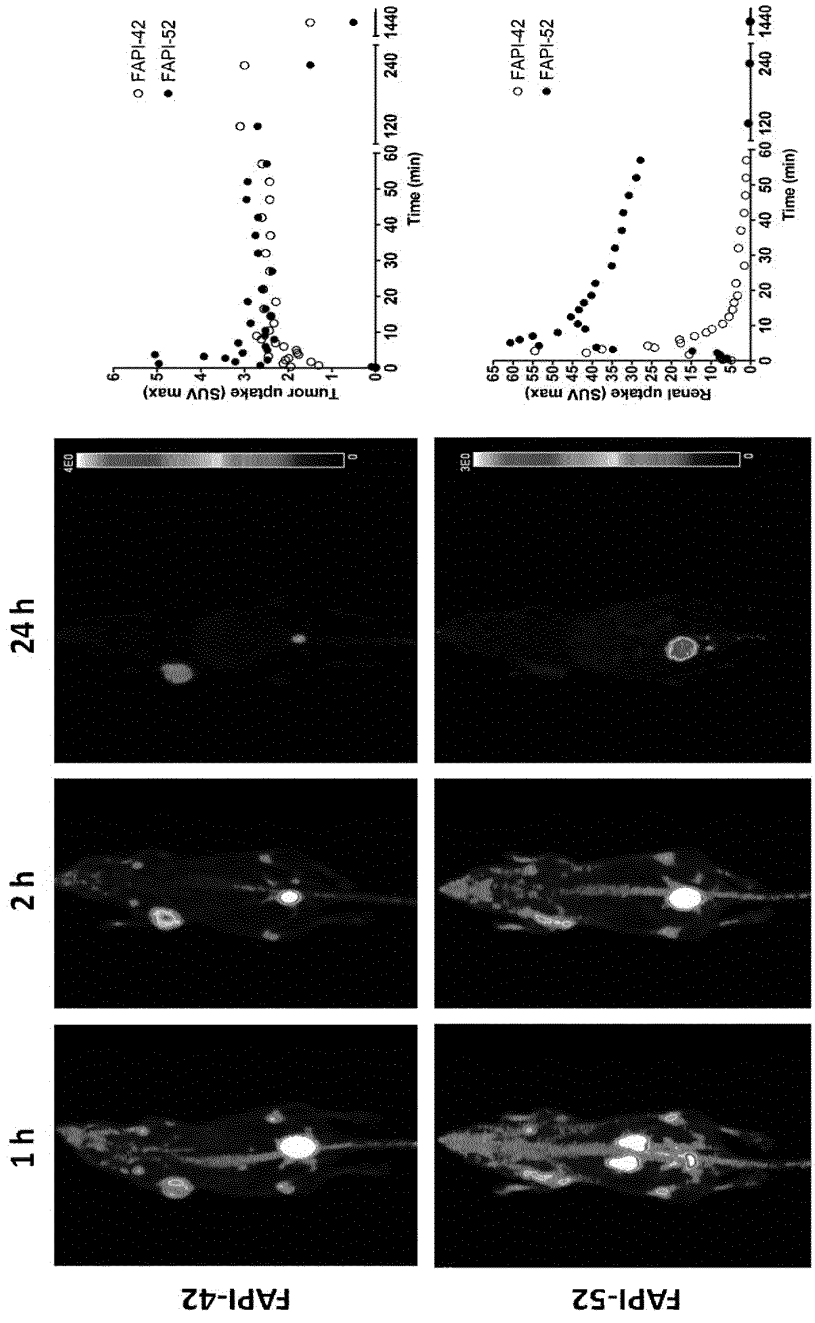

FAPI-42
FAPI-52
Tumor uptake (SUV max)
Renal uptake (SUV max)
Time (min)
0 10 20 30 40 50 60 120 240 1440
24 h
2 h
1 h
FAPI-42
FAPI-52

Figure 39

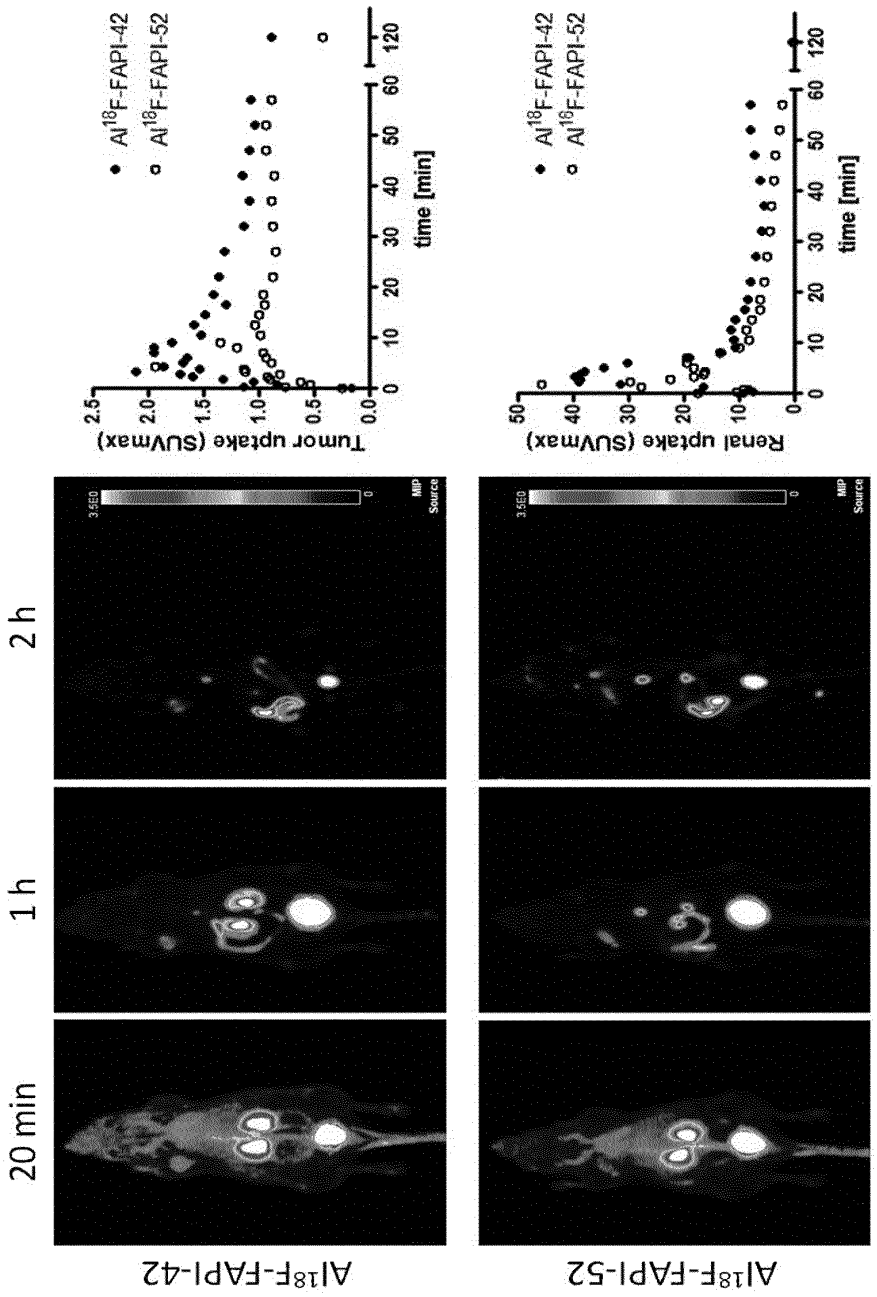

Al18F-FAPI-42
Al18F-FAPI-52
20 min
1 h
2 h
Tumor uptake (SUVmax)
Renal uptake (SUVmax)
time [min]
Al18F-FAPI-42
Al18F-FAPI-52

Figure 40

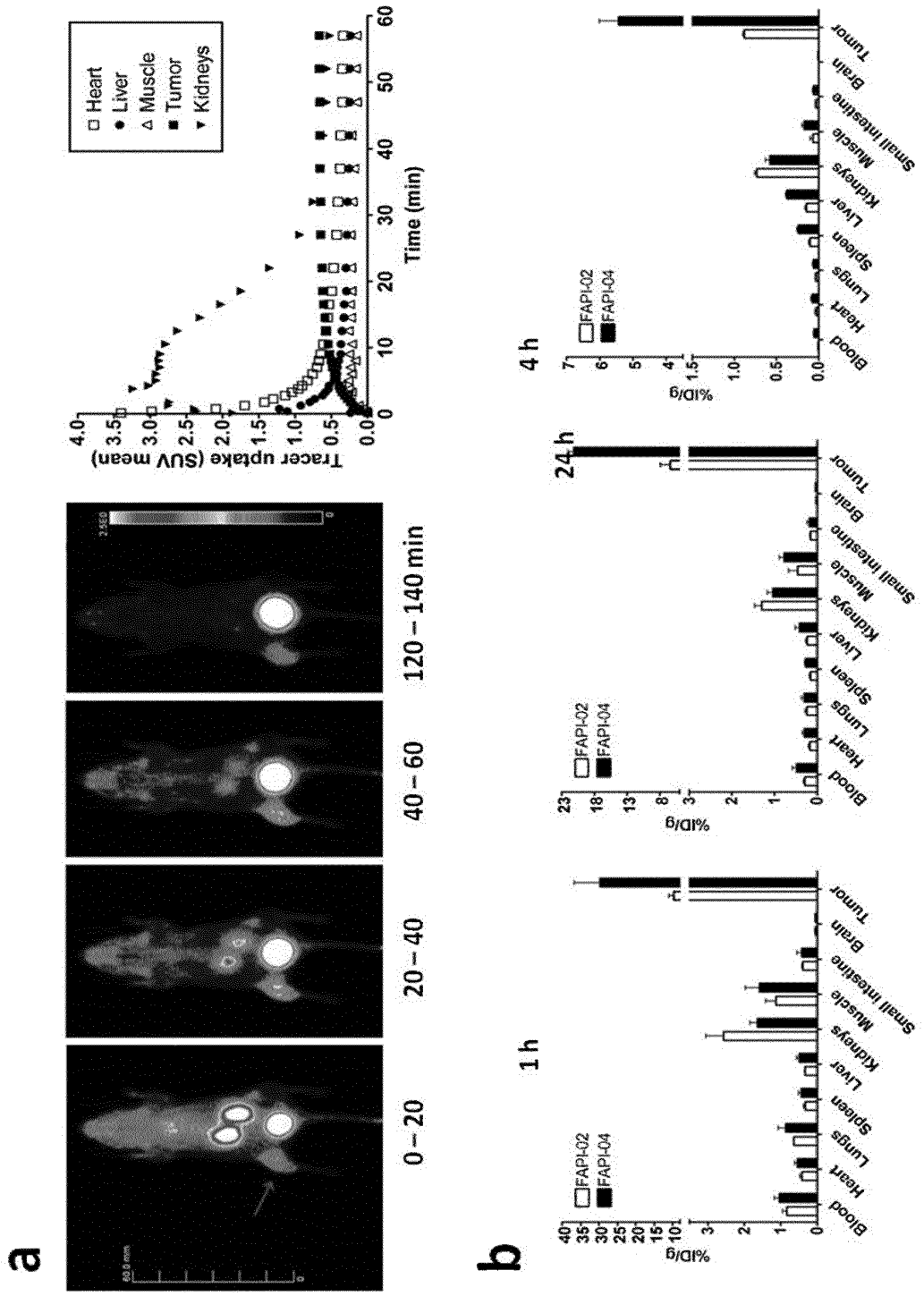

a
0 – 20
20 – 40
40 – 60
120 – 140 min
Tracer uptake (SUV mean)
Time (min)
Heart
Liver
Muscle
Tumor
Kidneys
b
1 h
4 h
24 h
%ID/g
FAPI-02
FAPI-04
Blood
Heart
Lungs
Spleen
Liver
Kidneys
Muscle
Small intestine
Brain
Tumor

Figure 41

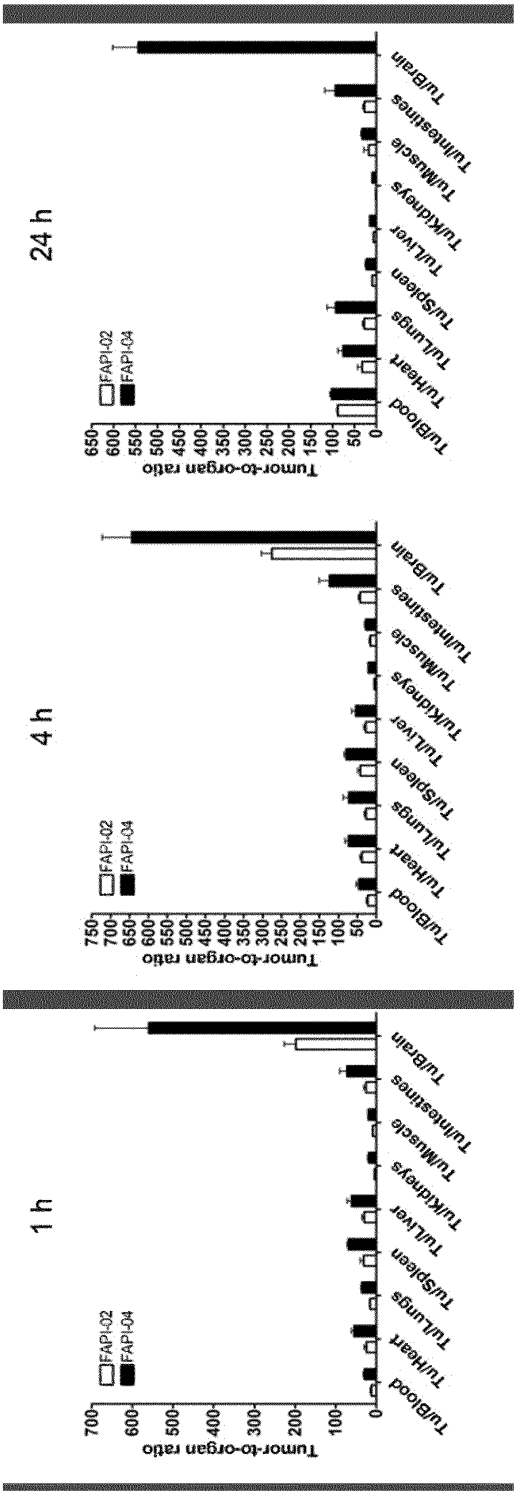

24 h
4 h
1 h
FAPI-02
FAPI-04
Tumor-to-organ ratio
Tu/Blood
Tu/Heart
Tu/Lungs
Tu/Spleen
Tu/Liver
Tu/Kidneys
Tu/Muscle
Tu/Intestines
Tu/Brain

Figure 42

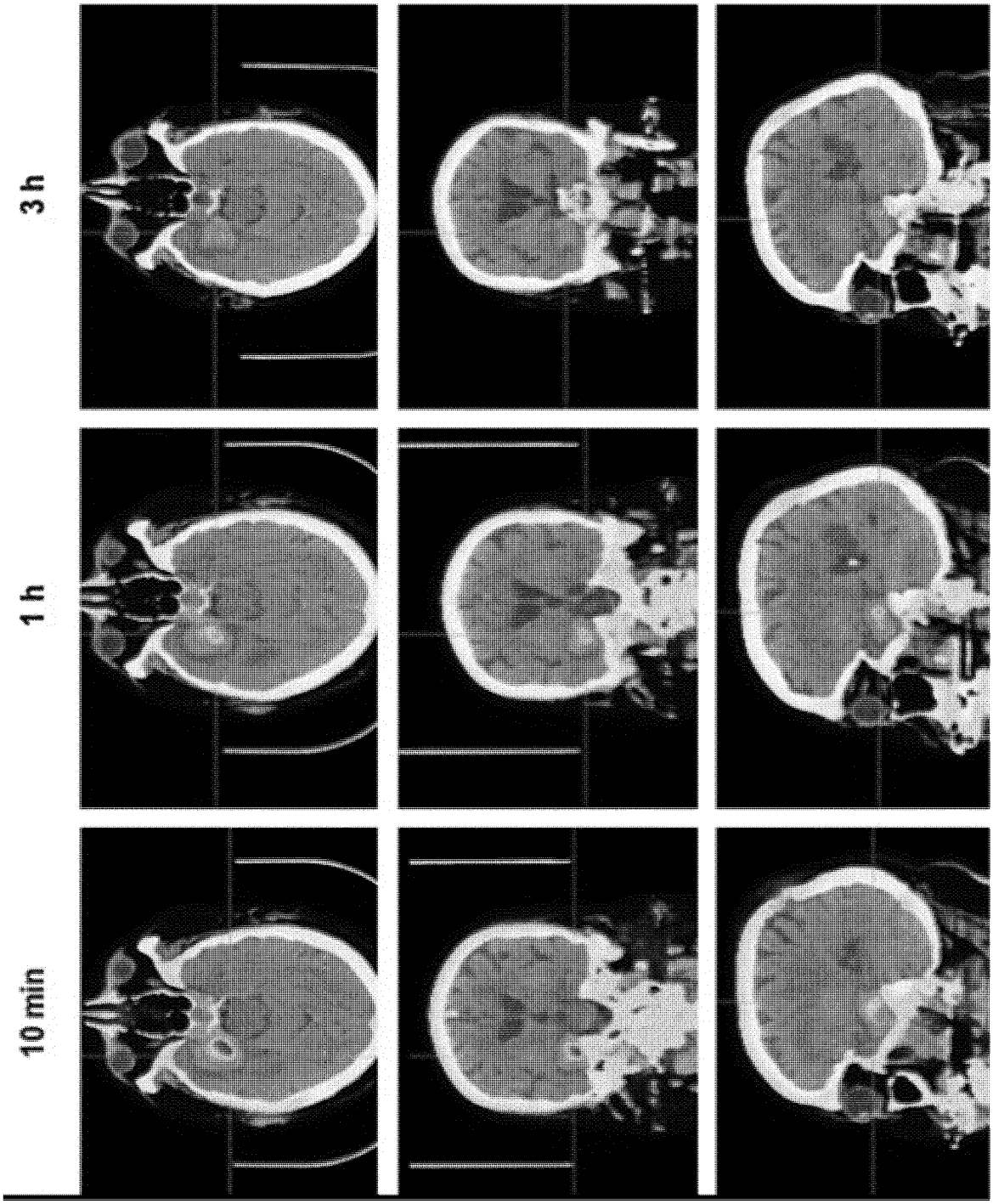


Figure 43

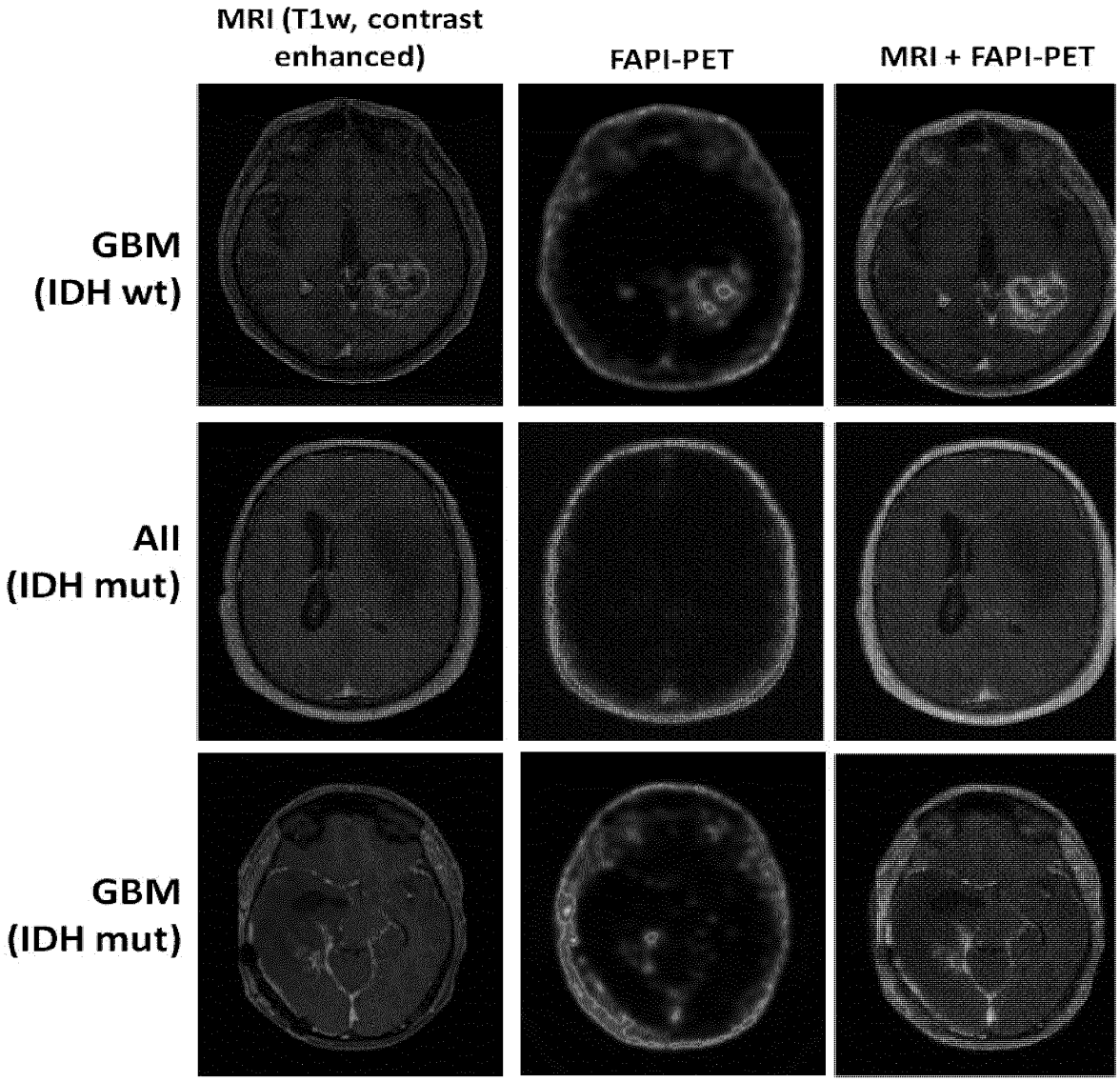

MRI (T1w, contrast enhanced)
FAPI-PET
MRI + FAPI-PET
GBM (IDH wt)
AII (IDH mut)
GBM (IDH mut)

Figure 44

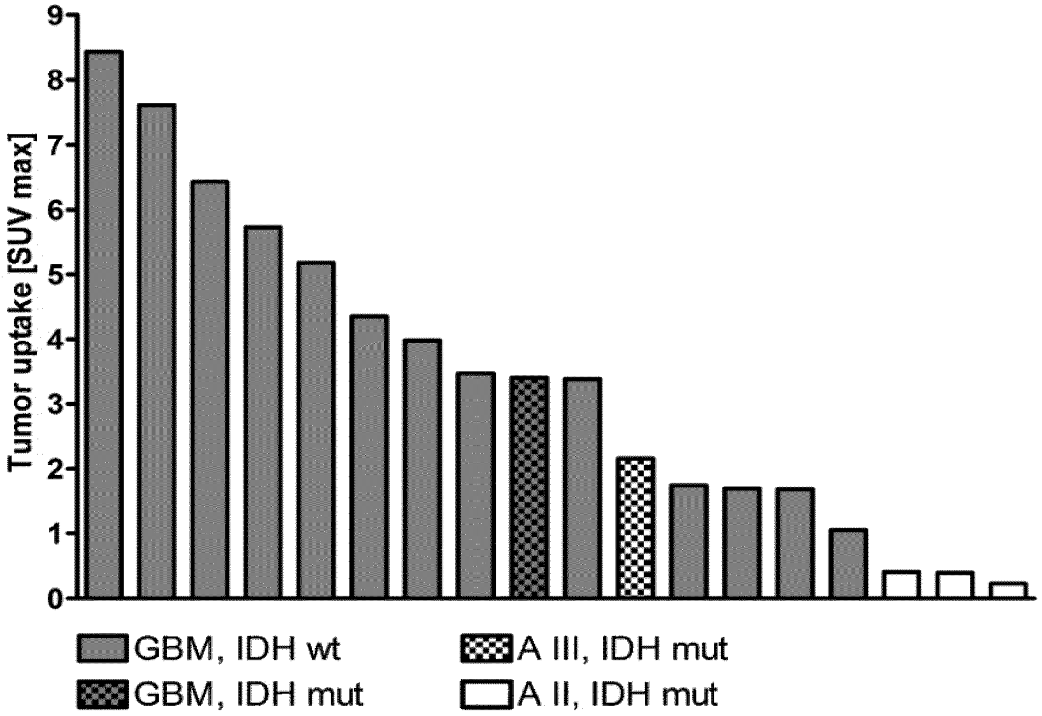

Tumor uptake [SUV max]
9
8
7
6
5
4
3
2
1
0
GBM, IDH wt
GBM, IDH mut
A III, IDH mut
A II, IDH mut

Figure 45

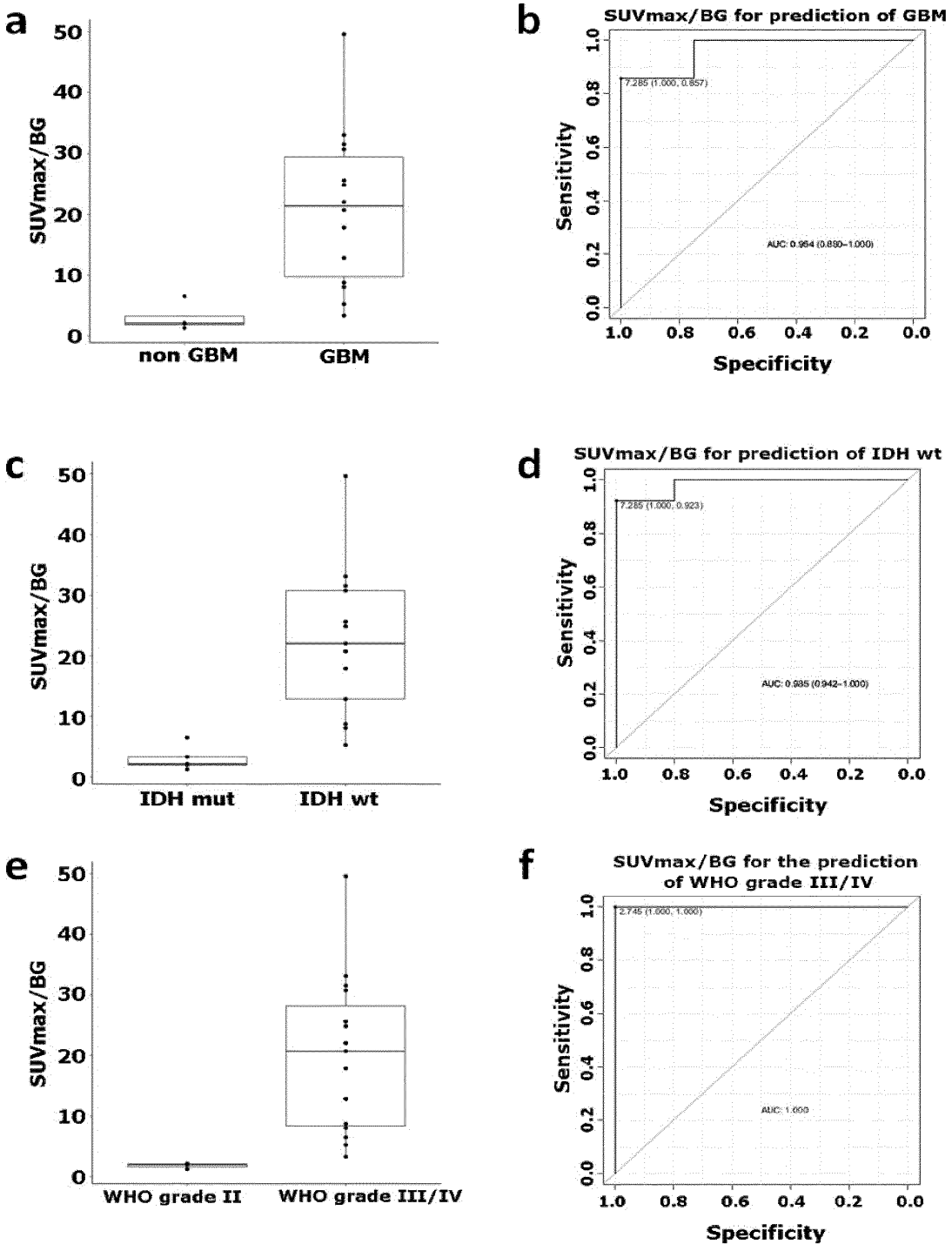

a
SUVmax/BG
50
40
30
20
10
0
non GBM
GBM
b
SUVmax/BG for prediction of GBM
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
7.285 (1.000, 0.857)
AUC: 0.964 (0.890–1.000)
c
SUVmax/BG
IDH mut
IDH wt
d
SUVmax/BG for prediction of IDH wt
7.285 (1.000, 0.923)
AUC: 0.985 (0.942–1.000)
e
SUVmax/BG
WHO grade II
WHO grade III/IV
f
SUVmax/BG for the prediction of WHO grade III/IV
2.745 (1.000, 1.000)
AUC: 1.000

Figure 46

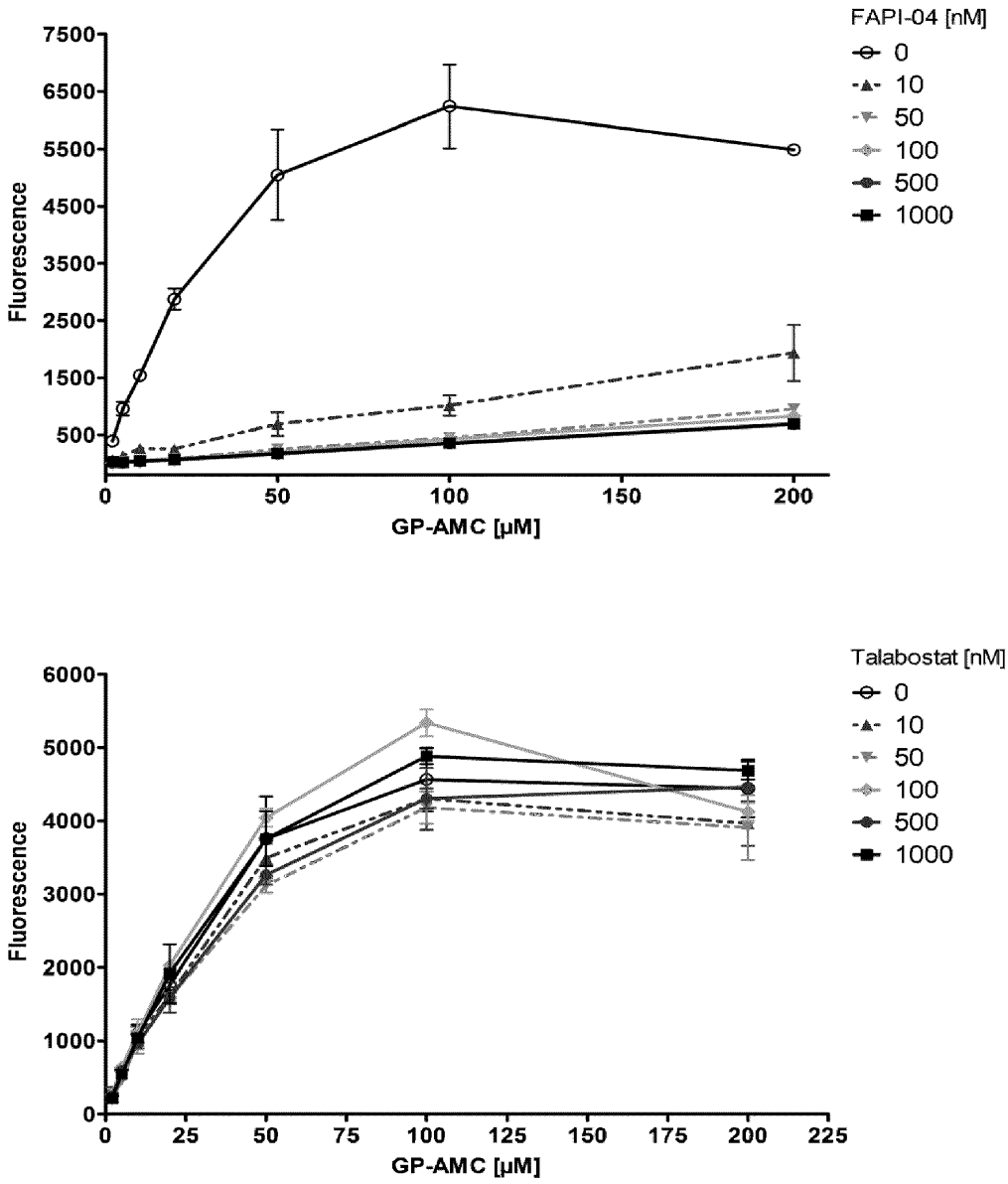
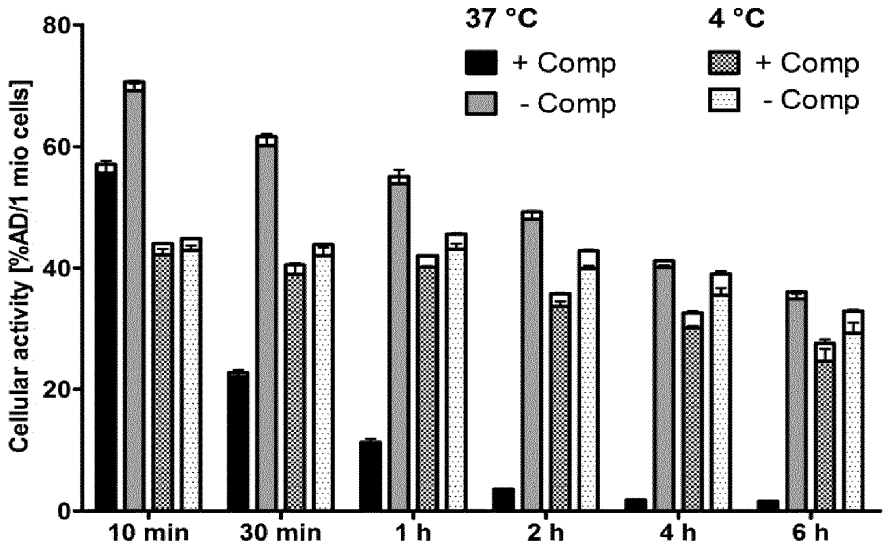

FAPI-04 [nM]
0
10
50
100
500
1000
Fluorescence
7500
6500
5500
4500
3500
2500
1500
500
0
50
100
150
200
GP-AMC [µM]
Talabostat [nM]
0
10
50
100
500
1000
Fluorescence
6000
5000
4000
3000
2000
1000
0
0
25
50
75
100
125
150
175
200
225
GP-AMC [µM]

Figure 47

FAPI-04



FAPI-46

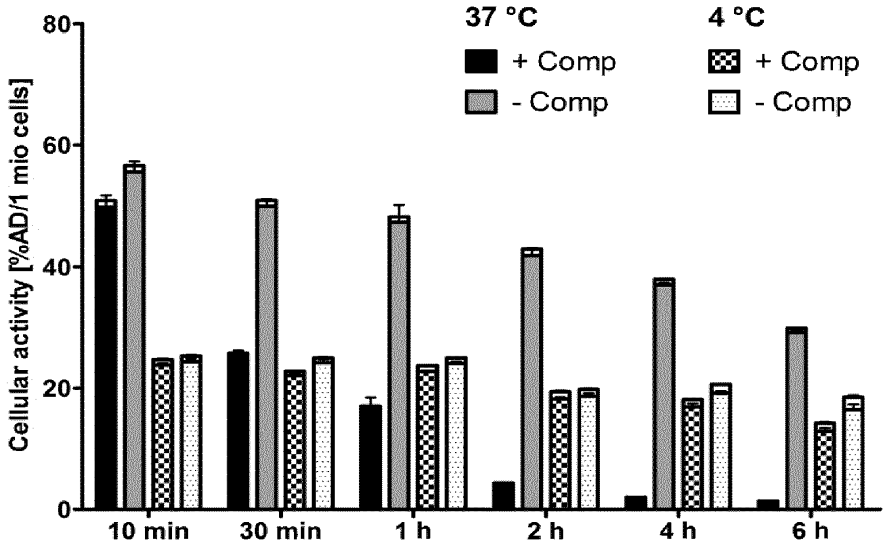


Figure 48

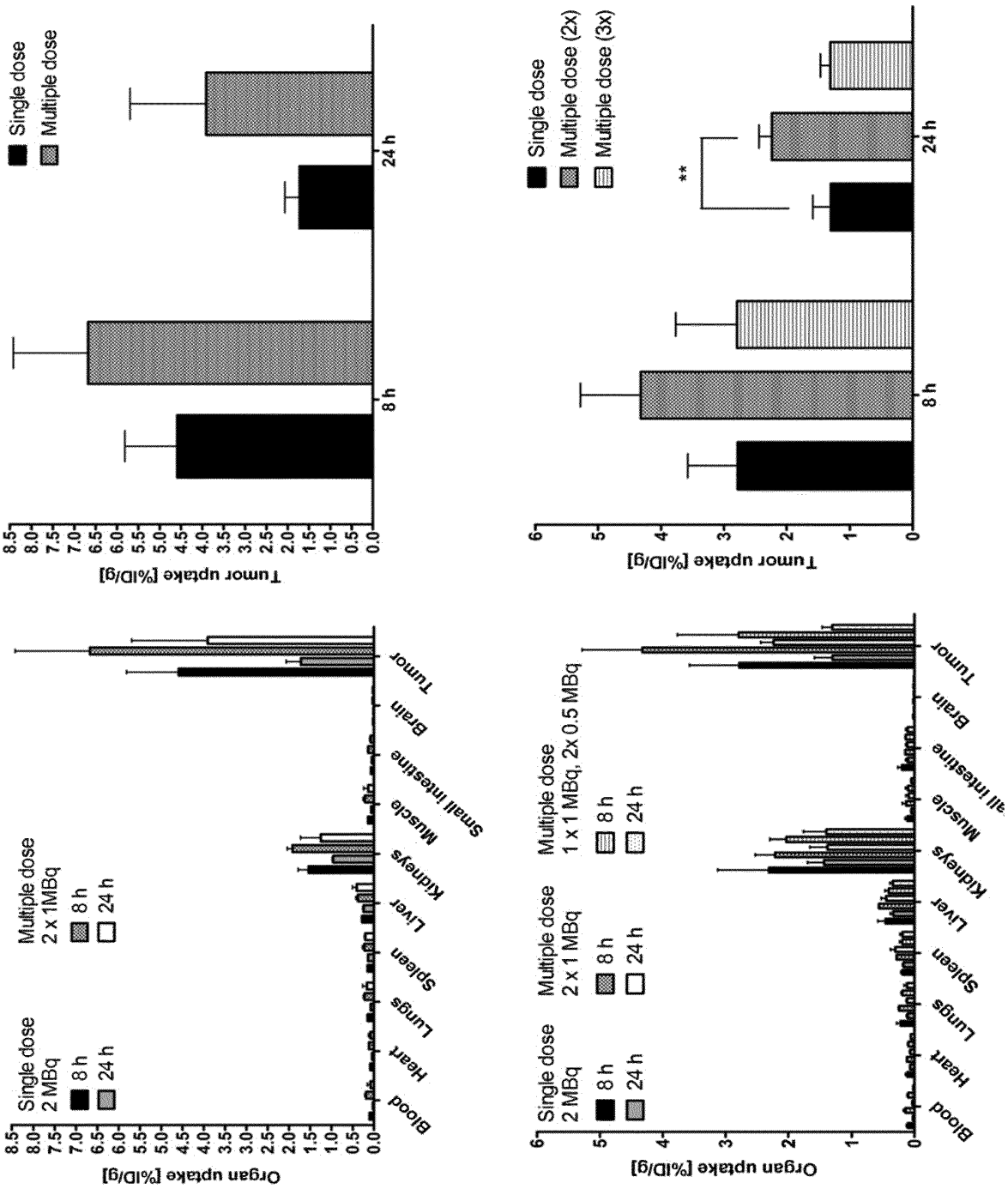

Single dose
Multiple dose
Tumor uptake [%ID/g]
8 h
24 h
Single dose
Multiple dose (2x)
Multiple dose (3x)
**
Organ uptake [%ID/g]
Single dose
2 MBq
8 h
24 h
Multiple dose
2 x 1MBq
Multiple dose
2 x 1 MBq
Multiple dose
1 x 1 MBq, 2x 0.5 MBq
Blood
Heart
Lungs
Spleen
Liver
Kidneys
Muscle
Small intestine
Brain
Tumor

Figure 49

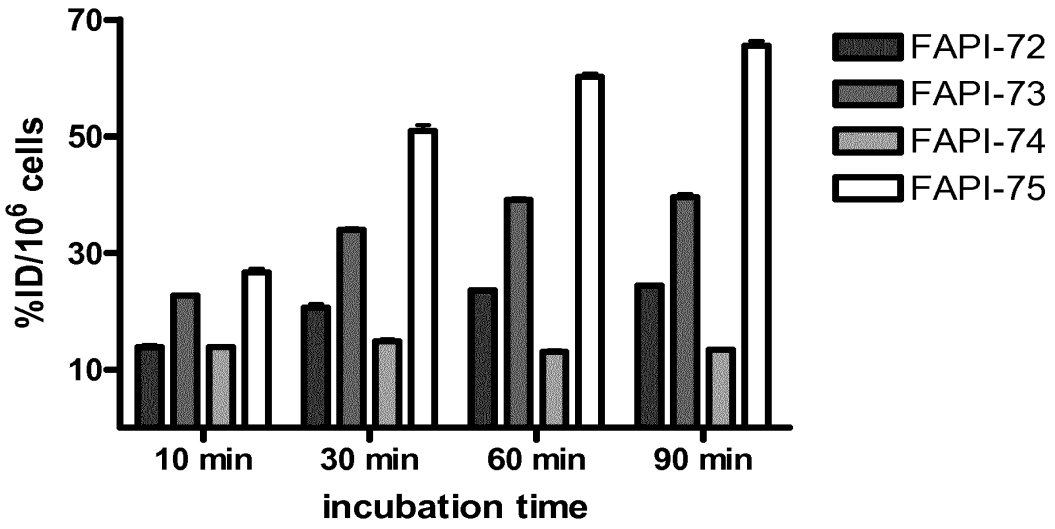

70
50
30
10
%ID/10^6 cells
10 min
30 min
60 min
90 min
incubation time
FAPI-72
FAPI-73
FAPI-74
FAPI-75

Figure 50

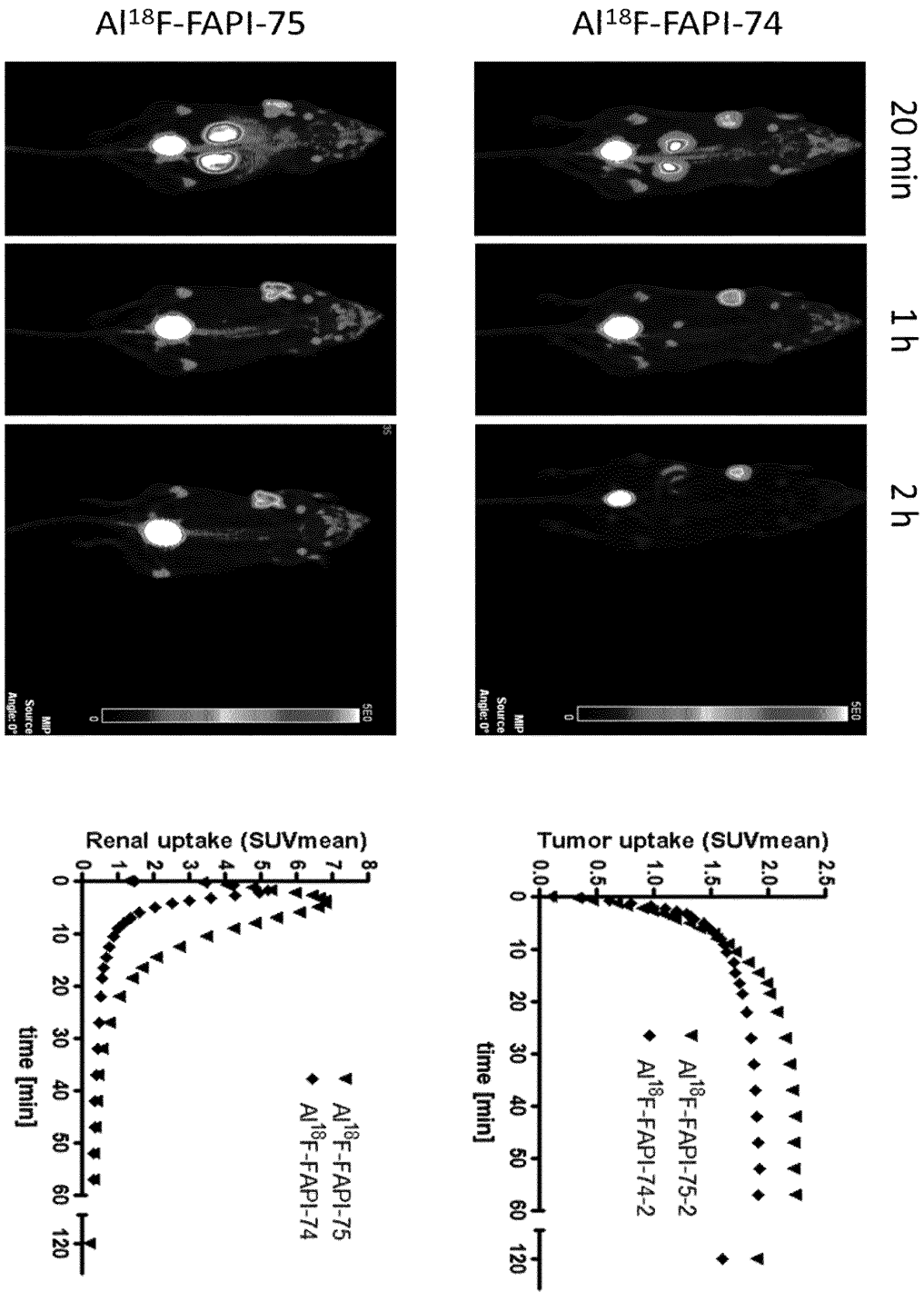

Al18F-FAPI-75
Al18F-FAPI-74
20 min
1 h
2 h
Renal uptake (SUVmean)
time [min]
Al18F-FAPI-75
Al18F-FAPI-74
Tumor uptake (SUVmean)
time [min]
Al18F-FAPI-75-2
Al18F-FAPI-74-2

Figure 51

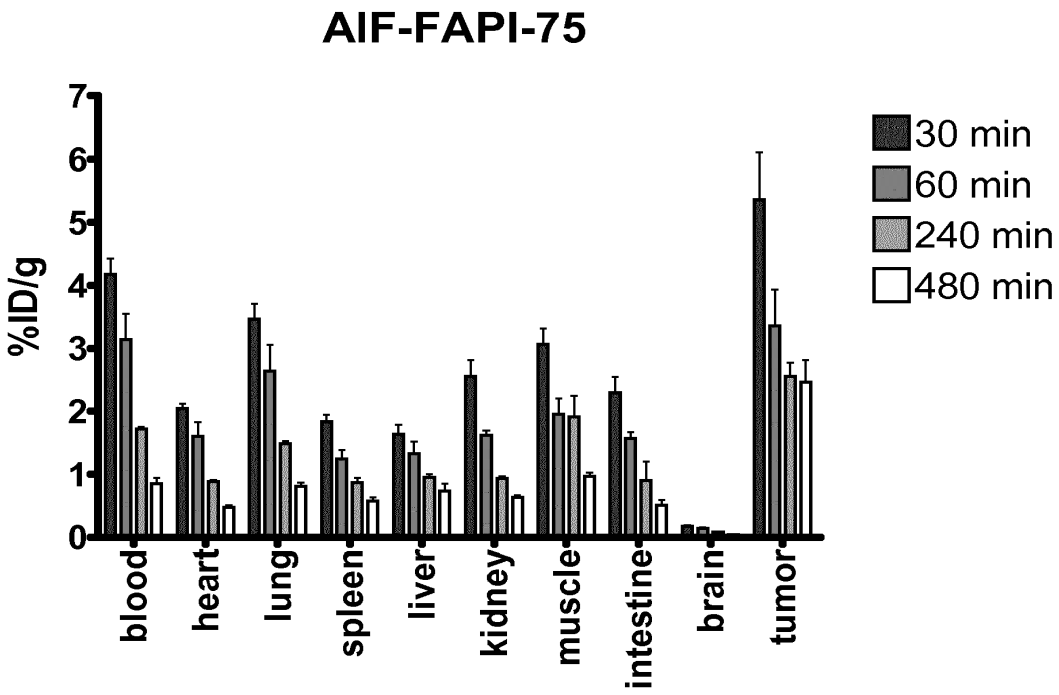
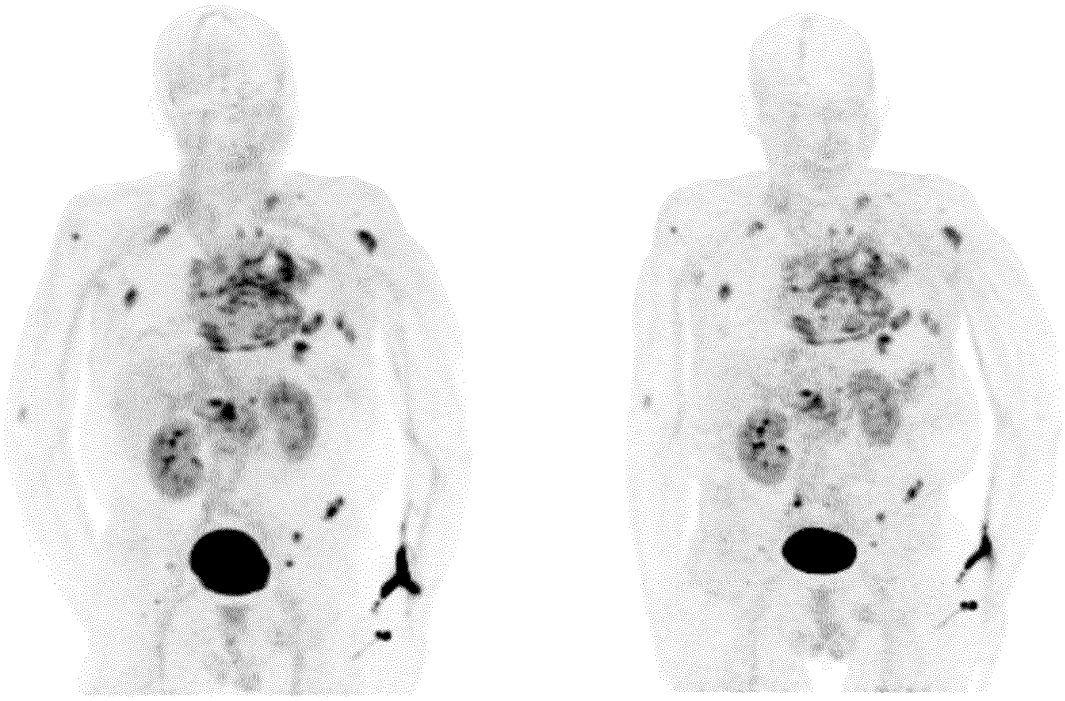
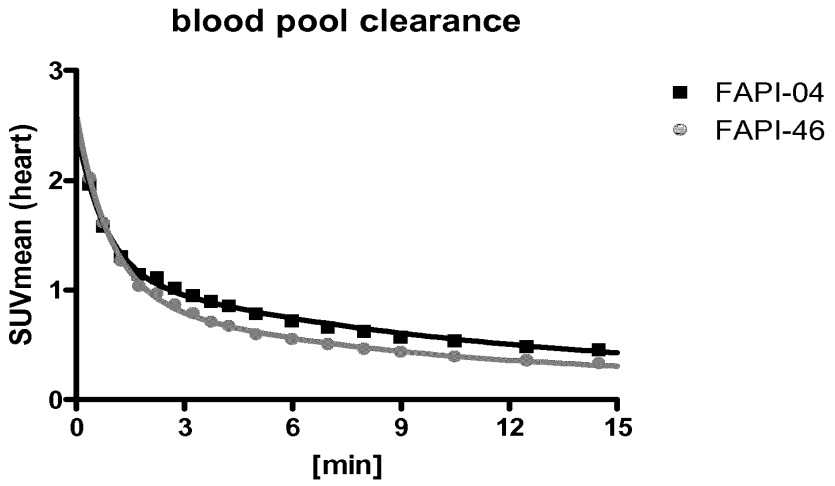

AlF-FAPI-75
%ID/g
0
1
2
3
4
5
6
7
blood
heart
lung
spleen
liver
kidney
muscle
intestine
brain
tumor
30 min
60 min
240 min
480 min

Figure 52



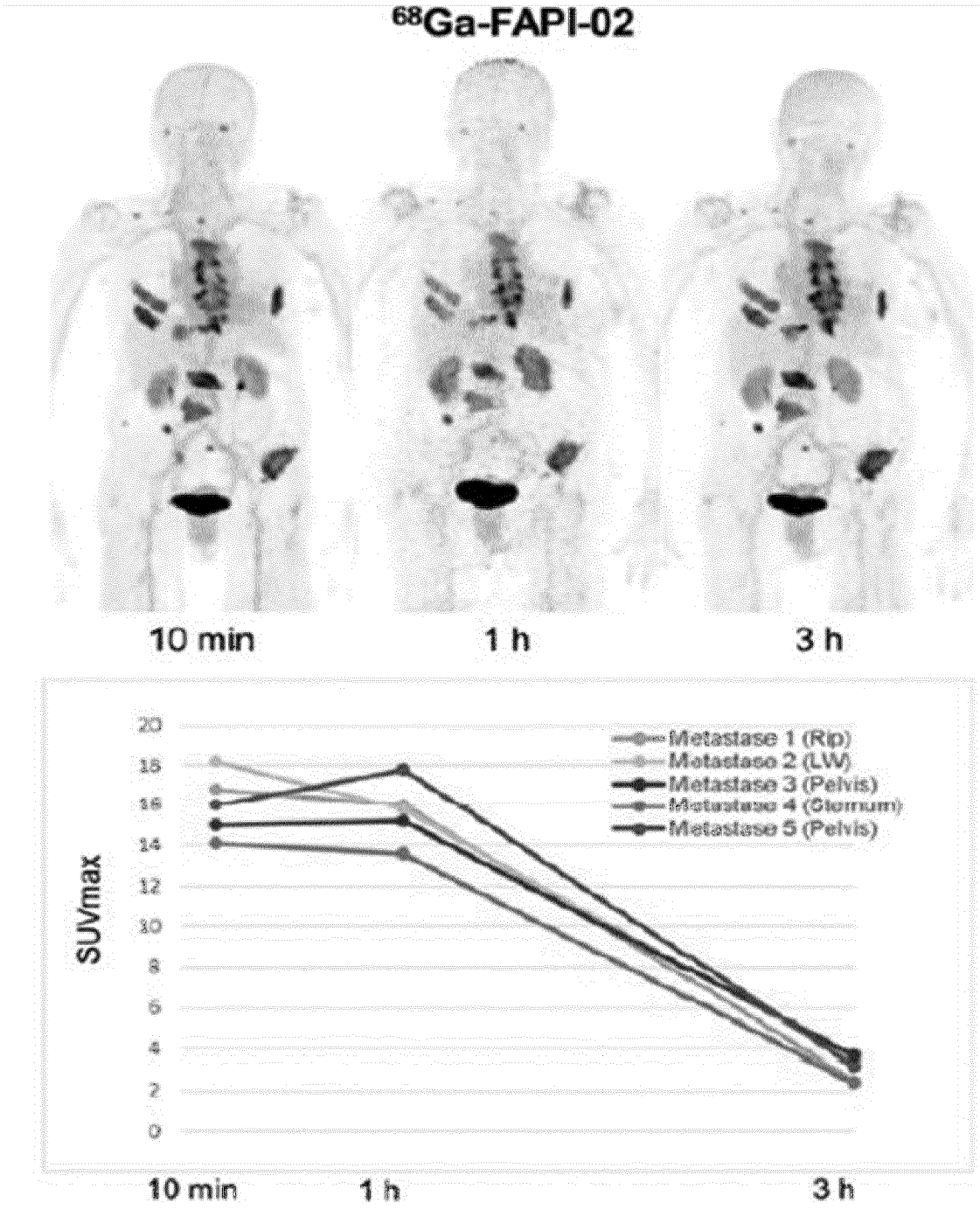
1 h p.i. 3 h p.i.

Figure 53



5

Figure 54



ITM Exhibit 1004, Page 1133 of 1652

Figure 54 continued

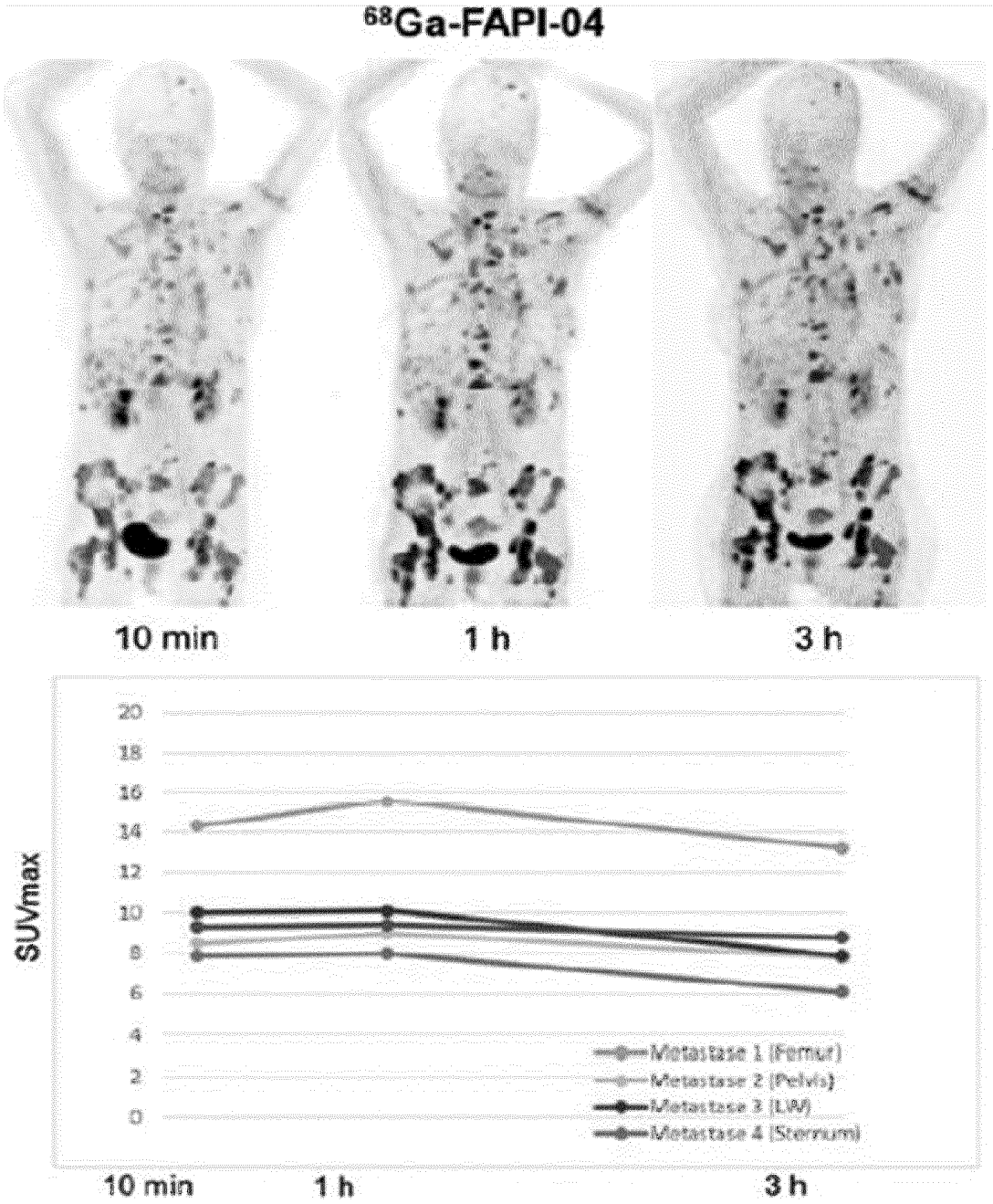


Figure 55

	FAPI-2	FAPI-4
Adrenals	1.23E-02	1.12E-02
Brain	9.54E-03	9.11E-03
Breasts	9.58E-03	8.88E-03
Gallbladder Wall	1.19E-02	1.13E-02
LLI Wall	1.23E-02	1.17E-02
Small Intestine	1.19E-02	1.13E-02
Stomach Wall	1.13E-02	1.06E-02
ULI Wall	1.17E-02	1.11E-02
Heart Wall	4.73E-02	2.02E-02
Kidneys	4.45E-02	4.43E-02
Liver	1.51E-02	1.46E-02
Lungs	1.09E-02	9.89E-03
Muscle	1.04E-02	9.91E-03
Ovaries	1.24E-02	1.19E-02
Pancreas	1.23E-02	1.13E-02
Red Marrow	3.28E-02	2.08E-02
Osteogenic Cells	2.94E-02	2.16E-02
Skin	9.01E-03	8.63E-03
Spleen	2.62E-02	1.05E-02
Testes	1.04E-02	1.01E-02
Thymus	1.15E-02	1.01E-02
Thyroid	1.03E-02	9.82E-03
Urinary Bladder Wall	8.89E-02	9.91E-02
Uterus	1.33E-02	1.30E-02
Total Body	1.19E-02	1.09E-02
Effective Dose (mSv/MBq)	1.80E-02	1.64E-02

Figure 56

A)

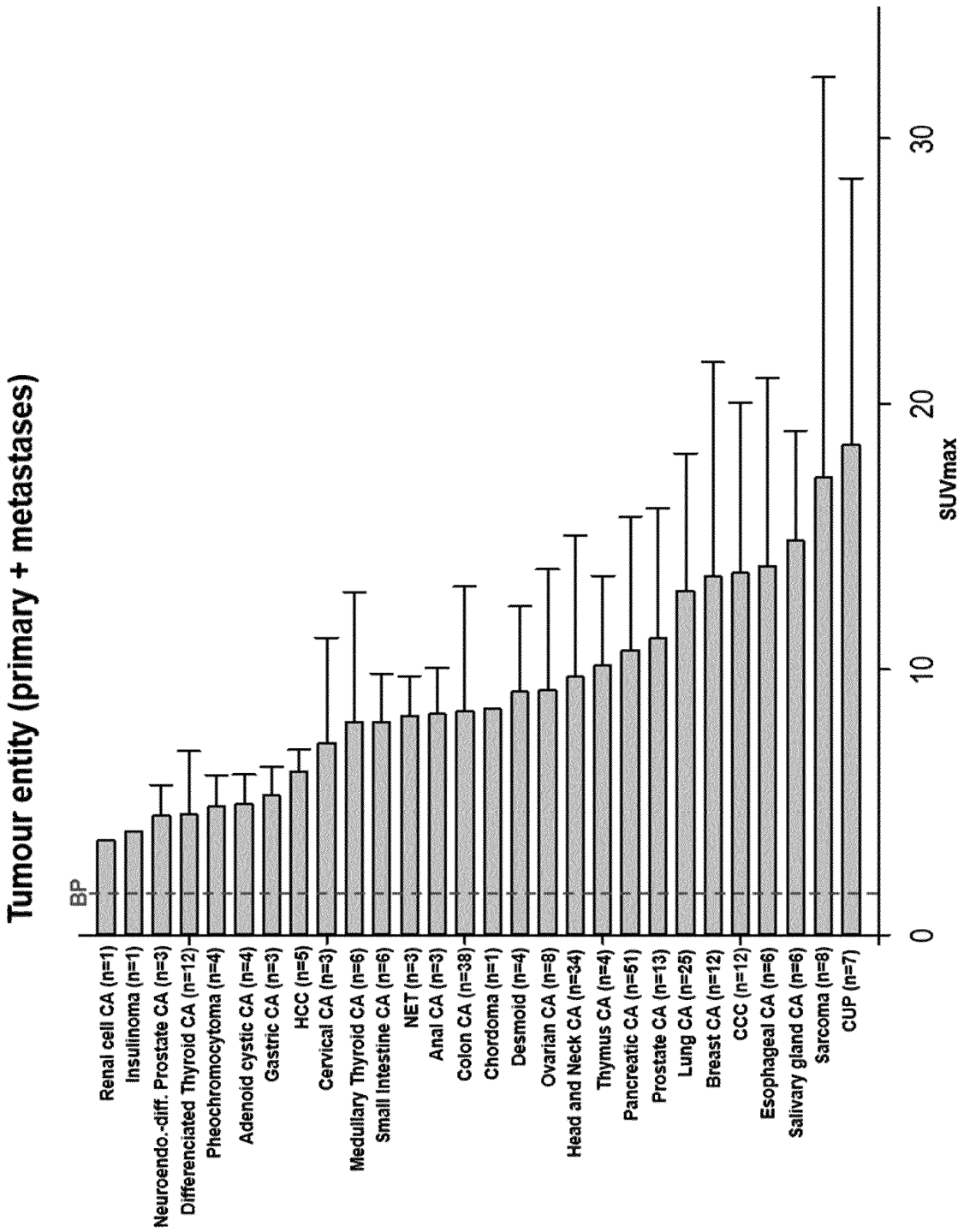

Tumour entity (primary + metastases)
BP
SUVmax
0
10
20
30
Renal cell CA (n=1)
Insulinoma (n=1)
Neuroendo.-diff. Prostate CA (n=3)
Differenciated Thyroid CA (n=12)
Pheochromocytoma (n=4)
Adenoid cystic CA (n=4)
Gastric CA (n=3)
HCC (n=5)
Cervical CA (n=3)
Medullary Thyroid CA (n=6)
Small Intestine CA (n=6)
NET (n=3)
Anal CA (n=3)
Colon CA (n=38)
Chordoma (n=1)
Desmoid (n=4)
Ovarian CA (n=8)
Head and Neck CA (n=34)
Thymus CA (n=4)
Pancreatic CA (n=51)
Prostate CA (n=13)
Lung CA (n=25)
Breast CA (n=12)
CCC (n=12)
Esophageal CA (n=6)
Salivary gland CA (n=6)
Sarcoma (n=8)
CUP (n=7)

Figure 56 continued

B)

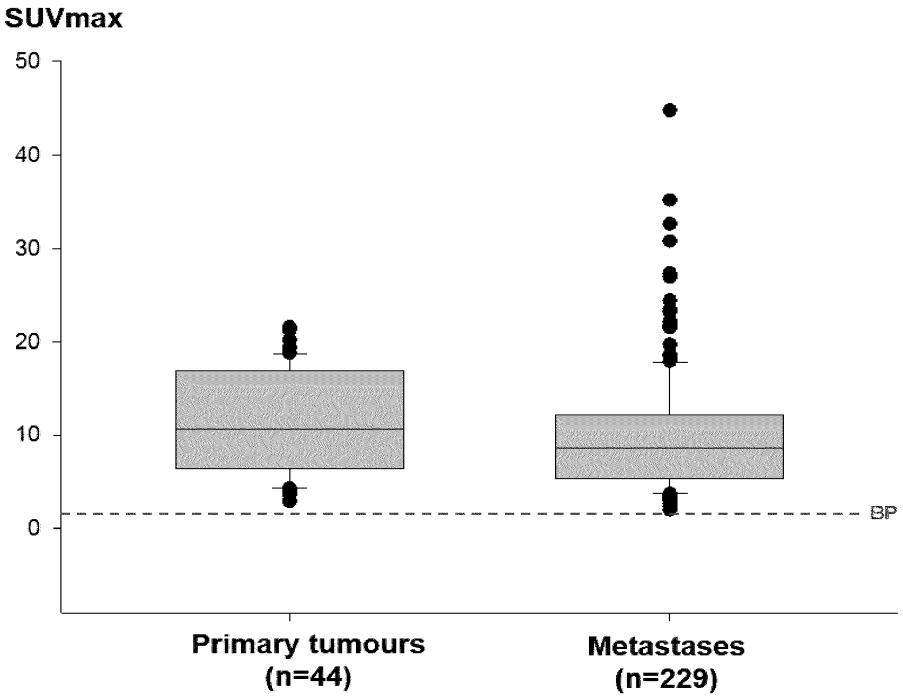
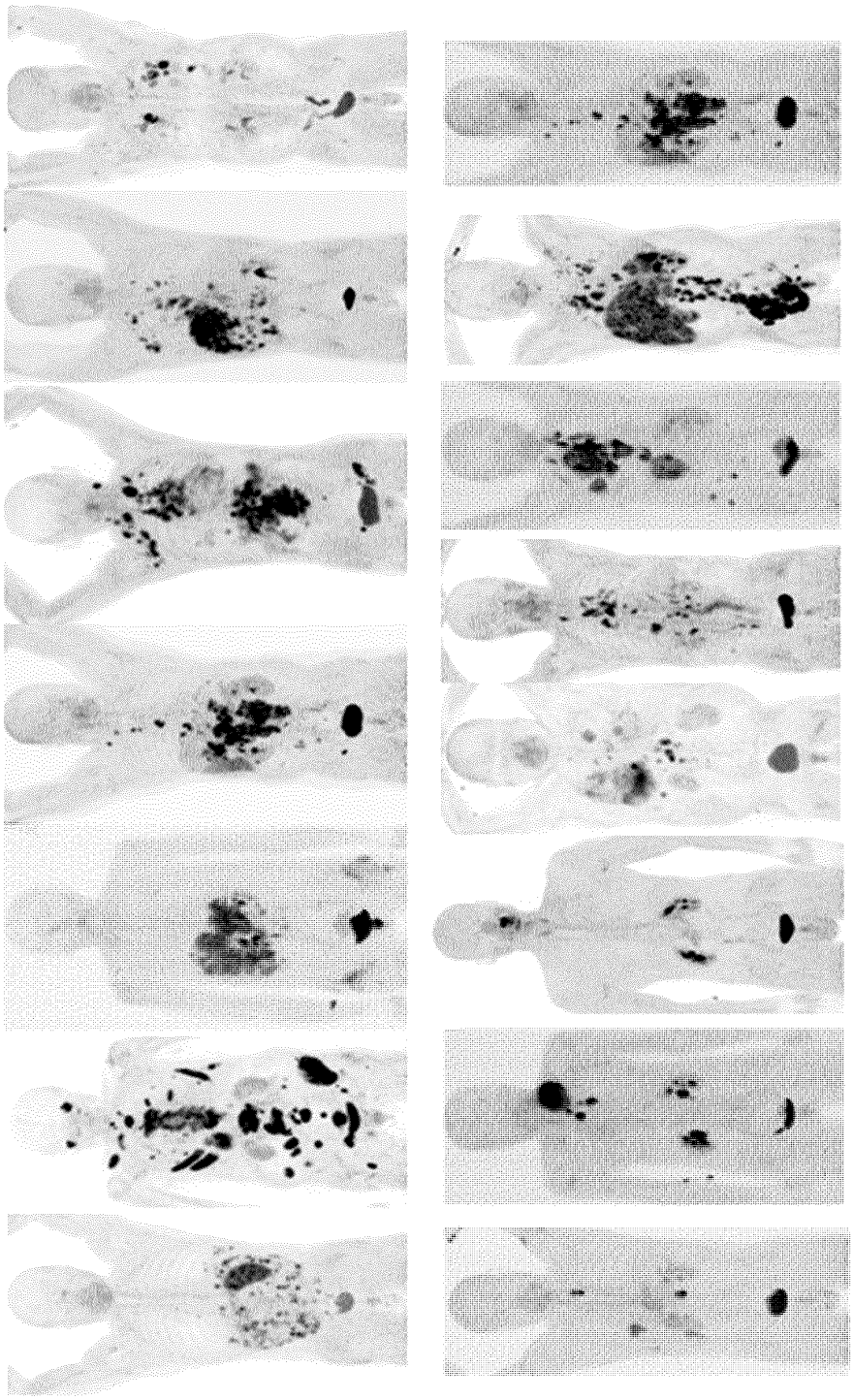


Figure 57



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/052952

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D401/14 C07D405/14 A61K31/4709 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)
C07D A61K A61P

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/107820 A1 (UNIV ANTWERPEN [BE]; FOX CHASE CANCER CT [US]) 25 July 2013 (2013-07-25) page 709, line 21 - page 88, line 15; claims	1-15
Y	WO 2013/033396 A2 (TUFTS COLLEGE [US]; BACHOVCHIN WILLIAM W [US]; LAI HUNG-SEN [US]; POPL) 7 March 2013 (2013-03-07) claims; examples	1-15
Y	WO 2017/165473 A1 (UNIV JOHNS HOPKINS [US]) 28 September 2017 (2017-09-28) claims; examples	1-15

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2019	29/03/2019

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	Gavriliu, Daniela

2

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

ITM Exhibit 1004, Page 1139 of 1652

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AL JAMMAZ ER AL.: "Rapid and efficient synthesis of [18F]fluoronicotinamides, [18F]fluoroisonicotinamides and [18F]fluorobenzamides as potential pet radiopharmaceuticals for melanoma imaging", JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, vol. 54, no. 6, 2011, pages 312-317, XP002782854, DOI: 10.1002/jlcr.1869 the whole document	1-15
Y	WO 2011/158189 A1 (CENTRE NAT RECH SCIENT [FR]; UNIV PARIS DESCARTES [FR]; DALKO PETER [F) 22 December 2011 (2011-12-22) the whole document	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2019/052952

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6, 8-15(all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-6, 8-15(all partially)

The present claim 1 relates to an extremely large number of possible compounds. Support and disclosure within the meaning of Articles 6 and 5 PCT are to be found, however, for only a very small proportion of the compounds claimed, namely for compounds as claimed in claim 7. Claim 1 can in no way be considered to be a reasonable generalisation of the actual examples since it include numerous possibilities which cannot be considered as equivalents, homologues or analogues of the examples (see the the present examples which contain all of them a quinoliyn-4-yl moiety as embodiment for the ring X, the substituents Q, R, U are always absent, R1/R2 are H or F, V=CO, W=NH, Y=CH2, Z=CO). Consequently, the search was carried out for those parts of the application which do appear to be clear (concise and supported by the examples), namely for the compounds as defined in Claims 7.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/052952

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013107820 A1	25-07-2013	EP 2804859 A1	26-11-2014
		US 2014357650 A1	04-12-2014
		WO 2013107820 A1	25-07-2013
WO 2013033396 A2	07-03-2013	AU 2012301810 A1	10-04-2014
		AU 2017204121 A1	06-07-2017
		CA 2846852 A1	07-03-2013
		CN 103945856 A	23-07-2014
		CN 108383893 A	10-08-2018
		EP 2753334 A2	16-07-2014
		JP 6207509 B2	04-10-2017
		JP 2014527070 A	09-10-2014
		JP 2018016629 A	01-02-2018
		US 2014255300 A1	11-09-2014
		US 2016346401 A1	01-12-2016
		US 2019054181 A1	21-02-2019
		WO 2013033396 A2	07-03-2013
WO 2017165473 A1	28-09-2017	AU 2017238181 A1	18-10-2018
		BR 112018069507 A2	29-01-2019
		CA 3018709 A1	28-09-2017
		CN 109311827 A	05-02-2019
		EP 3433238 A1	30-01-2019
		KR 20180134918 A	19-12-2018
		WO 2017165473 A1	28-09-2017
WO 2011158189 A1	22-12-2011	CA 2801807 A1	22-12-2011
		EP 2397466 A1	21-12-2011
		EP 2582672 A1	24-04-2013
		US 2013190284 A1	25-07-2013
		WO 2011158189 A1	22-12-2011

Electronic Acknowledgement Receipt

EFS ID:	48408930
Application Number:	18354282
International Application Number:	
Confirmation Number:	7536
Title of Invention:	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)
First Named Inventor/Applicant Name:	Xing Yang
Customer Number:	101943
Filer:	Jeffrey Childers./Aaron Bottjen
Filer Authorized By:	Jeffrey Childers.
Attorney Docket Number:	JHU-36631.303
Receipt Date:	08-AUG-2023
Filing Date:	18-JUL-2023
Time Stamp:	15:30:15
Application Type:	Utility under 35 USC 111(a)

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	Information Disclosure Statement (IDS) Form (SB08)	2023-08-08_36631-303-IDS_SB08.pdf	46022 247bb7f5587f230539953ed88b79c5bcca89799d	no	4

Warnings:

Information:					
This is not an USPTO supplied IDS fillable form					
2	Foreign Reference	EP18199641.pdf	17148949 f3a2a5725fd108ce02d07d18f88e834bd4100292	no	149
Warnings:					
Information:					
3	Foreign Reference	JP2021512949A.pdf	23045549 f5c29b108e53b17139acba43921c6ac626a69396	no	171
Warnings:					
Information:					
4	Foreign Reference	WO2010014933A2.pdf	3823640 1ec298234312be44fa6893719216d196d728435d	no	64
Warnings:					
Information:					
5	Foreign Reference	WO2010108125A2.pdf	8515844 506ba62b29e0bfb5e34964a46e1bfb51b26eddb2	no	159
Warnings:					
Information:					
6	Foreign Reference	WO2016065142A2.pdf	5159352 3b4a125bb48b122831526d523b31ae79aac5be79	no	128
Warnings:					
Information:					
7	Foreign Reference	WO2019154886A1_Original_document.pdf	18470573 440e432818dd839dc9f75574695f4559cae55b8f	no	195
Warnings:					
Information:					
8	Other reference-Patent/Application/ Search Documents	ThirdPartyPreissuance-16-758-182.pdf	384520 a06781ffdfe7e7ea44486db2b2dc7aae390ccfbf	no	6
Warnings:					
Information:					

9	Other reference-Patent/Application/ Search Documents	ThirdPartyObservation_JP2020-523010.pdf	281640 82e6ab8429dc3a5a5be498e97e6ef3ac1b4d40cf	no	7
Warnings:					
Information:					
10	Other reference-Patent/Application/ Search Documents	ThirdPartyObservation_EP2018 0871298.pdf	334885 f338935e84831506137afdea18cbccde0cf47493	no	7
Warnings:					
Information:					
11	Non Patent Literature	BERNHARD_2012.pdf	8749380 03284bc7c67fcc802ef3b247219049176ad023bf	no	8
Warnings:					
Information:					
12	Non Patent Literature	JAMOUS_2013.pdf	23794390 965b6f4ed231bfbd3c07a80c833b475d0dbae8c9	no	31
Warnings:					
Information:					
			Total Files Size (in bytes):	109754744	

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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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 08/30/2023

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
08/30/2023	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/354,282	**Applicant(s)** Yang et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 18 July 2023 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

Notice of References Cited	Application/Control No. 18/354,282	Applicant(s)/Patent Under Reexamination Yang et al.	
	Examiner MELISSA J PERREIRA	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-20100098633-A1	04-2010	ZIMMERMAN; Craig	C07D401/14	424/1.85
	B					
	C					
	D					
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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	Tahtis et al. (Mol. Cancer Therap. 2003, 2, 729-737)
	V	Terry et al. (J. Nucl. Med. 2016, 57, 467-472)
	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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*		
Symbol	Date	Examiner

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
google scholar	09/19/2023	MP
inventor search	09/19/2023	MP
PE2E search	09/19/2023	MP
STNext	09/20/2023	MP

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	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

CLAIM		DATE								
Final	Original	09/20/2023								
	1	-								
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	28	-								
	29	✓								

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L2	74816	FAP OR (fibroblast near2 activation)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 08:42 PM
L3	27353058	radionuclide OR radioisotop$6 OR radiolabel$3 OR dye OR optical OR cyanine OR IRdye800 OR DOTA OR chelat$3 OR BODIPY OR vivotag OR alexaflour OR Hilyte OR ADS780 OR ADS830 OR ADS832 OR Dy677 OR Dy676 OR Dy682 OR Dy752 OR Dy780 OR Dylight OR Cy5 OR cy7 OR cy5.5	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:00 PM
L4	49880	L2 AND L3	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:00 PM
L5	644	cyano near2 proline	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2023/09/19 09:01 PM

			IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L6	58	L4 AND L5	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:01 PM
L7	504	((("YANG") near3 ("Xing")) OR (("NIMMAGADDA") near3 ("Sridhar")) OR (("ROWE") near3 ("Steven")) OR (("SLANIA") near3 ("Stephanie")) OR (("POMPER") near3 ("Martin"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:08 PM
L8	7	L2 AND L7	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:08 PM
L9	2	L8 AND L3	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:11 PM
L10	5921	(A61K51/0485 OR A61K47/545 OR A61K51/0478 OR A61K51/0482).cpc.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM
L11	201	L2 AND L10	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM
L12	165	L3 AND L11	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM
L13	41	L12 AND ((@py<="2017"))	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	1	of	4	Attorney Docket Number	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		9346814	2016-05-24	JANSEN et al.	

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20080280856	2008-11-13	COHEN et al.	
		20140357650	2014-12-04	JANSEN et al.	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] *(if known)*	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
		WO 2013/107820	2013-07-25	UNIVERSITEIT ANTWERPEN et al.		
		WO 2014/001538	2014-01-03	GE HEALTHCARE LTD		
		WO 2015/114166	2015-08-06	PHILOCHEM AG		
		WO 2016/149188	2016-09-22	THE JOHNS HOPKINS UNIVERSITY		

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	2	of	4	Attorney Docket Number	JHU-36631.303

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
		ALLINEN et al., Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.	
		BAE et al., Fibroblast activation protein alpha identifies mesenchymal stromal cells from human bone marrow. Br J Haematol. 2008 Sep;142(5):827-30.	
		CHEN et al., Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. Biomed Res Int. 2014; 2014 : 819324. PMCID: PMC3943245.	
		COENEN et al., Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740.	
		CHO et al., Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2012; 53:1883–1891.	
		DVORAKOVA et al., Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein. J Med Chem. 2017;60:8385-8393.	
		EDOSADA et al., Peptide substrate profiling defines fibroblast activation protein as an endopeptidase of strict Gly(2)-Pro(1)-cleaving specificity. FEBS Lett. 2006 Mar 6;580(6):1581-6.	
		FISCHER et al., Radioimmunotherapy of fibroblast activation protein positive tumors by rapidly internalizing antibodies. Clin Cancer Res. 2012;18:6208–6218.	
		FRANCO et al., Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.	
		GARIN-CHESA et al., Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acad Sci U S A. 1990 Sep;87(18):7235-9. PMCID: PMC54718.	
		JANSEN et al., Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold. ACS Med Chem Lett. 2013 Mar 18;4(5):491-6.	
		JANSEN et al., Extended structure-activity relationship and pharmacokinetic investigation of (4-quinolinoyl)glycyl-2-cyanopyrrolidine inhibitors of fibroblast activation protein (FAP). J Med Chem. 2014 Apr 10;57(7):3053-74.	
		KELLY, Fibroblast activation protein-alpha and dipeptidyl peptidase IV (CD26): cell-surface proteases that activate cell signaling and are potential targets for cancer therapy. Drug Resist Updat. 2005 Feb-Apr;8(1-2):51-8.	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	3	of	4	Attorney Docket Number	JHU-36631.303

NONPATENT LITERATURE DOCUMENTS			
		KRAMAN et al., Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.	
		LAVERMAN et al., Immuno-PET and Immuno-SPECT of Rheumatoid Arthritis with Radiolabeled Anti-Fibroblast Activation Protein Antibody Correlates with Severity of Arthritis. J Nucl Med. 2015 May;56(5):778-83.	
		LI et al., Activatable Near-Infrared Fluorescent Probe for In Vivo Imaging of Fibroblast Activation Protein-alpha. Bioconjugate Chem. 2012 Jul. 19;23:1704-11	
		LO et al., Photodynamic molecular beacon triggered by fibroblast activation protein on cancer-associated fibroblasts for diagnosis and treatment of epithelial cancers. J Med Chem. 2009 Jan 22;52(2):358-68.	
		POPLAWSKI et al., Identification of selective and potent inhibitors of fibroblast activation protein and prolyl oligopeptidase. J Med Chem. 2013 May 9;56(9):3467-77.	
		REILLY et al., Advancing Novel Molecular Imaging Agents from Preclinical Studies to First-in-Humans Phase I Clinical Trials in Academia-A Roadmap for Overcoming Perceived Barriers. Bioconjugate chemistry. 2015; 26:625–632.	
		RETTIG et al., Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin Cancer Res. 1993 Jul 15;53(14):3327-35.	
		RYABTSOVA et al., Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity. Bioorg Med Chem Lett. 2012 May 15;22(10):3412-7.	
		SCANLAN et al., Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5657-61.	
		SCOTT et al., A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res. 2003 May;9(5):1639-47.	
		TSAI et al., Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein. J Med Chem. 2010 Sep 23;53(18):6572-83.	
		TUXHORN et al., Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. Clin Cancer Res. 2002 Sep;8(9):2912-23.	
		WELT et al., Antibody targeting in metastatic colon cancer: a phase I study of monoclonal antibody F19 against a cell-surface protein of reactive tumor stromal fibroblasts. J Clin Oncol. 1994 Jun;12(6):1193-203.	
		YOUN et al., In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59.	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	4	of	4	Attorney Docket Number	JHU-36631.303

NONPATENT LITERATURE DOCUMENTS			
		YU et al., The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.	
		International Search Report and Written Opinion for PCT/US2018/057086, mailed May 10, 2019, 12 pages	
		Extended EP Search Report for EP 18871298.8, mailed May 20, 2021, 7 pages	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	5	of	4	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____filed on_____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-07-18
Printed Name	Jeffrey W. Childers	Registration Number	58126

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

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[5] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[6] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[7] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[8] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.97 and 1.98. 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 CFR 1.14. This collection is estimated to take 2 hours 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**.

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Web Search History

date, time	web site	search string
9/19/2023 3:19:02 PM	Google Scholar	FAP-alpha radionuclide [after:2000] [before:2018]
9/19/2023 3:19:04 PM	Google Scholar	FAP-alpha radionuclide
9/19/2023 3:19:11 PM	Google Scholar	FAP-alpha DOTA
9/19/2023 3:38:51 PM	Google	fap ibody
9/19/2023 6:24:06 PM	Google	cyanoproline fap
9/19/2023 6:31:35 PM	Google Scholar	cyanoproline fap
9/19/2023 6:40:13 PM	Google Scholar	cyanoproline fibroblast activation protein
9/19/2023 6:41:11 PM	Google Scholar	radiolabeled fibroblast activation protein
9/19/2023 6:51:54 PM	Google Scholar	anit-fap ibody radiolabeled
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9/19/2023 8:55:44 PM	Google Scholar	cyanoproline fap cyanine dye
9/19/2023 8:55:50 PM	Google Scholar	fap cyanine dye
9/19/2023 8:58:06 PM	Google Scholar	fap targeting cyanine dye

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                  Derwent World Patents Index (R) Subscriber Files
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                  Manage Search Projects
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                  available on STNext
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                  a standalone database on STNext
 NEWS  6  JUN 22  Claims for Four Additional Patent Authorities Added to
                  CA/CAplus
 NEWS  7  JUN 24  SMARTracker SDI Option Now Supported in Derwent Files
 NEWS  8  JUN 24  Expanded Claims Coverage and Enhanced HIT Displays of
                  Claims Data in Derwent World Patents Index(R)
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                  Georgia Increases Comprehensiveness of INPADOC
 NEWS 10  SEP 14  New Preference Setting for Transcript Options Helps
                  Better Manage Transcripts, Increase Their Efficiency
 NEWS 11  SEP 22  CAS STNext Structure Editor Update Preserves Functionality,
                  Increases Flexibility
 NEWS 12  OCT 24  Links to National Patent Registers Now Available in Patent
                  Databases on CAS STNext
 NEWS 13  NOV  7  PCTFULL Reload Provides Additional Coverage, Independent
                  Claims and Assignee Searching Enhancements
 NEWS 14  NOV  7  EPFULL Reload on STNext Features New Independent Claims
                  Searching Capabilities
 NEWS 15  NOV 10  PS (Pharmaceutical Substances) Database Reloaded
 NEWS 16  DEC 05  Expanded access to Taiwanese patent information provided
                  by new full text database TWFULL and claims coverage
                  in CAplus(SM)
 NEWS 17  DEC 05  New Implementation of Derwent Drug File (DRUGU/DDFU)
                  Makes Searching More Convenient
 NEWS 18  DEC 23  New Interactive Claim Viewer in EPFULL and PCTFULL
                  Makes Claim Analysis More Efficient
 NEWS 19  DEC 30  2023 MeSH now available in MEDLINE on STNext
 NEWS 20  FEB 23  Derwent World Patents Index - Manual Code revision 2023
 NEWS 21  MAR 10  MEDLINE(R) Reloaded and MeSH Thesaurus Updated for
                  2023 on STNext
 NEWS 22  MAR 23  Expanded Patent Authority Coverage in CA/CAplus Means
                  Access to More Inventions, More Complete Patent
                  Families
 NEWS 23  MAY 12  Claim Tags Enhancement Extended to Include WO Patents
 NEWS 24  JUL 05  Reloaded Japanese Patent Full-Text Database JPFULL Provides
                  Expanded Content, New Search Options
 NEWS 25  JUL 06  Interactive Claims Viewer Enhancements: JPFULL Now Supported,
                  Links to the Interactive Claims Viewer Now Available in
                  Reports and Transcripts
 NEWS 26  SEP 04  September 2023 Update to Emtree(R) Provides Latest Biomedical
                  Terminology for Searching
 NEWS 27  SEP 08  Ultimate Owner Information Included in CA/CAplus Aids
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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:53:20 ON 20 SEP 2023

=> Fil BIOSIS BIOTECHNO CAPLUS CHEMCATS CHEMLIST EMBASE ESBIOBASE HCAPLUS
HCHEMLIST KOSMET LEMBASE MEDLINE REGISTRY SCISEARCH ZCAPLUS ZREGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.28	0.28

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SESSION RESUMED IN FILE 'BIOSIS, BIOTECHNO, CAPLUS, CHEMCATS, CHEMLIST, EMBASE, ESBIOBASE, HCAPLUS, HCHEMLIST, KOSMET, LEMBASE, MEDLINE, REGISTRY, SCISEARCH, ZCAPLUS, ZREGISTRY' AT 11:09:06 ON 20 SEP 2023
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FULL ESTIMATED COST	113.84	114.12

=> s "Fibroblast activation protein .alpha." OR "Fibroblast-activating protein .alpha." OR "Fibroblast activation protein" OR "FAP.alpha." OR "FAP alpha" OR "Proteins, FAP.alpha." OR "Fibroblast activation protein FAP.alpha." OR "FAP" OR "Fibroblast activation protein alpha" OR "Proteins, FAP"

L1	5762	FILE BIOSIS
L2	579	FILE BIOTECHNO
L3	7288	FILE CAPLUS
L4	58	FILE CHEMCATS
L5	9	FILE CHEMLIST
L6	11564	FILE EMBASE
L7	2202	FILE ESBIOBASE
L8	7288	FILE HCAPLUS
L9	9	FILE HCHEMLIST
L10	6	FILE KOSMET
L11	4	FILE LEMBASE
L12	7190	FILE MEDLINE
L13	355	FILE REGISTRY
L14	8627	FILE SCISEARCH
L15	7288	FILE ZCAPLUS
L16	355	FILE ZREGISTRY

TOTAL FOR ALL FILES

L17	58584	"FIBROBLAST ACTIVATION PROTEIN A" OR "FIBROBLAST-ACTIVATING PROTEIN A" OR "FIBROBLAST ACTIVATION PROTEIN" OR "FAP.ALPHA." OR "FAP ALPHA" OR "PROTEINS, FAPA" OR "FIBROBLAST ACTIVATION PROTEIN FAPA" OR "FAP" OR "FIBROBLAST ACTIVATIO

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               N PROTEIN ALPHA" OR "PROTEINS, FAP"

=> s radionuclide OR "Radioactive substances" OR "Radioisotopes" OR "Isotopic
radioelements" OR "Radioelement" OR "Radioelement isotopes" OR "Radioactive
elements" OR "Radioactive nuclides" OR "Radioactive isotopes" OR "Radioelement
complexes" OR "Radioelement conjugates"

L18       44015 FILE BIOSIS
L19        1432 FILE BIOTECHNO
L20      141489 FILE CAPLUS
L21          22 FILE CHEMCATS
L22         116 FILE CHEMLIST
L23       72885 FILE EMBASE
L24       18475 FILE ESBIOBASE
L25      141489 FILE HCAPLUS
L26         116 FILE HCHEMLIST
L27          23 FILE KOSMET
L28          35 FILE LEMBASE
L29      284572 FILE MEDLINE
L30           0 FILE REGISTRY
L31       70891 FILE SCISEARCH
L32      141489 FILE ZCAPLUS
L33           0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L34      917049 RADIONUCLIDE OR "RADIOACTIVE SUBSTANCES" OR "RADIOISOTOPES" OR
                "ISOTOPIC RADIOELEMENTS" OR "RADIOELEMENT" OR "RADIOELEMENT ISOT
                OPES" OR "RADIOACTIVE ELEMENTS" OR "RADIOACTIVE NUCLIDES" OR
                "RADIOACTIVE ISOTOPES" OR "RADIOELEMENT COMPLEXES" OR "RADIOELEM
                ENT CONJUGATES"

=> s l17 and l34

L35          38 FILE BIOSIS
L36           2 FILE BIOTECHNO
L37         156 FILE CAPLUS
L38           0 FILE CHEMCATS
L39           0 FILE CHEMLIST
L40         130 FILE EMBASE
L41           2 FILE ESBIOBASE
L42         156 FILE HCAPLUS
L43           0 FILE HCHEMLIST
L44           0 FILE KOSMET
L45           0 FILE LEMBASE
L46         278 FILE MEDLINE
L47           0 FILE REGISTRY
L48          81 FILE SCISEARCH
L49         156 FILE ZCAPLUS
L50           0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L51         999 L17 AND L34

=> s ibody or ibodies

L52          16 FILE BIOSIS
L53           1 FILE BIOTECHNO
L54          15 FILE CAPLUS
L55           0 FILE CHEMCATS
L56           0 FILE CHEMLIST
L57          23 FILE EMBASE
L58           4 FILE ESBIOBASE
L59          15 FILE HCAPLUS
L60           0 FILE HCHEMLIST
L61           0 FILE KOSMET
L62           0 FILE LEMBASE
L63           6 FILE MEDLINE
L64           0 FILE REGISTRY
L65          14 FILE SCISEARCH
L66          15 FILE ZCAPLUS
L67           0 FILE ZREGISTRY
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```
TOTAL FOR ALL FILES
L68        109 IBODY OR IBODIES

=> l51 and l68

L51 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l51 and l68

L69          0 FILE BIOSIS
L70          0 FILE BIOTECHNO
L71          0 FILE CAPLUS
L72          0 FILE CHEMCATS
L73          0 FILE CHEMLIST
L74          0 FILE EMBASE
L75          0 FILE ESBIOBASE
L76          0 FILE HCAPLUS
L77          0 FILE HCHEMLIST
L78          0 FILE KOSMET
L79          0 FILE LEMBASE
L80          0 FILE MEDLINE
L81          0 FILE REGISTRY
L82          0 FILE SCISEARCH
L83          0 FILE ZCAPLUS
L84          0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L85          0 L51 AND L68

=> s cyanoproline

L86          1 FILE BIOSIS
L87          0 FILE BIOTECHNO
L88          3 FILE CAPLUS
L89          3 FILE CHEMCATS
L90          0 FILE CHEMLIST
L91          3 FILE EMBASE
L92          0 FILE ESBIOBASE
L93          3 FILE HCAPLUS
L94          0 FILE HCHEMLIST
L95          0 FILE KOSMET
L96          0 FILE LEMBASE
L97          2 FILE MEDLINE
L98         16 FILE REGISTRY
L99          0 FILE SCISEARCH
L100         3 FILE ZCAPLUS
L101        16 FILE ZREGISTRY

TOTAL FOR ALL FILES
L102        50 CYANOPROLINE

=> s l51 and l102

L103         0 FILE BIOSIS
L104         0 FILE BIOTECHNO
L105         0 FILE CAPLUS
L106         0 FILE CHEMCATS
L107         0 FILE CHEMLIST
L108         0 FILE EMBASE
L109         0 FILE ESBIOBASE
L110         0 FILE HCAPLUS
L111         0 FILE HCHEMLIST
L112         0 FILE KOSMET
L113         0 FILE LEMBASE
L114         0 FILE MEDLINE
L115         0 FILE REGISTRY
L116         0 FILE SCISEARCH
L117         0 FILE ZCAPLUS
L118         0 FILE ZREGISTRY
```

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TOTAL FOR ALL FILES
L119         0 L51 AND L102

=> s dye OR "Fluorescent dyes" OR "IR-absorbing dyes" or cyanine or dylight or
imaging OR "Radioimmunoimaging" OR "Infrared imaging" OR "Spectral imaging" OR
"Luminescent imaging"

L120   1583858 FILE BIOSIS
L121     22740 FILE BIOTECHNO
L122   1616544 FILE CAPLUS
L123      2148 FILE CHEMCATS
L124      2311 FILE CHEMLIST
L125   2616449 FILE EMBASE
L126    282971 FILE ESBIOBASE
L127   1616544 FILE HCAPLUS
L128      2311 FILE HCHEMLIST
L129      3229 FILE KOSMET
L130       650 FILE LEMBASE
L131   2636196 FILE MEDLINE
L132     28650 FILE REGISTRY
L133   1545961 FILE SCISEARCH
L134   1616544 FILE ZCAPLUS
L135     28650 FILE ZREGISTRY

TOTAL FOR ALL FILES
L136  13605756 DYE OR "FLUORESCENT DYES" OR "IR-ABSORBING DYES" OR CYANINE OR
               DYLIGHT OR IMAGING OR "RADIOIMMUNOIMAGING" OR "INFRARED IMAGING"
                OR "SPECTRAL IMAGING" OR "LUMINESCENT IMAGING"

=> s l17 and l136

L137       530 FILE BIOSIS
L138         2 FILE BIOTECHNO
L139       626 FILE CAPLUS
L140         0 FILE CHEMCATS
L141         0 FILE CHEMLIST
L142      1431 FILE EMBASE
L143        76 FILE ESBIOBASE
L144       626 FILE HCAPLUS
L145         0 FILE HCHEMLIST
L146         0 FILE KOSMET
L147         0 FILE LEMBASE
L148       903 FILE MEDLINE
L149         1 FILE REGISTRY
L150       660 FILE SCISEARCH
L151       626 FILE ZCAPLUS
L152         1 FILE ZREGISTRY

TOTAL FOR ALL FILES
L153      5482 L17 AND L136

=> s l153 and l102

L154         0 FILE BIOSIS
L155         0 FILE BIOTECHNO
L156         0 FILE CAPLUS
L157         0 FILE CHEMCATS
L158         0 FILE CHEMLIST
L159         1 FILE EMBASE
L160         0 FILE ESBIOBASE
L161         0 FILE HCAPLUS
L162         0 FILE HCHEMLIST
L163         0 FILE KOSMET
L164         0 FILE LEMBASE
L165         1 FILE MEDLINE
L166         0 FILE REGISTRY
L167         0 FILE SCISEARCH
L168         0 FILE ZCAPLUS
L169         0 FILE ZREGISTRY

TOTAL FOR ALL FILES
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L170 2 L153 AND L102

=> d bib l179 1-2

L179 NOT FOUND
The L-number entered has not been defined in this session, or it
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session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d bib l170 1-2

L170 ANSWER 1 OF 2 EMBASE COPYRIGHT (c) 2023 Elsevier B.V. All rights
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AN 20230385996 EMBASE Full-text
DN 2024158278 PMID: 37117123
TI Advanced Fibroblast Activation Protein-Ligand Developments: FAP
Imaging Agents: A Review of the Structural Requirements.
AU DiMagno, Stephen G.; Babich, John W., PhD (correspondence)
CS Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston,
MA, 02210, United States. jbabich@ratiotx.com
SO PET Clinics, (July 2023) Vol. 18, No. 3, pp. 287-294.
Refs: 55
ISSN: 1556-8598; E-ISSN: 1879-9809
DOI 10.1016/j.cpet.2023.03.002
PB W.B. Saunders.
PUI S 1556-8598(23)00028-7
CY United States
DT Journal; General Review; (Review)
FS Intellectual Indexing
016 Cancer
023 Nuclear Medicine
037 Drug Literature Index
FS ClinicalTrials.gov
NCT NCT04939610
LA English
ED Entered Embase: 2 May 2023
Last Updated on Embase: 14 Jun 2023
Indexing Added: 14 Jun 2023
First Entered Embase or Embase Alert: 2 May 2023

L170 ANSWER 2 OF 2 MEDLINE ® on STN
AN 2027165793 MEDLINE Full-text
DN PubMed ID: 37117123
TI Advanced Fibroblast Activation Protein-Ligand Developments: FAP
Imaging Agents: A Review of the Structural Requirements.
AU DiMagno Stephen G
CS Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston,
MA 02210, USA.
AU Babich John W
CS Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston,
MA 02210, USA. jbabich@ratiotx.com
SO PET clinics, (2023 Jul) Vol. 18, No. 3, pp. 287-294. Electronic
Publication Date: 26 Apr 2023
Journal code: 101260152. E-ISSN: 1879-9809. L-ISSN: 1556-8598.
DOI http://dx.doi.org/10.1016/j.cpet.2023.03.002
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 202306
ED Entered STN: 30 Apr 2023
Last Updated on STN: 2 Jun 2023
Indexing Added: 2 Jun 2023
Entered Medline: 2 Jun 2023

=> s l153 and l68

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L171          1 FILE BIOSIS
L172          0 FILE BIOTECHNO
L173          1 FILE CAPLUS
L174          0 FILE CHEMCATS
L175          0 FILE CHEMLIST
L176          0 FILE EMBASE
L177          0 FILE ESBIOBASE
L178          1 FILE HCAPLUS
L179          0 FILE HCHEMLIST
L180          0 FILE KOSMET
L181          0 FILE LEMBASE
L182          0 FILE MEDLINE
L183          0 FILE REGISTRY
L184          0 FILE SCISEARCH
L185          1 FILE ZCAPLUS
L186          0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L187          4 L153 AND L68

=> d bib l187 1-4


L187 ANSWER 1 OF 4  BIOSIS  COPYRIGHT (c) 2023 Clarivate Analytics  on STN
AN   2018:61517  BIOSIS Full-text
DN   PREV201800061517
TI   Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation
     Protein.
AU   Dvorakova, Petra [Reprint Author]; Busek, Petr; Knedlik, Tomas; Schimer,
     Jiri; Etrych, Tomas; Kostka, Libor; Sromova, Lucie Stollinova; Subr,
     Vladimir; Sacha, Pavel [Reprint Author]; Sedo, Aleksi [Reprint Author];
     Konvalinka, Jan [Reprint Author]
CS   Czech Acad Sci, Inst Organ Chem and Biochem, Flemingovo Nam 2, Prague
     16610 6, Czech Republic
     pavelsacha@gmail.com; aleksi@cesnet.cz; jan.konvalinka@uochb.cas.cz
SO   Journal of Medicinal Chemistry, (OCT 26 2017) Vol. 60, No. 20, pp.
     8385-8393.
     CODEN: JMCMAR. ISSN: 0022-2623. E-ISSN: 1520-4804.
DOI  10.1021/acs.jmedchem.7b00767
DT   Article
LA   English
ED   Entered STN: 27 Dec 2017
     Last Updated on STN: 17 Jan 2018

L187 ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2023 ACS on STN
AN   2017:1570779  CAPLUS Full-text
DN   169:205864
TI   Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation
     Protein
AU   Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych,
     Tomas; Kostka, Libor; Stollinova Sromova, Lucie; Subr, Vladimir; Sacha,
     Pavel; Sedo, Aleksi; Konvalinka, Jan
CS   Institute of Organic Chemistry and Biochemistry of The Czech Academy of
     Sciences, Prague 6, 16610, Czech Rep.
SO   Journal of Medicinal Chemistry (2017), 60(20), 8385-8393
     CODEN: JMCMAR; ISSN: 0022-2623
DOI  10.1021/acs.jmedchem.7b00767
PB   American Chemical Society
DT   Journal; (online computer file)
LA   English
OS   CASREACT 169:205864
OSC.G   16    THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT  52    THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
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AN   2017:1570779  HCAPLUS Full-text
DN   169:205864
TI   Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation
     Protein
AU   Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych,
     Tomas; Kostka, Libor; Stollinova Sromova, Lucie; Subr, Vladimir; Sacha,
```

Pavel; Sedo, Aleksi; Konvalinka, Jan
CS Institute of Organic Chemistry and Biochemistry of The Czech Academy of Sciences, Prague 6, 16610, Czech Rep.
SO Journal of Medicinal Chemistry (2017), 60(20), 8385-8393
CODEN: JMCMAR; ISSN: 0022-2623
DOI 10.1021/acs.jmedchem.7b00767
PB American Chemical Society
DT Journal; (online computer file)
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OS CASREACT 169:205864
OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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AN 2017:1570779 ZCAPLUS Full-text
DN 169:205864
TI Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein
AU Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych, Tomas; Kostka, Libor; Stollinova Sromova, Lucie; Subr, Vladimir; Sacha, Pavel; Sedo, Aleksi; Konvalinka, Jan
CS Institute of Organic Chemistry and Biochemistry of The Czech Academy of Sciences, Prague 6, 16610, Czech Rep.
SO Journal of Medicinal Chemistry (2017), 60(20), 8385-8393
CODEN: JMCMAR; ISSN: 0022-2623
DOI 10.1021/acs.jmedchem.7b00767
PB American Chemical Society
DT Journal; (online computer file)
LA English
OS CASREACT 169:205864
OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

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				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number / Number-Kind Code[4] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2021/0038749	2021-02-11	HABERKORN et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document / Country Code[5] Number[6] Kind Code[7] (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
	1.	EP 18199641.4	2018-10-10	UNIV HEIDELBERG		
	2.	JP2021-512949A	2021-05-20	UNIV HEIDELBERG		X
	3.	WO 2010/014933	2010-02-04	THE JOHNS HOPKINS UNIVERSITY		
	4.	WO 2010/108125	2010-09-23	THE JOHNS HOPKINS UNIVERSITY		
	5.	WO 2016/065142	2016-04-28	THE JOHNS HOPKINS UNIVERSITY		
	6.	WO 2019/154886	2019-08-15	UNIV HEIDELBERG		

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303

FOREIGN PATENT DOCUMENTS						

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation [6]
	1.	Third Party Preissuance Submission filed in USSN 16/758, 182, filed February 23, 2022, 6 pages.	
	2.	Third Party Observations Japanese Patent Application no. 2020-523010. Dated 24 Oct 2022. 7 pages.	
	3.	Third Party Observations for application number EP20180871298. Dated 04/03/2022. 7 pages.	
	4.	BERNHARD et al., DOTAGA-anhydride: a valuable building block for the preparation of DOTA-like chelating agents. Chemistry. 2012 Jun 18;18(25):7834-41.	
	5.	JAMOUS et al., Synthesis of peptide radiopharmaceuticals for the therapy and diagnosis of tumor diseases. Molecules. 2013 Mar 14;18(3):3379-409.	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	3	of	3	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-08-08
Name/Print	Jeffrey W. Childers	Registration Number	58,126

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.
[5] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[6] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[7] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[8] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.97 and 1.98. 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 CFR 1.14. This collection is estimated to take 2 hours 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**.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 09/26/2023

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
09/26/2023	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

Office Action Summary	**Application No.** 18/354,282	**Applicant(s)** Yang et al.	
	Examiner MELISSA J PERREIRA	**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 7/24/23.

☐ 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) 29 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) 29 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 7/18/23 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 _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

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.

Claims Status

Claim 29 is pending in the application.

Drawings

Color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), one set of color drawings or color photographs, as appropriate, if submitted via EFS-Web or three sets of color drawings or color photographs, as appropriate, if not submitted via EFS-Web, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Rejections - 35 USC § 102

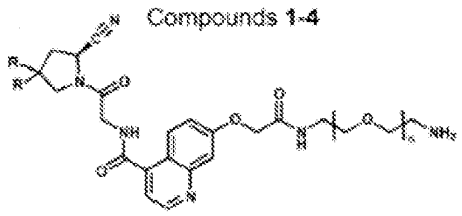
In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory

basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

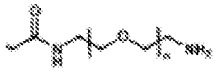
> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claim(s) 29 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Dvořáková et al. (*J. Med. Chem.* **2017**, *60*, 8385-8393).

Dvořáková et al. (*J. Med. Chem.* **2017**, *60*, 8385-8393) teaches of the anti-FAP iBody FAP inhibitors comprising 

(Scheme 1) bound to an ATTO488 dye via a HMPA copolymer (Figure 2).

The compounds 1-4 anticipate the targeting moiety for FAP-α, A, of the instant claims.

The  moiety bound to HMPA anticipates the linker, L, of the instant claims.

The ATTO488 dye anticipates the optical functional group, B, of the instant claims.

The anti-FAP iBody is for imaging of FAP-expressing cells (p8387, left column, first full paragraph; p8387, Use of Anti-FAP iBody 1 for detection and visualization of FAP; p8387, Application of Anti-FAP iBody 1 for imaging of FAP-expressing cells).

Claim Rejections - 35 USC § 103

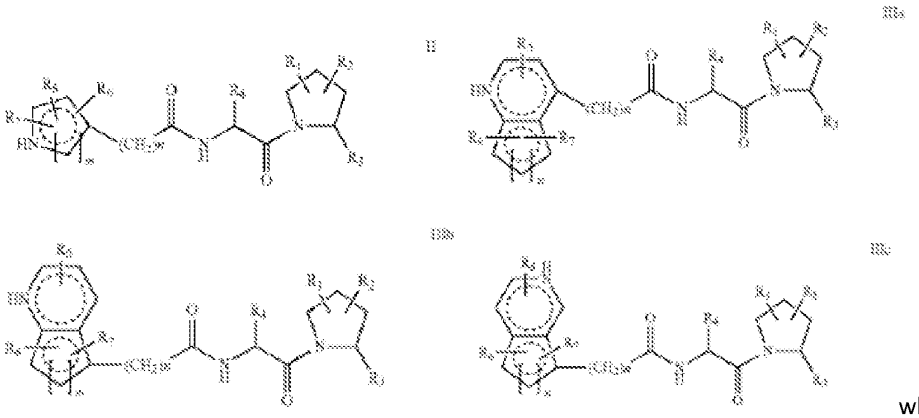
In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 29 is/are rejected under 35 U.S.C. 103 as being unpatentable over Jansen et al. (US2014/0357650A1) in view of Zimmerman et al. (US2010/0098633A1) and Jensen et al. (*ACS Med. Chem. Lett.* **2013**, *14*, 491-496).

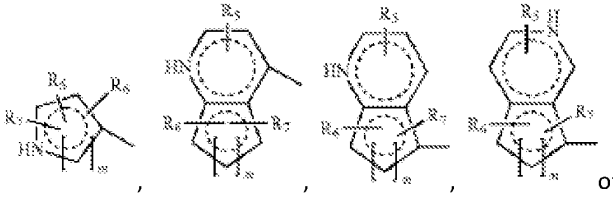
Jansen et al. (US2014/0357650A1) discloses the FAP inhibitors



wherein R_1 and R_2 are H, -OH, halogen, etc. and encompass the corresponding R_{1x} and R_{2x} are H, -OH, halogen, etc. of the instant claims.

The R_3 is H, -CN, -$B(OH)_2$, etc. of the disclosure encompasses the corresponding R_{3x} is H, -CN, -$B(OH)_2$, etc. of the instant claims.

The R_4 is H of the disclosure encompasses the corresponding R_{4x} is H of the instant claims.

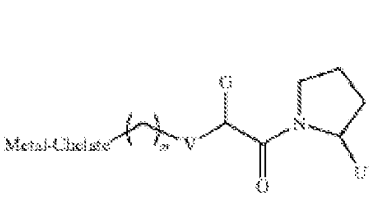
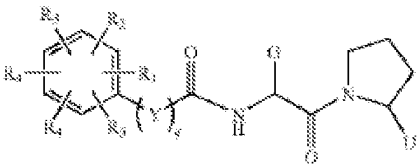
The  of the disclosure encompasses the corresponding  5 to 10-membered N-containing aromatic mono- or bicyclic heterocycle of the instant claims.

The R_5-R_7 are H, -OH, oxo, -halo, C_{1-6}alkyl, -O-C_{1-6}alkyl optionally substituted with 1-3 substituents selected from -halo, etc. of the disclosure encompasses the corresponding R_{5x}-R_{7x} are H, -OH, oxo, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, etc. of the instant claims. (p4-6, [0050-0089]; p10, [0113-0122]; p13-16, [0176-0215])

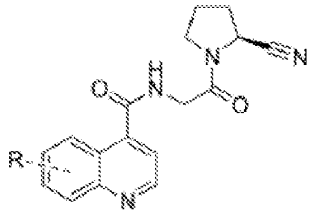
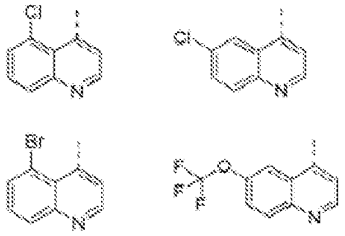
The inhibitors may comprise stereoisomers, tautomers, racemates, salts, hydrates or solvates thereof (p3, [0024]; p10, [0113]) which encompasses the stereoisomers, tautomers, racemates, salts, hydrates or solvates thereof of the instant claims.

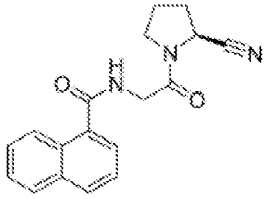
Jansen et al. (US2014/0357650A1) does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

Zimmerman et al. (US2010/0098633A1) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising

 , 

wherein U is -$B(OH)_2$, -CN, etc.; G is H, alkyl, etc.; V is a bond, etc.; the metal is a metallic moiety include a radionuclide for PET, SPECT; chelate is a chelating moiety that coordinates with the radionuclide; Y is -CH_2-, etc.; and R_1-R_5 may comprise radiohalogen, etc. (p1-2, [0008-0028]; p3, [0048-0049]; p6, [0087-0099]; p9, [0111-0117]; p13,).

Jensen et al. (*ACS Med. Chem. Lett.* **2013**, *14*, 491-496) discloses FAP inhibitors of the structure  wherein R comprises  , etc. (abstract; Table 3).

The quinoline containing compounds have 60 times more FAP-affinity than the initial N-(1-naphthoyl) based FAP inhibitors  (p492, right column, second full paragraph).

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the FAP inhibitors of Jansen et al. (US2014/0357650A1) with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jansen et al. (US2014/0357650A1) teaches that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated and Zimmerman et al. teaches of radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of Jansen et al. (US2014/0357650A1) with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jensen et al. (*ACS Med. Chem. Lett.* **2013**, *14*, 491-496) teaches that the quinoline containing FAP inhibitors have 60

times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Therefore, it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAP-affinity than the naphthoyl derivative.

Double Patenting

Claim 29 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1,2,13,15,16 and 21-25 of copending Application No. 16/762,873 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the compound of Formula (I) B-L-A of copending Application No. 16/762,873 encompasses the compound of Formula (I) B-L-A of the instant claims. The targeting moiety for FAP-α, A, of copending Application No. 16/762,873 is analogous to the targeting moiety for FAP-α, A, of the instant claims. The linker, L, of copending Application No. 16/762,873 is analogous to the linker, L, of the instant claims. The optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy, B, of copending Application No. 16/762,873 is analogous to the optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy, B, of the instant claims.

The compound of Formula (I) of copending Application No. 16/762,873 and the compound of Formula (I) of the instant claims, have the same properties and are capable of the same functions, such as being used for the method of inhibiting fibroblast-activation protein-α and the method for treating a fibroblast-activation protein-α disease or disorder.

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim

patentable and does not render the old composition patentably new to the discoverer. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Relevant Prior Art

Tahtis et al. (Mol. Cancer Therap. 2003, 2, 729-737) discloses iodine-131-labeled humanized anti-FAP monoclonal antibody (BIBH-7).

Terry et al. (J. Nucl. Med. 2016, 57, 467-472) discloses ^{111}In-28H1 (anti-FAP).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached M9-3, T9-3, W9-3, Th9-2, F9-2.

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, Michael Hartley 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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit

https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**10/30/2023 10:53:51 AM ET**	**J HU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63107112	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	E20230TA54136455	Van Nguyen

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	**$104.00**

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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	*Attorney Docket Number*	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS							
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document		Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
	1.	AZHDARINIA et al., "Characterization of chemical, radiochemical and optical properties of a dual-labeled MMP-9 targeting peptide". Bioorganic & Medicinal Chemistry, Vol. 19, Issue 12, May 6, 2011, 3769-3776.	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	*Attorney Docket Number*	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-10-30
Name/Print	Jeffrey W. Childers	Registration Number	58,126

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PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**10/30/2023 10:53:51 AM ET**	**J HU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63107112	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-10-30 - Supp IDS.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	33 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
Azhdarinia et.pdf	8	Non Patent Literature	770 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

2023-10-30 - Supp IDS.pdf	B954EE41A724E80D01515F926EB742F932937B05159CCC85A2 B3F397DC116FB6E53DB13026C69212CCCAEDC7FBD8CAD05 3AAC6C631B88AA045426ACDDA862DCD
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for 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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/354,282	07/18/2023	Xing Yang	JHU-36631.303

CONFIRMATION NO. 7536

101943
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PUBLICATION NOTICE

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Date Mailed: 11/16/2023

Title:IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Publication No.US-2023-0364274-A1
Publication Date:11/16/2023

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/.

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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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al. Confirmation No.: 7536

Serial No.: 18/354,282 Art Unit: 1618

Filed: July 18, 2023 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO ACCEPT COLOR DRAWINGS UNDER 37 C.F.R. § 1.84(a)(2)

This Petition is submitted to request acceptance of the color drawings previously filed in the above-referenced Application. Applicants submit that color drawings are the only practical medium by which to disclose the subject matter sought to be patented. The present application is directed to imaging and radiotherapeutics agents targeting fibroblast-activation protein-α. Specifically, Figures 6-8, show color images of tumor bearing mice using the exemplary imaging and radiotherapeutic agents. The figures illustrate the uptake of agents after set amounts of time. Thus, Applicant believes that color drawings are necessary as the only practicable medium by which to disclose the subject matter sought to be patented.

As the color drawings were filed electronically via EFS-Web, only one set of color drawings were submitted and were categorized as "Drawings-other than black and white line drawings." Please note that the specification incorporates the language regarding color drawings as required by 37 C.F.R. § 1.84(a)(2)(iii).

The small entity fee required under 37 C.F.R. § 1.17(h) in the amount of $56 is submitted herewith. No further fees are believed to be due. Please charge any additional fees or credit any overpayment of fees in connection with this Petition to Deposit Account No. 50-4302.

Respectfully,

Dated: December 13, 2023

/Jeffrey W. Childers/

Jeffrey W. Childers
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2275 Deming Way Suite 310
Middleton, WI 53562
608 662 1277

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al. Confirmation No.: 7536

Serial No.: 18/354,282 Art Unit: 1618

Filed: July 18, 2023 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

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

Examiner Perreira:

1. I, Martin Pomper, am the Principal Investigator and co-inventor of the subject matter described and claimed in the above-referenced patent application (the "Application"). The research leading to the subject matter of the Application was conducted in my laboratory.

2. I am currently Chair of the Department of Radiology at University of Texas Southwestern Medical Center. Previously, I was Professor of Radiology and Radiological Science, Professor of Oncology and Radiation Oncology and Molecular Radiation Services, Research Chief of Nuclear Medicine, Director of the Division of Nuclear Medicine and Molecular Imaging, Associate Dean of Entrepreneurship and Technology Development, and Director of the Johns Hopkins Center for Translational Molecular Imaging at the Johns Hopkins School of Medicine.

3. I received my B.Sc. degree, Ph.D. degree, and MD degrees all from the University of Illinois at Urbana-Champaign.

4. I completed my postgraduate medical training at Johns Hopkins that included a medical internship, residencies in diagnostic radiology and nuclear medicine, and a fellowship in neuroradiology, before I joined the Johns Hopkins faculty in 1996.

5. I have authored hundreds scientific articles and am inventor of numerous issued patents or patent applications in the field of medical diagnostic imaging.

6. I have read the non-final Office Action dated September 26, 2023, in the subject Application and the references cited therein.

7. I understand the Office Action rejected claim 29 on numerous grounds, including anticipation under 35 U.S.C. § 102(a) and obviousness under 35 U.S.C. § 103.

8. I understand that the pending claims are directed to a low molecular weight compound of Formula (I):

B-L-A

wherein A is a targeting moiety for FAP-α defined by a specific structure, B is an optical or radiolabeled functional group, and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

9. The office action asserts that prior claim 29 is anticipated under 35 U.S.C. § 102(a)(1) by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

10. Claim 29 is amended and further defines the compound of formula (I) as being "low molecular weight" ("LMW"). I distinguish the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, I characterize large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval.

11. I distinguish between the LMW compounds of the pending claims and larger biologic compounds such as antibodies and high relative molecule mass polymers, as cited below.

12. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

> [T]he presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP-α, i.e., an FAP-α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α [Page 8, lines 26-29, page 9, lines 1-2].

> Because FAP-α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP-α [Page 1, lines 28-34, page 2, lines 1-7].

13. Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

14. In contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound – as the Examiner correctly pointed out, comprising an anti-FAP moiety bound to an ATTO488 dye via a **HMPA copolymer**. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole.

15. Further, I have provided additional low molecular weight compounds of the current claims with molecular weights in the below table in paragraph 42.

16. I, upon reading and understanding of the instant specification in view of Dvořáková, would appreciate that the presently claimed compounds are "low molecular weight" compounds.

17. I observe that the term of "low molecular weight" is well accepted in the chemical arts. In particular, when used in the scientific references in the chemical arts, I recognize that low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. *See e.g.*, K Beebe et al., Clin Transl Sci. 2014 Feb; 7(1): 74–81 ("Metabolomics is often described as a systematic study of the low molecular weight (approximately 50–1,500 Da) metabolites (*chemicals*) within a given sample"); A. Ferreira et al., J. Agric. Food Chem. 2014, 62, 6784−6793 ("Metabolites are a group of low molecular weight substances (50−1500 Da) that includes amino acids, fatty acids …"); C. Llewellyn et al., Progress in Oceanography, Volume 137, p. 421-433 (Metabolomics involves the non-targeted unbiased analysis of large suites of low molecular weight organic molecules or metabolites (typically 50–1500 Da)…); *see also* https://www.ebi.ac.uk/training/online/courses/metabolomics-introduction/what-is/small-molecules/ ("A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product. Metabolomics usually studies small molecules within a mass range of 50 – 1500 daltons (Da).")

18. The Office Action asserts that claim 29 is obvious over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

19. I understand that the Office Action took the position that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Janssen I with a radiohalogen (taught in Zimmerman) via a linker, such as $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl as Jansen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

20. Based on my review of the Office Action and prior art references cited in the Office Action, I disagree with the obviousness rejections for the following reasons:

21. First, I found that there are no teachings or suggestions in the cited reference to make a compound with a linker having a bi-functionalization which binds to the FAP inhibitor moiety A and the optical or radiolabeled moiety B.

22. The Office Action took the position that the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl of Jansen I are modified with a radiohalogen.

23. I observed that $C_{1\text{-}6}$alkyl and the -O-$C_{1\text{-}6}$alkyl are among a variety of functional groups that may be attached to the heterocyclic group of the FAP inhibitor compounds disclosed in Jansen I, including —H, —OH, —oxo, —halo, —$C_{1\text{-}6}$alkyl, —O—$C_{1\text{-}6}$alkyl, —S—$C_{1\text{-}6}$alkyl, —NR_8R_9, —OR_{12}, —Het_2 and —Ar_2, wherein the $C_{1\text{-}6}$alkyl may be optionally substituted with —OH and —halo.

24. Further, I observed that the vast majority of the representative compounds disclosed in either Jansen I or Jansen II do not contain a halogenated $C_{1\text{-}6}$alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

25. FAP inhibitors substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl clearly do not stand out of the many FAP inhibitors including those unsubstituted or substituted with other functional groups or elements disclosed in Jansen I or Jansen II. There is no suggestion in the cited references as to why a FAP inhibitor substituted with a halogenated $C_{1\text{-}6}$alkyl should be selected for modification with a radiohalogen.

26. I notice that the single FAP inhibitor substituted with the halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl disclosed in Jansen I and Jansen II has worse bioactivities compared with the other compounds disclosed in the prior art. In particular, many FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II which is substituted with a trifluoromethoxy group. See Example 11, Table 4, Jansen I; Compound No. 28, Table 3, Jansen II. For example, compound Example 11 of

Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012 μm and a selectivity index of 59, which do not compare favorably to a number of compounds. For example, compound Example 15 of Jansen I has a IC_{50} of 0.0062 μm and a selectivity index of 193. Accordingly, one of ordinary skill in the art would not select the FAP inhibitor substituted with a trifluoromethoxy group for modification.

27. The Office Action appeared to correlate the substitution of a C_{1-6}alkyl or -O-C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

> It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy. [Office Action dated September 26, 2023, pages 6-7].

I would point out that Jansen II merely discloses that quinoline containing FAP inhibitors have 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Jansen II does not suggest that substitution of the quinoline ring of the quinoline containing FAP inhibitors will improve the FAP-affinity or selectivity of the FAP inhibitors.

28. On the contrary, Jansen II observed that substitution of the quinoline ring has little or negative effects on the FAP-affinity of the quinoline containing FAP inhibitors:

> Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19−24, having a clearly negative effect on this parameter. [Janssen II, page 493, left column].

In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e., Example 11 of Jansen I or Compound 28 of Jansen II, has an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without any substitution. Specifically, IC_{50} for FAP (an indicator of the FAP affinity; a higher value means a lower FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor. Selectivity index (a higher selectivity index means a higher selectivity) is 59 for the former versus 83 for the latter. *See* Jansen I, Table 4.

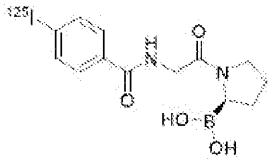
29. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl.

30. Further, due to the high unpredictability of the medical imaging art, I believe one of ordinary skill in the art would not reasonably expected success in modifying the cited prior art to arrive at the compounds of the pending claims for medical imaging applications.

31. There are numerous important parameters which need to be taken into consideration for successfully developing a FAP imaging agent. Those parameters include, for example, affinity for FAP, selectivity (specificity) for FAP, ease of synthesis, and biodistribution, and the like. It is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with a medical condition. The high specificity allows the imaging agent to bind selectively to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

32. The unpredictability of the art is clearly manifested by the documented failure of a compound disclosed in Zimmerman.

33. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic



[^{125}I]MIP-1232

plaque, and was determined as not suitable for the application. *See* Meletta et al., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta").

34. As provided on page 2089 of Meletta, while pronounced binding of [^{125}I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Based on these data, Maletta could not conclude on the selectivity of [^{125}I]MIP-1232 for FAP.

35. Accordingly, because of the low specificity MIP-1232 displayed in the testing, Meletta concluded that MIP-1232 was not suitable for the medical imaging application for the particular medical condition being tested in Meletta. *Id*. at 2095.

36. Based on my review, I am not aware of any other compounds disclosed in Zimmerman that fared better than MIP-1232 and that was developed successfully as a medical imaging agent.

37. The failure of investigations with MIP-1232, which is a compound disclosed in the cited prior art, is especially telling as it demonstrates the high unpredictability of the art and lack of reasonable expectation of success by combining the prior art to arrive at the compounds of the pending claims for medical imaging applications.

38. Further, I am of the opinion that there are unexpectedly superior FAP specificities associated with the compounds of the pending claims based on the testing results from my lab.

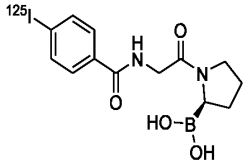
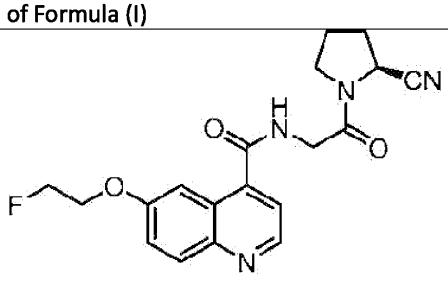
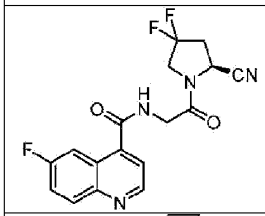
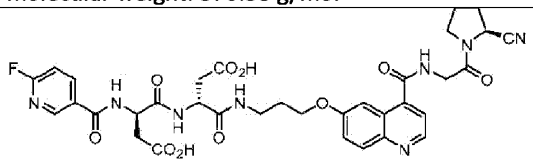
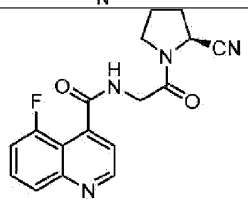
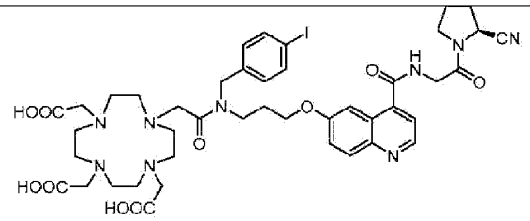
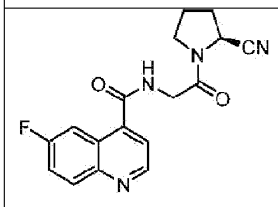
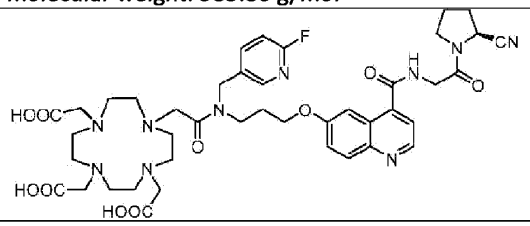
39. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

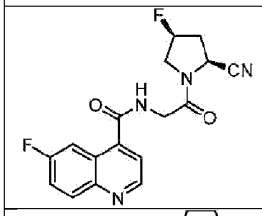
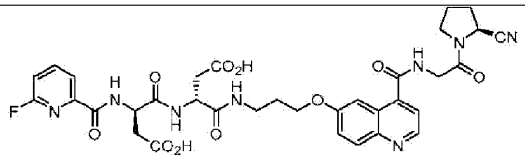
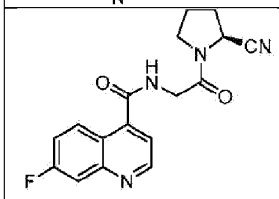
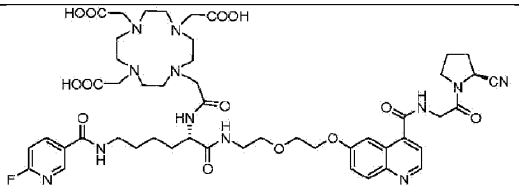
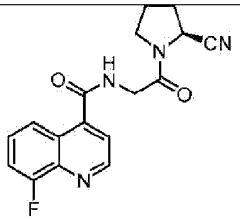
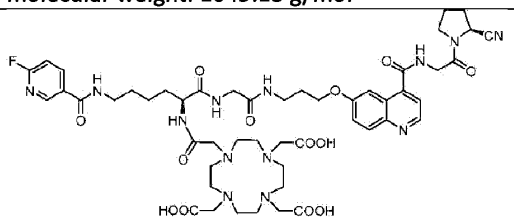
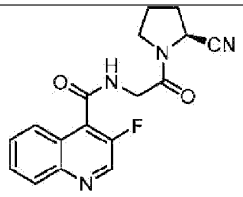
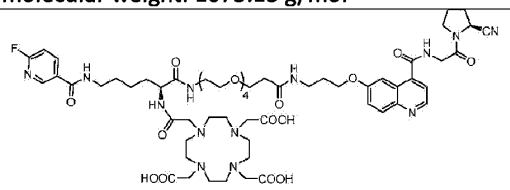
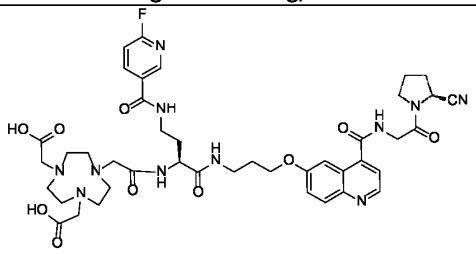
40. While Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above), we found the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents as shown in the current application US 2020/0330624 A1 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C).

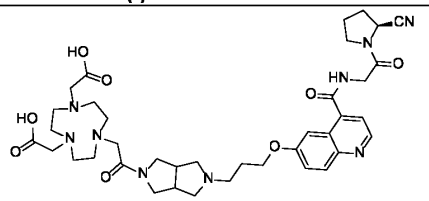
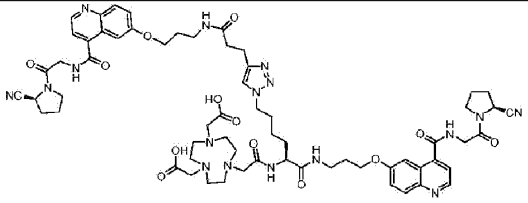
41. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase

(PREP) versus FAP. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4.

42. In the process of developing FAP imaging agents, my lab tested the specificity of a number of FAP imaging agents, some of which have molecular structures covered by the pending claims of this application, and some of which have molecular structures not covered by the pending claims and which are used as reference compounds. The results are summarized in the Table below, together with the specificity data for MIP-1232 extracted from Melleta. MIP-1232 and the compounds not covered by the pending claims tested in my lab are labeled as "Reference Compound" in the table below.

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *	 molecular weight: 370.38 g/mol	4,111
	152	 molecular weight: 734.70 g/mol	66,084
	20	 molecular weight: 983.86 g/mol	>1,418,440
	403		10,502

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
		molecular weight: 876.94 g/mol	
	15.7	 molecular weight: 734.70 g/mol	5,807
	241	 molecular weight: 1049.13 g/mol	779
	17	 molecular weight: 1073.15 g/mol	1,693
	3	 molecular weight: 1266.39 g/mol	407
		 molecular weight: 889.39 g/mol	10,694

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
		 molecular weight: 761.39 g/mol	11,893
		 molecular weight: 1282.43 g/mol	1,313

* Data from R. Meletta etc., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference

43. Surprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. In particular, as shown in the Table below, MIP-1232, which is a compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds of the pending claims. I also observe that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. Such differences in specificity between the reference compounds and the compounds of the pending claims are surprising and unexpected. The higher specificity of the compounds of the pending claims certainly is beneficial for successfully developing a medical imaging agent.

44. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully Submitted,



12/12/2023

Martin Pomper Date

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	12/13/2023 03:39:21 PM Z ET	JHU-36631.303

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63593228	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0636	E2023BCF40079520	Van Nguyen

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
2464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	56.00	1	56.00
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$330.00

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 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.

Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.	Confirmation No.: 7536
Serial No.: 18/354,282	Art Unit: 1618
Filed: July 18, 2023	Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Dear Examiner Perreira:

This communication is responsive to the non-final Office Action mailed September 26, 2023.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

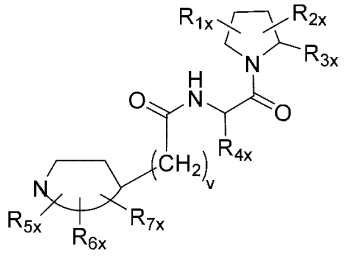
IN THE CLAIMS:

29. (Presently Amended) A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

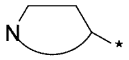
R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

ITM Exhibit 1004, Page 1210 of 1652

v is 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

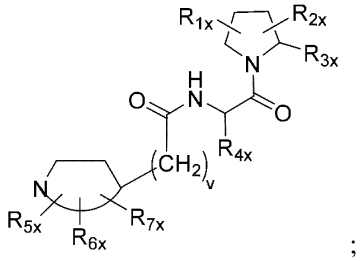
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

30. (New) The compound of claim 29, wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

31. (New) A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

ITM Exhibit 1004, Page 1211 of 1652

R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

v is 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

ITM Exhibit 1004, Page 1212 of 1652

Status

Claim 29 is pending in the Application and stands rejected. New claims 30 and 31 have been added. No new matter has been added. Upon entry of this Amendment, claims 29-31 will be pending in the Application.

Applicant-Initiated Interview Summary

Applicant appreciates the consideration of the Examiner during the telephonic interview of December 11, 2023. Participating in the interview were Examiner Perreira, Jeffrey W. Childers, Dr. Martin Pomper, Sangeeta Ray, Andrew G. Horti, Qi (Chee) Zhuo, and Don Ho. The rejection of claim 29 under 35 U.S.C. § 102(a)(1) and 35 U.S.C. § 103 was discussed. No agreement was reached.

Drawings

The Office Action notes that color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Applicant submits herewith a Petition under 37 CFR 1.84(a)(2) and accompanying fee. Applicant respectfully requests that the color drawings be accepted at this time.

Claim Rejections - 35 USC § 102

Claim 29 is rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

Claim 29 is amended and further defines the compound of formula (I) as being "low molecular weight" ("LMW"). The instant patent application distinguishes the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, the instant application characterizes the large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily

and may offer a shorter path to regulatory approval. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

> [T]he presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP-α, i.e., an FAP-α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α.

page 8, lines 26-29, page 9, lines 1-2.

> Because FAP-α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP-α.

page 1, lines 28-34, page 2, lines 1-7.

Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

In contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound – as the Examiner correctly pointed out, comprising an anti-FAP moiety bound to an ATTO488 dye via a **HMPA copolymer**. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole; further

LMW compounds of the current claims with molecular weights are presented in the table on pages 14-15 herein below. Thus, one of ordinary skill in the art upon reading and understanding of the instant specification in view of Dvořáková would appreciate that the presently claimed compounds are "low molecular weight" compounds.

The term of "low molecular weight" is well accepted in the chemical arts, and its meaning is clear to one of ordinary skill in the art. In particular, when used in the scientific references in the chemical arts, one of ordinary skill in the art would recognize that low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. *See e.g.*, K Beebe et al., Clin Transl Sci. 2014 Feb; 7(1): 74–81 ("Metabolomics is often described as a systematic study of the low molecular weight (approximately 50–1,500 Da) metabolites (*chemicals*) within a given sample"); A. Ferreira et al., J. Agric. Food Chem. 2014, 62, 6784−6793 ("Metabolites are a group of low molecular weight substances (50−1500 Da) that includes amino acids, fatty acids …"); C. Llewellyn et al., Progress in Oceanography, Volume 137, p. 421-433 (Metabolomics involves the non-targeted unbiased analysis of large suites of low molecular weight organic molecules or metabolites (typically 50–1500 Da)…); *see also* https://www.ebi.ac.uk/training/online/courses/metabolomics-introduction/what-is/small-molecules/ ("A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product. Metabolomics usually studies small molecules within a mass range of 50 – 1500 daltons (Da).")

New claim 30 further defines B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. Support for this amendment can be found in claim 29 as originally filed. Applicant notes that Dvořáková only discloses optical imaging agents.

New claim 31 includes the transitional phrase "consisting essentially of." As provided in MPEP § 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Applicant notes that in the present claims, the compound of formula (I) is limited then to components B-L-A, and would not include the HMPA copolymer carrier disclosed and which forms the basis of the iBodies disclosed in Dvořáková.

ITM Exhibit 1004, Page 1215 of 1652

Because every pending claim (claims 29-31) of the instant application requires the claimed compound to be "low molecular weight", Dvořáková cannot anticipate the pending claims because Dvořáková does not disclose a compound having low molecular weight.

Claim Rejections - 35 USC § 103

Claim 29 is rejected under 35 U.S.C. § 103 as being unpatentable over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

The Office Action asserts that Jansen I discloses FAP inhibitors that encompass aspects of the instant claims. The Office Action acknowledges, however, that Jansen I does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

The Office Action asserts that Zimmerman discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease, which, in some embodiments, include a metal chelating moiety that includes a radionuclide or, in other embodiments, a radiohalogen.

The Office Action asserts that Jensen II discloses quinoline-containing FAP inhibitors that are 60 times more FAP-affinity than the naphthoyl derivative of Jansen I.

The Office Action then concludes that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jansen I teaches that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated and Zimmerman teaches radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

The Office Action further concludes that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jensen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

The Office Action finally concludes that it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging

FAP with an expectation of success as the quinoline derivative provides 60 times more FAP-affinity than the naphthoyl derivative.

Applicant respectfully disagrees for the reasons set forth below.

i. <u>There was no motivation for one of ordinary skill in the art to select and modify any compounds of Jansen I and Jansen II to arrive at the claimed compounds</u>

As provided in MPEP § 2143(I)(E), in cases involving new chemical compounds, it is necessary to identify some reason that would have led a chemist to select a lead compound and subsequently modify the lead compound in a particular manner to establish prima facie obviousness of new claimed compounds. Takeda v. Alphapharm., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Office Action argues that the compounds of Jansen I may be modified with a radiohalogen via a linker. The Office Action appears to take the position that the C_{1-6}alkyl or -O-C_{1-6}alkyl that may be attached to the heterocyclic group of the FAP moiety in Jansen I may serve as a "linker" within the meaning of the pending claims. In particular, the Office Action points out that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated. An implicit but necessary position of the Office Action is that the C_{1-6}alkyl or the -O-C_{1-6}alkyl group may be interpreted as a "linker" only when it is selected as a substituent group in preference to the numerous other equally viable alternatives, and further, only when it is halogenated, and then further only when the halogen is a radiohalogen. Applicant respectfully points out that C_{1-6}alkyl and the -O-C_{1-6}alkyl are among a wide variety of alternative functional groups that may optionally be attached to the heterocyclic group of a generic structure of the FAP inhibitor compounds disclosed in Jansen I. See Pomper Affidavit, Para. 23. Furthermore, among 43 representative compounds disclosed in Jansen I and 39 representative compounds in Jansen II, only a single compound with a halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl is disclosed. *See* Pomper Affidavit, Para. 24; Jansen I, Example 11, Table 4; Jansen II, Compound No. 28, Table 3. Thus, the prior art provides no motivation or indication to select C_{1-6}alkyl or the -O-C_{1-6}alkyl from a large group of functional groups as a substituent group on the FAP inhibitors disclosed in Jansen I or Jansen II; even if C_{1-6}alkyl or the -O-C_{1-6}alkyl is selected as a substituent group, Jansen I or Jansen II provides no motivation to further substitute the C_{1-6}alkyl or the -O-C_{1-6}alkyl group with a halogen. In fact, in most of the halogenated compounds disclosed in Jansen I and Jansen II, the halogen is directly attached to the heterocyclic group, instead of via a C_{1-6}alkyl or the -O-C_{1-6}alkyl group.

Further, one of ordinary skill in the art also would not select the single FAP inhibitor substituted with the halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl disclosed in Jansen I and Jansen II as a starting point or a lead compound to modify, because this compound has mediocre bioactivities compared with the other compounds disclosed in the prior art. In particular, many other FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II, which is substituted with a trifluoromethoxy group. *See* Pomper Affidavit, Para. 26. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012 μm and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC_{50} of 0.0062 μm and a selectivity index of 193. *Id.*

Even assuming for arguments sake a skilled person made the non-obvious steps of selecting a compound with a halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl group of Jansen I or Jansen II for modification, there is still no explicit or implicit motivation in the cited prior art to substitute the alkyl group with a radiohalogenated group to render the C_{1-6}alkyl or -O-C_{1-6}alkyl as a "linker" within the meaning of the pending claims. In fact, the vast majority of the representative compounds disclosed in Jansen I and Jansen II do not have a halogenated C_{1-6}alkyl or the -O-C_{1-6}alkyl. To successfully argue that a new compound is obvious, the prior art must show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda,* 492 F.3d at 1356. The cited prior art clearly does not suggest anything that may motivate one of ordinary skill in the art to make the specific modification of substituting the C_{1-6}alkyl or -O-C_{1-6}alkyl with a radiohalogen.

The Office Action appears to correlate the substitution of a C_{1-6}alkyl or -O-C_{1-6}alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

> It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Office Action dated September 26, 2023, pages 6-7. Applicant respectfully points out that Jansen II merely discloses that quinoline-containing FAP inhibitors have a 60 times higher FAP-

affinity than the N-(1-naphthoyl) FAP inhibitors. Pomper Affidavit, Para. 27. Jansen II does not suggest that substitution of the quinoline ring of the quinoline-containing FAP inhibitors would, let alone could, improve the FAP affinity or selectivity of the FAP inhibitors. *Id.* On the contrary, Jansen II observed that substitution of the quinoline ring has little or even negative effects on the potency of the quinoline-containing FAP inhibitors:

> Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter.

Janssen II, page 493, left column. Pomper Affidavit, Para. 28. In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has both an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without the trifluoromethoxy substitution. [1] *Id.* Therefore, there is no motivation to substitute the quinoline moiety of the FAP inhibitor, not to mention to halogenate the quinoline moiety via a trifluoromethoxy substitution. Applicant would like to emphasize again that without a radiohalogenated trifluoromethoxy substitution on the FAP inhibitor of Jansen I or Jansen II, any FAP inhibitors modified based Jansen I or Jansen II cannot be interpreted as containing a "linker" within the meaning of the pending claims.

Accordingly, in view of the totality of the disclosure in Jansen I and Jansen II, there is no explicit or implicit teachings, suggestion, or motivation for one of ordinary skill in the art to select and modify any compounds in Jansen I and Jansen II to arrive at the claimed compounds. There is no prima facie obviousness because there is no reason that would have led a chemist to select and modify a known compound in a particular manner to establish prima facie obviousness of the compounds of the pending claims. *See* Takeda, 492 F.3d at 1357.

ii. <u>There was no reasonable expectation of success in modifying any compounds in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

The Office Action also fails to demonstrate a reasonable expectation of success in modifying and making the structural changes to the compounds of Jansen I and Jansen II to

[1] *See* Jansen I, Table 4. IC_{50} for FAP (an indicator of the FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor; selectivity index is 59 versus 83.

arrive at the compounds of the pending claims. The examiner is required to show a reasonable expectation of success when trying to establish prima facie obviousness by modifying or combing the prior art to achieve the claimed invention. MPEP § 2143.02; *see also* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so."). For a medical imaging agent used to diagnose disease, it is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with the medical condition. See the Pomper Affidavit, Para. 31. The high specificity allows the imaging agent to selectively bind to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical conditions from interfering with the binding between the imaging agent with the target protein. *Id.* The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. *Id.* Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

The Office Action takes the position that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen as Zimmerman teaches radiohalogenation of FAP inhibitors for diagnostic imaging and therapeutic treatment of diseases. However, at the time the instant application was filed, one of ordinary skill in the art recognized the unpredictability associated with the development of medical imaging agents, including the optimization of the specificity. Accordingly, there was no reasonable expectation of success for one of ordinary skill in the art to modify the compounds to arrive at the compounds of pending claims, even if the compound substituted with halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl were selected as the lead compound, which one of ordinary skill in the art had no motivation to do in the first place as discussed.

In fact, one of ordinary skill in the art knew that the FAP imaging agents of Zimmerman most likely would not function well because of the poor specificity associated with the compounds of Zimmerman. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for

atherosclerotic plaque, and was determined as not suitable for the application. *See* Meletta etc., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta"); Pomper Affidavit, Paras. 33-35. As provided on page 2089 of Meletta, although pronounced binding of [^{125}I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Pomper Affidavit, Para. 34. Based on these data, Maletta could not conclude on the selectivity of [^{125}I]MIP-1232 for FAP. Accordingly, because of the low specificity MIP-1232 displayed in the investigation, Meletta concluded that MIP-1232 was not suitable for the medical imaging for the medical condition. *See* Procter & Gamble v. Teva, 566 F.3d 989, 997 (Fed. Cir. 2009) (Upholding decision of the District Court that there was no reasonable expectation of success in modifying the prior art compound to produce a "improved, safe, and effective" drug because researchers had no basis to expect it to be as good as or better than the prior art compound). The lack of reasonable expectation of success is especially telling in view of the failure by others in the art to use the compounds of Zimmerman cited by the Office Action. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir.2003) ("While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."); In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("Failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.")

Applicant respectfully submits, based on the unpredictability in the art and failure and uncertainty observed by Maletta associated with the prior art compound, that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at a selective FAP imaging agent by merely modifying the FAP inhibitors of Jansen I and/or Jansen II with the radiohalogen of Zimmerman.

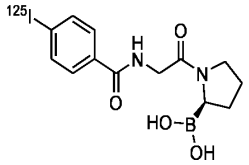
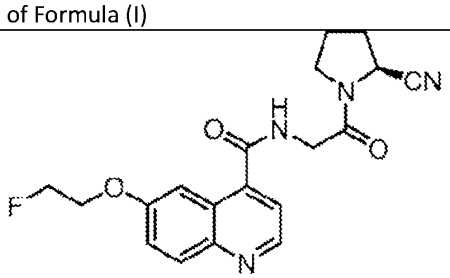
iii. <u>There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness</u>

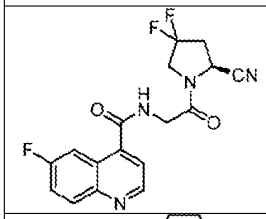
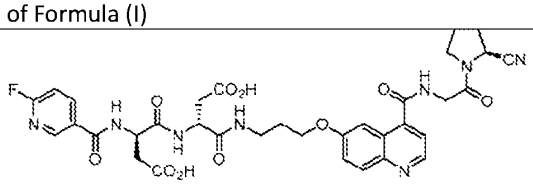
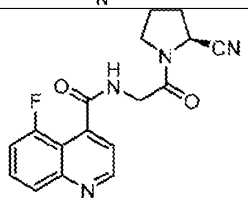
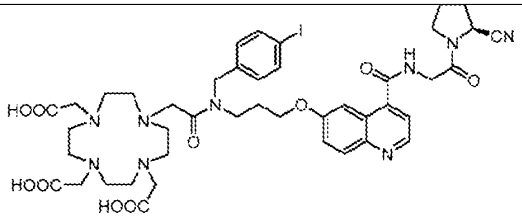
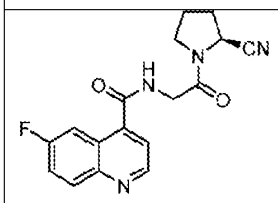
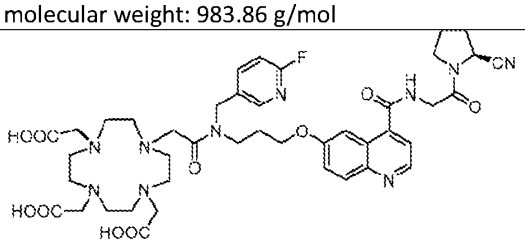
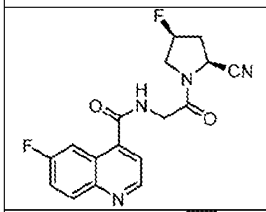
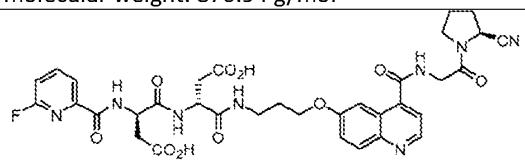
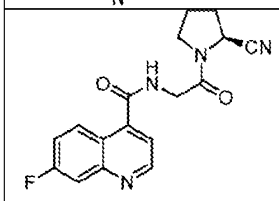
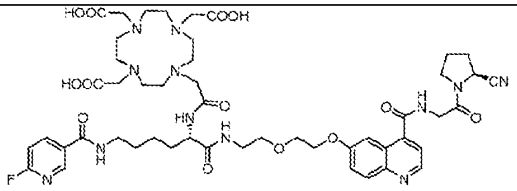
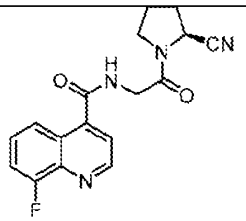
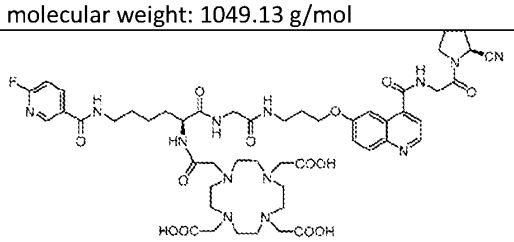
The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Pomper Affidavit, Paras. 38-42. As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to

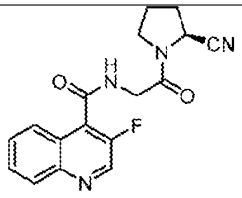
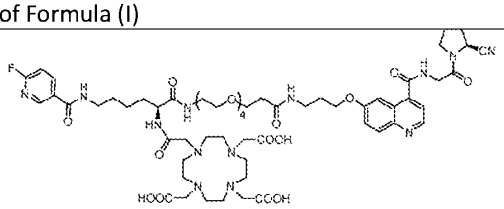
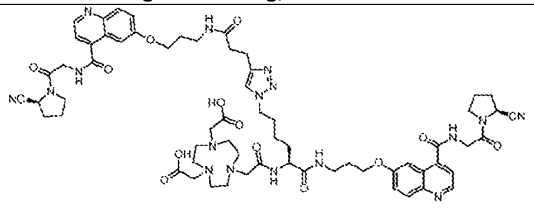
selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Pomper Affidavit, Para. 40.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Pomper Affidavit, Para. 42. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.,* Para. 42. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *	 molecular weight: 370.38 g/mol	4,111

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	152	 molecular weight: 734.70 g/mol	66,084
	20	 molecular weight: 983.86 g/mol	>1,418,440
	403	 molecular weight: 876.94 g/mol	10,502
	15.7	 molecular weight: 734.70 g/mol	5,807
	241	 molecular weight: 1049.13 g/mol	779
	17	 molecular weight: 1073.15 g/mol	1,693

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	3	 molecular weight: 1266.39 g/mol	407
		molecular weight: 889.39 g/mol	10,694
		molecular weight: 761.39 g/mol	11,893
		 molecular weight: 1282.43 g/mol	1,313

* Data from R. Meletta et al., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference.

Accordingly, Applicant respectfully submits that claim 29 is not obvious over Jansen I in view of Zimmerman and Jansen II. Applicant respectfully requests that the rejection of claim 29 under 35 U.S.C. § 103 as being unpatentable over Jansen I in view of Zimmerman and Jansen II be withdrawn at this time.

Double Patenting

Claim 29 is provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 2, 13, 15, 16 and 21-25 of copending Application No. 16/762,873.

Applicant notes that it appears that the Office Action intended to cite Application No. 16/758,182.

Without acquiescing to the assertions made in the Office Action, Applicant has submitted herewith a Terminal Disclaimer over Application No. 16/758,182.

Applicant respectfully requests that the rejection of claim 29 under nonstatutory double patenting over Application No. 16/758,182 be withdrawn at this time.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney at 919-724-8699 or 608-662-1277. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment associated with this filing to Deposit Account Number 50-4302. If an extension of time for this paper is required, petition for extension is herewith made.

Respectfully Submitted,

CASIMIR JONES, S.C.

Date: December 13, 2023

/JEFFREY W. CHILDERS/

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Customer No. 101943

PTO/AIA/25 (04-13)
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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) JHU-36631.303

In re Application of: YANG, et al.

Application No.: 18/354,282

Filed: July 18, 2023

For: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

The applicant, The Johns Hopkins University, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 16/758,182, filed, April 22, 2020, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 58126

/Jeffrey W. Childers/	December 13, 2023
Signature	Date
Jeffrey W. Childers	
Typed or printed name	
Attorney of Record	608.662.1277
Title	Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS							
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*		Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
		BEEBE et al., "Understanding the Apothecaries Within: The Necessity of a Systematic Approach for Defining the Chemical Output of the Human Microbiome". Clin Transl Sci. 2014 Feb; 7(1): 74–81.	
		FERREIRA et al., "Monitoring Alcoholic Fermentation: An Untargeted Approach". Journal of Agricultural and Food Chemistry, 2014, 62, 6784−6793.	
		LLEWELLYN et al., "Using community metabolomics as a new approach to discriminate marine microbial particulate organic matter in the western English Channel". Progress in Oceanography, Volume 137, Part B, September 2015, p. 421-433.	
		MELETTA et al., "Evaluation of the radiolabeled boronic acid-based FAP inhibitor MIP-1232 for atherosclerotic plaque imaging". Molecules, 2015 Jan 27;20(2):2081-99.	
		METABOLOMICS – EMBL-EBI, https://www.ebi.ac.uk/training/online/courses/metabolomics-introduction/what-is/small-molecules/, retrieved on 2023-12-12. 5 pages.	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	*Attorney Docket Number*	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	3	of	3	*Attorney Docket Number*	JHU-36631.303

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-12-13
Name/Print	Jeffrey W. Childers	Registration Number	58,126

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PTO Notes regarding this form:

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[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**12/13/2023 03:39:21 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63593228	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 12

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-12-13- 36631.303 Supp IDS.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	34 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
Small molecules __ Metabolomics.pdf	5	Non Patent Literature	209 KB
Meletta artic.pdf	20	Non Patent Literature	1061 KB
Beebe 2014.pdf	8	Non Patent Literature	1071 KB

Ferreira2014.pdf		10	Non Patent Literature	2597 KB
Llewellyn 201.pdf		7	Non Patent Literature	3383 KB
2023-12-13 - JHU-36631.303 TD.pdf		2	Terminal Disclaimer Filed	213 KB
2023-12-13 - 36631_303 RNFOApdf.pdf		17	-	442 KB
2023-12-13 - 36631_303 RNFOApdf-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	35 KB
2023-12-13 - 36631_303 RNFOApdf-CLM.pdf	(2-4)	3	Claims	55 KB
2023-12-13 - 36631_303 RNFOApdf-REM.pdf	(5-17)	13	Applicant Arguments/Remarks Made in an Amendment	396 KB
2023-12-13 - 36631_303 Declaration 1.132.pdf		12	Affidavit-traversing rejections or objections rule 132	615 KB
2023-12-13 -36631.303 Petition 1.84.pdf		2	A petition from Applicant to accept Color Drawings or Color Photographs	28 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-12-13- 36631.303 Supp IDS.pdf	7B4C838340F91E9A5BA30832A04FD5B424BD816CECACCCCA E4373F87A1EFD2EB69F056DCB1FD162CA8F732B814CE95C0 E826739563DE32C9738849C371CF1E16
Small molecules _ Metabolomics.pdf	F1E4BC35DAD24CA1195511593AEDBADE15BEEE47DDEF0C6 5677347D7A28D6DC39F309F28E8C3BDB0E99740D1D838D59C 134487CF7BA459F55C0511A860A4B85B

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2023-12-13 - 36631_303 RNFOApdf.pdf	B91DCF3CBC4BB5F3CC45181CDE559C67779D7C1060FA77E4B24CA7B7D156406D3E1DAD0844F8B1A5E426E9E2AA2CCF5354FBB7A923E4F536D69B1FE3EA033EC3
2023-12-13 - 36631_303 RNFOApdf-A....pdf	1AD2AA341DCF1F97E5144FE4CBD14C78AB0CF67C19674703B26069FA3874BADDE7953D147F4D76D4E93CE4CAFF2A3480FCEC15B70DF1543416EDB6DBD92C1861
2023-12-13 - 36631_303 RNFOApdf-CLM.pdf	116386194215398C9F8A60C2F2532272035F3305095B44AA38F43B52941177A0891AF2289D4BB1B2D6672228F1D3DBD2E299427256BC99D6DAD538746E67FFB2
2023-12-13 - 36631_303 RNFOApdf-REM.pdf	34D3B3FBE8C6834DB88450784B545EBCA964B9290FF65C8A969B4BC658D620A64C54B2EBC9F8D23C102381300A286AE7790867BC1AEAB86B2FD19BBFA9F9D9C3
2023-12-13 - 36631_303 Declaration 1.132.pdf	F3993FEF9318D0397B2409722BCDC279406FA612A0A350E24C715DADAAE459ADC65978ABEAA7A54F502AFB9B1109522113EC3189F5D4D388A94A0430CDD37D80

2023-12-13 -36631.303 Petition 1.84.pdf	B0699024CBFC974BCCF60C1AFB52FB7C00CD3A1DC93620FB F2DBB15AB984DA174FDFFE51A46F4D210C138176C38F48AD A29A88875B1B7E075997BC87B4994A9F

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 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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 12/15/2023

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
12/15/2023	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

Applicant-Initiated Interview Summary	**Application No.** 18/354,282	**Applicant(s)** Yang et al.		
	Examiner MELISSA J PERREIRA	**Art Unit** 1618	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
MELISSA J PERREIRA	Examiner	Telephonic
Jeffrey Childers	Attorney of Record	
Dr. Martin Pomper	Inventor	
Sangeeta Ray	Associate Professor	
Andrew Horti	Professor of Radiol	
Qi (Chee) Zhuo	Sr. Intellectual prop	
Don Ho	Licensee Representative	

Date of Interview: 11 December 2023

Issues Discussed:

Proposed Amendment(s)

The applicant asserts that the compounds of the instant claims are low molecular weight compounds wherein low molecular weight is defined as compounds under ~1500Da.
The proposed amendments and declaration were discussed as to include a number of representative examples of the low molecular weight compounds exhibiting the unexpected and advantageous results to be commensurate in scope with the instant claims.
The examples provided in the declaration have an identical quinoline but does not provide any compounds with other N-containing aromatic or non-aromatic mono- or bicyclic heterocycles.
The applicant stated that they have optimized the linkers.

Other

The examiner indicated that she used an incorrect application number in the NSDP rejection. The applicant stated that they corrected the application number in their response.

☑ Attachment

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant-Initiated Interview Summary	**Application No.** 18/354,282	**Applicant(s)** Yang et al.		
	Examiner MELISSA J PERREIRA	**Art Unit** 1618	**AIA (First Inventor to File) Status** Yes	**Page** **2 of 2**

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the 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.

FOR PURPOSES OF INTERVIEW ONLY – DO NOT ENTER

Application No. 18/354,282 JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al. Confirmation No.: 7536

Serial No.: 18/354,282 Art Unit: 1618

Filed: July 18, 2023 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

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

Examiner Perreira:

1. I, Martin Pomper, am the Principal Investigator and co-inventor of the subject matter described and claimed in the above-referenced patent application (the "Application"). The research leading to the subject matter of the Application was conducted in my laboratory.

2. I am currently Chair of the Department of Radiology at University of Texas Southwestern Medical Center. Previously, I was Professor of Radiology and Radiological Science, Professor of Oncology and Radiation Oncology and Molecular Radiation Services, Research Chief of Nuclear Medicine, Director of the Division of Nuclear Medicine and Molecular Imaging, Associate Dean of Entrepreneurship and Technology Development, and Director of the Johns Hopkins Center for Translational Molecular Imaging at the Johns Hopkins School of Medicine.

3. I received my B.Sc. degree, Ph.D. degree, and MD degrees all from the University of Illinois at Urbana-Champaign.

4. I completed my postgraduate medical training at Johns Hopkins that included a medical internship, residencies in diagnostic radiology and nuclear medicine, and a fellowship in neuroradiology, before I joined the Johns Hopkins faculty in 1996.

5. I have authored hundreds scientific articles and am inventor of numerous issued patents or patent applications in the field of medical diagnostic imaging.

6. I have read the non-final Office Action dated September 26, 2023, in the subject Application and the references cited therein.

7. I understand the Office Action rejected the claim 29 on numerous grounds, including anticipation under 35 U.S.C. § 102(a) and obviousness under 35 U.S.C. § 103. I will focus on the obviousness rejection under 35 U.S.C. § 103 in this Affidavit based on my technical expertise and knowledge in the art of medical diagnostic imaging.

8. I understand that the pending claims are directed to a low molecular weight compound of Formula (I):

B-L-A

wherein A is a targeting moiety for FAP-α defined by a specific structure, B is an optical or radiolabeled functional group, and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

9. The Office Action asserts that claim 29 is obvious over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

10. I understand that the Office Action took the position that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Janssen I with a radiohalogen (taught in Zimmerman) via a linker, such as C_{1-6}alkyl or -O-C_{1-6}alkyl as Jansen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

11. Based on my review of the Office Action and prior art references cited in the Office Action, I disagree with the obviousness rejections for the following reasons:

12. First, I found that there are no teachings or suggestions in the cited reference to make a compound with a linker having a bi-functionalization which binds to the FAP inhibitor moiety A and the optical or radiolabeled moiety B.

13. The Office Action took the position that the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl of Jansen I are modified with a radiohalogen.

14. I observed that $C_{1\text{-}6}$alkyl and the -O-$C_{1\text{-}6}$alkyl are among a variety of functional groups that may be attached to the heterocyclic group of the FAP inhibitor compounds disclosed in Jansen I, including —H, —OH, —oxo, —halo, —$C_{1\text{-}6}$alkyl, —O—$C_{1\text{-}6}$alkyl, —S—$C_{1\text{-}6}$alkyl, —NR_8R_9, —OR_{12}, —Het_2 and —Ar_2, wherein the $C_{1\text{-}6}$alkyl may be optionally substituted with —OH and —halo.

15. Further, I observed that the vast majority of the representative compounds disclosed in either Jansen I or Jansen II do not contain a halogenated $C_{1\text{-}6}$alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

16. FAP inhibitors substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl clearly do not stand out of the many FAP inhibitors including those unsubstituted or substituted with other functional groups or elements disclosed in Jansen I or Jansen II. There is no suggestion in the cited references as to why a FAP inhibitor substituted with a halogenated $C_{1\text{-}6}$alkyl should be selected for modification with a radiohalogen.

17. I notice that the single FAP inhibitor substituted with the halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl disclosed in Jansen I and Jansen II has worse bioactivities compared with the other compounds disclosed in the prior art. In particular, many FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II which is substituted with a trifluoromethoxy group. See Example 11, Table 4, Jansen I; Compound No. 28, Table 3, Jansen II. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012 μm and a selectivity index of 59, which do not compare favorably to a number of compounds. For example, compound

Example 15 of Jansen I has a IC_{50} of 0.0062 μm and a selectivity index of 193. Accordingly, one of ordinary skill in the art would not select the FAP inhibitor substituted with a trifluoromethoxy group for modification.

18. The Office Action appeared to correlate the substitution of a C_{1-6}alkyl or -O-C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

> It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy. [Office Action dated September 26, 2023, pages 6-7].

I would point out that Jansen II merely discloses that quinoline containing FAP inhibitors have 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Jansen II does not suggest that substitution of the quinoline ring of the quinoline containing FAP inhibitors will improve the FAP-affinity or selectivity of the FAP inhibitors.

19. On the contrary, Jansen II observed that substitution of the quinoline ring has little or negative effects on the FAP-affinity of the quinoline containing FAP inhibitors:

> Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19−24, having a clearly negative effect on this parameter. [Janssen II, page 493, left column].

In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without any substitution. Specifically, IC_{50} for FAP (an indicator of the FAP affinity; a higher value means a lower FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor. Selectivity index (a higher selectivity index means a higher selectivity) is 83 for the former versus 59 for the latter. *See* Jansen I, Table 4.

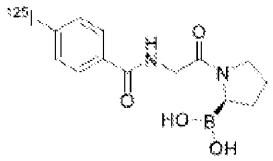
20. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the C_{1-6}alkyl or -O-C_{1-6}alkyl.

21. Further, due to the high unpredictability of the medical imaging art, I believe one of ordinary skill in the art would not reasonably expected success in modifying the cited prior art to arrive at the compounds of the pending claims for medical imaging applications.

22. There are numerous important parameters which need to be taken into consideration for successfully developing a FAP imaging agent. Those parameters include, for example, affinity for FAP, selectivity (specificity) for FAP, ease of synthesis, and biodistribution, and the like. It is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with a medical condition. The high specificity allows the imaging agent to bind selectively to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein. The affinity and specificity of the medical imaging agent is highly dependent on the molecular structure of the agent. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

23. The unpredictability of the art is clearly manifested by the documented failure of a compound disclosed in Zimmerman.

24. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic



[^{125}I]MIP-1232

plaque, and was determined as not suitable for the application. *See* Meletta et al., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta").

25. As provided on page 2089 of Meletta, while pronounced binding of [^{125}I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Based on these data, Maletta could not conclude on the selectivity of [^{125}I]MIP-1232 for FAP.

26. Accordingly, because of the low specificity MIP-1232 displayed in the testing, Meletta concluded that MIP-1232 was not suitable for the medical imaging application for the particular medical condition being tested in Meletta. *Id.* at 2095.

27. Based on my review, I am not aware of any other compounds disclosed in Zimmerman that fare better than MIP-1232 and that was developed successfully as a medical imaging agent.

28. The failure of investigations with MIP-1232, which is a compound disclosed in the cited prior art, is especially telling as it demonstrates the high unpredictability of the art and lack of reasonable expectation of success by combining the prior art to arrive at the compounds of the pending claims for medical imaging applications.

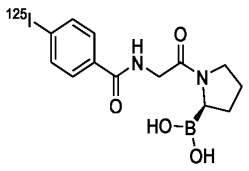
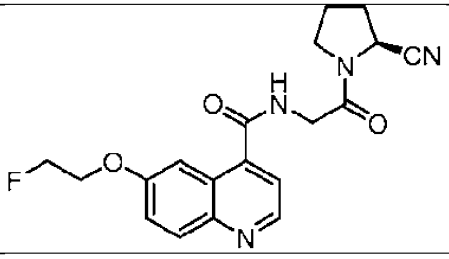
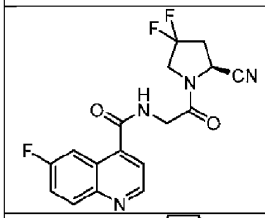
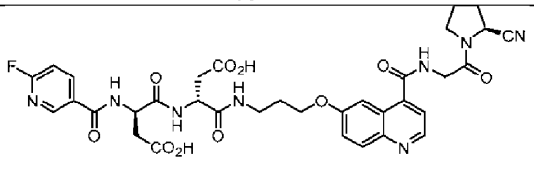
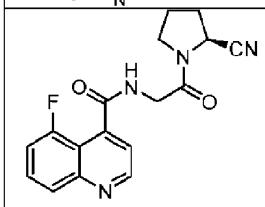
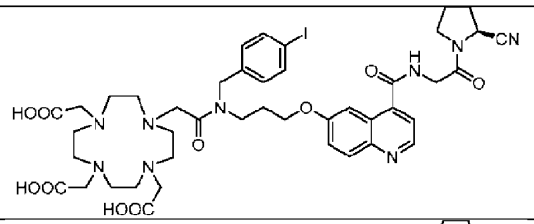
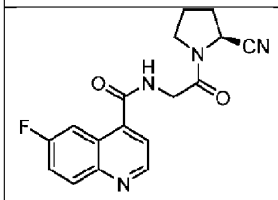
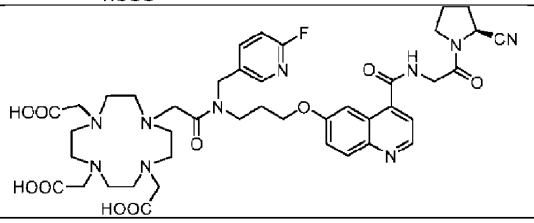
29. Further, I am of the opinion that there are unexpectedly superior FAP specificity associated with the compounds of the pending claims based on the testing results from my lab.

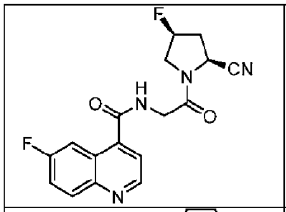
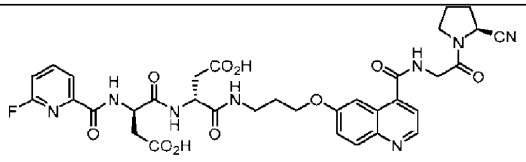
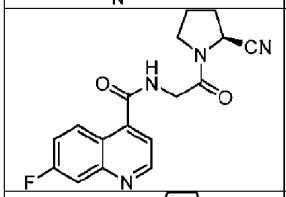
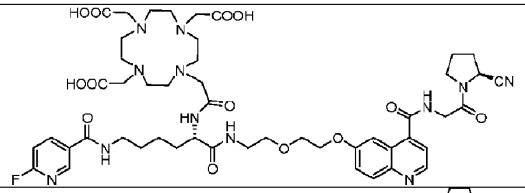
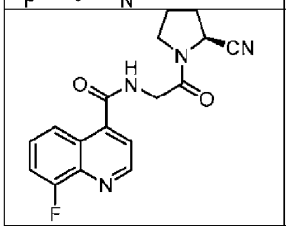
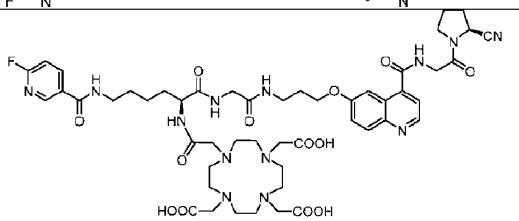
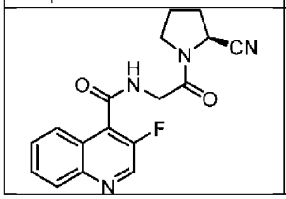
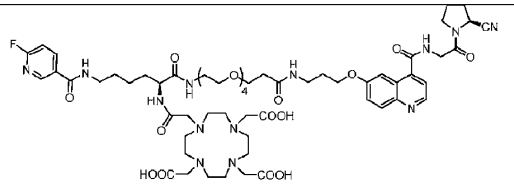
30. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

31. While Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above), we found the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents as shown in the current application US 2020/0330624 A1 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C).

32. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4.

33. In the process of developing FAP imaging agents, my lab tested the specificity of a number of FAP imaging agents, some of which have molecular structures covered by the pending claims of this application, and some of which have molecular structures not covered by the pending claims and which are used as reference compounds. The results are summarized in the Table below, together with the specificity data for MIP-1232 extracted from Melleta. MIP-1232 and the compounds not covered by the pending claims tested in my lab are labeled as "Reference Compound" in the table below.

Reference Compound Molecular Structure	PREP/FAP Ratio	Claimed Compound Molecular structure	PREP/FAP Ratio
	32 *		4,111
	152		66,084
	20		>1,418,440
	403		10,502

	15.7		5,807
	241		779
	17		1,693
	3		407

* Data from R. Meletta etc., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference

34. Surprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. In particular, as shown in the Table below, MIP-1232, which is a compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds of the pending claims. I also observe that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. Such differences in specificity between the reference compounds and the compounds of the pending claims are surprising and unexpected. The higher specificity of the compounds of the pending claims certainly is beneficial for successfully developing a medical imaging agent.

31. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully Submitted,

DRAFT-DRAFT-DRAFT

Martin Pomper Date

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INTERVIEW AGENDA

In re Application of: YANG, et al.
Serial No.: 18/354,282
Filed: July 18, 2023
Attorney Docket No.: JHU-36631.303

Confirmation No.: 7536
Art Unit: 1618
Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Date: December 11, 2023
Time: 11:00 am (EST)
Call-in Number: 1-877-304-9269
Pass code: 7695903

Attendees:

Examiner Melissa Jean Perreira, USPTO

Jeffrey W. Childers, Ph.D, Attorney of Record (Reg. No. 58,126)

Dr. Martin Pomper, Inventor, Chair of the Department of Radiology at University of Texas Southwestern Medical Center

Sangeeta Ray, Ph.D., M.S., Associate Professor of Radiology and Radiological Science, Johns Hopkins University School of Medicine

Andrew G. Horti, Ph.D., M.S., Professor of Radiology and Radiological Science, Johns Hopkins University School of Medicine

Qi (Chee) Zhuo, Sr. Intellectual Property Manager, Johns Hopkins Technology Ventures

Don Ho, Ph.D., Licensee Representative, Director of Intellectual Property, Neuraly, Inc.

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Agenda Outline

A. Summary of Claimed Invention

B. Claim Rejections and Distinction Over the Art

i. Rejection under 35 U.S.C. § 102(a)(1) as allegedly being anticipated by Dvořáková et al., J. Med. Chem. 2017, 60, 8385-8393.

ii. Rejection under 35 U.S.C. § 103 as allegedly being unpatentable over Jansen et al. (US2014/0357650A1) in view of Zimmerman et al. (US2010/0098633A1) and Jansen et al., ACS Med. Chem. Lett. 2013, 14, 491-496.

C. Proposed claim amendments

D. Proposed new claims

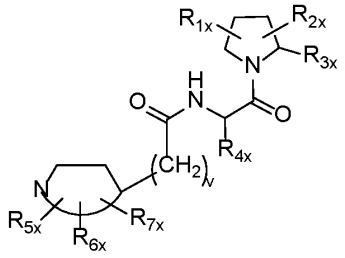
Proposed Claim Amendments

29. (Presently Amended) A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

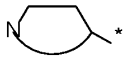
R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

v is 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

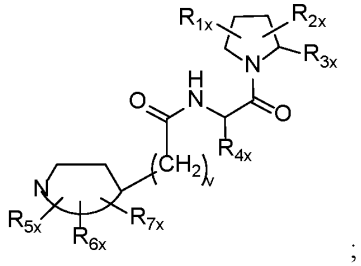
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

30. (New) The compound of claim 29, wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

31. (New) A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

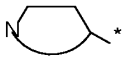
R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

v is 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

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Proposed Arguments

Claim Rejections - 35 USC § 102

Claim 29 is rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

Claim 29 is amended and further defines the compound of formula (I) as being "low molecular weight" ("LMW"). The instant patent application distinguishes the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, the instant application characterizes the large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

> [T]he presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP-α, i.e., an FAP-α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α.

page 8, lines 26-29, page 9, lines 1-2.

> Because FAP-α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010;

> Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP-α.

page 1, lines 28-34, page 2, lines 1-7.

Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

In contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound – as the Examiner correctly pointed out, comprising an anti-FAP moiety bound to an ATTO488 dye via a **HMPA copolymer**. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole. Thus, one of ordinary skill in the art upon reading and understanding of the instant specification in view of Dvořáková would appreciate that the presently claimed compounds are "low molecular weight" compounds.

The term of "low molecular weight" is well accepted in the chemical arts, and its meaning is clear to one of ordinary skill in the art. In particular, when used in the scientific references in the chemical arts, one of ordinary skill in the art would recognize that low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. *See e.g.*, K Beebe et al., Clin Transl Sci. 2014 Feb; 7(1): 74–81 ("Metabolomics is often described as a systematic study of the low molecular weight (approximately 50–1,500 Da) metabolites (*chemicals*) within a given sample"); A. Ferreira et al., J. Agric. Food Chem. 2014, 62, 6784−6793 ("Metabolites are a group of low molecular weight substances (50−1500 Da) that includes amino acids, fatty acids …"); C. Llewellyn et al., Progress in Oceanography, Volume 137, p. 421-433 (Metabolomics involves the non-targeted unbiased analysis of large suites of low molecular weight organic molecules or metabolites (typically 50–1500 Da)…); *see also* https://www.ebi.ac.uk/training/online/courses/metabolomics-introduction/what-is/small-

molecules/ ("A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product. Metabolomics usually studies small molecules within a mass range of 50 – 1500 daltons (Da).")

New claim 30 further defines B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. Support for this amendment can be found in claim 29 as originally filed. Applicant notes that Dvořáková only discloses optical imaging agents.

New claim 31 includes the transitional phrase "consisting essentially of." As provided in MPEP § 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Applicant notes that in the present claims, the compound of formula (I) is limited then to components B-L-A, and would not include the HMPA copolymer carrier disclosed and which forms the basis of the iBodies disclosed in Dvořáková.

Because every pending claim (claims 29-31) of the instant application requires the claimed compound to be "low molecular weight", Dvořáková cannot anticipate the pending claims because Dvořáková does not disclose a compound having low molecular weight.

Claim Rejections - 35 USC § 103

Claim 29 is rejected under 35 U.S.C. § 103 as being unpatentable over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

The Office Action asserts that Jansen I discloses FAP inhibitors that encompass aspects of the instant claims. The Office Action acknowledges, however, that Jansen I does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

The Office Action asserts that Zimmerman discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease, which, in some embodiments, include a metal chelating moiety that includes a radionuclide or, in other embodiments, a radiohalogen.

The Office Action asserts that Jensen II discloses quinoline-containing FAP inhibitors that are 60 times more FAP-affinity than the naphthoyl derivative of Jansen I.

The Office Action then concludes that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jansen I teaches that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated and Zimmerman teaches radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

The Office Action further concludes that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jensen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

The Office Action finally concludes that it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAP-affinity than the naphthoyl derivative.

Applicant respectfully disagrees for the reasons set forth below.

i. <u>There was no motivation for one of ordinary skill in the art to select and modify any compounds of Jansen I and Jansen II to arrive at the claimed compounds</u>

As provided in MPEP § 2143(I)(E), in cases involving new chemical compounds, it is necessary to identify some reason that would have led a chemist to select a lead compound and subsequently modify the lead compound in a particular manner to establish prima facie obviousness of new claimed compounds. Takeda v. Alphapharm., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Office Action argues that the compounds of Jansen I may be modified with a radiohalogen via a linker. The Office Action appears to take the position that the C_{1-6}alkyl or -O-C_{1-6}alkyl that may be attached to the heterocyclic group of the FAP moiety in Jansen I may serve as a "linker" within the meaning of the pending claims. In particular, the Office Action points out that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated. An implicit but necessary position of the Office Action is that the C_{1-6}alkyl or the -O-C_{1-6}alkyl group may be interpreted as a "linker" only when it is selected as a substituent group in preference to the numerous other equally viable alternatives, and further, only when it is halogenated, and then further only when the halogen is a radiohalogen. Applicant respectfully points out that C_{1-6}alkyl and the -O-C_{1-6}alkyl are among a

wide variety of alternative functional groups that may optionally be attached to the heterocyclic group of a generic structure of the FAP inhibitor compounds disclosed in Jansen I. See Pomper Affidavit, Para. 14. Furthermore, among 43 representative compounds disclosed in Jansen I and 39 representative compounds in Jansen II, only a single compound with a halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl is disclosed. *See* Pomper Affidavit, Para. 15; Jansen I, Example 11, Table 4; Jansen II, Compound No. 28, Table 3. Thus, the prior art provides no motivation or indication to select C_{1-6}alkyl or the -O-C_{1-6}alkyl from a large group of functional groups as a substituent group on the FAP inhibitors disclosed in Jansen I or Jansen II; even if C_{1-6}alkyl or the -O-C_{1-6}alkyl is selected as a substituent group, Jansen I or Jansen II provides no motivation to further substitute the C_{1-6}alkyl or the -O-C_{1-6}alkyl group with a halogen. In fact, in most of the halogenated compounds disclosed in Jansen I and Jansen II, the halogen is directly attached to the heterocyclic group, instead of via a C_{1-6}alkyl or the -O-C_{1-6}alkyl group.

Further, one of ordinary skill in the art also would not select the single FAP inhibitor substituted with the halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl disclosed in Jansen I and Jansen II as a starting point or a lead compound to modify, because this compound has mediocre bioactivities compared with the other compounds disclosed in the prior art. In particular, many other FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II, which is substituted with a trifluoromethoxy group. *See* Pomper Affidavit, Para. 17. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012μm and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC_{50} of 0.0062 μm and a selectivity index of 193. *Id.*

Even assuming for arguments sake a skilled person made the non-obvious steps of selecting a compound with a halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl group of Jansen I or Jansen II for modification, there is still no explicit or implicit motivation in the cited prior art to substitute the alkyl group with a radiohalogenated group to render the C_{1-6}alkyl or -O-C_{1-6}alkyl as a "linker" within the meaning of the pending claims. In fact, the vast majority of the representative compounds disclosed in Jansen I and Jansen II do not have a halogenated C_{1-6}alkyl or the -O-C_{1-6}alkyl. To successfully argue that a new compound is obvious, the prior art must show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda,* 492 F.3d at 1356. The cited prior art clearly does not suggest

anything that may motivate one of ordinary skill in the art to make the specific modification of substituting the C_{1-6}alkyl or -O-C_{1-6}alkyl with a radiohalogen.

The Office Action appears to correlate the substitution of a C_{1-6}alkyl or -O-C_{1-6}alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

> It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Office Action dated September 26, 2023, pages 6-7. Applicant respectfully points out that Jansen II merely discloses that quinoline-containing FAP inhibitors have a 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Pomper Affidavit, Para. 18. Jansen II does not suggest that substitution of the quinoline ring of the quinoline-containing FAP inhibitors would, let alone could, improve the FAP affinity or selectivity of the FAP inhibitors. *Id.* On the contrary, Jansen II observed that substitution of the quinoline ring has little or even negative effects on the potency of the quinoline-containing FAP inhibitors:

> Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19−24, having a clearly negative effect on this parameter.

Janssen II, page 493, left column. *Id.*, Para. 19. In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has both an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without the trifluoromethoxy substitution. [1] *Id.* Therefore, there is no motivation to substitute the quinoline moiety of the FAP inhibitor, not to mention to halogenate the quinoline moiety via a trifluoromethoxy substitution. Applicant would like to emphasize again that without a radiohalogenated trifluoromethoxy substitution on the FAP inhibitor of Jansen I or Jansen II, any

[1] *See* Jansen I, Table 4. IC_{50} for FAP (an indicator of the FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor; selectivity index is 83 versus 59.

FAP inhibitors modified based Jansen I or Jansen II cannot be interpreted as containing a "linker" within the meaning of the pending claims.

Accordingly, in view of the totality of the disclosure in Jansen I and Jansen II, there is no explicit or implicit teachings, suggestion, or motivation for one of ordinary skill in the art to select and modify any compounds in Jansen I and Jansen II to arrive at the claimed compounds. There is no prima facie obviousness because there is no reason that would have led a chemist to select and modify a known compound in a particular manner to establish prima facie obviousness of the compounds of the pending claims. *See* Takeda, 492 F.3d at 1357.

ii. <u>There was no reasonable expectation of success in modifying any compounds in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

The Office Action also fails to demonstrate a reasonable expectation of success in modifying and making the structural changes to the compounds of Jansen I and Jansen II to arrive at the compounds of the pending claims. The examiner is required to show a reasonable expectation of success when trying to establish prima facie obviousness by modifying or combing the prior art to achieve the claimed invention. MPEP § 2143.02; *see also* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.") For a medical imaging agent used to diagnose disease, it is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with the medical condition. See the Pomper Affidavit, Para. 22. The high specificity allows the imaging agent to selectively bind to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical conditions from interfering with the binding between the imaging agent with the target protein. *Id.* The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. *Id.* Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

The Office Action takes the position that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen as Zimmerman teaches radiohalogenation of FAP inhibitors for diagnostic imaging and therapeutic treatment of diseases. However, at the time the instant application was filed, one of ordinary skill in the art recognized the unpredictability associated with the development of medical imaging agents, including the optimization of the specificity. Accordingly, there was no reasonable expectation of success for one of ordinary skill in the art to modify the compounds to arrive at the compounds of pending claims, even if the compound substituted with halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl were selected as the lead compound, which one of ordinary skill in the art had no motivation to do in the first place as discussed.

In fact, one of ordinary skill in the art knew that the FAP imaging agents of Zimmerman most likely would not function well because of the poor specificity associated with the compounds of Zimmerman. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic plaque, and was determined as not suitable for the application. *See* Meletta etc., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta"); Pomper Affidavit, Para. 24 As provided on page 2089 of Meletta, although pronounced binding of [^{125}I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Pomper Affidavit, Para. 25. Based on these data, Maletta could not conclude on the selectivity of [^{125}I]MIP-1232 for FAP. Accordingly, because of the low specificity MIP-1232 displayed in the investigation, Meletta concluded that MIP-1232 was not suitable for the medical imaging for the medical condition. *See* Procter & Gamble v. Teva, 566 F.3d 989, 997 (Fed. Cir. 2009) (Upholding decision of the District Court that there was no reasonable expectation of success in modifying the prior art compound to produce a "improved, safe, and effective" drug because researchers had no basis to expect it to be as good as or better than the prior art compound). The lack of reasonable expectation of success is especially telling in view of the failure by others in the art to use the compounds of Zimmerman cited by the Office Action. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir.2003) ("While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."); In re

Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("Failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.")

Applicant respectfully submits, based on the unpredictability in the art and failure and uncertainty observed by Maletta associated with the prior art compound, that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at a selective FAP imaging agent by merely modifying the FAP inhibitors of Jansen I and/or Jansen II with the radiohalogen of Zimmerman.

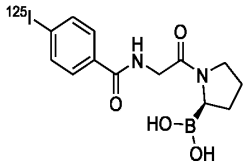
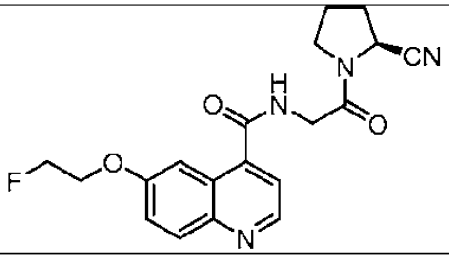
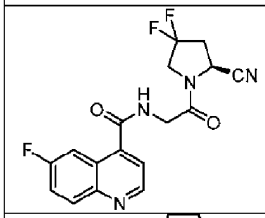
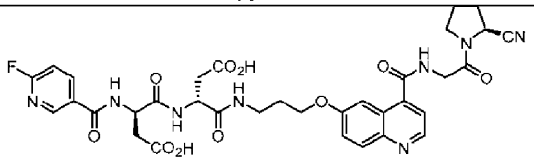
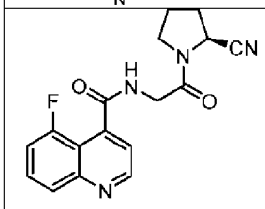
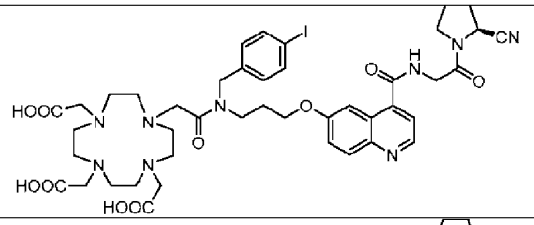
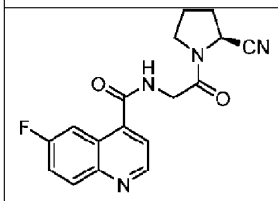
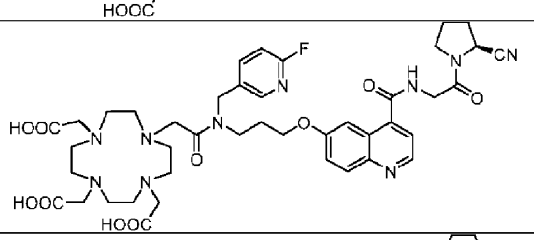
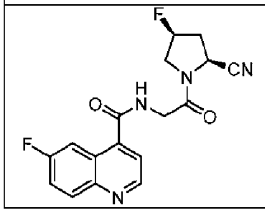
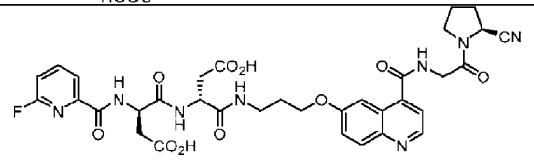
iii. <u>There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness</u>

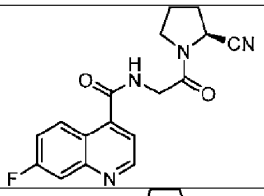
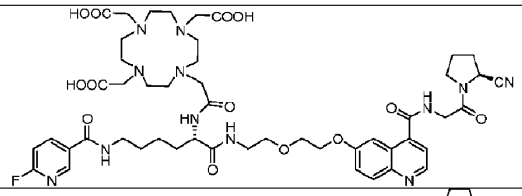
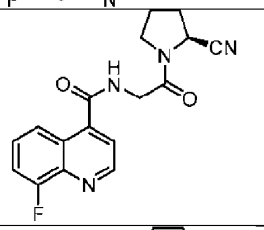
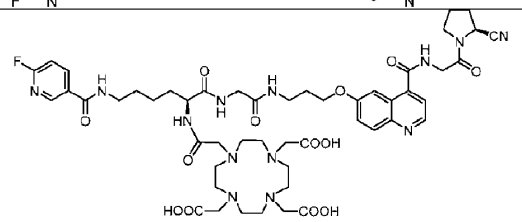
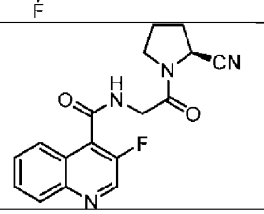
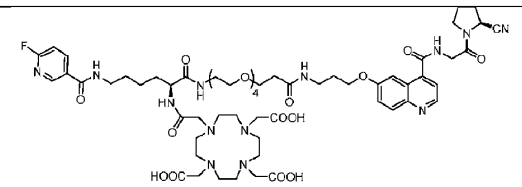
The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Dr. Pomper's Rule 132 Declaration (hereinafter "the Pomper Declaration"), Paragraphs 28-30. As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Id., Para. 31.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 32. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds <u>falling under the scope</u> of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Id., Para. 33. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32,

compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.*, Para. 34. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *		4,111
	152		66,084
	20		>1,418,440
	403		10,502
	15.7		5,807

	241		779
	17		1,693
	3		407

* Data from R. Meletta etc., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference

Accordingly, Applicant respectfully submits that claim 29 is not obvious over Jansen I in view of Zimmerman and Jansen II. Applicant respectfully requests that the rejection of claim 29 under 35 U.S.C. § 103 as being unpatentable over Jansen I in view of Zimmerman and Jansen II be withdrawn at this time.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 18/354,282	Filing Date 07/18/2023	☐ 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 $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 192 =	
☐ 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

AMENDMENT	12/18/2023	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 3	Minus	** 20	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $ 192 =	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

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) 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".	/MARISSA R BLYTHER/
*** 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.**

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**12/18/2023 01:35:41 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63647076	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
2023-12-18 - 36631.303 Supp Amendment NFOA.pdf		17	-	439 KB
2023-12-18 - 36631.303 Supp Amendment NFOA-SA...pdf	(1-1)	1	Supplemental Response or Supplemental Amendment	35 KB
2023-12-18 - 36631.303 Supp Amendment NFOA-CLM.pdf	(2-4)	3	Claims	57 KB
2023-12-18 - 36631.303 Supp Amendment NFOA-A....pdf	(5-17)	13	Amendment/Request for Reconsideration-After Non-Final Rejection	392 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-12-18 - 36631.303 Supp Amendment NFOA.pdf	A243C9BC115DAA8E31970D3E00A50693D766640C629D4D6F46257C622266E34EF3AA5EAE3250A1AE87C73E3217F86827B73589316A7F33472A0B7D598EA42578
2023-12-18 - 36631.303 Supp Amendment NFOA-SA...pdf	17956623C7889FECDEEF508489336787770BA4459EEC754E3C95A9F2C5A2318B6829CF9C26419249DA5C0E8F027BA36FA040B0D264F69F7F5E3ED4D763DE203500
2023-12-18 - 36631.303 Supp Amendment NFOA-CLM.pdf	B60C1AE0EBF4246B30CEEB95A807336E01ABF9E0322E79B743B5E860596DBE7A584DD90617C7754EFB83065234FED26592DD937821DCC48F655022B8CB525253
2023-12-18 - 36631.303 Supp Amendment NFOA-A....pdf	C7A6DD5081F86ABAB3900C09D15F01C3AC1A6DBABCACD75108CBAD2A64F668838A623DE25DCF3F9E0C5BDBCD3454B3E4A288DDF195BDA84B9F65417797E7C126

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 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.

Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.	Confirmation No.: 7536
Serial No.: 18/354,282	Art Unit: 1618
Filed: July 18, 2023	Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT TO NON-FINAL OFFICE ACTION

Dear Examiner Perreira:

This communication is responsive to the non-final Office Action mailed September 26, 2023, and the Applicant-Initiated Interview Summary mailed December 15, 2023.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

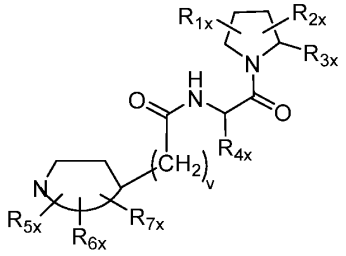
IN THE CLAIMS:

29. (Presently Amended) A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each ~~independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen~~;

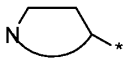
~~R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, and -Ar_3;~~

~~R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;~~

~~Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;~~

ITM Exhibit 1004, Page 1268 of 1652

v is 0;~~, 1, 2, or 3; and~~



represents a quinolinyl ring~~5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;~~

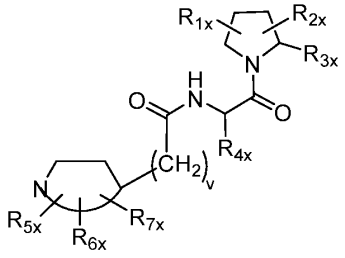
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

30. (New) The compound of claim 29, wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

31. (Currently amended) A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each ~~independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen~~;

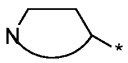
ITM Exhibit 1004, Page 1269 of 1652

~~R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and $-Ar_3$;~~

~~R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, and $-S-C_{1-6}$alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from $-NR_{10x}R_{11x}$, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, and $-S-C_{1-6}$alkyl;~~

~~Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, and $-S-C_{1-6}$alkyl;~~

v is 0~~;, 1, 2, or 3; and~~



represents a quinolinyl ring ~~5 to 10 membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;~~

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

ITM Exhibit 1004, Page 1270 of 1652

Status

Claim 29 is pending in the Application and stands rejected. New claims 30 and 31 have been added. Claim 29 and new claim 31 have been amended. No new matter has been added. Upon entry of this Amendment, claims 29-31 will be pending in the Application.

Applicant-Initiated Interview Summary

Applicant acknowledges the Applicant-Initiated Interview Summary mailed December 15, 2023.

Drawings

The Office Action notes that color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Applicant submits herewith a Petition under 37 CFR 1.84(a)(2) and accompanying fee. Applicant respectfully requests that the color drawings be accepted at this time.

Claim Amendments

Original claim 29 and new claim 31 have been amended to further define the 5- to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to be a quinolinyl ring. Support for this amendment can be found on page 8, line 5, of U.S. provisional patent application no. 62/575,607, filed October 23, 2017. Original claim 29 and new claim 31 also have been amended to define the variable "v" as being zero. No new matter has been added.

Claim Rejections - 35 USC § 102

Claim 29 is rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

Claim 29 is amended and further defines the compound of formula (I) as being "low molecular weight" ("LMW"). The instant patent application distinguishes the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, the instant application characterizes the large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In

contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

> [T]he presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP-α, i.e., an FAP-α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α.

page 8, lines 26-29, page 9, lines 1-2.

> Because FAP-α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP-α.

page 1, lines 28-34, page 2, lines 1-7.

Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

In contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound – as the Examiner correctly pointed out, comprising an anti-FAP moiety bound to an ATTO488 dye via a **HMPA copolymer**. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387,

left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole; further LMW compounds of the current claims with molecular weights are presented in the table on pages 14-15 herein below. Thus, one of ordinary skill in the art upon reading and understanding of the instant specification in view of Dvořáková would appreciate that the presently claimed compounds are "low molecular weight" compounds.

The term of "low molecular weight" is well accepted in the chemical arts, and its meaning is clear to one of ordinary skill in the art. In particular, when used in the scientific references in the chemical arts, one of ordinary skill in the art would recognize that low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. *See e.g.*, K Beebe et al., Clin Transl Sci. 2014 Feb; 7(1): 74–81 ("Metabolomics is often described as a systematic study of the low molecular weight (approximately 50–1,500 Da) metabolites (*chemicals*) within a given sample"); A. Ferreira et al., J. Agric. Food Chem. 2014, 62, 6784–6793 ("Metabolites are a group of low molecular weight substances (50–1500 Da) that includes amino acids, fatty acids …"); C. Llewellyn et al., Progress in Oceanography, Volume 137, p. 421-433 (Metabolomics involves the non-targeted unbiased analysis of large suites of low molecular weight organic molecules or metabolites (typically 50–1500 Da)…); *see also* https://www.ebi.ac.uk/training/online/courses/metabolomics-introduction/what-is/small-molecules/ ("A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product. Metabolomics usually studies small molecules within a mass range of 50 – 1500 daltons (Da).")

New claim 30 further defines B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. Support for this amendment can be found in claim 29 as originally filed. Applicant notes that Dvořáková only discloses optical imaging agents.

New claim 31 includes the transitional phrase "consisting essentially of." As provided in MPEP § 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel

characteristic(s)" of the claimed invention. Applicant notes that in the present claims, the compound of formula (I) is limited then to components B-L-A, and would not include the HMPA copolymer carrier disclosed and which forms the basis of the iBodies disclosed in Dvořáková.

Because every pending claim (claims 29-31) of the instant application requires the claimed compound to be "low molecular weight", Dvořáková cannot anticipate the pending claims because Dvořáková does not disclose a compound having low molecular weight.

Claim Rejections - 35 USC § 103

Claim 29 is rejected under 35 U.S.C. § 103 as being unpatentable over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

The Office Action asserts that Jansen I discloses FAP inhibitors that encompass aspects of the instant claims. The Office Action acknowledges, however, that Jansen I does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

The Office Action asserts that Zimmerman discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease, which, in some embodiments, include a metal chelating moiety that includes a radionuclide or, in other embodiments, a radiohalogen.

The Office Action asserts that Jensen II discloses quinoline-containing FAP inhibitors that are 60 times more FAP-affinity than the naphthoyl derivative of Jansen I.

The Office Action then concludes that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jansen I teaches that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated and Zimmerman teaches radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

The Office Action further concludes that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as Jensen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

The Office Action finally concludes that it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAP-affinity than the naphthoyl derivative.

Applicant respectfully disagrees for the reasons set forth below.

i. <u>There was no motivation for one of ordinary skill in the art to select and modify any compounds of Jansen I and Jansen II to arrive at the claimed compounds</u>

As provided in MPEP § 2143(I)(E), in cases involving new chemical compounds, it is necessary to identify some reason that would have led a chemist to select a lead compound and subsequently modify the lead compound in a particular manner to establish prima facie obviousness of new claimed compounds. Takeda v. Alphapharm., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Office Action argues that the compounds of Jansen I may be modified with a radiohalogen via a linker. The Office Action appears to take the position that the C_{1-6}alkyl or -O-C_{1-6}alkyl that may be attached to the heterocyclic group of the FAP moiety in Jansen I may serve as a "linker" within the meaning of the pending claims. In particular, the Office Action points out that the C_{1-6}alkyl, -O-C_{1-6}alkyl may be halogenated. An implicit but necessary position of the Office Action is that the C_{1-6}alkyl or the -O-C_{1-6}alkyl group may be interpreted as a "linker" only when it is selected as a substituent group in preference to the numerous other equally viable alternatives, and further, only when it is halogenated, and then further only when the halogen is a radiohalogen. Applicant respectfully points out that C_{1-6}alkyl and the -O-C_{1-6}alkyl are among a wide variety of alternative functional groups that may optionally be attached to the heterocyclic group of a generic structure of the FAP inhibitor compounds disclosed in Jansen I. See Pomper Affidavit, Para. 23. Furthermore, among 43 representative compounds disclosed in Jansen I and 39 representative compounds in Jansen II, only a single compound with a halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl is disclosed. *See* Pomper Affidavit, Para. 24; Jansen I, Example 11, Table 4; Jansen II, Compound No. 28, Table 3. Thus, the prior art provides no motivation or indication to select C_{1-6}alkyl or the -O-C_{1-6}alkyl from a large group of functional groups as a substituent group on the FAP inhibitors disclosed in Jansen I or Jansen II; even if C_{1-6}alkyl or the -O-C_{1-6}alkyl is selected as a substituent group, Jansen I or Jansen II provides no motivation to further substitute the C_{1-6}alkyl or the -O-C_{1-6}alkyl group with a halogen. In fact, in most of the halogenated

compounds disclosed in Jansen I and Jansen II, the halogen is directly attached to the heterocyclic group, instead of via a C_{1-6}alkyl or the -O-C_{1-6}alkyl group.

Further, one of ordinary skill in the art also would not select the single FAP inhibitor substituted with the halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl disclosed in Jansen I and Jansen II as a starting point or a lead compound to modify, because this compound has mediocre bioactivities compared with the other compounds disclosed in the prior art. In particular, many other FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II, which is substituted with a trifluoromethoxy group. *See* Pomper Affidavit, Para. 26. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012 μm and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC_{50} of 0.0062 μm and a selectivity index of 193. *Id.*

Even assuming for arguments sake a skilled person made the non-obvious steps of selecting a compound with a halogenated C_{1-6}alkyl or -O-C_{1-6}alkyl group of Jansen I or Jansen II for modification, there is still no explicit or implicit motivation in the cited prior art to substitute the alkyl group with a radiohalogenated group to render the C_{1-6}alkyl or -O-C_{1-6}alkyl as a "linker" within the meaning of the pending claims. In fact, the vast majority of the representative compounds disclosed in Jansen I and Jansen II do not have a halogenated C_{1-6}alkyl or the -O-C_{1-6}alkyl. To successfully argue that a new compound is obvious, the prior art must show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda,* 492 F.3d at 1356. The cited prior art clearly does not suggest anything that may motivate one of ordinary skill in the art to make the specific modification of substituting the C_{1-6}alkyl or -O-C_{1-6}alkyl with a radiohalogen.

The Office Action appears to correlate the substitution of a C_{1-6}alkyl or -O-C_{1-6}alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

> It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6}alkyl, -O-C_{1-6}alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Office Action dated September 26, 2023, pages 6-7. Applicant respectfully points out that Jansen II merely discloses that quinoline-containing FAP inhibitors have a 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Pomper Affidavit, Para. 27. Jansen II does not suggest that substitution of the quinoline ring of the quinoline-containing FAP inhibitors would, let alone could, improve the FAP affinity or selectivity of the FAP inhibitors. *Id.* On the contrary, Jansen II observed that substitution of the quinoline ring has little or even negative effects on the potency of the quinoline-containing FAP inhibitors:

> Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter.

Janssen II, page 493, left column. Pomper Affidavit, Para. 28. In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has both an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without the trifluoromethoxy substitution. [1] *Id.* Therefore, there is no motivation to substitute the quinoline moiety of the FAP inhibitor, not to mention to halogenate the quinoline moiety via a trifluoromethoxy substitution. Applicant would like to emphasize again that without a radiohalogenated trifluoromethoxy substitution on the FAP inhibitor of Jansen I or Jansen II, any FAP inhibitors modified based Jansen I or Jansen II cannot be interpreted as containing a "linker" within the meaning of the pending claims.

Accordingly, in view of the totality of the disclosure in Jansen I and Jansen II, there is no explicit or implicit teachings, suggestion, or motivation for one of ordinary skill in the art to select and modify any compounds in Jansen I and Jansen II to arrive at the claimed compounds. There is no prima facie obviousness because there is no reason that would have led a chemist to select and modify a known compound in a particular manner to establish prima facie obviousness of the compounds of the pending claims. *See* Takeda, 492 F.3d at 1357.

ii. <u>There was no reasonable expectation of success in modifying any compounds in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

[1] *See* Jansen I, Table 4. IC_{50} for FAP (an indicator of the FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor; selectivity index is 59 versus 83.

The Office Action also fails to demonstrate a reasonable expectation of success in modifying and making the structural changes to the compounds of Jansen I and Jansen II to arrive at the compounds of the pending claims. The examiner is required to show a reasonable expectation of success when trying to establish prima facie obviousness by modifying or combing the prior art to achieve the claimed invention. MPEP § 2143.02; *see also* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so."). For a medical imaging agent used to diagnose disease, it is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with the medical condition. See the Pomper Affidavit, Para. 31. The high specificity allows the imaging agent to selectively bind to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical conditions from interfering with the binding between the imaging agent with the target protein. *Id.* The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. *Id.* Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

The Office Action takes the position that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen as Zimmerman teaches radiohalogenation of FAP inhibitors for diagnostic imaging and therapeutic treatment of diseases. However, at the time the instant application was filed, one of ordinary skill in the art recognized the unpredictability associated with the development of medical imaging agents, including the optimization of the specificity. Accordingly, there was no reasonable expectation of success for one of ordinary skill in the art to modify the compounds to arrive at the compounds of pending claims, even if the compound substituted with halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl were selected as the lead compound, which one of ordinary skill in the art had no motivation to do in the first place as discussed.

In fact, one of ordinary skill in the art knew that the FAP imaging agents of Zimmerman most likely would not function well because of the poor specificity associated with the

compounds of Zimmerman. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic plaque, and was determined as not suitable for the application. *See* Meletta etc., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta"); Pomper Affidavit, Paras. 33-35. As provided on page 2089 of Meletta, although pronounced binding of [^{125}I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Pomper Affidavit, Para. 34. Based on these data, Maletta could not conclude on the selectivity of [^{125}I]MIP-1232 for FAP. Accordingly, because of the low specificity MIP-1232 displayed in the investigation, Meletta concluded that MIP-1232 was not suitable for the medical imaging for the medical condition. *See* Procter & Gamble v. Teva, 566 F.3d 989, 997 (Fed. Cir. 2009) (Upholding decision of the District Court that there was no reasonable expectation of success in modifying the prior art compound to produce a "improved, safe, and effective" drug because researchers had no basis to expect it to be as good as or better than the prior art compound). The lack of reasonable expectation of success is especially telling in view of the failure by others in the art to use the compounds of Zimmerman cited by the Office Action. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir.2003) ("While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."); In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("Failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.")

Applicant respectfully submits, based on the unpredictability in the art and failure and uncertainty observed by Maletta associated with the prior art compound, that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at a selective FAP imaging agent by merely modifying the FAP inhibitors of Jansen I and/or Jansen II with the radiohalogen of Zimmerman.

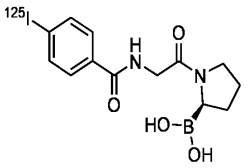
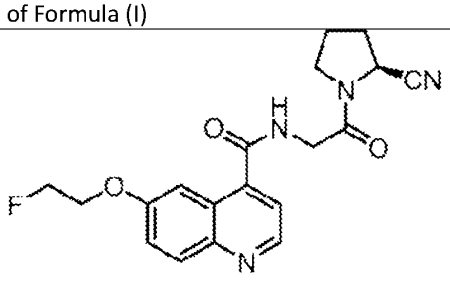
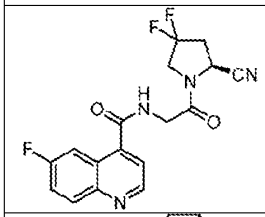
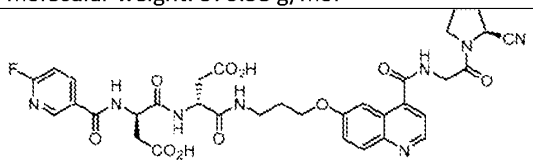
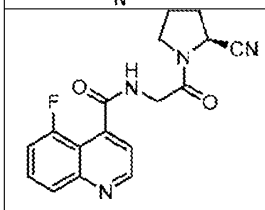
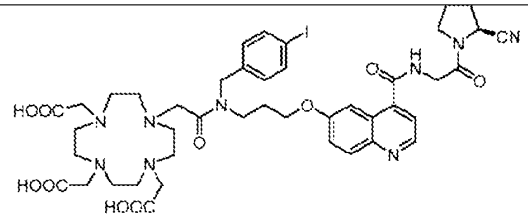
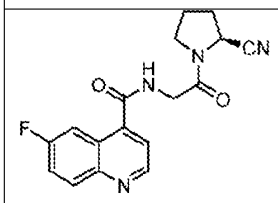
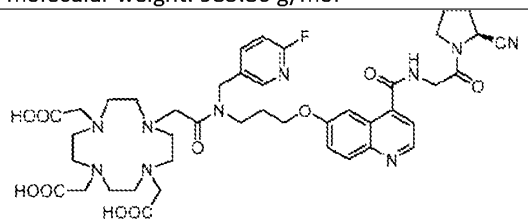
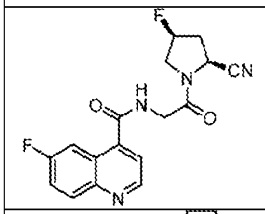
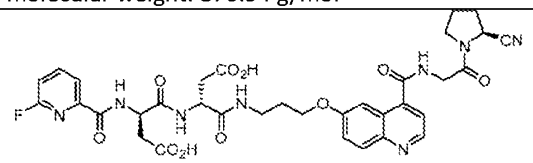
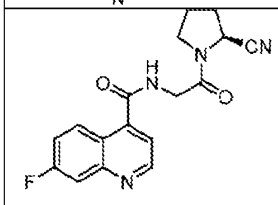
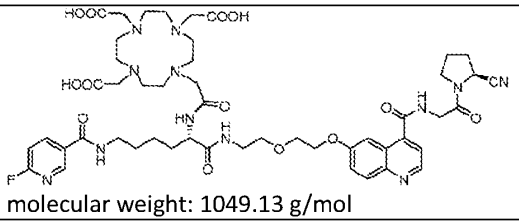
iii. <u>There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness</u>

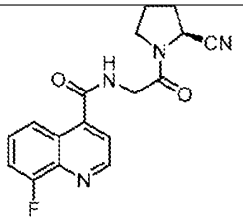
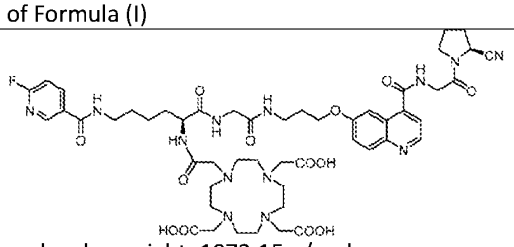
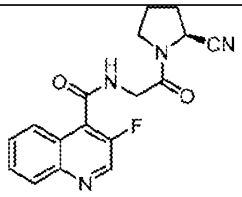
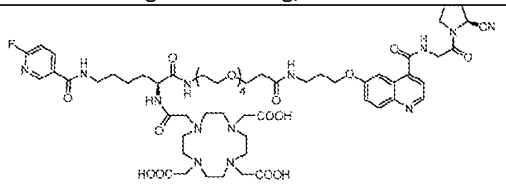
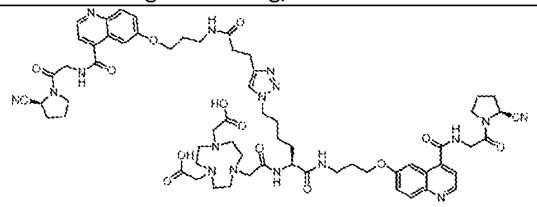
The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Pomper Affidavit, Paras. 38-42.

As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Pomper Affidavit, Para. 40.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Pomper Affidavit, Para. 42. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.,* Para. 42. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *	 molecular weight: 370.38 g/mol	4,111
	152	 molecular weight: 734.70 g/mol	66,084
	20	 molecular weight: 983.86 g/mol	>1,418,440
	403	 molecular weight: 876.94 g/mol	10,502
	15.7	 molecular weight: 734.70 g/mol	5,807
	241	 molecular weight: 1049.13 g/mol	779

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	17	 molecular weight: 1073.15 g/mol	1,693
	3	 molecular weight: 1266.39 g/mol	407
		molecular weight: 889.39 g/mol	10,694
		molecular weight: 761.39 g/mol	11,893
		 molecular weight: 1282.43 g/mol	1,313

* Data from R. Meletta et al., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference.

Accordingly, Applicant respectfully submits that claim 29 is not obvious over Jansen I in view of Zimmerman and Jansen II. Applicant respectfully requests that the rejection of claim 29

under 35 U.S.C. § 103 as being unpatentable over Jansen I in view of Zimmerman and Jansen II be withdrawn at this time.

Double Patenting

Claim 29 is provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 2, 13, 15, 16 and 21-25 of copending Application No. 16/762,873.

Applicant notes that it appears that the Office Action intended to cite Application No. 16/758,182.

Without acquiescing to the assertions made in the Office Action, Applicant has submitted herewith a Terminal Disclaimer over Application No. 16/758,182.

Applicant respectfully requests that the rejection of claim 29 under nonstatutory double patenting over Application No. 16/758,182 be withdrawn at this time.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney at 919-724-8699 or 608-662-1277. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment associated with this filing to Deposit Account Number 50-4302. If an extension of time for this paper is required, petition for extension is herewith made.

Respectfully Submitted,
CASIMIR JONES, S.C.

Date: December 18, 2023

/JEFFREY W. CHILDERS/

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Customer No. 101943

Application Number * 18/354,282 *	Application/Control No. 18/354,282	Applicant(s)/Patent under Reexamination Yang et al.	
	Examiner PERREIRA, MELISSA JEAN	Art Unit 1618	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 13 December 2023	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

/KIMBERLY R WHITE/

Technology Center: OPLC

Telephone: (571)272-6179

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	**Art Unit**
	MELISSA J PERREIRA	1618

CPC							
Symbol						**Type**	**Version**
A61K	/	51	/	0485		F	2013-01-01
A61K	/	47	/	545		I	2017-08-01
A61K	/	51	/	0478		I	2013-01-01
A61K	/	51	/	0482		I	2013-01-01

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

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 January 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 January 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20240105

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	**Art Unit**
	MELISSA J PERREIRA	1618

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	51	/	00	
A61M	/	36	/	14	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
424	1.89

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

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 January 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 January 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office — Part of Paper No.: 20240105

ITM Exhibit 1004, Page 1286 of 1652

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	**Art Unit**
	MELISSA J PERREIRA	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
	1		10		19		28								
	2		11		20	1	29								
	3		12		21	2	30								
	4		13		22	3	31								
	5		14		23										
	6		15		24										
	7		16		25										
	8		17		26										
	9		18		27										

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 January 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 January 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office Part of Paper No.: 20240105

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*		
Symbol	Date	Examiner

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
google scholar	09/19/2023	MP
inventor search	09/19/2023	MP
PE2E search	09/19/2023	MP
STNext	09/20/2023	MP
PE2E search	12/24/2023	MP
google scholar	12/19/2023	MP
allowability conference (SPE Mike Hartley)	01/04/2024	MP

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K	51/0485	12/24/2023	MP
A61K	47/545	12/24/2023	MP
A61K	51/0478	12/24/2023	MP
A61K	51/0482	12/24/2023	MP
A61K	49/0032	12/24/2023	MP
A61K	49/0052	12/24/2023	MP
A61K	51/0455	12/24/2023	MP
A61K	51/0497	12/24/2023	MP
A61K	51/0474	12/24/2023	MP
A61K	2121/00	12/24/2023	MP
A61K	2123/00	12/24/2023	MP
A61P	5/00	12/24/2023	MP
A61P	7/04	12/24/2023	MP
A61P	29/00	12/24/2023	MP
A61P	35/00	12/24/2023	MP
A61P	43/00	12/24/2023	MP
C07D	403/14	12/24/2023	MP
C07D	401/14	12/24/2023	MP
C07B	2200/07	12/24/2023	MP

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

PE2E SEARCH - Search History (Prior Art)

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	21238	FAP OR (fibroblast near2 activation)	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:23 PM
N2	1519	(cyano OR boron OR sulfona$3 OR phospho$5 OR carboxyl$4) near2 proline	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:26 PM
N3	122	N1 AND N2	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:26 PM
N4	87	N3 AND ((@py<="2017"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:26 PM
N5	7715089	optical OR fluoresce$4 OR chelate OR radionuclide OR radioisotop$6 OR radioactive OR imag$4 OR PET OR SPECT	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:27 PM
N6	18611	N1 AND N5	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:27 PM
N7	65	N4 AND N5	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:27 PM
N8	247117	quinolin$4	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:34 PM
N9	3079	N6 AND N8	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:34 PM
N10	19	N7 AND N8	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:34 PM
N11	448	((("YANG") near3 ("Xing")) OR (("NIMMAGADDA") near3 ("Sridhar")) OR (("ROWE") near3 ("Steven")) OR (("SLANIA") near3 ("Stephanie")) OR (("POMPER") near3 ("Martin"))).INV.	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:39 PM
N12	7	N1 AND N11	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:39 PM
N14	363857	(A61K51/0485 OR A61K47/545 OR A61K51/0478 OR A61K51/0482 OR A61K49/0032 OR	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:41 PM

		A61K49/0052 OR A61K51/0455 OR A61K51/0497 OR C07D403/14 OR A61P5/00 OR A61P7/04 OR A61P29/00 OR A61P35/00 OR A61P43/00 OR C07D401/14 OR C07B2200/07 OR A61K51/0474 OR A61K2121/00 OR A61K2123/00).cpc.					
N15	9891	N1 AND N14	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:41 PM
N16	2339	N8 AND N15	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:41 PM
N17	1162	N16 AND ((@py<="2017"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:42 PM
N18	1067	N5 AND N17	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:42 PM

Web Search History

date, time	web site	search string
12/19/2023 10:09:56 AM	Google Scholar	proline quinoline FAP
12/19/2023 10:10:36 AM	Google Scholar	proline quinoline FAP [after:2000] [before:2017]
12/19/2023 10:17:42 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP imaging
12/19/2023 10:20:10 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP 18F
12/19/2023 10:20:13 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP DOTA
12/19/2023 10:21:21 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP radiolabeling
12/19/2023 10:25:23 AM	Google Scholar	proline quinoline FAP radiolabeling [after:2000] [before:2017]
12/19/2023 10:28:12 AM	Google Scholar	[after:2000] [before:2017] radiolabeled proline FAP
12/19/2023 10:29:44 AM	Google Scholar	radiolabeled proline FAP [after:2000] [before:2017]
12/19/2023 10:30:54 AM	Google Scholar	[after:2000] [before:2017] quinoline proline FAP PET
12/19/2023 10:31:03 AM	Google Scholar	quinoline proline FAP PET [after:2000] [before:2017]
12/19/2023 10:35:01 AM	Google Scholar	[after:2000] [before:2017] proline FAP PET
12/19/2023 10:35:25 AM	Google Scholar	proline FAP PET [after:2000] [before:2017]
12/19/2023 10:40:39 AM	Google Scholar	[after:2000] [before:2017] proline FAP SPECT
12/19/2023 11:00:22 AM	Google Scholar	[after:2000] [before:2017] proline FAP cyanine dye
12/19/2023 11:48:35 AM	Google Scholar	proline FAP cyanine dye [after:2000] [before:2017]
12/19/2023 11:49:30 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP PET
12/19/2023 11:49:32 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP cyanine dye
12/19/2023 11:50:09 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP imaging

ok to enter

/M.J.P/

Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.	Confirmation No.: 7536
Serial No.: 18/354,282	Art Unit: 1618
Filed: July 18, 2023	Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT TO NON-FINAL OFFICE ACTION

Dear Examiner Perreira:

This communication is responsive to the non-final Office Action mailed September 26, 2023, and the Applicant-Initiated Interview Summary mailed December 15, 2023.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Bibliographic Data

Application No: 18/354,282

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /MELISSA J PERREIRA/ (Examiner's Signature) (Initials)

Title: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/18/2023	424	1618	JHU-36631.303
RULE			

APPLICANTS

The Johns Hopkins University, Baltimore, MD, UNITED STATES

INVENTORS

Xing Yang,

Sridhar Nimmagadda, Balimore, MD, UNITED STATES

Steven Rowe, Parkville, MA, UNITED STATES

Stephanie Slania, Baltimore, MD, UNITED STATES

Martin G. Pomper, Baltimore, MD, UNITED STATES

CONTINUING DATA

This application is a CON of 16758182 04/22/2020

16758182 is a 371 of PCT/US18/57086 10/23/2018

PCT/US18/57086 has PRO of 62575607 10/23/2017

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

08/04/2023

**** SMALL ENTITY ****

STATE OR COUNTRY

ADDRESS

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562
UNITED STATES

FILING FEE RECEIVED

$2,400

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS						
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
		BEEBE et al., "Understanding the Apothecaries Within: The Necessity of a Systematic Approach for Defining the Chemical Output of the Human Microbiome". Clin Transl Sci. 2014 Feb; 7(1): 74–81.	
		FERREIRA et al., "Monitoring Alcoholic Fermentation: An Untargeted Approach". Journal of Agricultural and Food Chemistry, 2014, 62, 6784–6793.	
		LLEWELLYN et al., "Using community metabolomics as a new approach to discriminate marine microbial particulate organic matter in the western English Channel". Progress in Oceanography, Volume 137, Part B, September 2015, p. 421-433.	
		MELETTA et al., "Evaluation of the radiolabeled boronic acid-based FAP inhibitor MIP-1232 for atherosclerotic plaque imaging". Molecules, 2015 Jan 27;20(2):2081-99.	
		METABOLOMICS – EMBL-EBI, https://www.ebi.ac.uk/training/online/courses/metabolomics-introduction/what-is/small-molecules/, retrieved on 2023-12-12. 5 pages.	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	12/19/2023

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	3	of	3	*Attorney Docket Number*	JHU-36631.303

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-12-13
Name/Print	Jeffrey W. Childers	Registration Number	58,126

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
	1.	AZHDARINIA et al., "Characterization of chemical, radiochemical and optical properties of a dual-labeled MMP-9 targeting peptide". Bioorganic & Medicinal Chemistry, Vol. 19, Issue 12, May 6, 2011, 3769-3776.	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	12/19/2023

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

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☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-10-30
Name/Print	Jeffrey W. Childers	Registration Number	58,126

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

101943 7590 01/10/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER
PERREIRA, MELISSA JEAN

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 01/10/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

TITLE OF INVENTION: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/10/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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.

PTOL-85 (Rev. 11/23)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

101943 7590 01/10/2024
The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

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 the USPTO patent electronic filing system 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.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

TITLE OF INVENTION: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/10/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
PERREIRA, MELISSA JEAN	1618	424-001890

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/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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)

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

❑ Electronic Payment via the USPTO patent electronic filing system ❑ 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

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.

❑ Applicant asserting small entity status. See 37 CFR 1.27

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.

❑ Applicant changing to regular undiscounted fee 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. _____

ITM Exhibit 1004, Page 1304 of 1652

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 01/10/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 01/10/2024

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.

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

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6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
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8) 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));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/354,282	Applicant(s) Yang et al.	
	Examiner MELISSA J PERREIRA	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 12/18/23.
   ☐ 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 29-31 . 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. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

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.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: the low molecular weight quinolinyl-containing compounds of the instant claims surprisingly have a specificity (PREP/FAP ratio) for FAP that is several orders of magnitude higher than other small molecule FAP inhibitors found in the prior art.

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."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached M9-3, T9-3, W9-3, Th9-2, F9-2.

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, Michael Hartley 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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To

file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] *(if known)*	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
	1.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY		

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
	1.	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages.	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	*Attorney Docket Number*	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-01-16
Name/Print	Jeffrey W. Childers	Registration Number	58,126

.

PTO Notes regarding this form:

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	01/16/2024 05:15:59 PM Z ET	JHU-36631.303

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968554	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0636	E20241FN16479846	Van Nguyen

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	$104.00

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 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.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2016 (08.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/196628 A1

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C07D 417/12 (2006.01) *A61K 51/04* (2006.01)
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1 June 2016 (01.06.2016)

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(26) Publication Language: English

(30) Priority Data:
62/169,338 1 June 2015 (01.06.2015) US
62/336,043 13 May 2016 (13.05.2016) US

(71) Applicant: **THE JOHNS HOPKINS UNIVERSITY** [US/US]; 3400 North Charles Street, Baltimore, Maryland 21218 (US).

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(74) Agent: **CHILDERS, Jeffrey W.**; Wade II, Suite 400, 5430 Wade Park Blvd., Raleigh, North Carolina 27607 (US).

(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, 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.

(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, 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))*

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

(54) **Title**: NUCLEAR IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING CARBONIC ANHYDRASE IX AND USES THEREOF

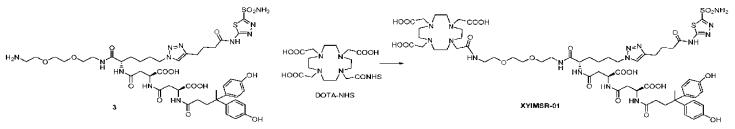


Fig. 6

(57) **Abstract**: Highly potent and selective radionuclide-based imaging and therapy agents targeting carbonic anhydrase IX with minimum non-specific organ uptake are disclosed. Methods of imaging and/or treating carbonic anhydrase IX-expressing cells or tumors also are disclosed.

WO 2016/196628 A1

NUCLEAR IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING CARBONIC ANHYDRASE IX AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 62/169,338, filed June 1, 2015, and 62/336,043 filed May 13, 2016, which are incorporated herein by reference in their entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under CA183031, CA197470, CA184228, and CA134675 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

BACKGROUND

Renal cell carcinoma (RCC) is the most common neoplasm of the kidney (Srigley et al., 2013), with an estimated 60,000 patients diagnosed annually in the United States (Siegel et al., 2015). Among cases of RCC, the clear cell subtype (ccRCC) is the most prevalent, accounting for up to 70 % of RCCs (Pichler et al., 2010; Lipworth et al., 2014; Umbreit et al., 2012). Common to ccRCC is loss of the Von Hippel-Lindau (VHL) tumor suppressor gene (Shuch et al., 2015). Loss of VHL in turn leads to over-expression of carbonic anhydrase IX (CAIX) (Bragmaier et al., 2004), a membrane-associated enzyme responsible for catalyzing the reversible hydration of carbon dioxide to a bicarbonate anion and a proton (Supuran, 2008; Alterio et al., 2012). Over-expression of CAIX has been demonstrated in approximately 95 % of ccRCC tumor specimens (Bui et al., 2003; Atkins et al., 2005; Leibovitch et al., 2007), making it a useful biomarker for this disease.

CAIX has limited expression in normal tissues and organs with the exception of the gastrointestinal tract, gallbladder and pancreatic ducts (Alterio et al., 2012; Clare and Supuran, 2006; Ivanov et al., 2001; Potter and Harris, 2004). No report has demonstrated CAIX expression in normal renal parenchyma or benign renal masses (Supuran, 2008; Alterio et al., 2012; Clare and Supuran, 2006; Ivanov et al., 2001; Potter and Harris, 2004). Feasibility for the non-invasive diagnosis of ccRCC based on CAIX expression has been proved with the radiolabeled antibody G250 (Oosterwijk et al., 1986) and its clinical potential has been reviewed (Smaldone et al.,

2012). However, antibodies as molecular imaging agents suffer from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low-molecular-weight (LMW) agents demonstrate faster pharmacokinetics and higher specific signal within clinically convenient times after administration. They also offer site specific radiolabeling often by a wider range of chemical methods and radionuclides, and may offer a shorter path to regulatory approval (Coenen et al., 2010; Cho et al., 2012; Reilly et al., 2015).

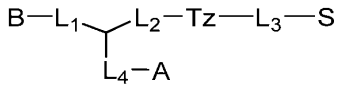
Targeting CAIX with LMW inhibitors has proved challenging in part because fifteen human isoforms of carbonic anhydrase, with high sequence homology, have been identified. Those isoforms share common structural features, including a zinc-containing catalytic site, a central twisted β-sheet surrounded by helical connections, and additional β-strands. The isoforms, however, do vary widely in terms of intracellular location, expression levels, and tissue and organ distribution (Supuran, 2008; Alterio et al., 2012). Significant effort has been expended on development of sulfonamides and other LMW CAIX ligands for nuclear imaging of CAIX, but most reported agents have been fraught with low tumor uptake and significant off-target accumulation (Pan et al., 2014; Akurathi et al., 2010; Lu et al., 2013; Doss et al., 2014; Rana et al., 2012; Peeters et al., 2015).

A new LMW CAIX targeting agent has recently been reported that is composed of two binding motifs, one accessing the CAIX active site and the other binding to an as yet unidentified site (Wichert et al., 2015). Conjugated with the infrared dye IRDye®750, the dual-motif inhibitor showed 10 % injected dose per gram of tumor (ID/g) tumor uptake. In comparison, agents targeting only the active site show 2 % ID/g tumor uptake (Wichert et al., 2015). However, this optical agent also demonstrated high kidney as well as other non-specific organ uptake at 24 h post-administration. Additionally, utility of this agent for *in vivo* studies is somewhat limited due to the substantial attenuation of light emission through tissue inherent to optical agents. Such limitations call for an agent that retains affinity for CAIX, but clears rapidly from non-target tissues and can be detected with existing clinical instrumentation.

ITM Exhibit 1004, Page 1317 of 1652

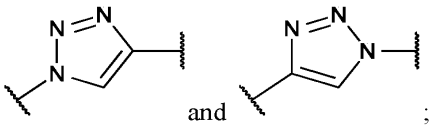
SUMMARY

In some aspects, the presently disclosed subject matter provides compounds of Formula (I):



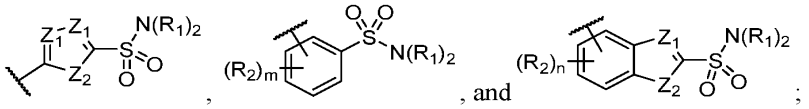
(I);

wherein: B is a metal chelating moiety optionally comprising a metal or a radiometal, or a halogenated or radio-halogenated prosthetic group; L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-; each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl; Tz is a triazole group selected from the group consisting of



and ;

S is a sulfonamide selected from the group consisting of:

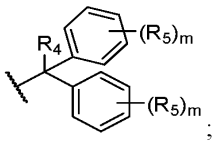


, , and ;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; m is an integer selected from the group consisting of 1, 2, 3, and 4; n is an integer selected from the group consisting of 1, 2, and 3; each Z_1 is independently selected from the group consisting of CR_3, and N; each Z_2 is

ITM Exhibit 1004, Page 1318 of 1652

independently selected from the group consisting of CR_3, and S; each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; A is



;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; R_5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In other aspects, the presently disclosed subject matter provides a method for imaging or treating one or more Carbonic Anhydrase IX-expressing tumors or cells, the method comprising contacting the one or more tumors or cells with an effective amount of a compound of formula (I), and making an image.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Figures as best described herein below.

ITM Exhibit 1004, Page 1319 of 1652

BRIEF DESCRIPTION OF THE FIGURES

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying Figures, which are not necessarily drawn to scale, and wherein:

FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D show (A) optical imaging agents **1** and **2** reported with dual-targeting moiety to CAIX (Wichert et al., 2015); (B) the epi-fluorescence imaging of two mice harboring CAIX expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1, 2, 4, 6, 8, 11 and 23h after injection of 3 nmol of compounds **1** and **2** via the tail vein; (C) quantitative biodistribution analysis of compounds **1** and **2**; compound accumulations in organs are reported as the percentage of injected dose per gram of tissue (% ID g−1) 24 h after intravenous administration of 3 nmol of **1** and of **2**; data points are averages of three mice; error bars indicate standard deviations; and (D) the epi-fluorescence imaging of various organs in a mouse; images were obtained at 24h after injection of 3 nmol of compound **1** via the tail vein;

FIG. 2A, FIG. 2B, and FIG. 2C show (A) the structure of FITC conjugated fluorescent ligand **8**; (B) FACS analysis of **8** for binding to CAIX-negative BxPC3 cells; and (C) FACS analysis of **8** for binding to CAIX-expressing SK-RC-52 cells; flow cytometry was done with **8** at 10 nM, 100 nM and 1μM with 30 min incubation;

FIG. 3A, FIG. 3B, and FIG. 3C show IC_{50} values of (A) positive control CAIX targeting agent **3**; (B) **XYIMSR-01**; and (C) [$^{113/115}$In]**XYIMSR-01**; the IC_{50} values were determined relative to the inhibition of fluorescence polarization of FITC labeled **8** with a known K_d of 0.2 nM for CAIX ; Compounds **3**, **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** demonstrate high binding affinity to CAIX;

FIG. 4A, FIG. 4B, FIG. 4C, and FIG. 4D show binding affinity of (A) **3**, (B) [$^{63/65}$Cu]**XYIMSR-06**, (C) [Al^{19}F]**XYIMSR-04**, and (D) [^{175}Lu]**XYIMSR-01**;

FIG.5 shows the synthesis scheme for compound **3**;

FIG.6 shows the synthesis scheme for compound **XYIMSR-01**;

FIG.7 shows the synthesis scheme for compound **XYIMSR-01**-[In];

FIG.8 shows the synthesis scheme for compound **XYIMSR-01**-[Ga];

FIG.9 shows the synthesis scheme for compound **XYIMSR-01**-[Lu];

FIG.10 shows the synthesis scheme for compound **XYIMSR-02**;

FIG.11 shows the synthesis scheme for compound **XYIMSR-03**;

FIG.12 shows the synthesis scheme for compound **XYIMSR-04**;

FIG.13 shows the synthesis scheme for compound **XYIMSR-04**-[AlF];

FIG.14 shows the synthesis scheme for compound **XYIMSR-05**;

FIG.15 shows the synthesis scheme for compound **XYIMSR-06**;

FIG.16 shows the synthesis scheme for compound **XYIMSR-06**-Cu;

FIG.17 shows the SPECT/CT imaging of two mice harboring CAIX-expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1, 4, 8, 24 and 48 h after injection of 14.8 MBq (400 μCi) of [^{111}In]**XYIMSR-01** via the tail vein; arrows indicate tumors; [^{111}In]**XYIMSR-01** enabled specific imaging of CAIX-expressing SK-RC-52 tumors;

FIG.18 shows the SPECT/CT imaging of two mice harboring CAIX-expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1, 4, 8, 24 and 48 h after injection of 740 kBq (20 μCi) of [^{177}Lu]**XYIMSR-01** via the tail vein; arrows indicate tumors;

FIG.19 shows the PET/CT imaging of [Al^{18}F]**XYIMSR-04** in mice harboring CAIX-expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1h after injection of 7.4 MBq (200 μCi) of [Al^{18}F]**XYIMSR-04** via the tail vein;

FIG. 20 shows PET/CT imaging of [^{64}Cu]**XYIMSR-06** in mice harboring CAIX-expressing SK-RC-52 tumors within the upper right flank; images were obtained at 1h after injection of 22.2 MBq (600 μCi) of[^{64}Cu]**XYIMSR-06** via the tail vein; arrows indicate tumors; and

FIG. 21 shows the treatment response of [^{177}Lu]**XYIMSR-01** in SK-RC-52 tumor mice.

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

DETAILED DESCRIPTION

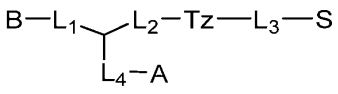
The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Figures, in which some, but not all embodiments of the inventions are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of

the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated Figures. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

I. NUCLEAR IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING CARBONIC ANHYDRASE IX AND USES THEREOF

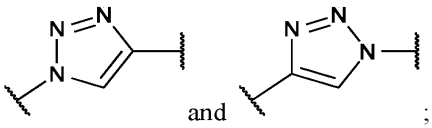
A. Compounds of Formula (I)

Accordingly, in some embodiments, the presently disclosed subject matter provides a compound of formula (I):



(I);

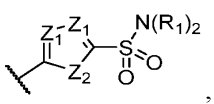
wherein: B is a metal chelating moiety optionally comprising a metal or a radiometal, or a halogenated or radio-halogenated prosthetic group; L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by -O-, -S-, or -(NR')-; each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl; Tz is a triazole group selected from the group consisting of



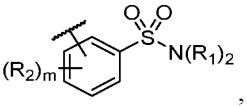
and

;

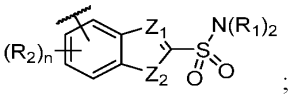
S is a sulfonamide selected from the group consisting of:



,



, and

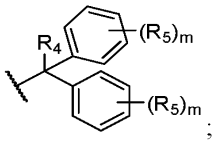


;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;each R_2 is selected from the group consisting of

ITM Exhibit 1004, Page 1322 of 1652

hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; m is an integer selected from the group consisting of 1, 2, 3, and 4; n is an integer selected from the group consisting of 1, 2, and 3;each Z_1 is independently selected from the group consisting of CR_3, and N; each Z_2 is independently selected from the group consisting of CR_3, and S; each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; A is

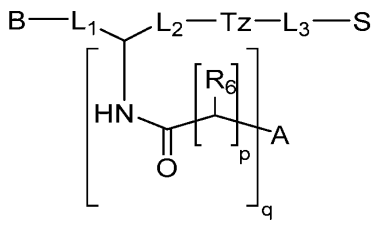


;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; R_5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of formula (I) is a compound of formula (II):

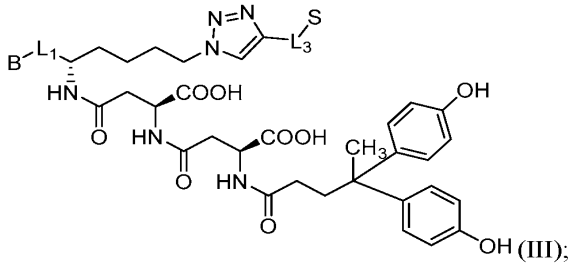
ITM Exhibit 1004, Page 1323 of 1652



(II);

wherein: p is an integer selected from the group consisting of 0, 1, 2, 3, and 4; q is an integer selected from the group consisting of 1, 2, 3, and 4; each R_6 is independently selected from the group consisting of H and –COOR; or a pharmaceutically acceptable salt thereof.

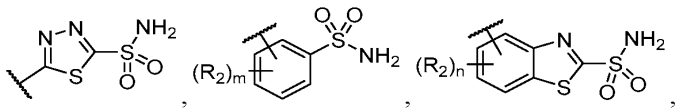
In further embodiments, the compound of formula (II) is a compound of formula (III):

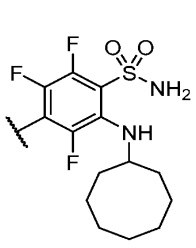


(III);

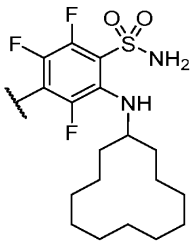
or a pharmaceutically acceptable salt thereof.

In yet further embodiments, S is selected from the group consisting of:



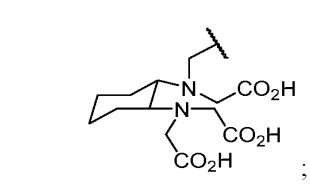
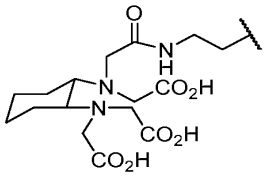
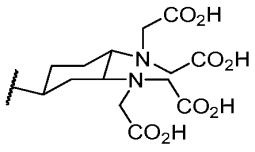
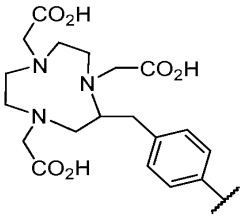
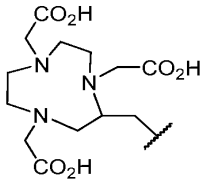
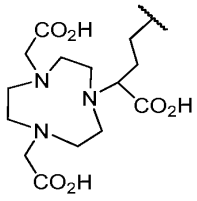
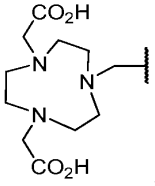
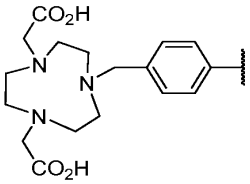
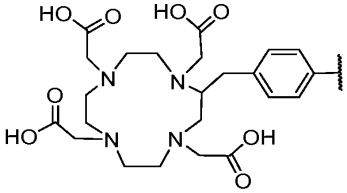
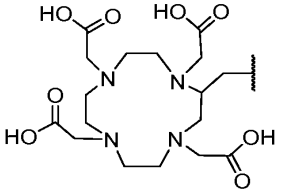
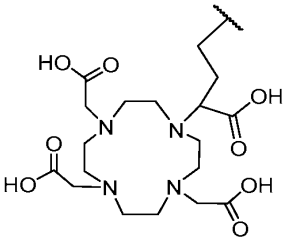
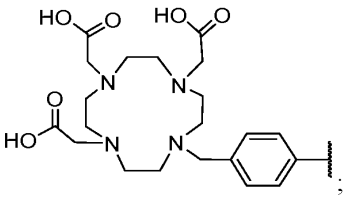
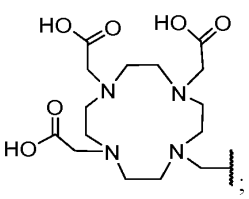
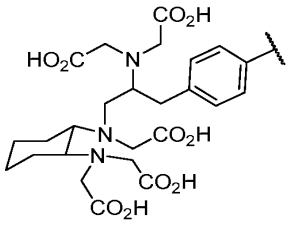
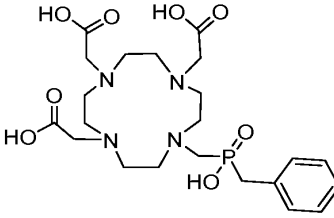
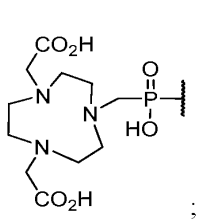


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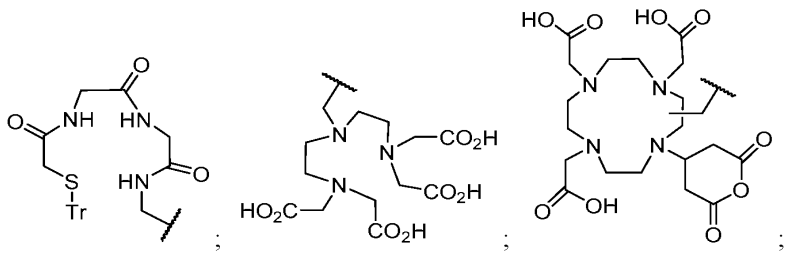


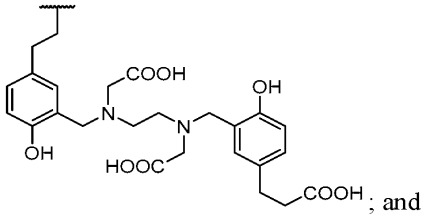
; or a pharmaceutically acceptable salt thereof.

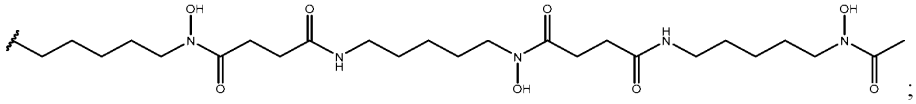
In particular embodiments, B is a metal chelating moiety optionally comprising a metal or a radiometal selected from the group of:


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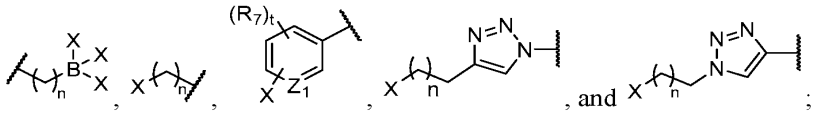
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; and


;

or B is a halogenated or radio-halogenated prosthetic group selected from the group consisting of:


; and ;

wherein: X is a halogen or a radio-halogen; n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6; t is an integer selected from the group consisting of 1, 2, and 3; each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

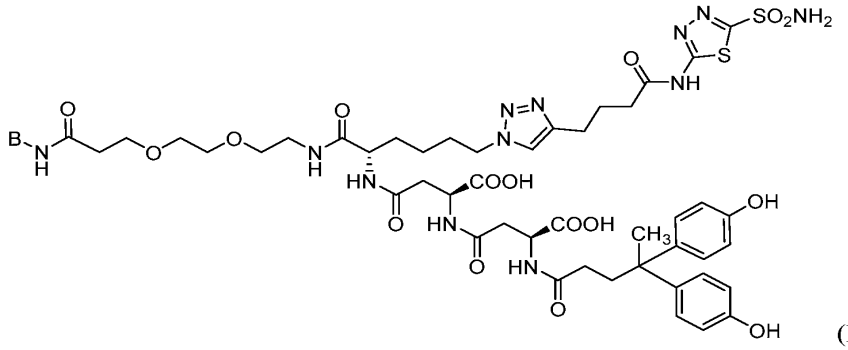
In certain embodiments, the metal chelating agent comprises a metal selected from the group consisting of: Y, Lu, Tc, Zr, In, Sm, Re, Cu, Pb, Ac, Bi, Al, Ga, Re, Ho and Sc. In other embodiments, the metal is a radiometal and is selected from the

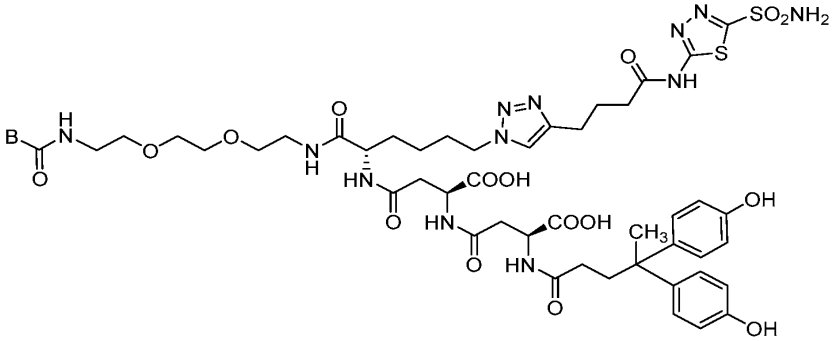
ITM Exhibit 1004, Page 1326 of 1652

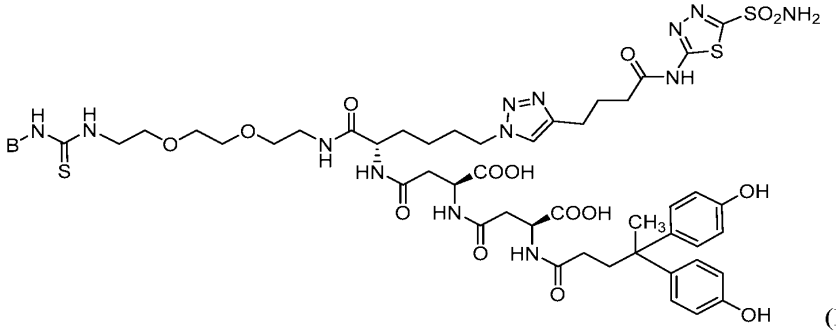
group consisting of ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho.

In further embodiments, halogen is selected from the group consisting of: F, Br, I, and At. In yet further embodiments, the radio-halogen is selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At.

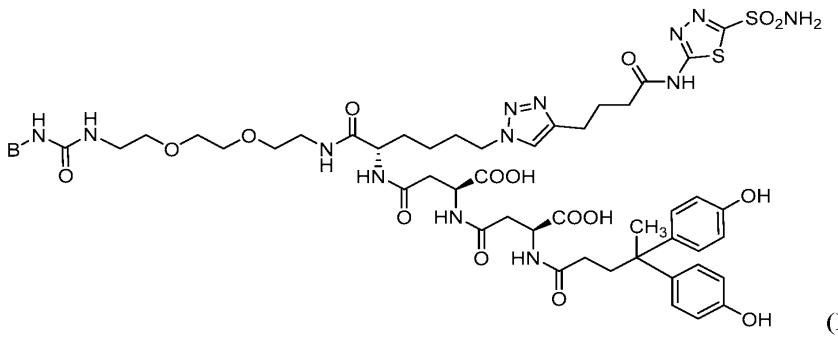
In certain embodiments, the compound of Formula (I) is selected from the group consisting of:


(IVa);


(IVb);


(IVc); and

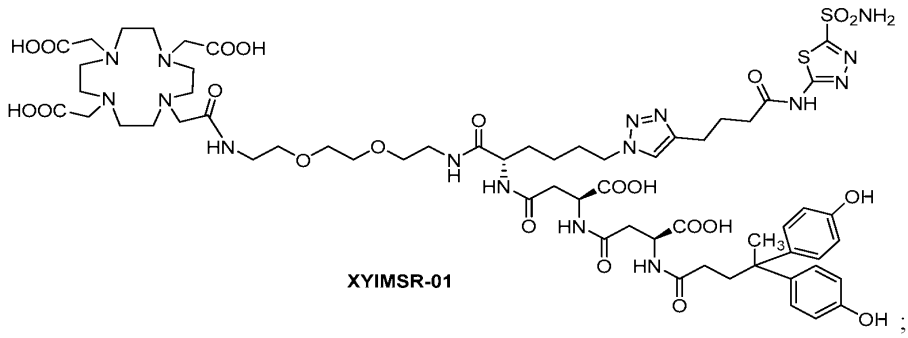
ITM Exhibit 1004, Page 1327 of 1652



(IVd);

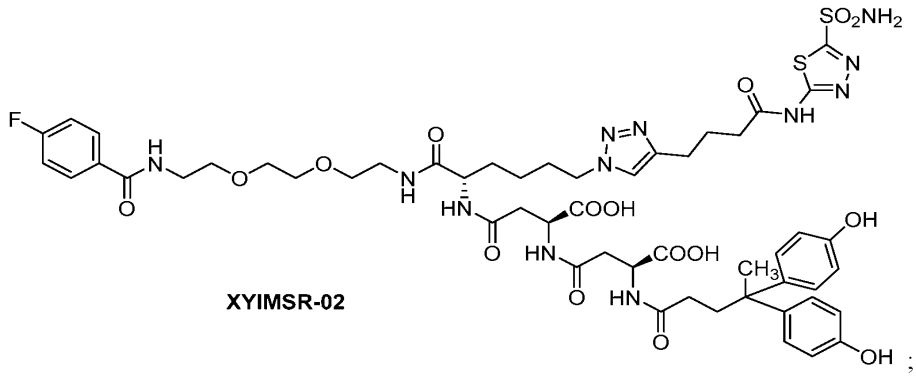
or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of Formula (I) is selected from the group consisting of:



XYIMSR-01

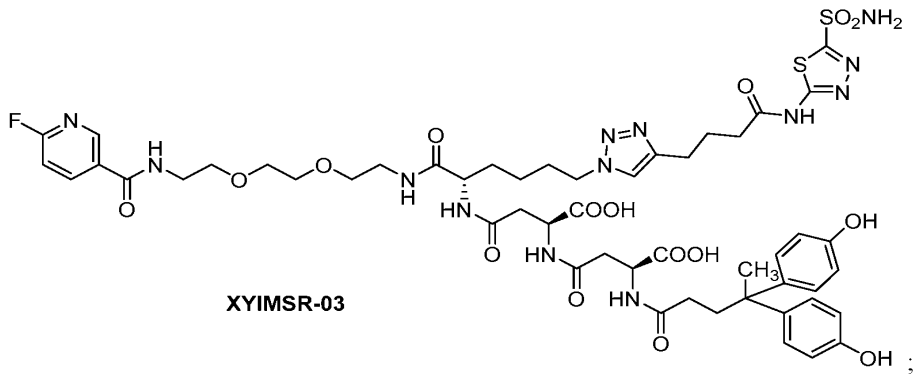
;



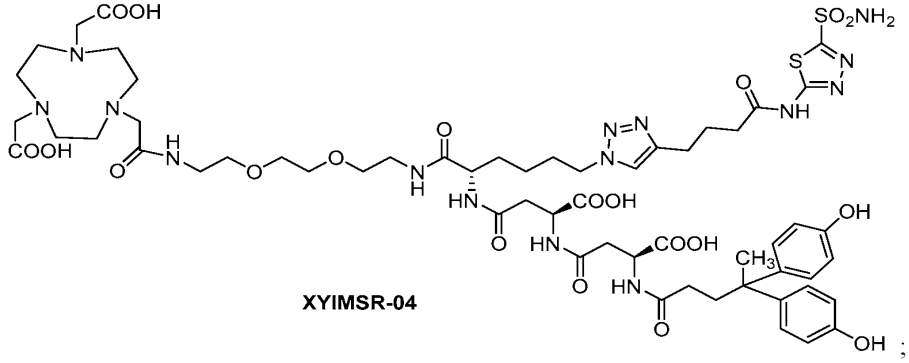
XYIMSR-02

;

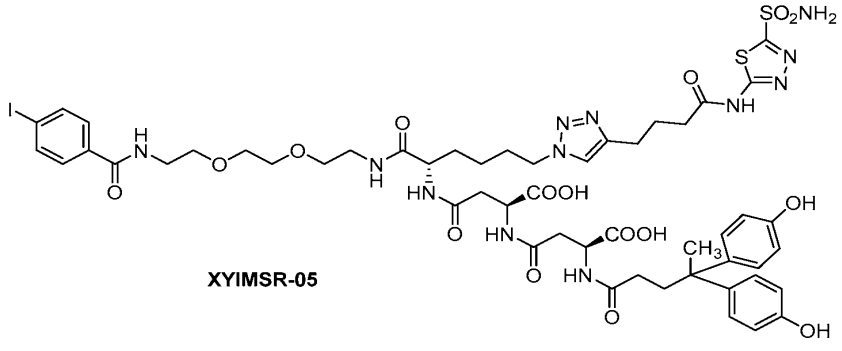
ITM Exhibit 1004, Page 1328 of 1652



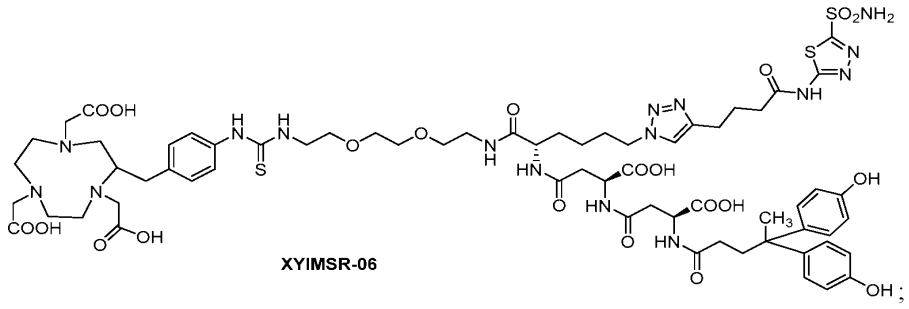
XYIMSR-03 ;



XYIMSR-04 ;



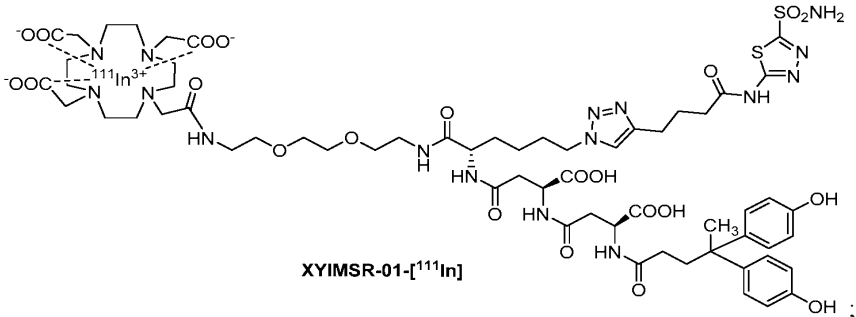
XYIMSR-05 ; and



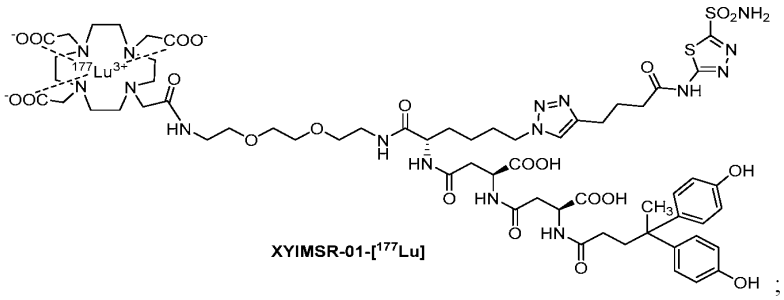
XYIMSR-06 ;

or a pharmaceutically acceptable salt thereof.

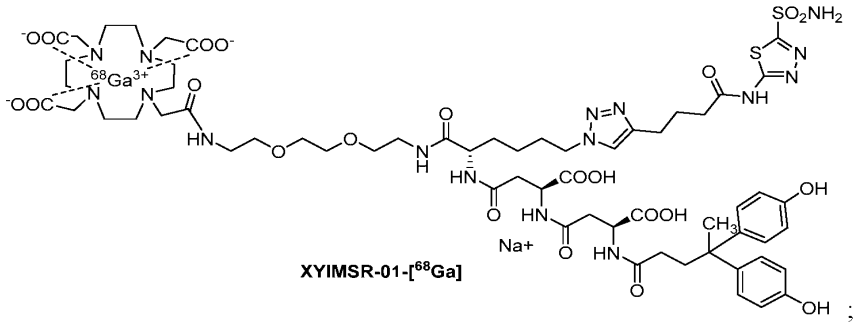
In other particular embodiments, the compound of formula (I) is selected from the group consisting of:



XYIMSR-01-[^{111}In] ;

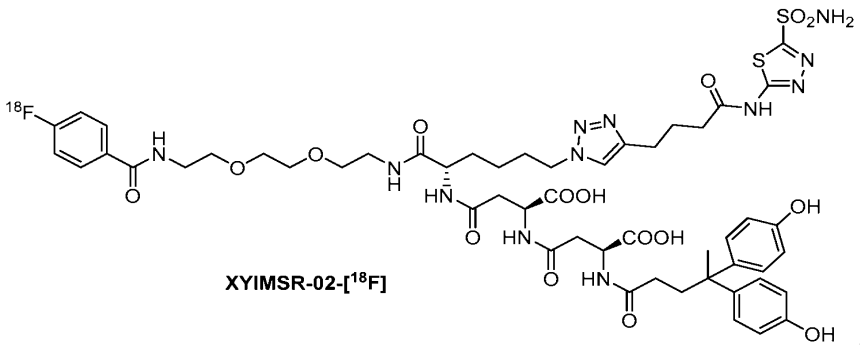


XYIMSR-01-[^{177}Lu] ;

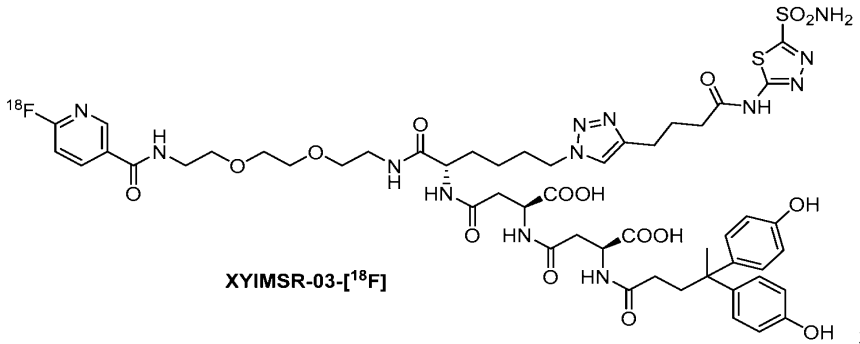


XYIMSR-01-[^{68}Ga] ;

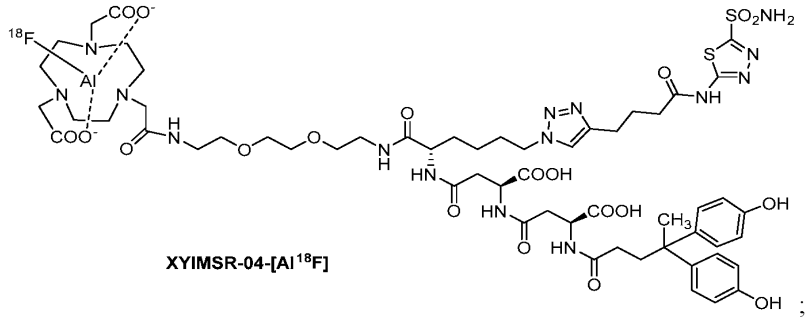
ITM Exhibit 1004, Page 1330 of 1652



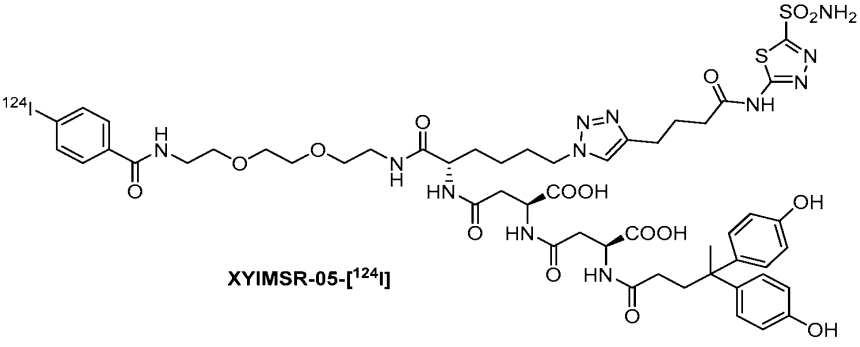
XYIMSR-02-[^{18}F] ;



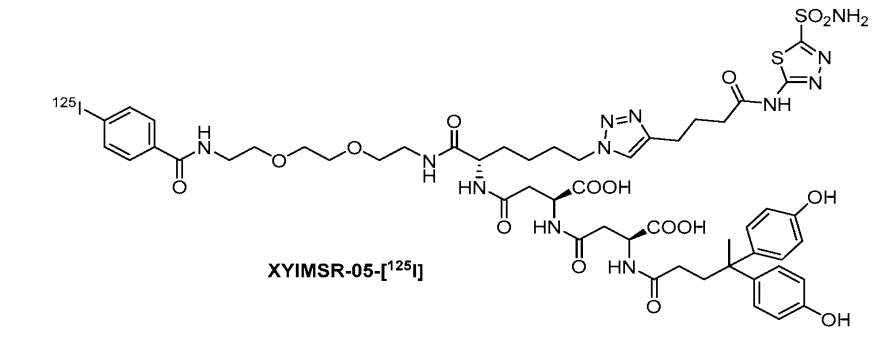
XYIMSR-03-[^{18}F] ;



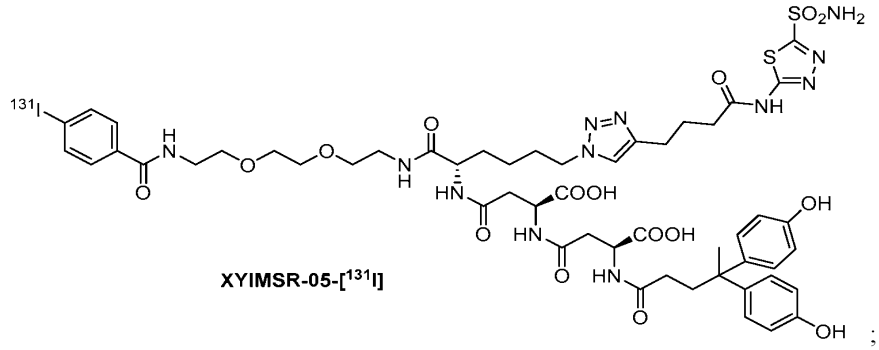
XYIMSR-04-[Al^{18}F] ;



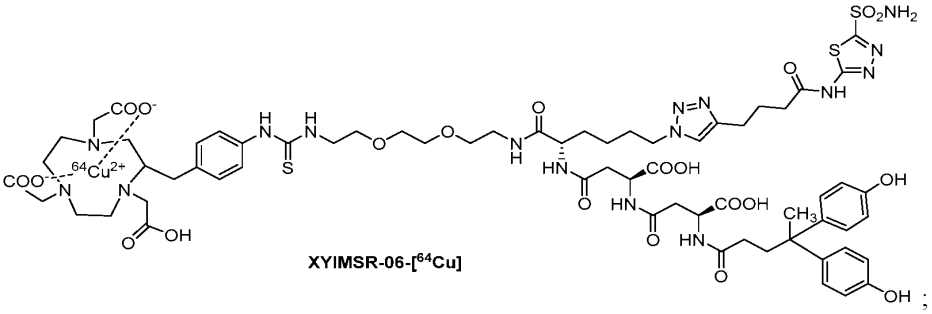
XYIMSR-05-[^{124}I] ;



XYIMSR-05-[^{125}I] ;



XYIMSR-05-[^{131}I] ; and

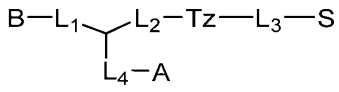


XYIMSR-06-[^{64}Cu] ;

or a pharmaceutically acceptable salt thereof.

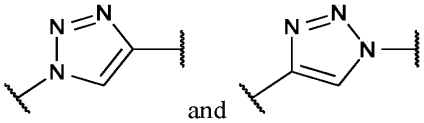
B. Methods of Using Compounds of Formula (I) for Imaging or Treating a Carbonic Anhydrase IX-Expressing Tumor or Cell

Accordingly, in some embodiments, the presently disclosed subject matter provides a method for imaging or treating one or more Carbonic Anhydrase IX expressing tumors or cells, the method comprising contacting the one or more tumors or cells with an effective amount of a compound of formula (I) and making an image, the compound of formula (I) comprising:



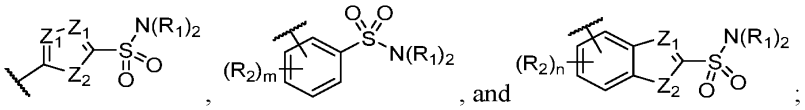
(I);

wherein: B is a metal chelating moiety comprising a radiometal, or a radio-halogenated prosthetic group; L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-; each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl; Tz is a triazole group selected from the group consisting of



and ;

S is a sulfonamide targeting a catalytic pocket of CAIX selected from the group consisting of:

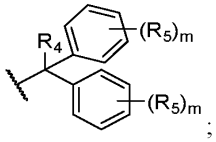


, , and ;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl; each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; m is an integer selected from the group consisting of 1, 2, 3, and 4; n is an integer selected from the group consisting of 1, 2, and 3; each Z_1 is independently selected from the group consisting of CR_3, and N; each Z_2 is independently selected from the group consisting of CR_3, and S; each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl,

ITM Exhibit 1004, Page 1333 of 1652

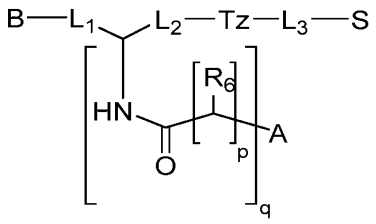
substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; A is



;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; R_5 is independently selected from the group consisting hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of formula (I) is a compound of formula (II):

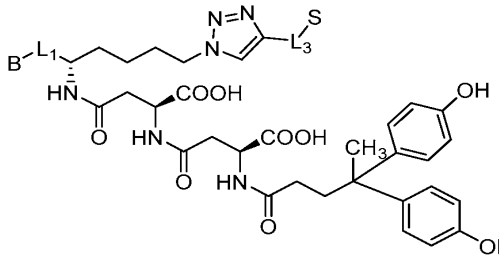


(II);

wherein: p is an integer selected from the group consisting of 0, 1, 2, 3, and 4; q is an integer selected from the group consisting of 1, 2, 3, and 4; each R_6 is independently selected from the group consisting of H and –COOR; or a pharmaceutically acceptable salt thereof.

In further embodiments, the compound of formula (II) is a compound of formula (III):

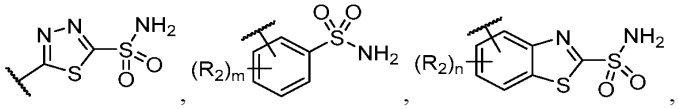
ITM Exhibit 1004, Page 1334 of 1652

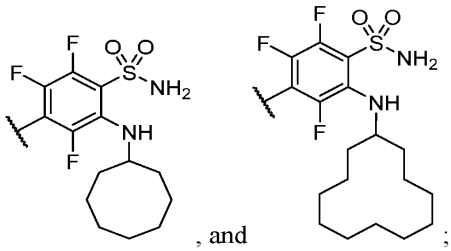


(III);

or a pharmaceutically acceptable salt thereof.

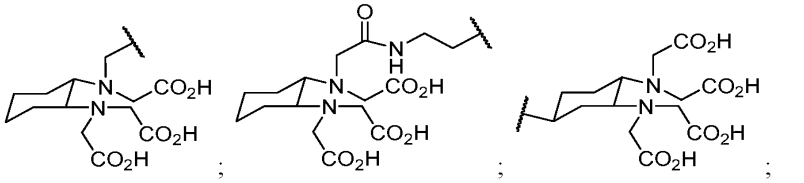
In yet further embodiments, S is selected from the group consisting of:

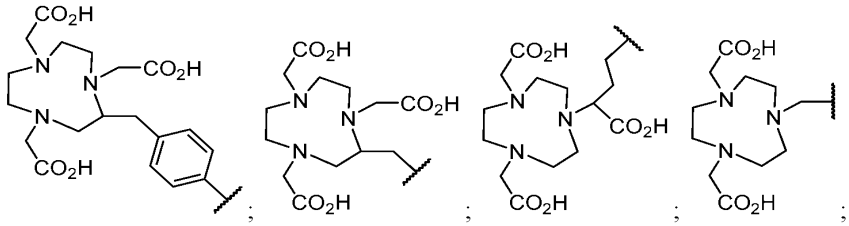




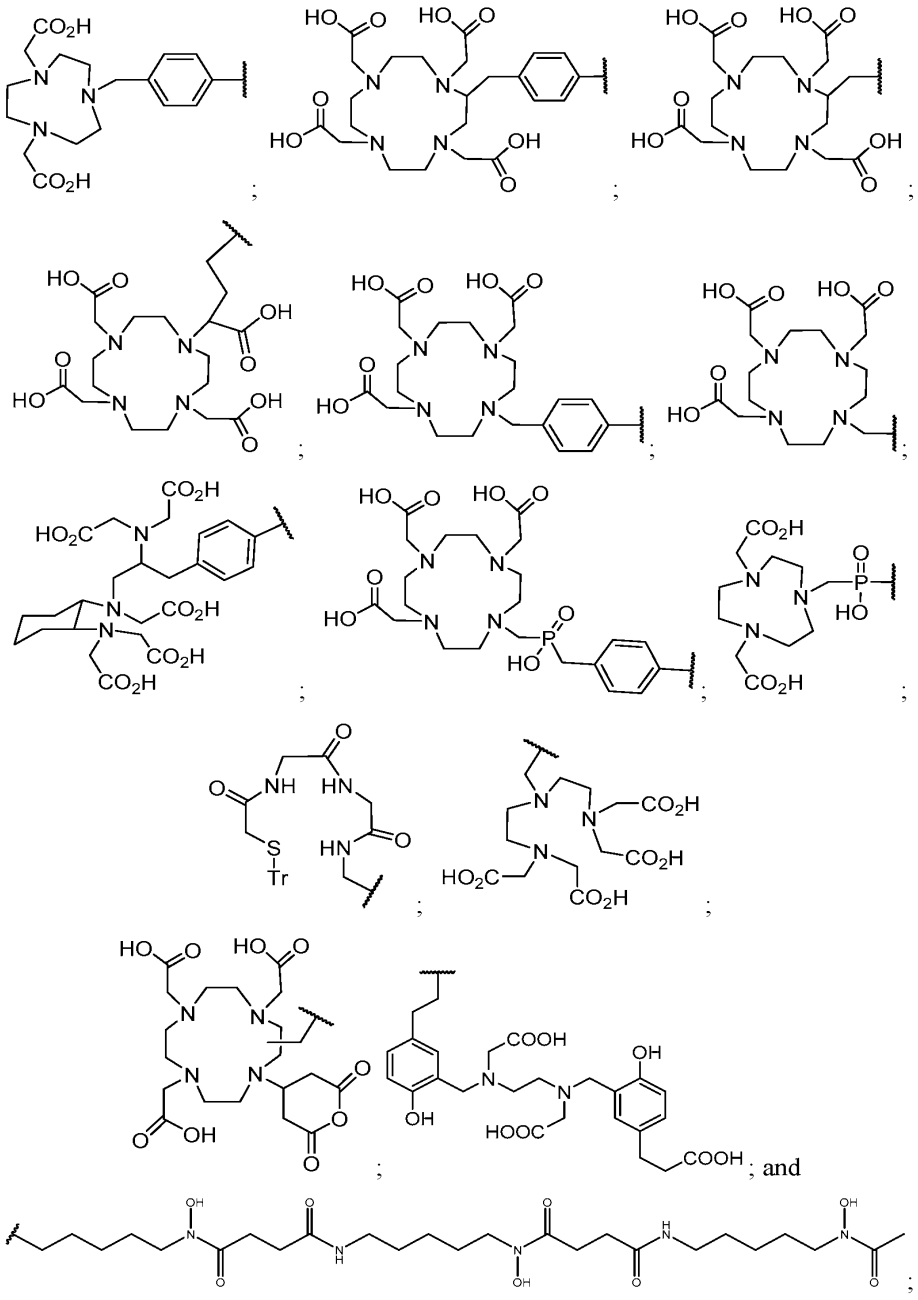
, and ; or a pharmaceutically acceptable salt thereof.

In particular embodiments, B is a metal chelating moiety comprising a radiometal selected from the group of:

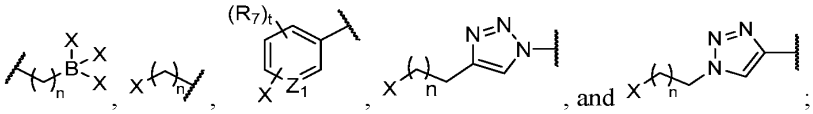




ITM Exhibit 1004, Page 1335 of 1652



or B is a radio-halogenated prosthetic group selected from the group consisting of:

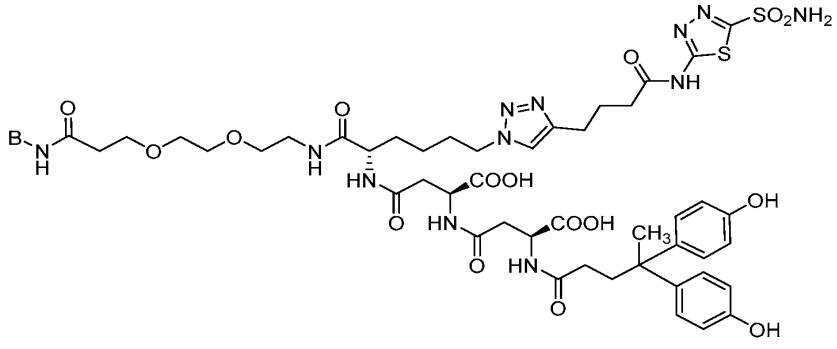


wherein: X is a radio-halogen; n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6; t is an integer selected from the group consisting of 1, 2, and 3; each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the radiometal is selected from the group consisting of ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho.

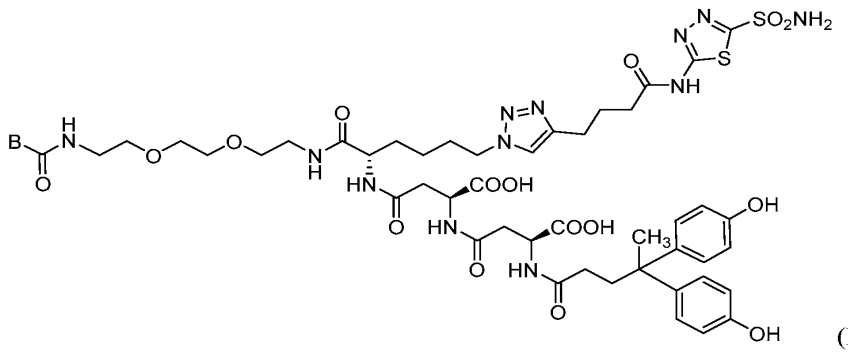
In other embodiments, the radio-halogen is selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At.

In certain embodiments, the compound of Formula (I) is selected from the group consisting of:

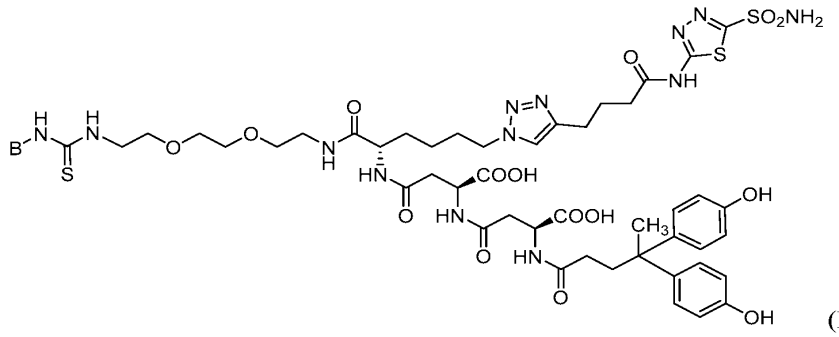


(IVa);

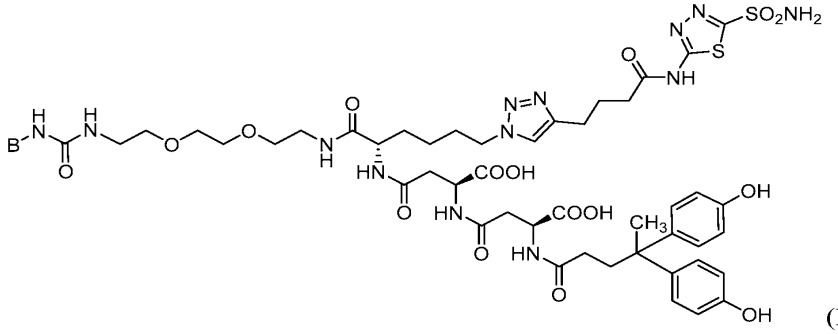
ITM Exhibit 1004, Page 1337 of 1652



(IVb);



(IVc); and

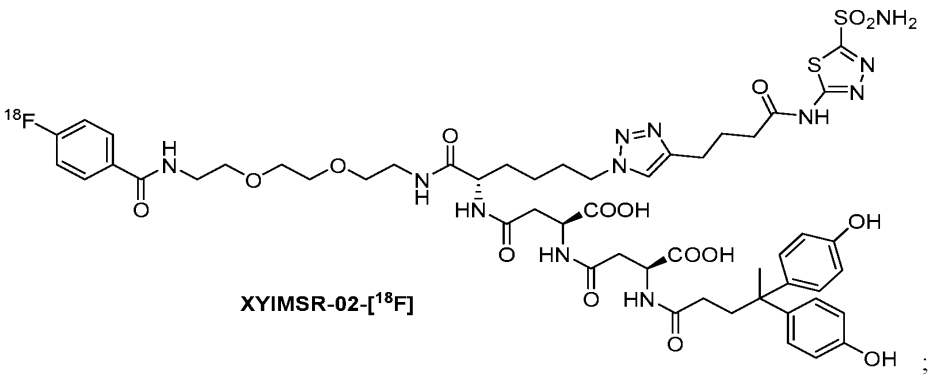


(IVd);

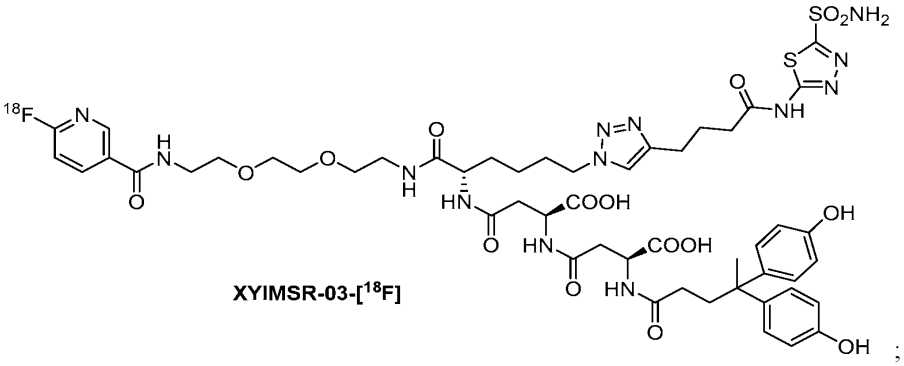
or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of Formula (I) is selected from the group consisting of:

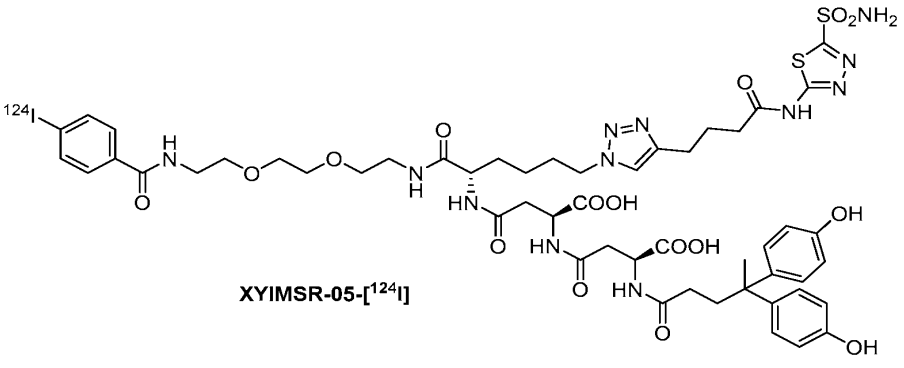
ITM Exhibit 1004, Page 1338 of 1652



XYIMSR-02-[^{18}F] ;

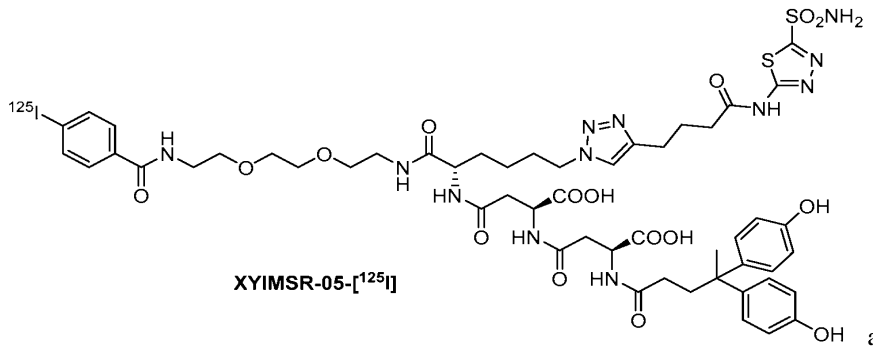


XYIMSR-03-[^{18}F] ;



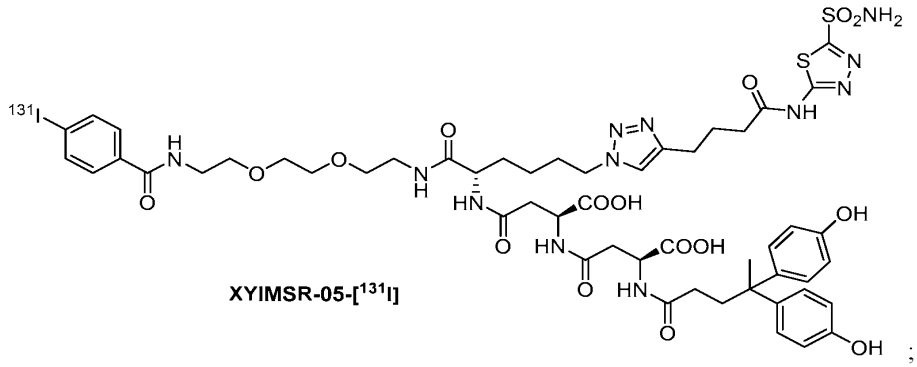
XYIMSR-05-[^{124}I] ;

ITM Exhibit 1004, Page 1339 of 1652



XYIMSR-05-[^{125}I]

and

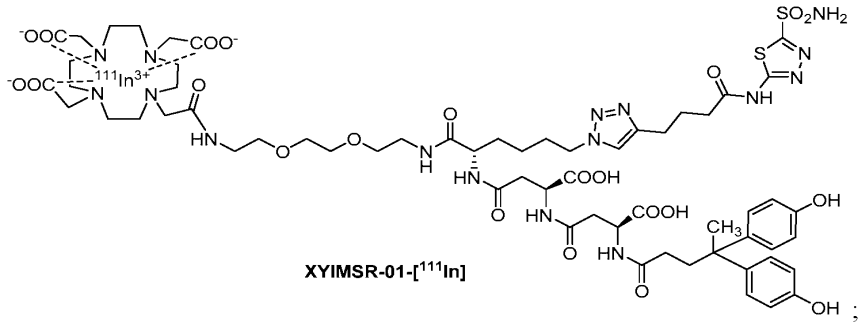


XYIMSR-05-[^{131}I]

;

or a pharmaceutically acceptable salt thereof.

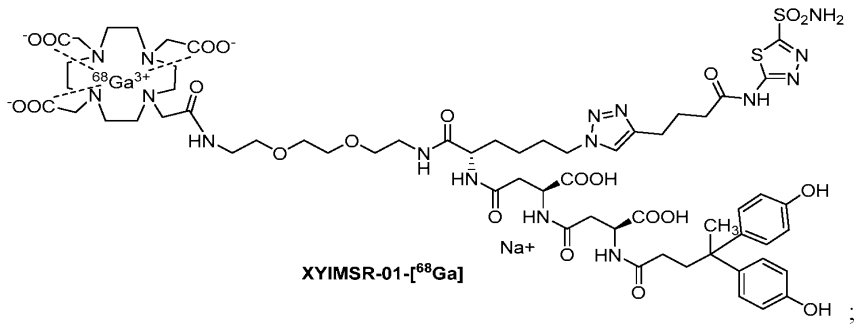
In other particular embodiments, the compound of formula (I) is selected from the group consisting of:



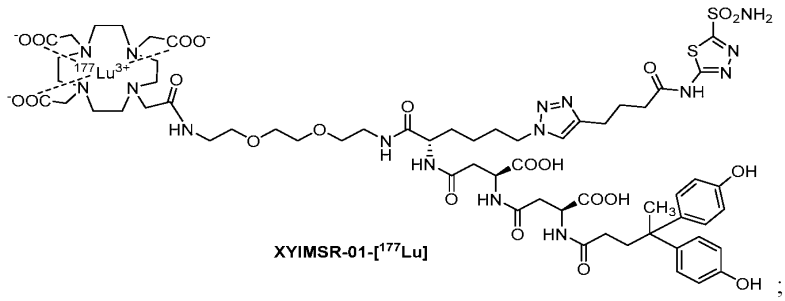
XYIMSR-01-[^{111}In]

;

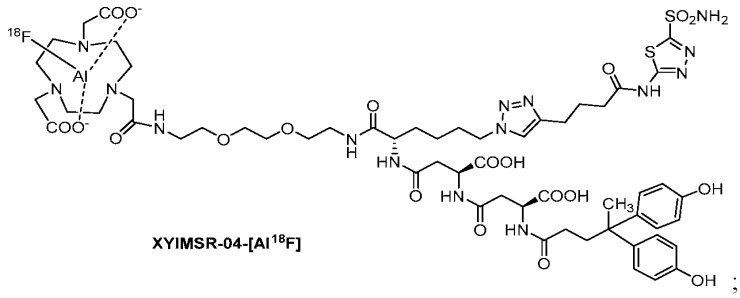
ITM Exhibit 1004, Page 1340 of 1652



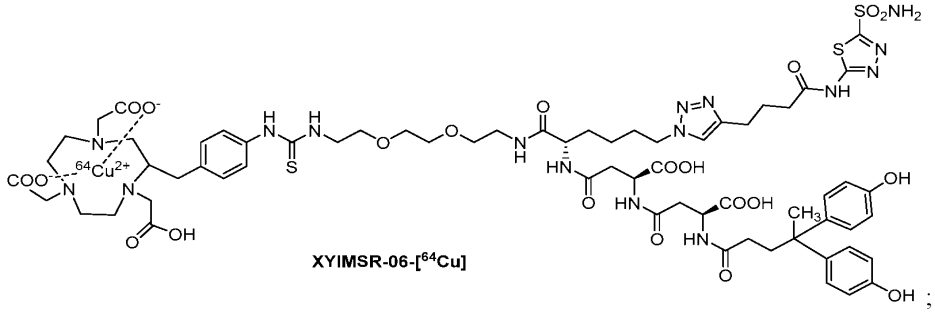
XYIMSR-01-[^{68}Ga] ;



XYIMSR-01-[^{177}Lu] ;



XYIMSR-04-[Al^{18}F] ; and



XYIMSR-06-[^{64}Cu] ;

or a pharmaceutically acceptable salt thereof.

"Contacting" means any action which results in at least one compound comprising the imaging agent of the presently disclosed subject matter physically contacting at least one CAIX-expressing tumor or cell. Contacting can include

exposing the cell(s) or tumor(s) to the compound in an amount sufficient to result in contact of at least one compound with at least one cell or tumor. The method can be practiced *in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube. The method can be practiced *in vivo*, in which case contacting means exposing at least one cell or tumor in a subject to at least one compound of the presently disclosed subject matter, such as administering the compound to a subject via any suitable route. According to the presently disclosed subject matter, contacting may comprise introducing, exposing, and the like, the compound at a site distant to the cells to be contacted, and allowing the bodily functions of the subject, or natural (e.g., diffusion) or man-induced (e.g., swirling) movements of fluids to result in contact of the compound and cell(s) or tumor(s).

By "making an image," it is meant using PET or SPECT to form an image of a cell, tissue, tumor, part of body, and the like.

As used herein, the term "treating" can include reversing, alleviating, inhibiting the progression of, preventing or reducing the likelihood of the cancer to which such term applies, or one or more symptoms or manifestations of such disease, disorder or condition, including killing or eliminating an infectious agent. Preventing refers to causing a disease, disorder, condition, or symptom or manifestation of such, or worsening of the severity of such, not to occur.

In other embodiments, the one or more Carbonic Anhydrase IX-expressing tumors or cells is selected from the group consisting of: a renal cell carcinoma, a prostate tumor or cell, a metastasized prostate tumor or cell, a lung tumor or cell, a renal tumor or cell, a glioblastoma, a pancreatic tumor or cell, a bladder tumor or cell, a sarcoma, a melanoma, a breast tumor or cell, a colon tumor or cell, a germ cell, a pheochromocytoma, an esophageal tumor or cell, a stomach tumor or cell, and combinations thereof. In specific embodiments, the one or more Carbonic Anhydrase IX-expressing tumors or cells is a renal cell carcinoma. In other embodiments, the one or more Carbonic Anhydrase IX expressing tumors or cells is *in vitro*, *in vivo*, or *ex vivo*. In particular embodiments, the one or more Carbonic Anhydrase IX-expressing tumors or cells is present in a subject.

The subject treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which

are intended to be included in the term "subject." Accordingly, a "subject" can include a human subject for medical purposes, such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal (non-human) subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but not limited to, primates, e.g., humans, monkeys, apes, and the like; bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a "subject" can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms "subject" and "patient" are used interchangeably herein.

In some embodiments, a detectably effective amount of the imaging agent of the presently disclosed methods is administered to a subject. In accordance with the presently disclosed subject matter, "a detectably effective amount" of the imaging agent is defined as an amount sufficient to yield an acceptable image using equipment which is available for clinical use. A detectably effective amount of the imaging agent may be administered in more than one injection. The detectably effective amount of the imaging agent can vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual, the dosimetry, and instrument and film-related factors. Optimization of such factors is well within the level of skill in the art.

It is preferable that the compounds of the presently disclosed subject matter are excreted from tissues of the body quickly. Typically compounds of the presently disclosed subject matter are eliminated from the body in less than about 48 hours. More preferably, compounds of the presently disclosed subject matter are eliminated from the body in less than about 24 hours, 16 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 90 minutes, or 60 minutes.

In some embodiments, the presently disclosed methods comprise clearance of the compound comprising the imaging agent from the tumor or cell in the subject. In

ITM Exhibit 1004, Page 1343 of 1652

some other embodiment, the imaging agent is cleared more rapidly from a subject's kidneys than from a tumor in the subject.

In some embodiments, the presently disclosed methods use compounds that are stable *in vivo* such that substantially all, e.g., more than about 50%, 60%, 70%, 80%, or more preferably 90% of the injected compound is not metabolized by the body prior to excretion. In other embodiments, the compound comprising the imaging agent is stable *in vivo*.

In general, the "effective amount" of an active agent refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent or device may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target tissue, and the like.

In some embodiments, the disease or condition is a cancer. Accordingly, the presently disclosed compounds can be administered prophylactically to prevent or reduce the incidence or recurrence of the cancer.

A "cancer" in a subject refers to the presence of cells possessing characteristics typical of cancer-causing cells, for example, uncontrolled proliferation, loss of specialized functions, immortality, significant metastatic potential, significant increase in anti-apoptotic activity, rapid growth and proliferation rate, and certain characteristic morphology and cellular markers. In some circumstances, cancer cells will be in the form of a tumor; such cells may exist locally within a subject, or circulate in the blood stream as independent cells, for example, leukemic cells.

A cancer can include, but is not limited to, renal cancer, head cancer, neck cancer, head and neck cancer, lung cancer, breast cancer, prostate cancer, colorectal cancer, esophageal cancer, stomach cancer, leukemia/lymphoma, uterine cancer, skin cancer, endocrine cancer, urinary cancer, pancreatic cancer, gastrointestinal cancer, ovarian cancer, cervical cancer, and adenomas. In some embodiments, a detectably effective amount of the therapeutic agent of the presently disclosed methods is administered to a subject.

In any of the above-described methods, the administering of a compound can result in at least about a 10% , 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100% decrease in the amount of Carbonic Anhydrase IX released.

C. Pharmaceutical Compositions and Administration

In another aspect, the present disclosure provides a pharmaceutical composition including one compounds of formula (I), formula (II), formula (III) formula (IVa), formula (IVb), formula (IVc), and/or formula (IVd), alone or in combination with one or more additional therapeutic agents in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the compounds described above. Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

The term "combination" is used in its broadest sense and means that a subject is administered at least two agents, more particularly a compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and optionally, one or more therapeutic agents. More particularly, the term "in combination" refers to the concomitant administration of two (or more) active agents for the treatment of a, e.g., single disease state. As used herein, the active agents may be combined and administered in a single dosage form, may be administered as separate dosage forms at the same time, or may be administered as separate dosage forms that are administered alternately or sequentially on the same or separate days. In one embodiment of the presently disclosed subject matter, the active agents are combined and administered in a single dosage form. In another embodiment, the active agents are administered in separate dosage forms (e.g., wherein it is desirable to vary the amount of one but not the other). The single dosage form may include additional active agents for the treatment of the disease state.

Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

The timing of administration of a compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent can be varied so long as the beneficial effects of the combination of these agents are achieved. Accordingly, the phrase "in combination with" refers to the administration of a compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent either simultaneously, sequentially, or a combination thereof. Therefore, a subject administered a combination of a compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent can receive compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent at the same time (i.e., simultaneously) or at different times (i.e., sequentially, in either order, on the same day or on different days), so long as the effect of the combination of both agents is achieved in the subject.

When administered sequentially, the agents can be administered within 1, 5, 10, 30, 60, 120, 180, 240 minutes or longer of one another. In other embodiments, agents administered sequentially, can be administered within 1, 5, 10, 15, 20 or more days of one another. Where the compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd),), and at least one additional therapeutic agent are administered simultaneously, they can be administered to the subject as separate pharmaceutical compositions, each comprising either a compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), or at least one additional therapeutic agent, or they can be administered to a subject as a single pharmaceutical composition comprising both agents.

When administered in combination, the effective concentration of each of the agents to elicit a particular biological response may be less than the effective concentration of each agent when administered alone, thereby allowing a reduction in the dose of one or more of the agents relative to the dose that would be needed if the agent was administered as a single agent. The effects of multiple agents may, but need not be, additive or synergistic. The agents may be administered multiple times.

ITM Exhibit 1004, Page 1346 of 1652

In some embodiments, when administered in combination, the two or more agents can have a synergistic effect. As used herein, the terms "synergy," "synergistic," "synergistically" and derivations thereof, such as in a "synergistic effect" or a "synergistic combination" or a "synergistic composition" refer to circumstances under which the biological activity of a combination of a compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent is greater than the sum of the biological activities of the respective agents when administered individually.

Synergy can be expressed in terms of a "Synergy Index (SI)," which generally can be determined by the method described by F. C. Kull et al., Applied Microbiology 9, 538 (1961), from the ratio determined by:

$$Q_a/Q_A + Q_b/Q_B = \text{Synergy Index (SI)}$$

wherein:

Q_A is the concentration of a component A, acting alone, which produced an end point in relation to component A;

Q_a is the concentration of component A, in a mixture, which produced an end point;

Q_B is the concentration of a component B, acting alone, which produced an end point in relation to component B; and

Q_b is the concentration of component B, in a mixture, which produced an end point.

Generally, when the sum of Q_a/Q_A and Q_b/Q_B is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated. When the sum is less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. Thus, a "synergistic combination" has an activity higher that what can be expected based on the observed activities of the individual components when used alone. Further, a "synergistically effective amount" of a component refers to the amount of the component necessary to elicit a synergistic effect in, for example, another therapeutic agent present in the composition.

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable

acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-toluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by

inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra -sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption promoters; and fluorocarbons.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the

form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl- cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

D. Kits

In yet other embodiments, the presently disclosed subject matter provides a kit comprising a compound of formula (I), formula (II), formula (III), formula (IVa), formula (IVb), formula (IVc), and/or formula (IVd). In certain embodiments, the kit provides packaged pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent, or excipient, and a presently disclosed compound. In certain embodiments the packaged pharmaceutical composition will comprise the reaction precursors necessary to generate the compound of the invention upon combination with a radio labeled precursor. Other packaged pharmaceutical compositions provided by the present invention further comprise indicia comprising at least one of: instructions for preparing compounds according to the invention from supplied precursors, instructions for using the composition to image cells or tissues expressing Carbonic Anhydrase IX, or instructions for using the composition to image glutamatergic neurotransmission in a patient suffering from a stress-related disorder, or instructions for using the composition to image prostate cancer.

II. Definitions

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of Formula (I) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term "optionally" or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art, to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position.

The substituents also may be further substituted (e.g., an aryl group substituent may have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$; $-C(=O)O-$ is equivalent to $-OC(=O)-$; $-OC(=O)NR-$ is equivalent to $-NRC(=O)O-$, and the like.

When the term "independently selected" is used, the substituents being referred to (e.g., R groups, such as groups R_1, R_2, and the like, or variables, such as "m" and "n"), can be identical or different. For example, both R_1 and R_2 can be substituted alkyls, or R_1 can be hydrogen and R_2 can be a substituted alkyl, and the like.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named "R" or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise herein. For the purposes of illustration, certain representative "R" groups as set forth above are defined below.

Description of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

Unless otherwise explicitly defined, a "substituent group," as used herein, includes a functional group selected from one or more of the following moieties, which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions. The hydrocarbon may be unsaturated, saturated, branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term "alkyl" refers to C_{1-20} inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., "straight-chain"), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers thereof.

"Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. "Lower alkyl" refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C_{1-8} alkyl), e.g., 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "Higher alkyl" refers to an alkyl group having about 10 to about 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, "alkyl" refers, in particular, to C_{1-8} straight-chain alkyls. In other embodiments, "alkyl" refers, in particular, to C_{1-8} branched-chain alkyls.

ITM Exhibit 1004, Page 1353 of 1652

Alkyl groups can optionally be substituted (a "substituted alkyl") with one or more alkyl group substituents, which can be the same or different. The term "alkyl group substituent" includes but is not limited to alkyl, substituted alkyl, halo, arylamino, acyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, lower alkyl (also referred to herein as "alkylaminoalkyl"), or aryl.

Thus, as used herein, the term "substituted alkyl" includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_{25}-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)NR', -NR'R", -OR', -SR, -S(O)R, and/or $-S(O_2)R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific

ITM Exhibit 1004, Page 1354 of 1652

heteroalkyl groups, such as -NR'R" or the like.

"Cyclic" and "cycloalkyl" refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The cycloalkyl group can be optionally partially unsaturated. The cycloalkyl group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor, camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

The term "cycloalkylalkyl," as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkyl group, also as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "cycloheteroalkyl" or "heterocycloalkyl" refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10-member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from the group consisting of nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocylic refers to a non-aromatic 5-, 6-, or 7-membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has

ITM Exhibit 1004, Page 1355 of 1652

0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4- morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C_{1-20} inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadiene, cyclohexenyl, 1,3-cyclohexadiene, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

ITM Exhibit 1004, Page 1356 of 1652

The term "alkynyl" as used herein refers to a monovalent group derived from a straight or branched C_{1-20} hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term "alkylene" by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene ($–CH_2–$); ethylene ($–CH_2–CH_2–$); propylene ($–(CH_2)_3–$); cyclohexylene ($–C_6H_{10}–$); –CH=CH–CH=CH–; –CH=CH–CH_2–; -$CH_2CH_2CH_2CH_2$-, -CH_2CH=$CHCH_2$-, -CH_2CsCCH_2-, -$CH_2CH_2CH(CH_2CH_2CH_3)CH_2$-, -$(CH_2)_q$-N(R)-$(CH_2)_r$–, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxyl (–O–CH_2–O–); and ethylenedioxyl (-O-$(CH_2)_2$–O–). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- and –R'OC(O)-.

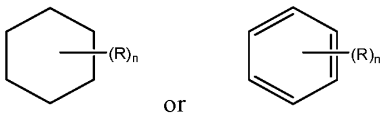
ITM Exhibit 1004, Page 1357 of 1652

The term "aryl" means, unless otherwise stated, an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4- oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4- pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5- isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl" and "heteroarylalkyl" are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

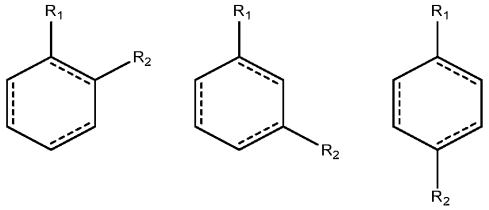
Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



or

as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable "n," which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from the group consisting of a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

The symbol (~~~~) denotes the point of attachment of a moiety to the remainder of the molecule.

When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being "absent," the named atom is replaced by a direct bond.

Each of above terms (e.g. , "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl," "phosphonate," and "sulfonate" as well as their divalent derivatives) are meant to include both substituted and unsubstituted forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent

ITM Exhibit 1004, Page 1359 of 1652

and divalent derivative groups (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R',-C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"C(O)OR', -NR-C(NR'R")=NR'", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 in a number ranging from zero to (2m'+l), where m' is the total number of carbon atoms in such groups. R', R", R'" and R"" each may independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'" and R"" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7- membered ring. For example, -NR'R" is meant to include, but not be limited to, 1- pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF_3 and -CH_2CF_3) and acyl (e.g., -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"C(O)OR', -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'" -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxo, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R'" and R"" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

ITM Exhibit 1004, Page 1360 of 1652

unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'" and R"" groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R'")_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R" and R'" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term "acyl" refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula RC(=O)-, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocylic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term "acyl" specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl)- and a 2-phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, -RC(=O)NR', esters, -RC(=O)OR', ketones, -RC(=O)R', and aldehydes, -RC(=O)H.

The terms "alkoxyl" or "alkoxy" are used interchangeably herein and refer to a saturated (i.e., alkyl–O–) or unsaturated (i.e., alkenyl–O– and alkynyl–O–) group attached to the parent molecular moiety through an oxygen atom, wherein the terms "alkyl," "alkenyl," and "alkynyl" are as previously described and can include C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

"Aryloxyl" refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term "aryloxyl" as used herein can refer to phenyloxyl or hexyloxyl, and alkyl, substituted alkyl, halo, or alkoxyl substituted phenyloxyl or hexyloxyl.

"Aralkyl" refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described, and included substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

"Aralkyloxyl" refers to an aralkyl-O– group wherein the aralkyl group is as previously described. An exemplary aralkyloxyl group is benzyloxyl, i.e., C_6H_5-CH_2-O-. An aralkyloxyl group can optionally be substituted.

"Alkoxycarbonyl" refers to an alkyl-O-C(=O)– group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl, and *tert*-butyloxycarbonyl.

"Aryloxycarbonyl" refers to an aryl-O-C(=O)– group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxy-carbonyl.

"Aralkoxycarbonyl" refers to an aralkyl-O-C(=O)– group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" refers to an amide group of the formula –C(=O)NH_2. "Alkylcarbamoyl" refers to a R'RN–C(=O)– group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described. "Dialkylcarbamoyl" refers to a R'RN–C(=O)– group wherein each of R and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxyl, as used herein, refers to a carbonate group of the formula -O-C(=O)-OR.

"Acyloxyl" refers to an acyl-O- group wherein acyl is as previously described.

The term "amino" refers to the –NH_2 group and also refers to a nitrogen containing group as is known in the art derived from ammonia by the replacement of one or more hydrogen radicals by organic radicals. For example, the terms "acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups respectively.

An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and

trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure –NHR' wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group having the structure –NR'R", wherein R' and R" are each independently selected from the group consisting of alkyl groups. The term trialkylamino refers to a group having the structure –NR'R"R"', wherein R', R", and R"' are each independently selected from the group consisting of alkyl groups. Additionally, R', R", and/or R"' taken together may optionally be $-(CH_2)_k-$ where k is an integer from 2 to 6. Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl–S–) or unsaturated (i.e., alkenyl–S– and alkynyl–S–) group attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

"Acylamino" refers to an acyl-NH– group wherein acyl is as previously described. "Aroylamino" refers to an aroyl-NH– group wherein aroyl is as previously described.

The term "carbonyl" refers to the –C(=O)– group, and can include an aldehyde group represented by the general formula R-C(=O)H.

The term "carboxyl" refers to the –COOH group. Such groups also are referred to herein as a "carboxylic acid" moiety.

The terms "halo," "halide," or "halogen" as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "hydroxyl" refers to the –OH group.

The term "hydroxyalkyl" refers to an alkyl group substituted with an –OH group.

The term "mercapto" refers to the –SH group.

The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term "nitro" refers to the $–NO_2$ group.

The term "thio" refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term "sulfate" refers to the $–SO_4$ group.

The term thiohydroxyl or thiol, as used herein, refers to a group of the formula –SH.

More particularly, the term "sulfide" refers to compound having a group of the formula –SR.

The term "sulfone" refers to compound having a sulfonyl group $–S(O_2)R$.

The term "sulfoxide" refers to a compound having a sulfinyl group –S(O)R

The term ureido refers to a urea group of the formula $–NH—CO—NH_2$.

Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms. Optically active (R)- and (S)-, or D- and L-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefenic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each

asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures with the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

The compounds of the present disclosure may exist as salts. The present disclosure includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous

acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Following long-standing patent law convention, the terms “a,” “an,” and “the” refer to “one or more” when used in this application, including the claims. Thus, for example, reference to “a subject” includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

Throughout this specification and the claims, the terms “comprise,” “comprises,” and “comprising” are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term “include” and its grammatical variants

ITM Exhibit 1004, Page 1366 of 1652

are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about" even though the term "about" may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some embodiments, ± 100% in some embodiments ± 50%, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ±1%, in some embodiments ± 0.5%, and in some embodiments ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term "about" when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can

be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

EXAMPLE 1

Carbonic Anhydrase IX and Applications Thereof

Carbonic Anhydrase IX. Carbonic anhydrase IX (CAIX) is a membrane-associated member of the carbonic anhydrase (CA) family (Krishnamurthy et al., 2008; Supuran, 2008; Alterio et al., 2012). These enzymes catalyze the reversible hydration of carbon dioxide to a bicarbonate anion and a proton. Fifteen human isoforms of CA have been identified. These isoforms show high sequence homology and share common structural features, including a zinc-containing catalytic site, a central twisted β-sheet surrounded by helical connections and additional β-strands (Altero et al., 2006; Lindskog et al., 1997; Hakansson et al., 1992; Christianson and Fierke, 1996). At the same time they are differ widely in molecular features, cellular localization, expression levels and tissue distribution (Clare and Supuran, 2006). CAIX is one of the transmembrane isoforms (along with CAIV, CAXII and CAXIV) and has limited expression in normal tissues with the exception of the gastrointestinal tract, gallbladder and pancreatic ducts (Supuran, 2008; Alterio et al., 2012; Christianson and Fierke, 1996).

CAIX as a Biomarker of Clear Cell RCC. RCC is a primary epithelial malignancy of the renal paryncyma. To date, a number of different histologic variants of RCC have been described (Srigley et al., 2013). Most common among these is the clear cell (ccRCC) subtype. CcRCC is characterized by loss of the Von Hippel-Lindau (VHL) gene located at 3p25 (Cancer Genome Atlas Research Network, 2013). Under normoxic conditions, the VHL protein is responsible for ubiquitination of the hypoxia-inducible factor (HIF) (Gossage, 2015). Upon sensing hypoxia, the VHL gene releases its control over HIF leading to its localization to the nucleus where it up regulates the expression of a number of genes including CAIX and vascular endothelial growth factor (VEGF). Over-expression of CAIX has been demonstrated in approximately 95 % of ccRCC specimens (Bui et al., 2003; Atkins et al., 2005; Leibovich et al., 2007). Given the ubiquitous overexpression of CAIX in cases of ccRCC, CAIX represents a rationale imaging and therapeutic target of this

disease. Moreover, CAIX is unregulated in a number of other cancer types, both due to VHL loss and tissue hypoxia (include citations). Thus, ligands capable of selectively binding CAIX would have widespread utility in cancer imaging and therapeutics.

Significance for CAIX imaging with low-molecular-weight (LMW) agents. Feasibility for the non-invasive diagnosis of ccRCC via CAIX expression level has been extensively studied with the radiolabeled antibody G250, a murine monoclonal antibody (mAbG250) developed by immunization of mice with human ccRCC homogenates in 1986 (Oosterwijk et al., 1986). The clinical applications of this agent have been reviewed (Smaldone et al., 2012) and it was reported to identify ccRCC with 86 % sensitivity, 87 % specificity and 95 % positive predictive value (Uzzo et al., 2010). However, antibodies as molecular imaging agents suffer from certain pharmacokinetic limitations, including slow blood/tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. LMW imaging agents, especially ^{18}F-labeled LMW agents, in principle, could provide superior imaging quality within 2 hours (Alauddin et al., 2012; Coenen et al., 2010; Cho et al., 2012). LMW agents are also more convenient to synthesize and to distribute to imaging centers. Although significant effort has been spent on sulfonamides and other CAIX ligands (Supuran, 2008; Alterio et al., 2012; Askoxylakis et al., 2010), no successful radionuclide-based molecular imaging agent has been reported (Pan et al., 2014; Akurathi et al., 2010; Lu et al., 2013; Doss et al., 2014; Rana et al., 2012). Most imaging results were reported with optical agents (Cecchi et al., 2005; Groves et al., 2012; Bao et al., 2012; Krall et al., 2014), but suffer from low tumor uptake (<2% ID/g) and highly variable imaging quality. Recently, significant progress in the field of CAIX imaging was reported by Wichert and coworkers with the identification of an additional surface binding pocket (Wichert et al., 2015). This dramatically reinforced the binding affinity of common sulfonamides over CAIX up to 0.2 nM and improved the tumor uptake by more than five times in ccRCC xenografts model as disclosed in FIG. 1A through FIG 1D. In addition, the amino-containing western part of the molecule, was prove to expose to water and suitable for various modification. However, there are still two issues with this new generation dual-targeting agents: (1) the limited tissue penetration of optical agents and (2) the high kidney uptake precluding the use of this agent for imaging primary renal tumors apart from kidney background.

ITM Exhibit 1004, Page 1369 of 1652

Fueled by the recent success of optical imaging of CAIX, PET/SPECT radioisotope labeled ligands have been investigated. As shown in FIG. 2A, the molecule contains an acetazolamide analog, 4,4-bis(4-hydroxyphenyl)valeric acid, an optimized linker and a modifiable amino group. FITC conjugated fluorescent ligand 1 has been synthetized, which reported with 0.2 nM Ki and excellent cellular uptake property on CAIX+ SK-RC-52 cells have been demonstrated, which is consistent with the earlier report (Wichert et al., 2015).

Significance for nuclear imaging and radiotherapy. Radionuclide molecular imaging including PET is the most mature molecular imaging technique without tissue penetration limitations. Due to its advantages of high sensitivity and quantifiability, radionuclide molecular imaging plays an important role in clinical and preclinical research (Youn and Honk, 2012; Chen et al., 2014). Many radionuclides, primarily β- and alpha emitters, have been investigated for targeted radioimmunotherapy and include both radiohalogens and radiometals (Table 1). The highly potent and specific binding moiety targeting CAIX enables its nuclear imaging and radiotherapy.

Table 1. Therapeutic Radionucleotides

β-particle emitters	^{90}Y, ^{131}I, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{212}Pb, ^{166}Ho, ^{47}Sc
α-particle emitters	^{225}Ac, ^{213}Bi, ^{212}Bi, ^{211}At, ^{212}Pb
Auger electron emitters	^{125}I, ^{123}I, ^{67}Ga, ^{111}In, ^{80m}Br

Herein, the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to CAIX is described. A new scaffold for radionuclide-based imaging and therapy of clear cell renal cell carcinoma (ccRCC) targeting carbonic anhydrase IX (CAIX) has been developed. The bivalent and low-molecular-weight ligands **XYIMSR-01**, a DOTA-conjugated, **XYIMSR-04**, a NOTA-conjugated, and **XYIMSR-06**, a Bz-NOTA-conjugated, have two moieties that target two separate sites on CAIX, imparting high affinity.

[^{111}In]**XYIMSR-01** in 73.8-75.8 % (n = 3) yield has been synthetized with specific radioactivities ranging from 118 – 1,021 GBq/μmol (3,200 – 27,600 Ci/mmol). Single photon emission computed tomography of [^{111}In]**XYIMSR-01** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 h post-injection. Rapid clearance from non-

ITM Exhibit 1004, Page 1370 of 1652

target tissues, including kidneys, allowed for high and specific signal by 24 h. Biodistribution studies demonstrated 26 % injected dose per gram of radioactivity within tumor at 1 h. Tumor-to- blood, muscle and kidney ratios were 178.1± 145.4, 68.4 ± 29.0 and 1.7 ± 1.2, respectively, at 24 h post-injection. Retention of radioactivity was exclusively observed in tumors by 48 h, the latest time point evaluated.

[^{177}Lu]**XYIMSR-01** in 69.0% yield has been synthetized with specific radioactivity of 2,340 Ci/mmol; 73.0% with specific radioactivity of 2239 Ci/mmol, and in average yield of 60% (n=12), with average specific activity of 1,900 Ci/mmol (ranging from 1,200 Ci/mmol to 2,500 Ci/mmol). Single photon emission computed tomography of [^{177}Lu]**XYIMSR-01** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 h post-injection. Rapid clearance from non-target tissues, including kidneys, allowed for high and specific signal by 24 h. Biodistribution studies confirmed the SPECT/CT data. Tumor-to-blood, muscle, and kidney ratios were 607.4 ± 200.7, 128.4 ± 25.4 and 4.5 ± 1.4, respectively, at 24 h post-injection.

[Al^{18}F]**XYIMSR-04** in 4.3% (n = 3) yield has been synthetized with specific radioactivities of 2.1 – 3.4 GBq/μM (57-92 Ci/mmol). Positron emission tomography of [Al^{18}F]**XYIMSR-04** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor at 1 h post-injection. Biodistribution studies demonstrated 14.40% injected dose per gram of radioactivity within tumor at 1 h. Tumor-to –blood, -muscle and –kidney ratio were 22.1, 9.74 and 0.28 respectively, at 1h post-injection.

[^{64}Cu]**XYIMSR-06**, in 51.0 ± 4.5% (n=5) yield has been synthetized with specific radioactivities of 4.1 – 8.9 GBq/μM (110-240 Ci/mmol). Positron emission tomography of [^{64}Cu]**XYIMSR-06** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 h post-injection. By 24 h radioactivity within the tumors dropped to 6.2 % injected dose per gram of radioactivity. Within 24 h, no significant radiotracer uptake within liver was observed, indicative of the *in vivo* stability of NOTA-^{64}Cu chelation.

The dual targeting strategy to engage CAIX enabled specific detection of ccRCC in this xenograft model, with pharmacokinetics surpassing those of previously described radionuclide-based probes against CAIX.

EXAMPLE 2

Material and Methods

General Procedures. Solvents and chemicals obtained from commercial sources were of analytical grade or better and used without further purification. Fmoc-protected azidolysine, HBTU, and N-α-fmoc-L-aspartic acid α-tert-butyl ester were purchased from Chem Impex International, Inc. (Wooddale, IL). Carrier-free [^{111}In]$InCl_3$ was purchased from MDS Nordion (Ottawa, ON, Canada). DOTA-NHS-ester (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid mono N-hydroxysuccinimide ester) was purchased from Macrocyclics, Inc. (Dallas, TX). Indium (III) nitrate, triethylsilane (Et_3SiH), N,N-diisopropylethylamine (DIEA), triethylamine (TEA), piperidine, 4,4-bis(4-hydroxyphenyl)valeric acid, copper iodide (CuI), and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA) were purchased from Sigma-Aldrich (Saint Louis, MO). Pre-loaded O-bis-(aminoethyl)ethylene glycol on trityl resin was purchased from EMD Millipore (Billerica, MA). Flash chromatography was performed using MP SiliTech 32-63 D 60Å silica gel purchased from Bodman (Aston, PA). Recombinant human CAIX was purchased from R&D Systems (Minneapolis, MN). 1H NMR spectra were recorded on a Bruker Ultrashield 500 MHz spectrometer. Chemical shifts (δ) were reported in ppm downfield by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. ESI mass spectra were obtained on a Bruker Daltonics Esquire 3000 Plus spectrometer (Billerica, MA).

HPLC purification of non-labeled compounds were performed using a Phenomenex C18 Luna 10 × 250 mm column on a Agilent 1260 infinity LC system (Santa Clara, CA). HPLC purification of radiolabeled (^{111}In) ligand was performed on another Phenomenex C18 Luna 10 × 250 mm and a Varian Prostar System (Palo Alto, CA), equipped with a Varian ProStar 325 UV-Vis variable wavelength detector and a Bioscan (Poway, CA) Flow-count in-line radioactivity detector, all controlled by Galaxie software. The specific radioactivity was calculated as the ratio of the radioactivity eluting at the retention time of product during the preparative HPLC purification to the mass corresponding to the area under the curve of the UV absorption. The purity of tested compounds as determined by analytical HPLC with absorbance at 254 nm was > 95%.

Synthesis of N^4-((S)-1-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-1-oxo-6-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-

*yl)hexan-2-yl)-N^2-((S)-3-(4,4-bis(4-hydroxyphenyl)pentanamido)-3-carboxypropanoyl)-L-asparagine (**3**).* Referring to FIG. 5, **3** was synthesized through an established solid phase based procedure (Wichert et al., 2015).

*Synthesis of 2,2',2''-(10-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**XYIMSR-01**).* Referring to FIG. 6, N^4-((S)-1-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-1-oxo-6-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)hexan-2-yl)-N^2-((S)-3-(4,4-bis(4-hydroxyphenyl)pentanamido)-3-carboxypropanoyl)-L-asparagine (**3**) 19 mg (0.017 mmol), DOTA-NHS **7** 16 mg (0.021 mmol) and N,N-diisopropylethylamine 150 µL were mixed in 2 mL DMSO. The reaction was stirred at room temperature for 2 h. Solvent was removed under vacuum. 21 mg (0.014 mmol) of product **XYIMSR-01** was obtained as a white powder after purification by HPLC in 82 % yield. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 10/90/0.1 to 50/50/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product eluted at 6.3 min. ^{1}H-NMR (500 MHz, DMSO-d6): δ 13.01 (s, 1H), 12.77 (br. 2H), 9.17 (br. s, 2H), 8.53 (br, 1H), 8.33 (s, 2H), 8.19 (d, J = 8.0, 1H), 8.09 (d, J =7.9, 1H), 7.91 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.84 (s, 1H), 7.45 (br. 2H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J =8.4, 4H), 4.54 – 4.44 (m, 2H), 4.24 (t, J = 7.2, 2H), 4.17 (td, J = 8.3, 5.5, 1H), 4.0-3.0 (36H, overlap with water signal), 2.65 (t, J = 7.5, 2H), 2.64 – 2.55 (m, 4H), 2.51 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H) 1.94 (m, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.75 (m, J = 7.5, 2H), 1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{61}H_{88}N_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1483.6; Found: 1483.4.

*Synthesis of DOTA-In conjugated compound [In]-**XYIMSR-01**.* Referring to FIG. 7, **XYIMSR-01** 2 mg (0.0013 mmol) was dissolved in 1 mL of 0.2 M NaOAc. Then, 20 µL of $In(NO_3)_3$ solution was added (containing 0.6 mg of $In(NO_3)_3$). The solution was kept at 60°C for 30 min. 2.0 mg [In]-**XYIMSR-01**was obtained as white crystal, after HPLC purification. Yield is 98 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/TFA MeCN/H_2O/TFA, flow 10 mL/min. Product was eluded at 10.6 min. MS, calculated for $C_{61}H_{85}InN_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1595.4; Found: 1595.3.

ITM Exhibit 1004, Page 1373 of 1652

*Synthesis of DOTA-Ga conjugated compound [Ga]-**XYIMSR-01***. Referring to FIG. 8, **XYIMSR-01** 2 mg (0.0013 mmol) was dissolved in 1 mL of pure water. Then, 20 µL of $Ga(NO_3)_3$ solution was added (containing 0.5 mg of $Ga(NO_3)_3$). The solution was kept at 60 °C for 30 min. 1.8 mg [Ga]-**XYIMSR-01**was obtained as white crystal, after HPLC purification. Yield is 90 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/TFA MeCN/H_2O/TFA, flow 10 mL/min. Product was eluded at 10.2 min. MS, calculated for $C_{61}H_{85}GaN_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1549.5; Found: 1549.7.

*Synthesis of DOTA-Lu conjugated compound [^{175}Lu]2,2',2''-(10-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid ([Lu]**XYIMSR-01**)* Synthesis of DOTA-Lu conjugated compound [^{175}Lu]**XYIMSR-01**. Referring to FIG. 9, **XYIMSR-01** 1 mg (0.0007 mmol) was dissolved in 1 mL of 0.2 M NaOAc. Then, 10 µL of $Lu(NO_3)_3$ solution was added (containing 0.4 mg of $Lu(NO_3)_3$). The solution was kept at 60°C for 30 min. 1.0 mg [^{175}Lu]**XYIMSR-01** was obtained as white crystal, after HPLC purification. Yield is 90 %. MS, calculated for $C_{61}H_{85}LuN_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1655.4766; Found: 1655.4787. HPLC, Column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/0.1 MeCN/H_2O/TFA, flow 10 mL/min. Product was eluded at 14.1 min, with free ligand eluted first at 13.1. It is applied to preparative runs.

*Synthesis of SFB conjugated compound **XYIMSR-02***. Referring to FIG. 10, compound **3** 10 mg (0.009 mmol), **4** 5 mg (0.021 mmol) and di-isopropylethylamine 10 µL were dissolved in 1 mL DMF. The reaction was kept at room temperature for 1.5 hour. The solvent was removed under vacuum. 9 mg **XYIMSR-02** was obtained after HPLC as white powder. Yield is 81 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 15/85/0.1 to 60/40/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 7.1 min. ^{1}H-NMR (500 MHz, DMSO-d6): δ 13.01 (s, 1H), 12.62(br, 1H), 12.49(br, 1H), 9.16 (br. s, 2H), 8.55(br, 1H), 8.32 (s, 2H), 8.17 (d, J = 8.0, 1H), 8.09 (d, J = 7.9, 1H) 7.91 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.84 (s, 1H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J = 8.4, 4H), 6.54(br, 2H), 4.51 – 4.45 (m, 2H), 4.26 (t, J = 7.2, 2H), 4.21 (td, J = 8.3, 5.5, 1H), 3.53 (t, J = 5.3, 2H), 3.56 – 3.50 (m, 4H), 3.38 (t, J = 6.1, 2H), 3.24 – 3.15 (m, 2H), 2.65 (t, J = 7.5, 2H),

ITM Exhibit 1004, Page 1374 of 1652

2.64 – 2.55 (m, 4H), 2.51 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H) 1.95 (quin, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.76 (quin, J = 7.5, 2H),1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{52}H_{65}FN_{12}NaO_{16}S_2^+$ $[M+Na]^+$: 1219.4; Found: 1219.3.

*Synthesis of 6-fluoro-pyridine-3-carbonyl conjugated compound (**XYIMSR-03**).* Referring to FIG. 11, compound **3** 5 mg (0.0045 mmol), **5** 4 mg and di-isopropylethylamine 20 µL were dissolved in 1 mL DMF. The reaction was kept at room temperature for 2 hour. The solvent was removed under vacuum. 2.8 mg **XYIMSR-03** was obtained after HPLC as white powder. Yield is 52 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 15/85/0.1 to 60/40/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 6.9 min. MS, calculated for $C_{51}H_{63}FN_{13}O_{15}S_2^+$ $[M+H-H_2O]^+$: 1180.4; Found: 1180.4.

Synthesis of NOTA conjugated compound 2,2'-(7-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (***XYIMSR-04***). Referring to FIG. 12, **3** 14 mg (0.0126 mmol), NOTA-NHS 10 mg (0.0151 mmol) and triethylamine 50 µL were mixed in 2 mL DMF. The reaction was stirred at room temperature for 2 hours. All the solvent was removed under vacuum. 9.0 mg product **XYIMSR-04** was obtained as white powder, after HPLC purification. Yield is 52%. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 10/90/0.1 to 50/50/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 6.9 min. ^{1}H-NMR (500 MHz, DMSO-d6): δ 12.99 (s, 1H), 12.25(br. 2H), 9.15 (br. s, 2H), 8.31 (s, 2H), 8.24(m, 1H), 8.16 (d, J = 8.0, 1H), 8.05 (d, J =7.9, 1H), 7.90 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.83 (s, 1H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J =8.4, 4H), 6.50(br, 2H), 4.52 – 4.46 (m, 2H), 4.24 (t, J = 7.2, 2H), 4.17 (td, J = 8.3, 5.5, 1H), 4.0-2.84(overlap with water signal), 2.65 (t, J = 7.5, 2H), 2.64 – 2.55 (m, 4H), 2.47 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H), 1.94 (m, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.75 (m, J = 7.5, 2H), 1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{57}H_{81}N_{15}NaO_{20}S_2^+$ $[M+Na]^+$: 1382.5; Found: 1382.8.

Synthesis of NOTA-Al-F conjugated compound [Al^{19}F] 2,2'-(7-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-

*6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (**[Al^{19}F]XYIMSR-04**)*. Referring to FIG. 13, **XYIMSR-04** 1 mg (0.0007 mmol) was dissolved in 1 mL water/Ethanol 1:1. To the solution, 500 µL of $AlCl_3$ 2 mmol/NaOAc 2 mmol water solution (pH = 4) was added. Then, 500 µL of 10 mmol KF solution was added, together with 1 mL of ethanol. The resulting solution was heated at 110 °C for 30 min. 0.6 mg of [Al^{19}F]**XYIMSR-04** was obtained as white crystal, after HPLC purification. Yield is 61 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/TFA MeCN/H_2O/TFA, flow 4 mL/min. Product was eluded at 35.5 min. MS, calculated for $C_{57}H_{79}AlFN_{15}NaO_{20}S_2^+$ $[M+Na]^+$: 1426.4759; Found: 1426.4777.

*Synthesis of conjugated compound **XYIMSR-05**.* Referring to FIG. 14, compound **3** 4 mg (0.0036 mmol), **6** 4 mg and di-isopropylethylamine 20 µL were dissolved in 1 mL DMF. The reaction was kept at room temperature for 2 hour. The solvent was removed under vacuum. 2.9 mg **XYIMSR-05** was obtained after HPLC as white powder. Yield is 62%. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 15/85/0.1 to 60/40/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 7.6 min. MS, calculated for $C_{52}H_{66}IN_{12}O_{16}S_2^+$ [M+H]+: 1305.3; Found: 1305.2.

*Synthesis of NOTA conjugated compound 2,2',2''-(2-(4-(3-((11S,15S,19S)-15,19-dicarboxy-24,24-bis(4-hydroxyphenyl)-10,13,17,21-tetraoxo-11-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-3,6-dioxa-9,12,16,20-tetraazapentacosyl)thioureido)benzyl)-1,4,7-triazonane-1,4,7-triyl)triacetic acid (**XYIMSR-06**)*. Referring to FIG. 15, compound **3** (Wichert et al., 2015) 12 mg (0.0111 mmol), p-SCN-Bn-NOTA 8 mg (0.0143 mmol) and *N,N*-diisopropylethylamine 50 µL were mixed in 2 mL DMF. The reaction was stirred at room temperature for 2 h. Solvent was removed under vacuum. 14.0 mg of product **XYIMSR-06** was obtained as a white powder after HPLC purification. Yield was 83%. HPLC conditions: column Phenomenex, Luna 10 × 250 mm, 10 µm. 25/75/0.1 MeCN/H_2O/TFA, flow 10 mL/min. Product eluted at 12.0 min. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.98 (s, 1H), 12.63 (br. 2H), 9.60 (m, 1H), 9.15 (br. s, 2H), 8.31 (s, 2H), 8.16 (d, J = 8.0, 1H), 8.05 (d, J =7.9, 1H), 7.90 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.83 (s, 1H), 7.69(br, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J =8.4, 4H), 6.50 (br, 2H), 4.52 – 4.46 (m, 2H), 4.24 (t, J = 7.2, 2H), 4.17 (td, J = 8.3, 5.5, 1H), 4.0-2.90 (overlaps with water signal), 2.65 (t, J =

7.5, 2H), 2.64 – 2.55 (m, 4H), 2.47 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H), 1.94 (m, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.75 (m, J = 7.5, 2H), 1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{65}H_{89}N_{16}O_{21}S_3^+$ $[M+H]^+$: 1525.5545; Found: 1525.5527.

*Synthesis of [$^{63/65}$Cu]2,2',2''-(2-(4-(3-((11S,15S,19S)-15,19-dicarboxy-24,24-bis(4-hydroxyphenyl)-10,13,17,21-tetraoxo-11-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-3,6-dioxa-9,12,16,20-tetraazapentacosyl)thioureido)benzyl)-1,4,7-triazonane-1,4,7-triyl)triacetic acid([$^{63/65}$Cu]**XYIMSR-06**).* Referring to FIG. 16, **XYIMSR-06** 1 mg (0.0007mmol) was dissolved in 0.5 mL 0.2 M NaOAc solution. To the solution 0.2 mg $Cu(NO_3)_23H_2O$ was added in 0.1 mL of water. The reaction was heated at 100°C for 10 min and then loaded onto HPLC for purification. 0.5 mg of product was obtained as blue crystals. Yield was 48%. HPLC conditions: column Phenomenex, Luna 10 × 250 mm, 10 µm. 25/75/TFA MeCN/H_2O/TFA, flow 10 mL/min. Product eluted at 8.3 min with the starting material eluting at 12.6 min. MS, calculated for $C_{65}H_{87}CuN_{16}O_{21}S_3^+$ [M+H]+: 1586.4684; Found: 1586.4683.

Radiolabeling of [^{111}In]XYIMSR-01. 20 µg **XYIMSR-01** was dissolved in 10 µL of 0.2 M NaOAc followed by addition of 3.3 mCi of $^{111}InCl_3$ solution to provide a final pH = 5.5-6. The mixture was heated in a water bath at 65°C for 30 min. Radiolabeling was monitored by HPLC. At completion, the reaction mixture was diluted with 1 mL of water then loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, [^{111}In]**XYIMSR-01**, and starting material, **XYIMSR-01**, were optimized to the point of baseline separation, with [^{111}In]**XYIMSR-01** eluting first. 2.5 mCi of [^{111}In]**XYIMSR-01** was obtained at a radiochemical yield of 75.8 % in specific radioactivities of 118.4 GBq/µmol (3,200 Ci/mmol). The identity of the radiolabeled product was confirmed by co-injection with [$^{113/115}$In]**XYIMSR-01** and co-elution on HPLC with the same condition. Another two syntheses were performed under similar conditions. The average yield was 74 % (n = 3). The specific activities ranged from 118 to 1021.2 GBq/µmol (3,200 to 27,600 Ci/mmol). For preparative runs, the HPLC solvent was removed under vacuum. [^{111}In]**XYIMSR-01** was formulated in phosphate-buffered saline (PBS) for the imaging study. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10µm. 19/81/0.1 MeCN/H_2O/TFA, flow 4 mL/min. Product eluted at 28.3 min, while starting material eluted at 30.2 min.

ITM Exhibit 1004, Page 1377 of 1652

*Radiolabeling of **XYIMSR-01**-[^{177}Lu].* 20 μg **XYIMSR-01** was dissolved in 10 μL of 0.2M NaOAc followed by addition of 10.1 mCi of $^{177}LuCl_3$ solution to provide a final pH = 5.5-6. The mixture was heated in a water bath at 65°C for 30 min. Radiolabeling was monitored by HPLC. At completion, the reaction mixture was diluted with 0.2 mL of water then loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, [^{177}Lu]**XYIMSR-01**, and starting material, **XYIMSR-01**, were optimized to the point of baseline separation, with **XYIMSR-01**-[^{177}Lu] eluting first. 6.97 mCi of **XYIMSR-01**-[^{177}Lu] was obtained at a radiochemical yield of 69.0% in specific radioactivities of 2,340 Ci/mmol. The identity of the radiolabeled product was confirmed by co-injection with **XYIMSR-01**-[Lu] and co-elution on HPLC with the same condition. Another one syntheses were performed under similar conditions, starting with 10.2 mCi and obtaining 7.30 mCi at yield of 73.0% and specific radioactivity of 2239 Ci/mmol. The product was diluted with water, loaded onto Sep-Pak and eluded with 2 mL pure ethanol. After the concentrated under nitrogen gas, **XYIMSR-01**-[^{177}Lu] was formulated in phosphate-buffered saline (PBS) for the study. HPLC conditions: Phenomenex, Luna 4.6 × 250 mm, 5μm. 22/78/0.1 MeCN/H2O/TFA, flow 0.5 mL/min. Product eluted at 24.5 min, while starting material eluted at 29.0 min.

Yet other syntheses were performed under similar conditions, starting with 8.4-20.7 mCi. At completion, the reaction mixture was diluted with 200 μL of water, loaded onto a HPLC column for purification. With Method B, [^{177}Lu]**XYIMSR-01** got eluted first and collected. Base line separation between radiolabel product and starting material was achieved. The average radiochemical yield is 60% (n=12), with average specific activity of 1,900 Ci/mmol (ranging from 1,200 Ci/mmol to 2,500 Ci/mmol). HPLC column Phenomenex, Luna 4.6 × 250 mm, 5 μm. 21/79/0.1 MeCN/H2O/TFA, flow 0.5 mL/min. Product was eluded at 30.5 min, with free ligand eluted second at 36.1 min.

*Radiolabeling of **XYIMSR-04**-[Al^{18}F].* 20μL of 1 mM **XYIMSR-04** in water/EtOH 1/1 was added to 200 μL of Na^{18}F in 0.9% saline containing 1.3 mCi activity. To this mixture, 1 μL of 2 mM $AlCl_3$/NaOAc solution and 200 μL of ethanol were added. The reaction was kept at 105 °C for 20 min, then diluted with 1.5 mL of water and loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, **XYIMSR-04**-[Al^{18}F], and starting material,

XYIMSR-04, were optimized to the point of baseline separation, with **XYIMSR-04**-[$Al^{18}F$] eluting first. 180 μCi of **XYIMSR-04**-[$Al^{18}F$] was obtained a radiochemical yield of 13.8% in specific radioactivity of >1000 Ci/mmol in 1 hour. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10μm. 20/80/0.1 MeCN/H2O/TFA, flow 0.5 mL/min. Product eluted at 35.5 min, while starting material eluted at 39.0 min.

Another radiosynthesis of ***XYIMSR-04***-*[$Al^{18}F$]* was performed. $Na^{18}F$ in saline was purchased from PETNET (Hackensack, NJ) and was directly used in the synthesis 400 μg of **XYIMSR-04** in 200 μL water/ethanol 1:1 was added to 1 mL of $Na^{18}F$ in 0.9% saline containing 0.17 – 0.52 GBq (4.6-14.0 mCi) of radioactivity. To this mixture 20 μL of 2 mM $AlCl_3$/NaOAc solution and 200 μL of ethanol were added. The reaction was kept at 105°C for 20 min, then diluted to 2.0 mL with water and loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, [$Al^{18}F$]**XYIMSR-04**, and starting material, **XYIMSR-04**, were optimized to the point of baseline separation, with [$Al^{18}F$]**XYIMSR-04** eluting first. [$Al^{18}F$]**XYIMSR-04** was obtained in a radiochemical yield of 4.3% (n=3) in specific radioactivity of 2.1 – 3.4 GBq/μmol (57-92 Ci/mmol) in 1.5 h. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10 μm. 20/80/0.1 MeCN/H_2O/TFA, flow 4 mL/min. Product eluted at 35.5 min, while starting material eluted at 39.0 min. The collected activity was diluted with 20 mL of water and loaded onto an activated Sep-Pak column (WAT020515, Waters, Milford MA). After the Sep-Pak was washed with 10 mL of water, [$Al^{18}F$]**XYIMSR-04** was eluted with 2 mL of ethanol. The ethanol was evaporated under a gentle stream of N_2 (to a total volume of < 50 μL). The resulting solution was formulated in saline for the imaging and biodistribution studies.

*Radiolabeling of [^{64}Cu]**XYIMSR-06***. 40 μg of **XYIMSR-06** in 20 μL 0.2 M NaOAc solution was added to 60 μL $^{64}CuCl_2$ with 0.16 – 0.26 GBq (4.2 – 6.9 mCi) of radioactivity. The reaction was heated in a water bath at 65°C and pH 5.5−6 for 0.5 h. The reaction was then diluted with 1.5 mL of water and injected onto the HPLC for purification. Baseline separation was achieved between [^{64}Cu]**XYIMSR-06** and **XYIMSR-06** with [^{64}Cu]**XYIMSR-06** eluting first. The average non-decay corrected radiochemical yield was 51.0 ± 4.5% (n=5) and specific activities were 4.1 – 8.9 GBq/μmol (110-240 Ci/mmol). HPLC conditions: column Phenomenex, Luna 10 × 250 mm, 10 μm. 23/77/TFA MeCN/H_2O/TFA, flow 4 mL/min. Product eluted at

29.2 min. The collected radioactivity was diluted with 20 mL of water and loaded onto activated Sep-Pak (WAT020515, Waters, Milford MA). After the Sep-Pak was washed with 10 mL of water, [^{64}Cu]**XYIMSR-06** was eluted with 2 mL of ethanol. The ethanol was evaporated under a gentle stream of N_2 (to a total volume of < 50 μL). The resulting solution was formulated in saline for the imaging and biodistribution studies.

Cell Lines and Mouse Models. Animal experiments were performed in accordance with protocols approved by the Johns Hopkins Animal Care and Use Committee (ACUC). Six-week-old female NOD/SCID mice were purchased from the Animal Resource Core of the Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins and were subcutaneously injected in the lower left flank or upper right flank with 1 x 10^6 SK-RC-52 cells in RPMI 1640 GlutaMAX™ media (Life Technologies, Frederick, MD) supplemented with 1% fetal bovine serum (FBS). Mice were monitored for tumor size and used for SPECT/CT imaging when the size of the tumor reached 100 mm^3.

FACS Analysis. CAIX-positive SK-RC-52 and CAIX-negative BxPC3 cells were maintained in RPMI 1640 media supplemented with 10% FBS and 1 x penicillin-streptomycin in a 37°C humidified incubator. Cells were detached from the flask with trypsin and reconstituted in RPMI 1640 media supplemented with 1% FBS at a density of 1 x 10^6 cells per mL. FITC-labeled **8** was added to the cells at the indicated concentration and incubated at room temperature for 30 min. Cells were washed twice with the same media for staining and analyzed using the FACSCalibur (BD Bioscience, San Jose, CA) instrument.

*Competitive Fluorescence Polarization Assay for [$^{113/115}$In]**XYIMSR-01.*** Fluorescence polarization (FP) experiments were performed in 21 μL of the assay buffer (12.5 mM Tris-HCl, pH 7.5, 75 mM NaCl) in black flat bottom 384-well microplates (Corning, Inc., New York, NY) The FP reaction employed 100 nM of purified CAIX (R&D systems, Minneapolis, MN) and 80 nM FITC-labeled **8** (Wichert, et al., 2015) within the assay buffer. The FP values were measured as mP units using the Victor3 multi-label plate reader equipped with excitation (485 nm) and emission (535 nm) filters (Perkin Elmer, Waltham, MA). 100 nM CAIX was incubated with serially diluted (from 1 μM to 61 fM) concentrations of the three targeting molecules, **2**, **XYIMSR-01**, and [$^{113/115}$In]**XYIMSR-01** for 30 min at room temperature in 384-well plates. 80 nM **8** was added to each well and the reaction was

incubated for 30 min at room temperature followed by FP measurement. Experiments were carried out in triplicate and the concentration resulting in 50% response (IC_{50}) was calculated in GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using the sigmoidal dose-response regression function.

*Competitive Fluorescence Polarization Assay for [$Al^{19}F$]**XYIMSR-04**, [$^{63/65}Cu$]**XYIMSR-06**, and [^{175}Lu]**XYIMSR-01***. Fluorescence polarization (FP) experiments were performed in 21 µL of the assay buffer (12.5 mM Tris-HCl, pH 7.5, 75 mM NaCl) in transparent flat bottom 384 well Small Volume™ LoBase Microplates (Greiner Bio-One, Frickenhausen Germany). The FP reaction employed 100 nM of purified CAIX (R&D systems, Minneapolis, MN) and 80 nM FITC-labeled ligand within the assay buffer. The FP values were measured as mP units using the Safire2™ plate reader (Tecan, Morrisville, NC) with excitation at 475 nm and emission at 532 nm emission. 100 nM CAIX was incubated with serially diluted (from 8 µM to 488.2 fM) concentrations of the three targeting molecules, [$Al^{19}F$]**XYIMSR-04**, [$^{63/65}Cu$]**XYIMSR-06** and [^{175}Lu]**XYIMSR-01** for 30 min at room temperature in 384 well plates. 80 nM FITC-labeled ligand was added to each well and the reaction was incubated for 30 min at room temperature followed by FP measurements. Experiments were carried out in triplicate and the concentration resulting in 50% response (IC_{50}) was calculated in GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using the sigmoidal dose-response regression function.

*SPECT/CT imaging of [^{111}In]**XYIMSR-01***. Mice harboring subcutaneous SK-RC-52 tumors with the lower left flank were injected with 14.8 MBq (400 µCi) of [^{111}In]**XYIMSR-01** in 250 µL of PBS (pH = 7.0) intravenously (tail vein). Anesthesia was then induced with 3% isofluorane and maintained at 2% isoflurane. Physiologic temperature was maintained with an external light source while the mouse was on the gantry. Imaging employed a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA). SPECT data were acquired in 64 projections at 65 s per projection using medium energy pinhole collimators. A CT scan was performed in 512 projections at the end of each SPECT scan for anatomic co-registration. CT and SPECT scans were performed at 1, 4, 8, 24, and 48 h post-injection of [^{111}In]**XYIMSR-01**. Imaging data sets were reconstructed using the manufacturer's software. Display of images utilized Amide software (Dice Holdings, Inc. NY).

*SPECT/CT imaging of [^{177}Lu]**XYIMSR-01***. Mice were injected with 1.7 mCi of **[^{177}Lu]XYIMSR-01** in 250uL of PBS (pH7.0) intravenously, anesthetized under

3% isofluorane prior to being placed on the scanner bed and kept warm with an external light source while being scanned. Isofluorane levels were decreased to 1% throughout the scanning process in order to ensure mouse survival. Imaging of mice was then carried out using a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA). A CT scan was performed at the end of each SPECT scan for anatomical co-registration. CT and SPECT scans were performed at 1, 4, 8, 24, and 48 hrs post injection of the **[^{177}Lu]XYIMSR-01**. Obtained data sets were subsequently reconstructed using the provided Gamma Medica-Ideas software. Final data visualization and image generation was accomplished using Amide software (Dice Holdings, Inc. NY).

*PET/CT imaging of [Al^{18}F]**XYIMSR-04***. Mice harboring subcutaneous SK-RC-52 tumors with the lower left flank were injected with 7.4 MBq (200 μCi) of [Al^{18}F]**XYIMSR-04** in 250 μL of PBS (pH = 7.0) intravenously (tail vein). Anesthesia was then induced with 3% isofluorane and maintained at 2% isoflurane. Physiologic temperature was maintained with an external light source while the mouse was on the gantry. Imaging employed a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA). Whole body 2-bed PET scan was performed using ARGUS small-animal PET/CT scanner (Sedecal, Madrid, Spain) at 250-700 keV energy window. PET acquisition times were: 5 min/bed (1 h) post-injection of [Al^{18}F]**XYIMSR-04**. PET images were co-registered with the corresponding 360-slice CT images. Imaging datasets were reconstructed using the 3D-FORE/2D-OSEM iterative algorithm with 2 iterations and 16 subsets, using the manufacturer's software. Display of images utilized Amide software (Dice Holdings, Inc. NY).

*PET/CT imaging of [^{64}Cu]**XYIMSR-06***. Mice harboring subcutaneous SK-RC-52 tumors within the upper right flank were injected intravenously (tail vein) with 22.2 MBq (600 μCi) of [^{64}Cu]**XYIMSR-06** in 250 μL of PBS (pH = 7.0). Anesthesia was then induced with 3% isoflurane and maintained with 2% isoflurane. Physiologic temperature was maintained with an external light source while the mouse was on the gantry. Whole body, 2-bed PET/CT imaging was performed using the SuperArgus small animal PET/CT scanner (Sedecal, Madrid, Spain), CT employing a 250-700 keV energy window. PET acquisition times were: 5 min/bed position (1 h post-injection of [^{64}Cu]**XYIMSR-06**); 10 min/bed position (4 and 8 h) and 20 min/bed position (24 h). PET images were co-registered with the corresponding 360-slice CT images. Imaging datasets were reconstructed using the 3D-FORE/2D-OSEM iterative

ITM Exhibit 1004, Page 1382 of 1652

algorithm with 2 iterations and 16 subsets, using the manufacturer's software. Imaging data sets were reconstructed using the manufacturer's software. Display of images utilized the software package PMOD (v3.3, PMOD Technologies Ltd, Zurich, Switzerland).

*Biodistribution of [^{111}In]**XYIMSR-01** and [^{177}Lu]**XYIMSR-01***. Mice bearing SK-RC-52 xenografts at lower left flank were injected intravenously with 740 kBq (20 μCi) of [^{111}In]**XYIMSR-01**, or [^{177}Lu]**XYIMSR-01** in 200 μL of PBS. For competitive blocking, same tumor bearing mice were injected with 740 kBq (20 μCi) of [^{111}In]**XYIMSR-01** and 200 nmole of **8** in 200 μL of PBS. At 1 h, 4 h, 8 h, 24 h and 48 h post-injection, mice were sacrificed by cervical dislocation and the blood was immediately collected by cardiac puncture. Heart, lungs, pancreas, spleen, fat, brain, muscle, small intestines, liver, stomach, kidney, urinary bladder, and tumor were collected. Each organ was weighed and the tissue radioactivity was measured with an automated gamma counter (1282 Compugamma CS, Pharmacia/ LKBNuclear, Inc., Mt. Waverly, Vic. Australia). The percentage of injected dose per gram of tissue (% ID/g) was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for radioactive decay.

Data were expressed as mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, California) was used to determine statistical significance. Statistical significance was calculated using a paired t test. *P*-values < 0.0001 were considered significant.

*Biodistribution of [Al^{18}F]**XYIMSR-04***. Mice bearing SK-RC-52 xenografts within the lower left flank were injected intravenously with 740 kBq (20 μCi) of [Al^{18}F]**XYIMSR-04** in 200 μL of PBS. At specific 1 hour time point mentioned in the paper, mice (n = 5) were sacrificed by cervical dislocation and the blood was immediately collected by cardiac puncture. Heart, lungs, pancreas, spleen, fat, brain, muscle, small intestines, liver, bone, stomach, kidney, urinary bladder, and tumor were collected. Each organ was weighed and the tissue radioactivity was measured with an automated gamma counter (1282 Compugamma CS, Pharmacia/ LKBNuclear, Inc., Mt. Waverly, Vic. Australia). The percentage of injected dose per gram of tissue (% ID/g) was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for radioactive decay. Data were expressed as mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, California) was used to determine statistical significance. Statistical

significance was calculated using a paired t test. *P*-values < 0.0001 were considered significant.

*Biodistribution of [^{64}Cu]**XYIMSR-06***. Mice bearing SK-RC-52 xenografts within the upper right flank were injected intravenously with 740 kBq (20 μCi) of [^{64}Cu]**XYIMSR-06** in 200 μL of PBS. For *in vivo* competition (binding specificity) studies, tumor-bearing mice were injected with 740 kBq (20 μCi) of [^{64}Cu]**XYIMSR-06** and 200 nmole of **8** in 200 μL of PBS concurrently. At specific times after injection (1 h, 4 h, 8 h and 24 h), mice (n = 5) were sacrificed by cervical dislocation with blood immediately collected by cardiac puncture. Heart, lungs, pancreas, spleen, fat, brain, muscle, small intestines, liver, stomach, kidney, urinary bladder, and tumor were also collected. Each organ was weighed and the tissue radioactivity was measured with an automated gamma counter (1282 Compugamma CS, Pharmacia/ LKBNuclear, Inc., Mt. Waverly, Vic. Australia). The percentage of injected dose per gram of tissue (%ID/g) was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for radioactive decay. Data were expressed as mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, California) was used to determine statistical significance. Statistical significance was calculated using a paired t test. *P*-values < 0.0001 were considered significant.

*Radio-therapy of [^{177}Lu]**XYIMSR-01***. Mice bearing SK-RC-52 xenografts at lower left flank were injected intravenously with PBS, 11.1 MBq (300 μCi) and 18.5 MBq (500 μCi) of [^{177}Lu]**XYIMSR-01** in 200 μL of PBS (n=4). Size of the tumors was measured twice a week after the injection. Delays in tumor growth were observed from mice injected with [^{177}Lu]**XYIMSR-01** in compared with control non-treated mice. The *P*-values were 0.042 and 0.031 for the 11.1 and 18/5 MBq doses, respectively.

EXAMPLE 3

Results

Chemical synthesis of **XYIMSR-01**, **XYIMSR-04**, and **XYIMSR-06** were achieved as in FIG. 5, FIG. 6, FIG.12 and FIG.15 respectively. Following a reported procedure, key intermediate **3** was obtained *via* solid support synthetic methods (Wichert et al., 2015). **XYIMSR-01** has been generated by conjugating the commercially available DOTA-NHS ester with **3** in 82 % yield. In(III) was

incorporated into DOTA in nearly quantitative yield in 0.2 M NaOAc buffer at 60°C, providing the non-radiolabeled standard, [$^{113/115}$In]**XYIMSR-01** (FIG. 7). After optimization, baseline separation between **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** could be achieved by high performance liquid chromatography (HPLC). Lu(III) was incorporated into DOTA in excellent yield in 0.2 M NaOAc buffer at 60 °C, providing the non-radiolabeled standard, [^{175}Lu]**XYIMSR-01** (FIG. 9). After optimization, baseline separation between **XYIMSR-01** and [^{175}Lu]**XYIMSR-01** could be achieved by high performance liquid chromatography (HPLC). **XYIMSR-04** has been generated by conjugating the commercially available NOTA-NHS ester with **3** in 52 % yield. Al(III) was incorporated into NOTA in fair yield in 0.2 M NaOAc buffer at 60°C, providing the non-radiolabeled standard, [Al^{19}F]**XYIMSR-04** (FIG. 13). After optimization, baseline separation between **XYIMSR-04** and [Al^{19}F]**XYIMSR-04** could be achieved by high performance liquid chromatography (HPLC). **XYIMSR-06** has been generated by conjugating the commercially available p-SCN-Bn-NOTA with **3** in 83 % yield. Cu(II) was incorporated into Bn-NOTA in fair yield in 0.2 M NaOAc buffer at 60°C, providing the non-radiolabeled standard, [$^{63/65}$Cu]**XYIMSR-06** (FIG. 16). After optimization, baseline separation between **XYIMSR-06** and [$^{63/65}$Cu]**XYIMSR-06** could be achieved by high performance liquid chromatography (HPLC).

Fluorescein isothiocyanate (FITC)-labeled **8**, as shown on FIG. 2A, has been synthesized as a standard to measure CAIX binding affinities of the corresponding radiotracers. Compound **8** bound specifically to CAIX-expressing SK-RC-52 cells, but not to CAIX-negative BxPC3 cells (FIG. 2B and FIG. 2C) (Rana et al., 2012; Wichert et al., 2015). In order to test the relative binding of **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** to CAIX a competitive fluorescence polarization assay (Alquicer et al., 2012) for use with **8** has been modified. For the competitive binding assay, after optimization for background fluorescence, concentrations of 80 nM and 100 nM have been chosen for **8** and CAIX, respectively. As a positive control, non-fluorescent **3** has been employed, which has a reported K_d value of 2.6 nM (Wichert et al., 2015). Increasing concentrations of **3**, **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** were incubated with CAIX for 30 min at room temperature. After **8** was added, fluorescence polarization signal was recorded. The IC_{50} values determined for **3**, **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** were 75.9, 67.0, and 108.2 nM, respectively (FIG. 3A, FIG. 3B, and FIG. 3C). Using a similar method, the IC_{50} value determined

ITM Exhibit 1004, Page 1385 of 1652

for **3**, [$^{63/65}$Cu]**XYIMSR-06,** [Al^{19}F]**XYIMSR-04**, and [^{175}Lu]**XYIMSR-01** were 63.6 ± 2.8, 156.5 ± 4.3 nM, 96.7±3.3 nM, and 122.4 ± 3.8 nM (FIG. 4A, FIG. 4B, FIG. 4C and FIG. 3D). These findings suggest that the DOTA/NOTA-modified adducts were capable of binding CAIX with high affinity, on the order of positive control **3**.

The capacity for [^{111}In]**XYIMSR-01,** [^{177}Lu]**XYIMSR-01**], [Al^{18}F] **XYIMSR-04**, and [^{64}Cu]**XYIMSR-06**, to detect CAIX-expressing tumors *in vivo* using PET or SPECT imaging was further investigated. The synthesis and purification of [^{111}In]**XYIMSR-01** were achieved within 1.5 h in yield of 73.8-75.8% (n = 3) and with specific radioactivities of 118.4 – 1021.2 GBq/μM (3,200 -27,600 Ci/mmol). The synthesis and purification of [^{177}Lu]**XYIMSR-01** was achieved within 1.5 h in yield of 69.0% with specific radioactivity of 2,340 Ci/mmol; 73.0% with specific radioactivity of 2239 Ci/mmol, and in average yield of 60% (n=12), with average specific activity of 1,900 Ci/mmol (ranging from 1,200 Ci/mmol to 2,500 Ci/mmol). The synthesis and purification of [Al^{18}F]**XYIMSR-04,** were achieved within 1.5 h in yield of 4.3% (n = 3) and with specific radioactivity of 2.1 – 3.4 GBq/μM (57-92 Ci/mmol).The synthesis and purification of [^{64}Cu]**XYIMSR-06,** were achieved within 1.5 h in yield of 51.0 ± 4.5% (n=5) and with specific radioactivities of 4.1 – 8.9 GBq/μM (110-240 Ci/mmol).

*SPECT/CT imaging of [^{111}In]**XYIMSR-01***. [^{111}In]**XYIMSR-01** was administered intravenously to two mice with SK-RC-52 flank tumors, followed by SPECT/CT. As shown in FIG. 17, radiotracer uptake was observed within the tumors at 1 h post-injection. By 24 h post-injection, nearly all the radioactivity in the kidneys and other organs had been eliminated, with tumor still retaining significant amounts of radiotracer. Image contrast improved even further by 48 h post-injection.

*SPECT/CT imaging of [^{177}Lu]**XYIMSR-01***. [^{177}Lu]**XYIMSR-01**was administered intravenously to mice with SK-RC-52 flank tumors, followed by SPECT/CT. [^{177}Lu]**XYIMSR-01** exhibited CAIX specific uptake in vitro. As shown in FIG. 18, SPECT/CT imaging demonstrated tumor visualization by 1 h post-injection and achieved high signal contrast by 24 h.

*PET/CT imaging of [Al^{18}F]**XYIMSR-04***. [Al^{18}F]**XYIMSR-04**was administered intravenously to mice with SK-RC-52 flank tumors, followed by PET/CT. As shown in FIG 19, PET/CT imaging demonstrated tumor visualization by 1 h post-injection.

*PET/CT imaging of [^{64}Cu]**XYIMSR-06***. As shown in FIG. 20, the imaging findings closely matched the results of the biodistribution study (Table 3). At 1 h, tumor could be observed distinctly with additional visible signal in the kidneys and urinary bladder. Relatively selective tumor imaging could be achieved at 8 h with target selectivity continuing to improve by 24 h, with the SK-RC-52 ccRCC tumor xenografts as the only remaining visible radiotracer-avid structures. There was no significant background signal from blood or muscle. The liver did not retain significant radioactivity at any time.

*Biodistribution of [^{111}In]**XYIMSR-01***. Table 2 shows the biodistribution of [^{111}In]**XYIMSR-01** at 1 h, 4 h, 8h, 24 h and 48 h post-injection; results are expressed as the percentage injected dose per gram (% ID/g) of tissue, n = 5; block was done by simultaneously injecting 200 nmole of non-labeled **1** with **[^{111}In]XYIMSR-01**. Biodistribution confirmed tumor-selective uptake and retention of [^{111}In]**XYIMSR-01** observed in imaging studies (Table 2). At 1 h post-injection, 26.0% ID/g of radiotracer uptake was observed within the tumor. Tumor/blood, and tumor/muscle ratios reached 19.7 and 12.7, respectively. Major non-specific organ uptake was observed in kidney, lung, stomach, small intestine and liver (Table 2).

Biodistribution studies conducted at later time points showed that the radiotracer continued to wash out from those organs while being retained within the tumor. At 24 h post-injection, tumor/blood and tumor/muscle ratios reached 178 and 68, respectively. Importantly, tumor/kidney ratio reached 1.7, suggesting that it might be possible to detect local ccRCC in the kidney at 24 h. The enhanced hydrophilicity of [^{111}In]**XYIMSR-01,** relative to the reported optical analog (Wichert et al., 2015), may have contributed to the low liver uptake. Tumor/liver ratio for [^{111}In]**XYIMSR-01** and optical agent were 8.5 and 4.0 at 24 h, respectively (Wichert et al., 2015). All other organs showed tumor/organ ratio close to or higher than 10, indicating that good image contrast can be expected from these imaging agents. Biodistribution of [^{111}In]**XYIMSR-01** simultaneously injected with non-radioactive competitor **8** at 24h and 48h post injection showed competitive inhibition of the uptake to tumors to 1% level (Table 2). The fast normal tissue clearance and the long lasting tumor retention may enable applications to radiopharmaceutical therapy with appropriately selected therapeutic radiometals.

ITM Exhibit 1004, Page 1387 of 1652

Table 2. Biodistribution of [^{111}In]**XYIMSR-01** at 1 h, 4 h, 8h, 24 h and 48 h post-injection

Organs	**1hr**	**4hr**	**8hr**	**24hr**	**24hr +Block**	**48hr**	**48hr +Block**
Blood	1.34 ±0.17	0.65 ±0.06	0.48 ±0.02	0.15 ±0.02	0.03 ±0.00	0.06 ±0.02	0.03 ±0.00
Heart	5.98 ±0.53	2.91 ±0.45	2.61 ±0.35	1.16 ±0.20	0.04 ±0.01	0.84 ±0.16	0.04 ±0.01
Lung	45.85 ±19.89	17.85 ±3.55	17.39 ±8.99	11.01 ±3.71	0.12 ±0.02	9.22 ±1.25	0.09 ±0.02
Pancreas	3.81 ±0.72	1.54 ±0.40	1.61 ±0.28	0.69 ±0.18	0.03 ±0.00	0.59 ±0.18	0.03 ±0.01
Spleen	0.52 ±0.04	0.51 ±0.08	0.64 ±0.07	0.69 ±0.39	0.08 ±0.01	0.67 ±0.13	0.11 ±0.03
Fat	1.03 ±0.24	0.42 ±0.22	0.45 ±0.08	0.28 ±0.19	0.02 ±0.01	0.25 ±0.08	0.03 ±0.01
Brain	1.23 ±1.10	0.45 ±0.06	0.59 ±0.09	0.71 ±0.85	0.03 ±0.00	0.41 ±0.05	0.03 ±0.01
Muscle	2.34 ±2.19	1.01 ±0.28	1.09 ±0.15	0.35 ±0.12	0.02 ±0.00	0.39 ±0.28	0.02 ±0.00
Small intestine	9.37 ±1.26	4.27 ±0.69	4.31 ±0.67	2.11 ±0.33	0.08 ±0.01	1.22 ±0.44	0.08 ±0.02
Liver	8.36 ±0.73	4.00 ±0.8	3.65 ±0.65	3.02 ±3.46	0.10 ±0.02	1.65 ±0.26	0.13 ±0.04
Stomach	16.71 ±2.46	7.91 ±1.28	8.74 ±1.26	3.31 ±1.25	0.14 ±0.02	1.82 ±0.43	0.14 ±0.03
Kidney	71.26 ±8.74	41.52 ±6.07	28.79 ±21.35	15.29 ±1.69	0.68 ±0.14	8.78 ±1.89	0.45 ±0.09
Bladder	4.90 ±4.96	2.68 ±1.89	2.28 ±0.51	0.74 ±0.17	0.20 ±0.07	0.38 ±0.18	0.14 ±0.03
Tumor	26.01 ±5.74	20.83 ±6.25	34.00 ±15.16	25.62 ±17.67	1.41 ±0.20	13.92 ±6.67	1.22 ±0.54
Tumor/ Blood	19.7 ±4.8	31.9 ±9.4	77.0 ±32.5	178.1 ±145.4	45.2 ±9.7	212.0 ±41.4	45.4 ±13.8
Tumor/ Muscle	12.7 ±5.8	21.4 ±7.2	34.2 ±16.0	68.4 ±29.0	91.4 ±11.1	52.0 ±21.0	75.1 ±17.7
Tumor/ Kidney	0.36 ±0.06	0.50 ±0.15	3.1 ±3.1	1.7 ±1.2	2.1 ±0.3	1.5 ±0.5	2.7 ±0.8

*Biodistribution of [^{177}Lu]**XYIMSR-01***. Biodistribution studies confirmed the SPECT/CT data. Tumor-to-blood, muscle, and kidney ratios were 607.4 ± 200.7, 128.4 ± 25.4 and 4.5 ± 1.4, respectively, at 24 h post-injection.

Table 3. Biodistribution of [^{177}Lu]**XYIMSR-01**

Organs	**1hr**	**4hr**	**8hr**	**24hr**	**24hr +Block**	**48hr**	**48hr +Block**
Blood	0.55 ±0.06	0.18 ±0.02	0.16 ±0.05	0.02 ±0.01	0.04 ±0.02	0.04 ±0.01	0.04 ±0.07

Heart	3.59 ±0.73	1.52 ±0.54	1.49 ±0.59	0.28 ±0.14	0.08 ±0.04	0.12 ±0.17	0.04 ±0.01
Lung	23.72 ±6.49	10.35 ±1.86	8.87 ±3.30	1.48 ±0.59	0.73 ±0.58	0.90 ±0.05	0.18 ±0.05
Pancreas	2.03 ±0.25	0.99 ±0.19	1.03 ±0.50	0.16 ±0.07	0.05 ±0.03	0.06 ±0.01	0.02 ±0.00
Spleen	0.29 ±0.07	0.15 ±0.03	0.29 ±0.05	0.20 ±0.07	0.38 ±0.32	0.13 ±0.04	0.15 ±0.06
Fat	1.07 ±0.58	0.56 ±0.14	0.46 ±0.17	0.05 ±0.04	0.03 ±0.03	0.03 ±0.01	0.02 ±0.01
Brain	0.49 ±0.08	0.33 ±0.04	0.44 ±0.08	0.28 ±0.10	0.04 ±0.01	0.17 ±0.03	0.02 ±0.00
Muscle (mm)	1.42 ±0.40	0.65 ±0.19	0.47 ±0.18	0.10 ±0.05	0.03 ±0.01	0.04 ±0.01	0.01 ±0.00
Sm. intestine	6.11 ±0.68	2.64 ±0.17	3.67 ±0.93	0.96 ±0.32	0.18 ±0.07	0.20 ±0.05	0.05 ±0.01
Liver	4.15 ±0.39	1.79 ±0.44	1.87 ±0.77	0.47 ±0.21	0.46 ±0.34	0.19 ±0.03	0.23 ±0.04
Stomach	12.20 ±1.66	6.06 ±1.57	6.15 ±2.65	1.02 ±0.56	0.21 ±0.07	0.35 ±0.04	0.09 ±0.02
Kidney (kid)	40.77 ±6.68	19.17 ±2.82	18.99 ±6.14	3.11 ±1.59	1.54 ±1.44	0.76 ±0.11	0.39 ±0.05
Bladder	26.55 ±11.08	6.60 ±3.66	6.00 ±3.52	1.29 ±1.10	0.73 ±0.55	0.20 ±0.01	0.28 ±0.09
Tumor	26.91 ±6.06	26.28 ±4.25	27.48 ±4.32	12.51 ±3.02	1.70 ±0.79	5.82 ±2.14	0.65 ±0.10
Tumor/ Blood	47.9 ±13.4	150.3 ±34.6	178.6 ±36.6	607.4 ±200.7	42.0 ±20.9	200.2 ±101.7	42.7 ±23.7
Tumor/mm	18.8 ±5.0	43.7 ±16.8	65.0 ±19.0	128.4 ±25.4	58.6 ±25.3	141.5 ±71.7	62.5 ±34.5
Tumor/kid	0.6 ±0.2	1.4 ±0.4	1.5 ±0.3	4.5 ±1.4	1.4 ±0.6	7.1 ±1.8	1.7 ±0.3

*Biodistribution of [Al^{18}F]**XYIMSR-04***. The biodistribution data at 1 h is shown in Table 4. The tumor uptake is 14.40%ID/g, with tumor-to –blood, -muscle and –kidney of 22.1, 9.74 and 0.28.

Table 4. Biodistribution of [Al^{18}F]**XYIMSR-04**

Organs	**1 h (%ID/g)**
Blood	0.65 ± 0.11
Heart	5.03 ± 0.51
Lung	34.07 ± 5.85
Pancreas	3.47 ± 0.16
Spleen	0.54 ± 0.18
Fat	1.54 ± 0.25
Brain	0.66 ± 0.04
Muscle (mm)	1.74 ± 0.58
Sm. intestine	9.59 ± 1.04

Liver	5.55 ± 0.91
Stomach	21.62 ± 1.85
Kidney (kid)	50.84 ± 2.65
Bladder	20.12 ± 12.51
Bone	1.91 ± 1.39
Tumor	14.40±2.18
Tumor/Blood	22.1 ± 1.5
Tumor/mm	9.74 ± 2.9
Tumor/kid	0.28 ± 0.03

*Biodistribution of [^{64}Cu]**XYIMSR-06***. Table 5 shows the radiotracer uptake in selected organs. Radiotracer uptake within tumor was 14.5 %ID/g at 1 h with tumor-to-blood and muscle ratios >10. After the radiotracer reached a maximum of 19.3 %ID/g in tumor at 4 h, it began to wash out from tumors slowly. By 24 h radioactivity within the tumors dropped to 6.2 %ID/g. Compared with [^{111}In]**XYIMSR-01** (20.8 %ID/g at 4 h, 34.0 %ID/g at 8 h, 25.6 %ID/g at 24h and 13.9%ID/g at 48 h)[33], [^{64}Cu]**XYIMSR-06** demonstrated faster clearance, likely due to the more hydrophilic nature of NOTA-Cu(II), which has an additional non-coordinated free carboxylate not present for DOTA-In(III). At 8 h post-injection tumor signal was predominant, with kidney, lung and stomach as the only readily visible organs. Tumor-to-blood, muscle and kidney ratios were 129.6 ± 18.8, 84.3 ± 21.0 and 2.1 ± 0.26, respectively. In principle those ratios would allow the detection of localized tumor in kidney. At 24 h, tumor-to-kidney and -lung ratios were further improved to 7.1 and 4.9, with all other tumor-to-organ ratios tested ≥ 10.0. Co-injection of 200 nmole of **8** along with [^{64}Cu]**XYIMSR-06** blocked tumor uptake of the latter (Table 3) indicating specific, CAIX-mediated binding of this radiotracer. Within 24 h, no significant radiotracer uptake within liver was observed, indicative of the *in vivo* stability of NOTA-^{64}Cu chelation.

Table 5. Biodistribution of [^{64}Cu]**XYIMSR-06**

Organs	**1h**	**4h**	**8h**	**8h +block**	**24h**	**24h +block**
Blood	0.66 ±0.05	0.33 ±0.06	0.13 ±0.02	0.08 ±0.01	0.00 ±0.06	0.01 ±0.08
Heart	3.41 ±0.79	1.78 ±0.33	0.65 ±0.10	0.16 ±0.03	0.12 ±0.03	0.08 ±0.01
Lung	25.52 ±3.35	12.03 ±1.61	4.64 ±0.58	0.77 ±0.14	1.27 ±0.38	0.29 ±0.05
Pancreas	2.94 ±0.24	1.36 ±0.19	0.47 ±0.21	0.14 ±0.03	0.21 ±0.29	0.07 ±0.02

Spleen	0.36 ±0.08	0.24 ±0.04	0.18 ±0.02	0.14 ±0.02	0.09 ±0.01	0.11 ±0.04
Fat	0.80 ±0.17	0.52 ±0.29	0.28 ±0.27	0.05 ±0.01	0.03 ±0.01	0.01 ±0.01
Brain	1.46 ±2.23	0.29 ±0.06	0.24 ±0.06	0.04 ±0.01	0.13 ±0.02	0.02 ±0.01
Muscle (mm)	1.28 ±0.27	0.70 ±0.18	0.21 ±0.05	0.05 ±0.02	0.02 ±0.01	0.04 ±0.06
Sm. intestine	7.35 ±0.78	4.15 ±0.69	1.98 ±0.14	0.38 ±0.06	0.47 ±0.03	0.19 ±0.05
Liver	3.25 ±0.97	2.18 ±0.57	0.99 ±0.22	0.55 ±0.08	0.38 ±0.03	0.42 ±0.04
Stomach	14.80 ±2.27	8.19 ±0.97	4.02 ±0.53	0.69 ±0.18	0.65 ±0.04	0.29 ±0.04
Kidney (kid)	33.65 ±3.91	19.99 ±2.88	8.14 ±1.15	1.82 ±0.39	0.90 ±0.12	0.48 ±0.09
Bladder	11.12 ±6.33	17.05 ±8.86	7.43 ±7.72	1.45 ±1.53	0.34 ±0.09	0.45 ±0.50
Tumor	14.47 ±2.69	19.31 ±4.51	16.74 ±1.58	2.39 ±0.24	6.23 ±1.41	1.20 ±0.47
Tumor/ Blood	21.9 ±4.6	57.7 ±9.3	129.6 ±18.8	32.0 ±3.8	142.6 ±115.8	27.1 ±26.7
Tumor/mm	10.8 ±3.7	29.4 ±9.9	84.3 ±21.0	53.0 ±12.6	261.3 ±47.3	49.0 ±28.7
Tumor/kid	0.4 ±0.1	1.0 ±0.1	2.1 ±0.26	1.3 ±10.2	7.1 ±2.5	2.4 ±0.4

*Radio-therapy of [^{177}Lu]**XYIMSR-01***. Delays in tumor growth were observed from mice injected with [^{177}Lu]**XYIMSR-01** in compared with control non-treated mice. The *P*-values were 0.042 and 0.031 for the 11.1 and 18/5 MBq doses, respectively.

EXAMPLE 4

Discussion

Recently, Wichert and co-workers (Wichert et al., 2015) identified 4,4-bis(4-hydroxyphenyl)valeric acid/acetazolamide as a dual-motif CAIX inhibitor, from a DNA-encoded chemical library(Krall et al., 2013; Franzini et al., 2014; Brenner and Lerner, 1992; Dower et al., 1993). The addition of a second binding motif significantly improved the potency of sulfonamide inhibitors (up to 40 times) (Wichert et al., 2015), while also suggesting a solution to the problem of generating an isoform-selective CAIX inhibitor caused by conserved structures at the active site. It has been hypothesized that the slow renal clearance and high liver uptake of the reported optical agent might derive from the hydrophobicity of the molecule. To

ITM Exhibit 1004, Page 1391 of 1652

improve the pharmacokinetics, the IRDye®750 portion of the molecule has been replaced with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), a more hydrophilic species that also enables convenient radiolabeling with metal isotopes for positron emission tomography (PET), single photon emission computed tomography (SPECT), and radiopharmaceutical therapy (Wadas et al., 2010; Cutler et al., 2013). Indium-111 has been chosen as the initial radionuclide for its relatively long half-life (2.8 day) to enable extended monitoring of pharmacokinetics.

Despite intensive effort expended in the development of CAIX inhibitors designed to engage only the active site, nuclear imaging analogs continued to demonstrate limited success, showing < 2% ID/g within tumor and high radiotracer uptake within kidney and liver (Pan et al., 2014; Akurathi et al., 2010; Lu et al., 2013; Doss et al., 2014; Peeters et al., 2015). Peptides that bind to the surface of CAIX may provide an alternative solution to selective targeting, but they are limited by low potency and *in vivo* stability (Rana et al., 2012). Dual-motif ligands that may concurrently engage the CAIX active site and surface binding demonstrated high potency and tumor uptake for [^{111}In]**XYIMSR-01,** [^{177}Lu]**XYIMSR-01**, [Al^{18}F]**XYIMSR-04**, and [^{64}Cu]**XYIMSR-06**, and for the previously reported optical agent (Wichert et al., 2015). The hydrophilicity of these compounds, with multiple carboxylates and heteroatoms, improved non-targeted organ clearance, including that from kidney and liver.

In summary, highly potent and selective low-molecular-weight (LMW) ligands of carbonic anhydrase IX (CAIX) with a dual-targeting moiety were conjugated with metal chelators, metal complexes and fluorine prosthetic groups, enabling radio-labeling with a wide array of PET, SPECT and radiotherapeutic isotopes. As examples, a ^{111}In labeled ligand ([^{111}In]**XYIMSR-01**) a ^{177}Lu labeled ligand ([^{177}Lu]**XYIMSR-01**), a ^{18}F labeled ligand ([Al^{18}F]**XYIMSR-04**), and a ^{64}Cu labeled ligand ([^{64}Cu]**XYIMSR-06**), were successfully synthesized in high yield and purity. These compounds were then injected into mice bearing CA IX+ tumors (SK-RC-52) and allowed for successful imaging with rapid uptake and minimum non-specific organ uptake. In addition, [^{111}In]**XYIMSR-01** showed long lasting tumor residence, and also demonstrates improved pharmacokinetics, with fast clearance from non-targeted tissues, including kidney. Further, PET imaging ligands, such as [^{64}Cu]**XYIMSR-06** and [Al^{18}F]**XYIMSR-04**, enabled detecting CAIX expressing tumor in higher sensitivity and resolution. Moreover, the structure modifications on

[^{64}Cu]**XYIMSR-06** and [^{177}Lu]**XYIMSR-01** enabled significant improvement on *in vivo* pharmacokinetics for both imaging and therapy applications. Finally, [^{177}Lu]**XYIMSR-01** showed significant therapeutic effect in controlling tumor growth.

Radioisotope labeled CA IX targeting agents stand to enable a wide range of imaging and therapeutic applications, including but not limited to renal cell carcinoma (RCC). Based on the structural similarity of the ligands synthesized, kinetic data of these ligands could help to predict the *in vivo* properties of other PET/SPECT/radiotherapeutic isotope labeled ligands. These analogs of [^{111}In]**XYIMSR-01,** [^{177}Lu]**XYIMSR-01**, [Al^{18}F]**XYIMSR-04** and [^{64}Cu]**XYIMSR-06**, with other radiometals should allow for their use in other nuclear imaging modalities and targeted radiopharmaceutical therapy, including but not limited to renal cell carcinoma (RCC).

REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references are herein incorporated by reference to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art. In case of a conflict between the specification and any of the incorporated references, the specification (including any amendments thereof, which may be based on an incorporated reference), shall control. Standard art-accepted meanings of terms are used herein unless indicated otherwise. Standard abbreviations for various terms are used herein.

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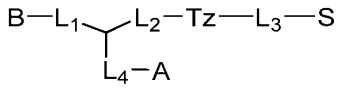
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Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims.

ITM Exhibit 1004, Page 1399 of 1652

THAT WHICH IS CLAIMED:

1. A compound of formula (I):



(I);

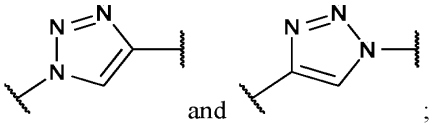
wherein:

B is a metal chelating moiety optionally comprising a metal or a radiometal, or a halogenated or radio-halogenated prosthetic group;

L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-;

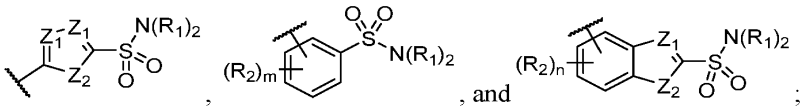
each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl;

Tz is a triazole group selected from the group consisting of



and ;

S is a sulfonamide selected from the group consisting of:



, , and ;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;

each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted

ITM Exhibit 1004, Page 1400 of 1652

heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

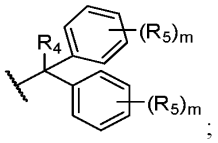
n is an integer selected from the group consisting of 1, 2, and 3;

each Z_1 is independently selected from the group consisting of CR_3, and N;

each Z_2 is independently selected from the group consisting of CR_3, and S;

each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

A is



;

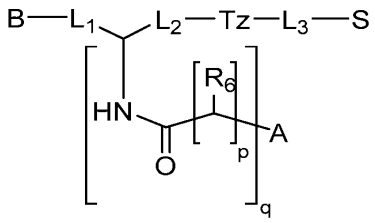
R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl;

R_5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound of formula (I) is a compound of formula (II):

ITM Exhibit 1004, Page 1401 of 1652



(II);

wherein:

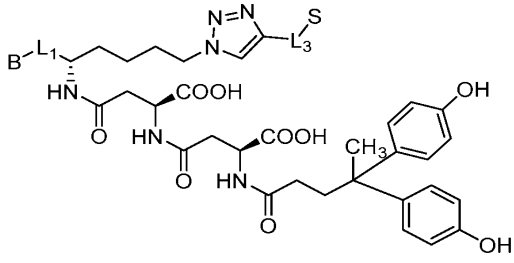
p is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

q is an integer selected from the group consisting of 1, 2, 3, and 4;

each R_6 is independently selected from the group consisting of H and –COOR;

or a pharmaceutically acceptable salt thereof.

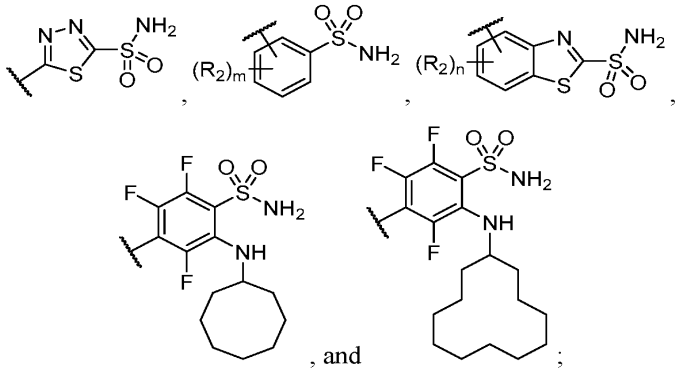
3. The compound of claim 2, wherein the compound of formula (II) is a compound of formula (III):



(III);

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein S is selected from the group consisting of:

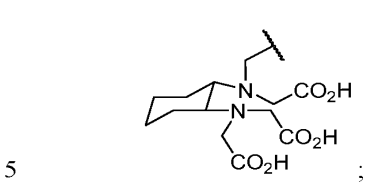
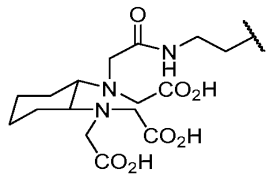
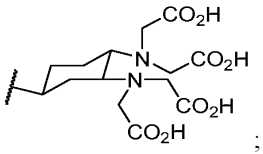
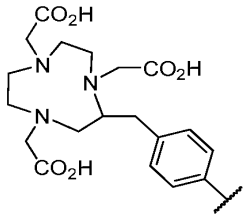
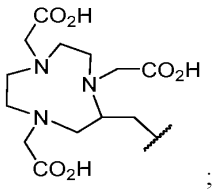
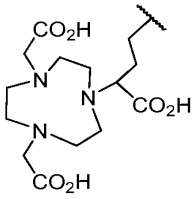
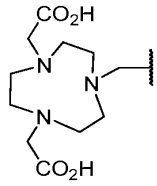
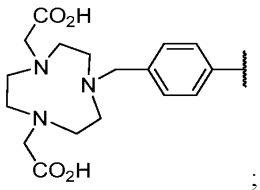
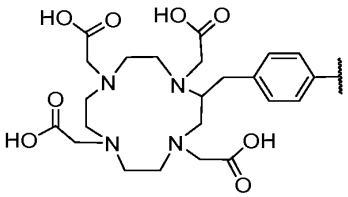
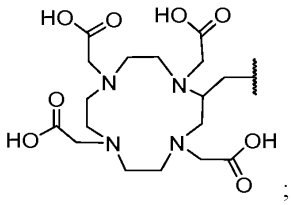
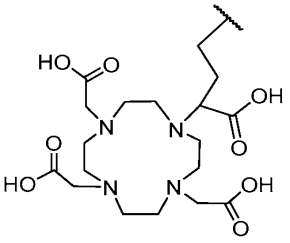
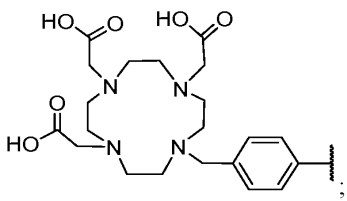
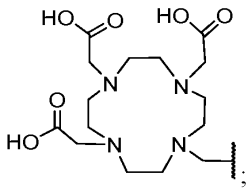
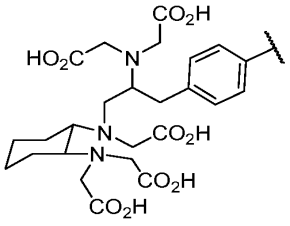
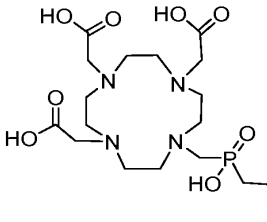
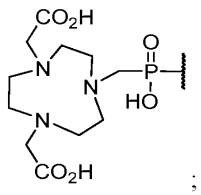


, and ;

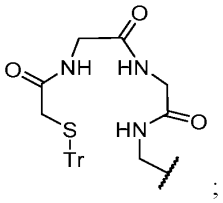
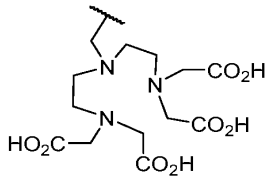
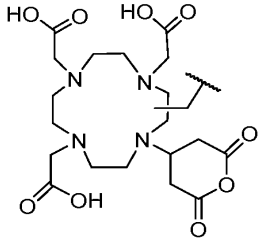
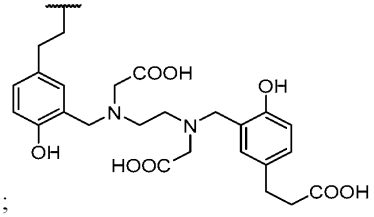
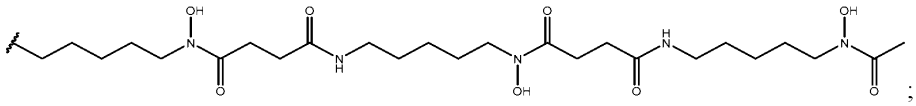
ITM Exhibit 1004, Page 1402 of 1652

or a pharmaceutically acceptable salt thereof.

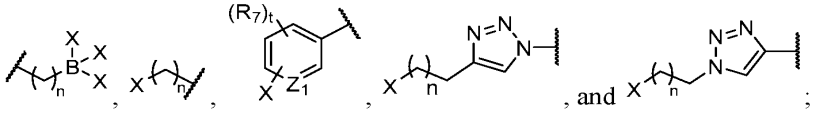
5. The compound of claim 1, wherein B is a metal chelating moiety optionally comprising a metal or a radiometal selected from the group of:


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;

ITM Exhibit 1004, Page 1403 of 1652


;

;

;

; and

;

or wherein B is a halogenated or radio-halogenated prosthetic group selected from the group consisting of:


, and ;

wherein:

X is a halogen or a radio-halogen;

n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6;

t is an integer selected from the group consisting of 1, 2, and 3;

each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

ITM Exhibit 1004, Page 1404 of 1652

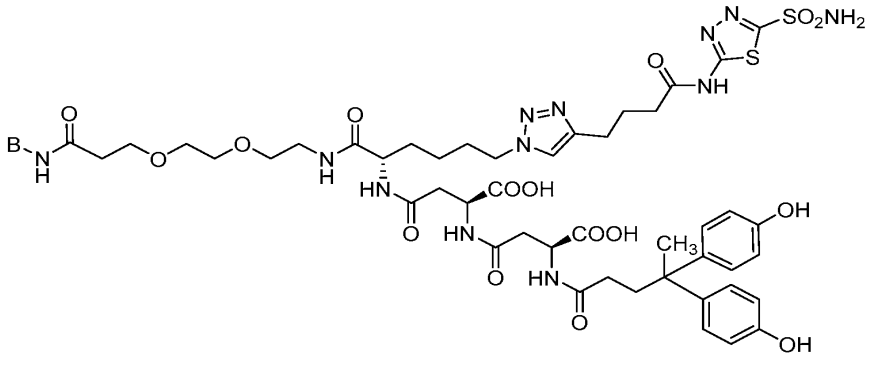
6. The compound of claim 5, wherein the metal chelating agent comprises a metal selected from the group consisting of: Y, Lu, Tc, Zr, In, Sm, Re, Cu, Pb, Ac, Bi, Al, Ga, Re, Ho and Sc.

7. The compound of claim 5, wherein the metal is a radiometal and is selected from the group consisting of: ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho.

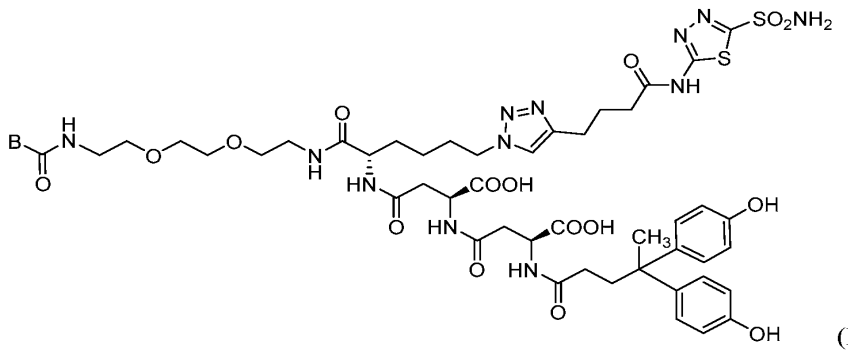
8. The compound of claim 5, wherein the halogen is selected from the group consisting of: F, Br, I, and At.

9. The compound of claim 5, wherein the radio-halogen is selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At.

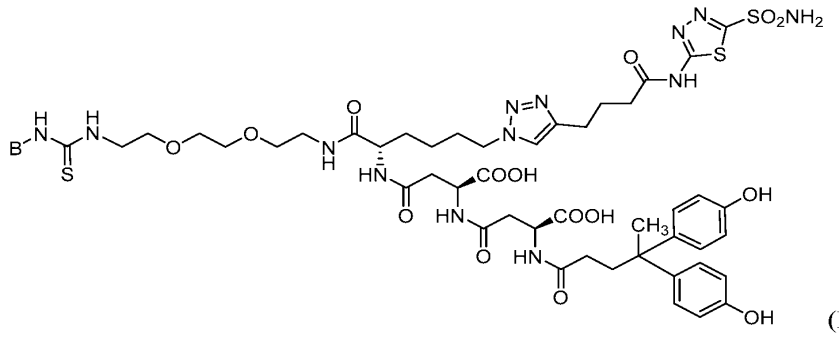
10. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



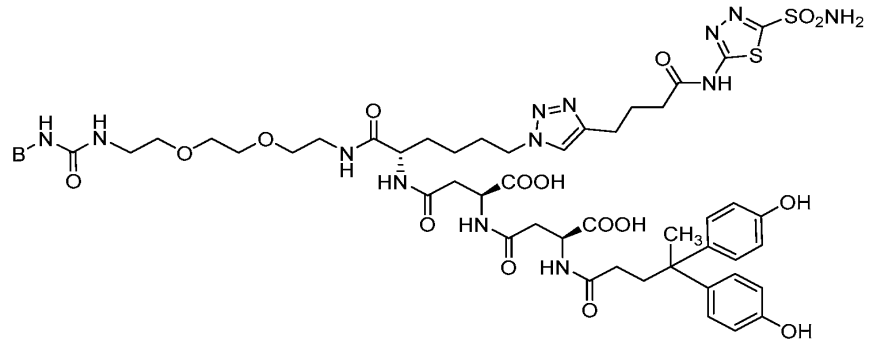
(IVa);



(IVb);



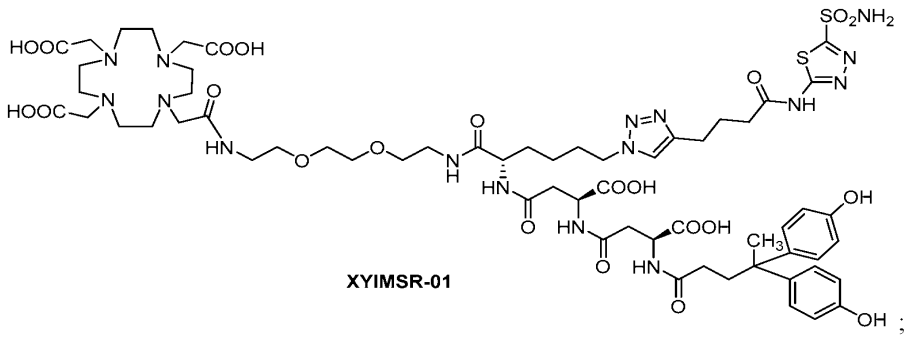
(IVc); and



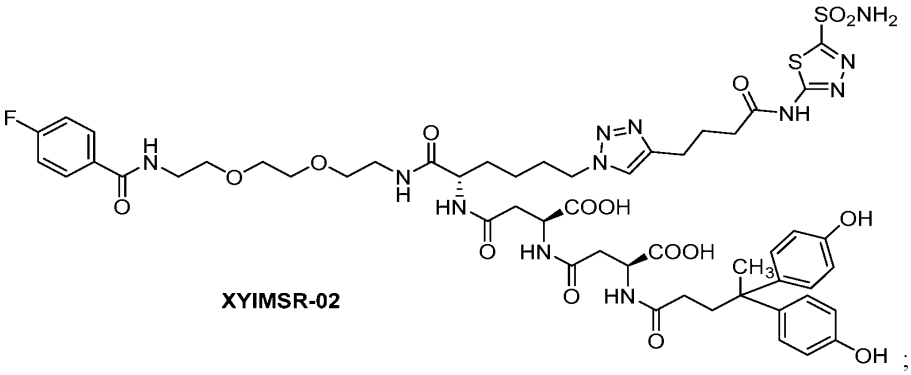
(IVd);

or a pharmaceutically acceptable salt thereof.

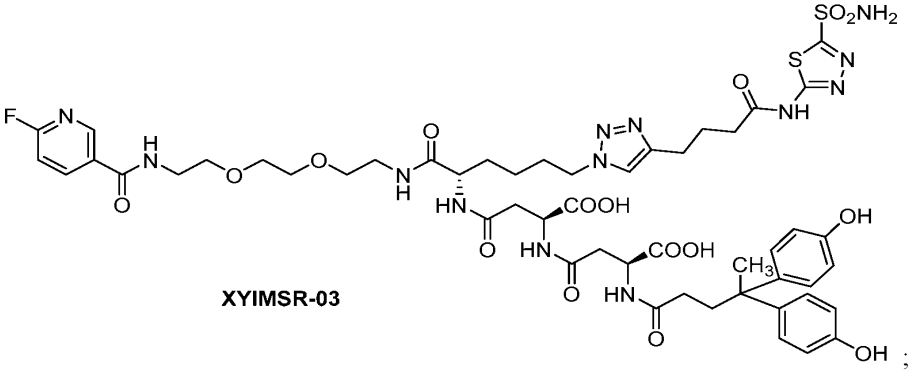
11. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



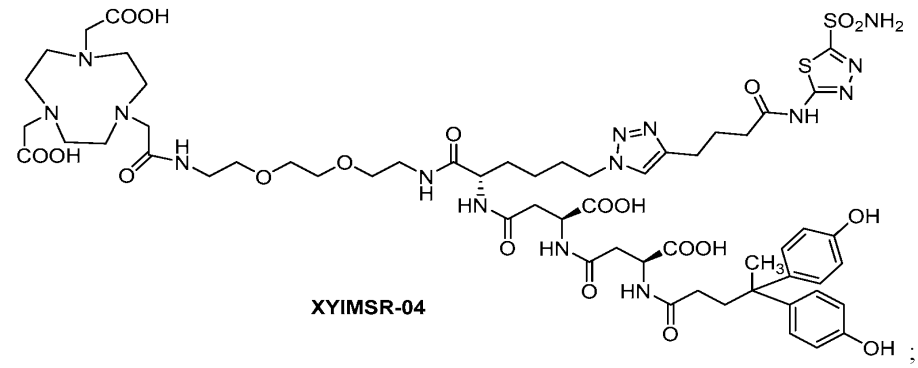
XYIMSR-01 ;



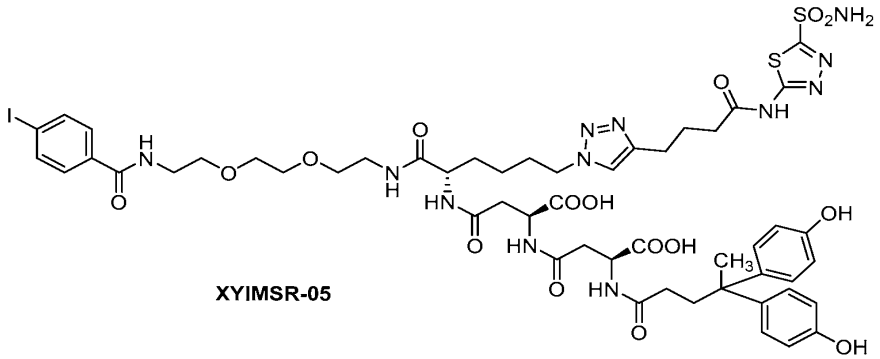
XYIMSR-02 ;



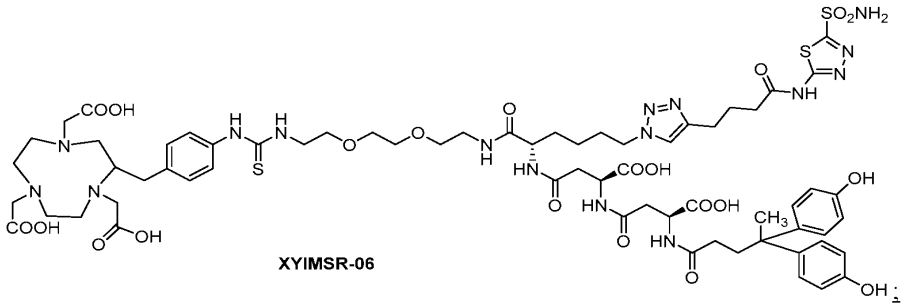
XYIMSR-03 ;



XYIMSR-04 ;



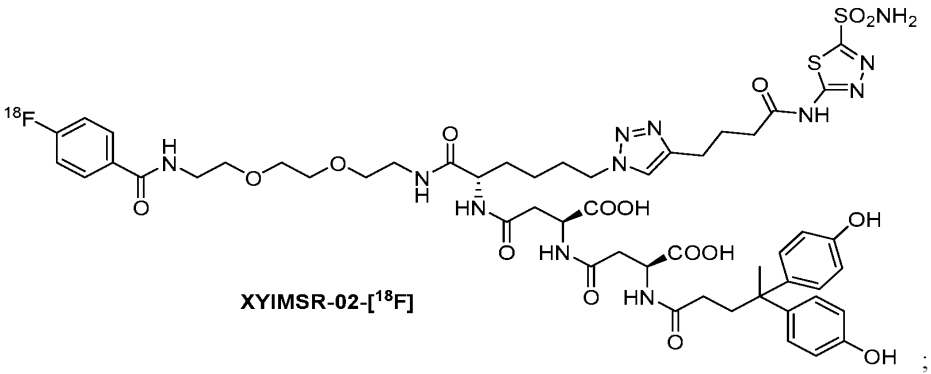
XYIMSR-05 ; and



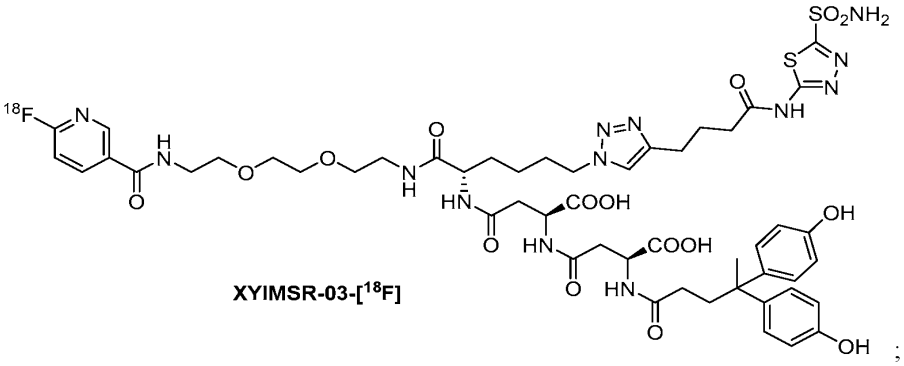
XYIMSR-06 ;

or a pharmaceutically acceptable salt thereof.

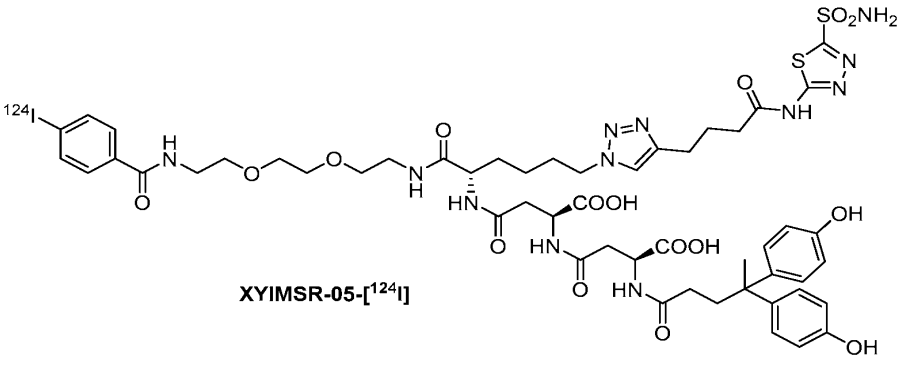
12. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



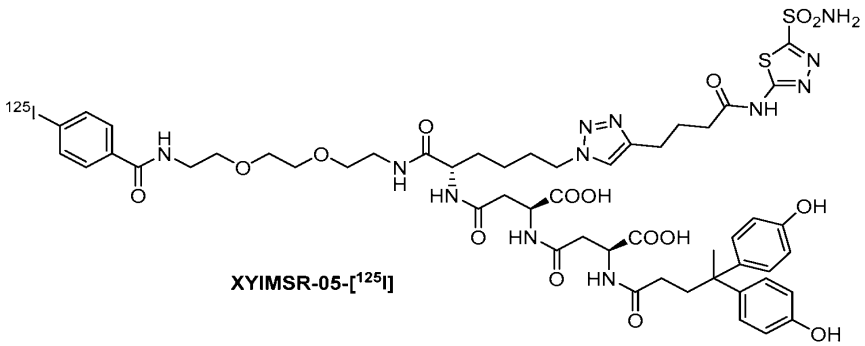
XYIMSR-02-[^{18}F] ;



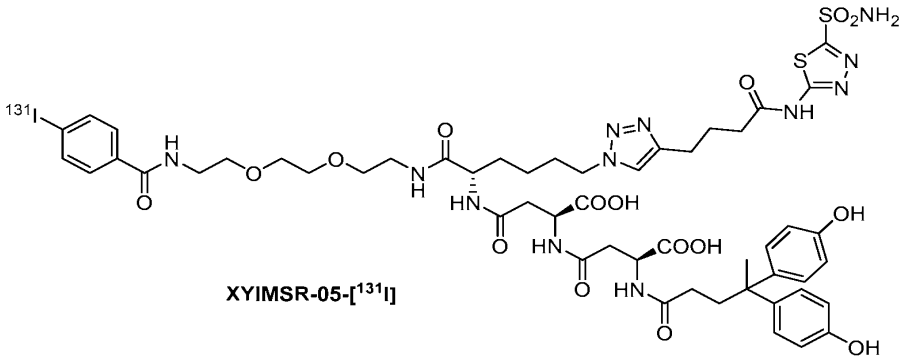
XYIMSR-03-[^{18}F] ;



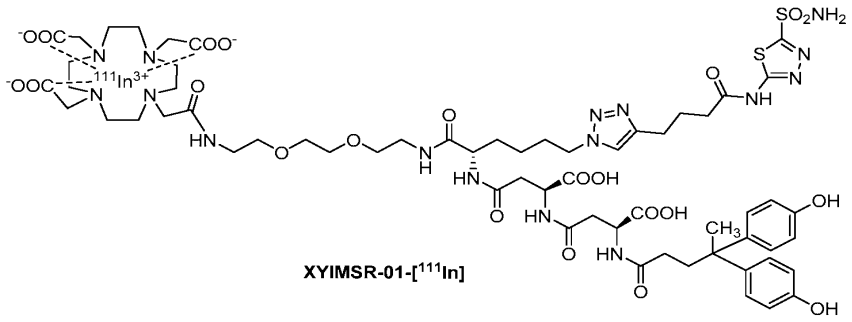
XYIMSR-05-[^{124}I] ;



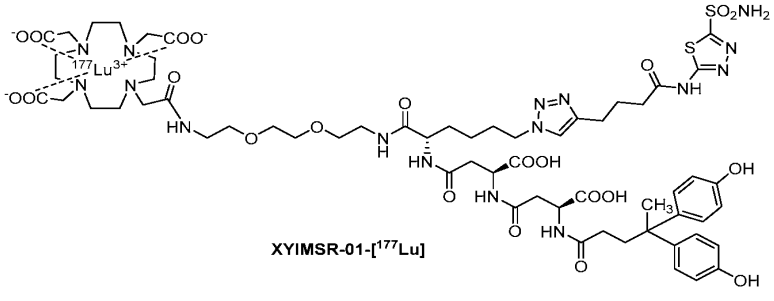
XYIMSR-05-[^{125}I] ;



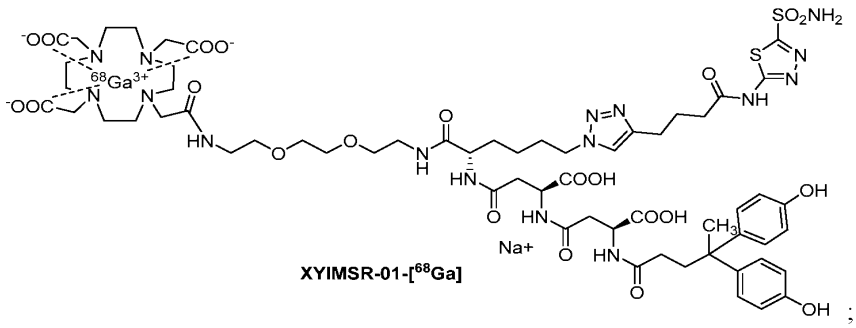
XYIMSR-05-[^{131}I] ;



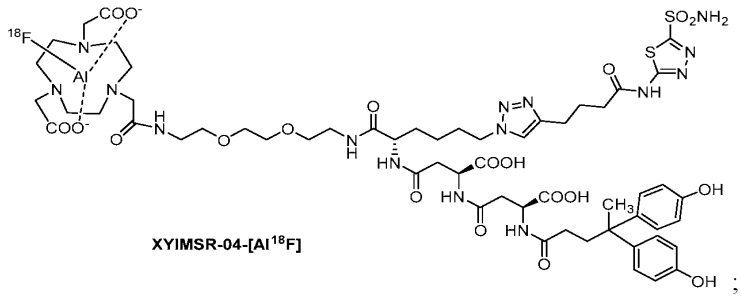
XYIMSR-01-[^{111}In] ;



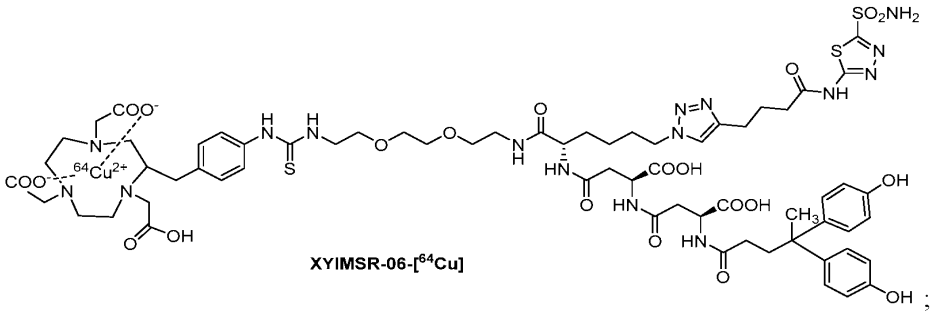
XYIMSR-01-[^{177}Lu] ;



XYIMSR-01-[^{68}Ga] ;



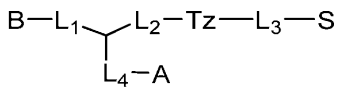
XYIMSR-04-[Al^{18}F] ; and



XYIMSR-06-[^{64}Cu] ;

or a pharmaceutically acceptable salt thereof.

13. A method for imaging or treating one or more Carbonic Anhydrase IX expressing tumors or cells, the method comprising contacting the one or more tumors or cells with an effective amount of a compound of formula (I) and making an image, the compound of formula (I) comprising:



(I);

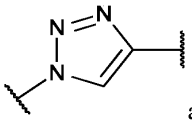
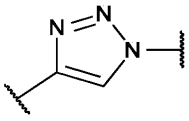
wherein:

B is a metal chelating moiety comprising a radiometal, or a radio-halogenated prosthetic group;

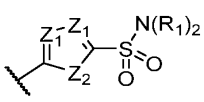
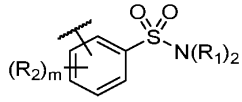
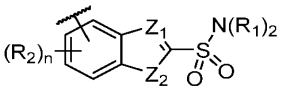
L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-;

each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl;

Tz is a triazole group selected from the group consisting of


and

;

S is a sulfonamide targeting a catalytic pocket of CAIX selected from the group consisting of:


,

, and

;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;

each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

n is an integer selected from the group consisting of 1, 2, and 3;

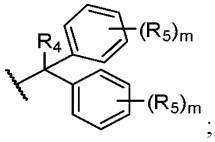
each Z_1 is independently selected from the group consisting of CR_3, and N;

each Z_2 is independently selected from the group consisting of CR_3, and S;

ITM Exhibit 1004, Page 1412 of 1652

each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

A is



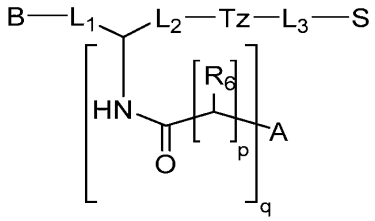
;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl;

R_5 is independently selected from the group consisting hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the compound of formula (I) is a compound of formula (II):



(II);

ITM Exhibit 1004, Page 1413 of 1652

wherein:

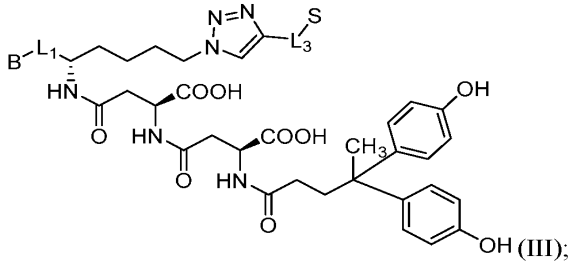
p is an integer selected from the group consisting of 1, 2, 3, and 4;

q is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

each R_6 is independently selected from the group consisting of H and –COOR;

or a pharmaceutically acceptable salt thereof.

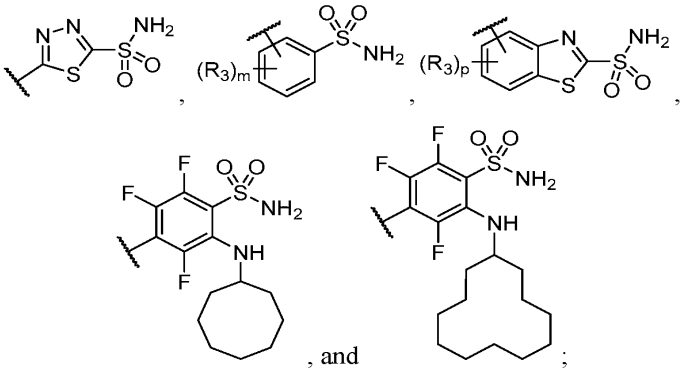
15. The method of claim 14, wherein the compound of formula (II) is a compound of formula (III):



(III);

or a pharmaceutically acceptable salt thereof.

16. The method of claim 13, wherein S is selected from the group of:

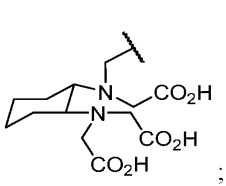
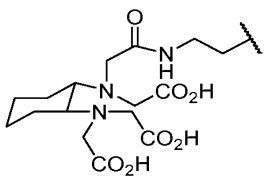
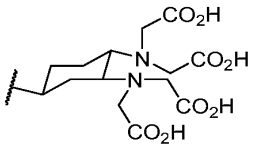
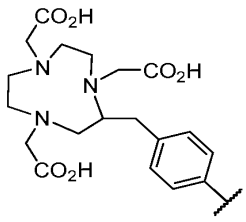
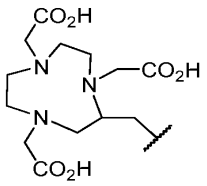
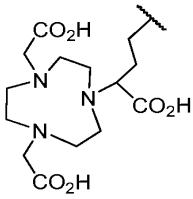
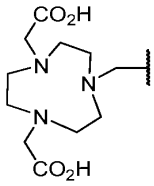
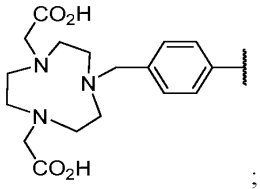
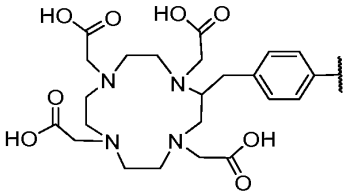
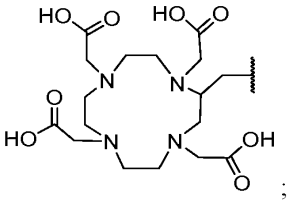
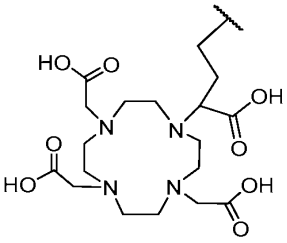
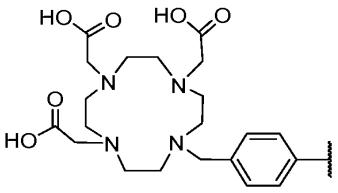
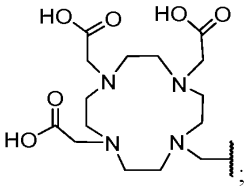
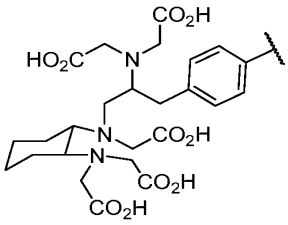
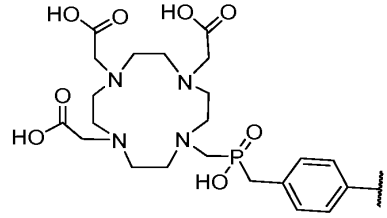
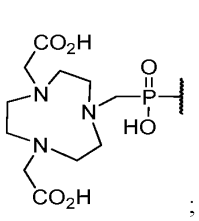


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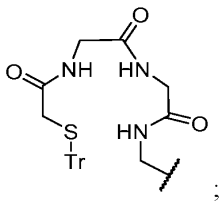
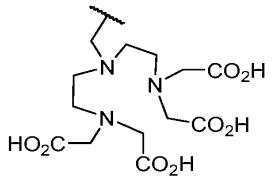
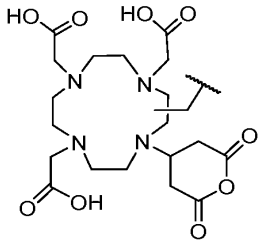
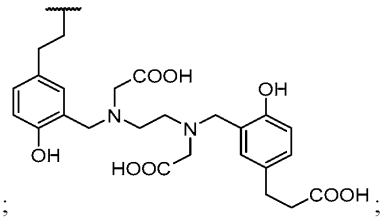
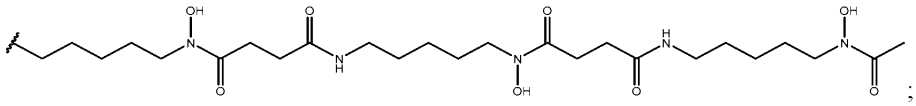
or a pharmaceutically acceptable salt thereof.

17. The method of claim 13, wherein B is a metal chelating moiety comprising a radiometal selected from the group of:

ITM Exhibit 1004, Page 1414 of 1652

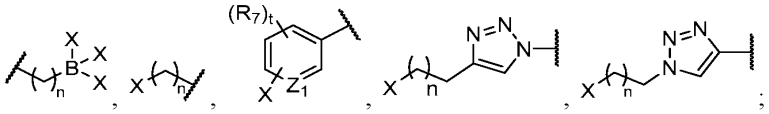

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; and

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and the radiometal and is selected from the group consisting of: ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho;

or wherein B is a radio-halogenated prosthetic group selected from the group consisting of:


;

wherein:

X is a radio-halogen selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At;

n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6;

t is an integer selected from the group consisting of 1, 2, and 3;

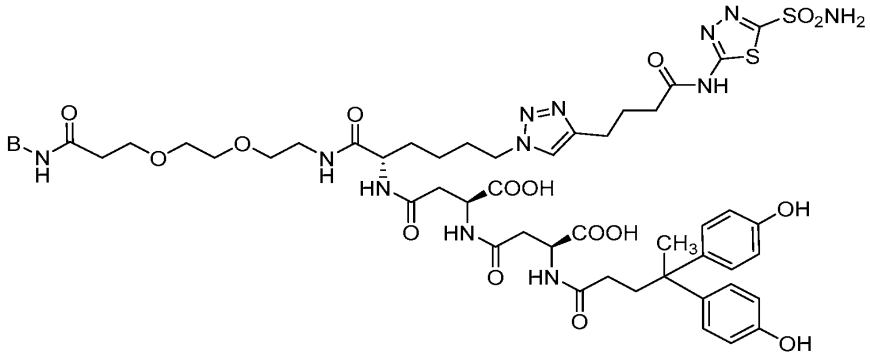
each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted

ITM Exhibit 1004, Page 1416 of 1652

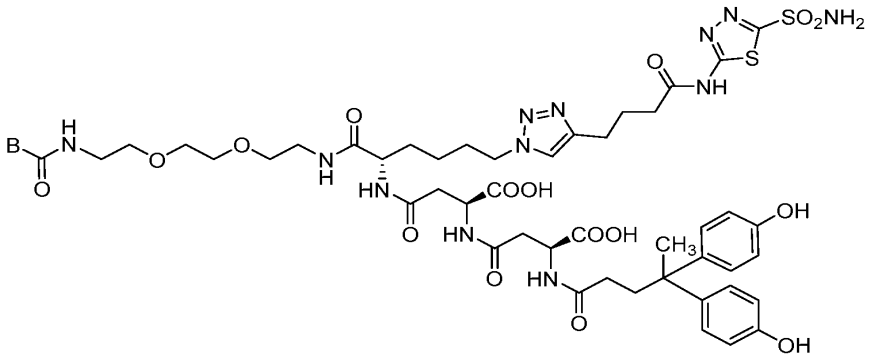
heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

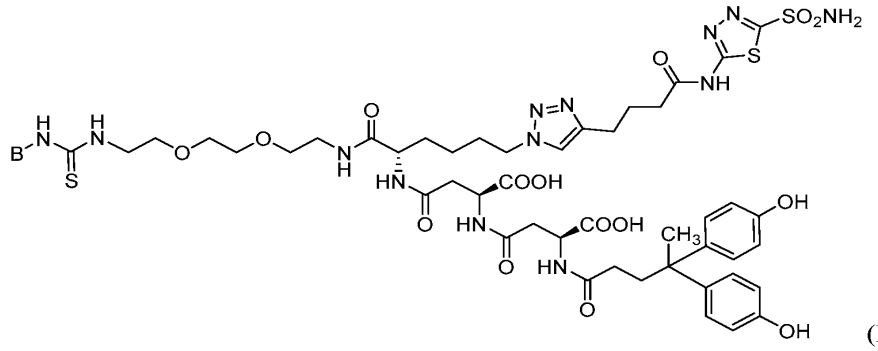
18. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:



(IVa);



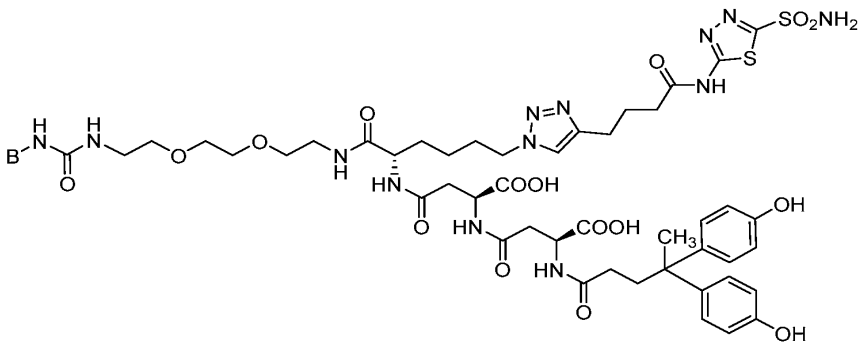
(IVb);



(IVc);

and

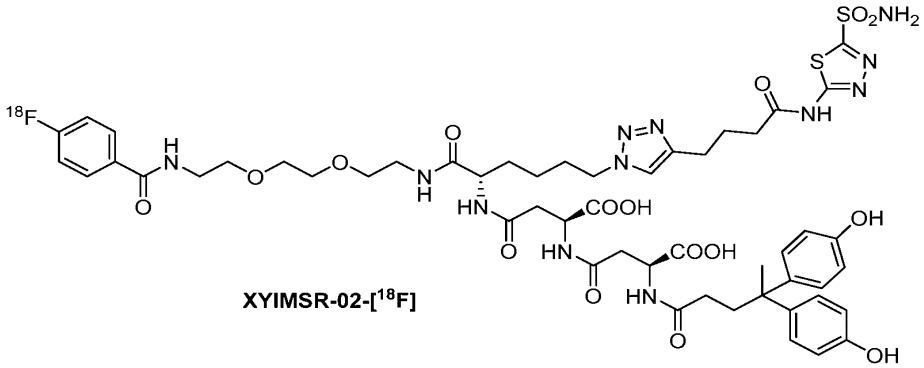
ITM Exhibit 1004, Page 1417 of 1652



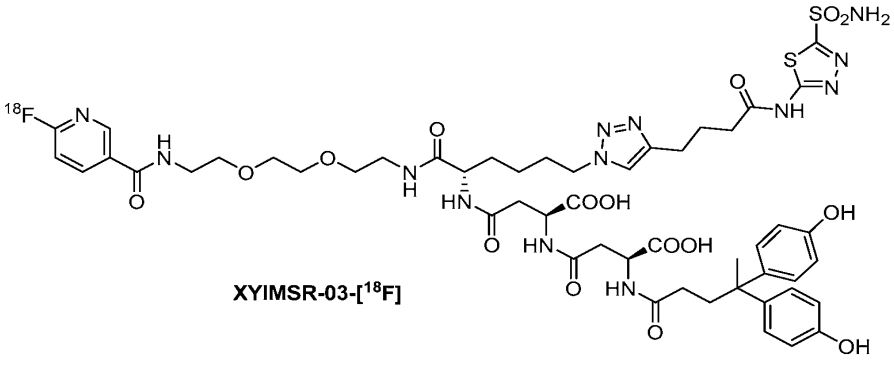
(IVd);

or a pharmaceutically acceptable salt thereof.

19. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:

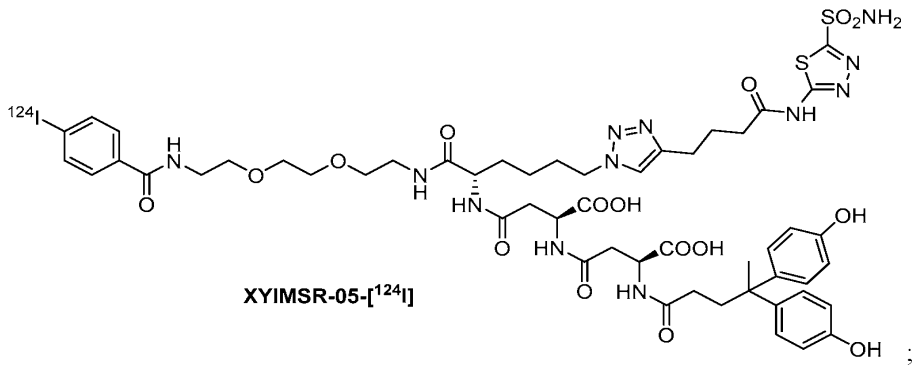


XYIMSR-02-[^{18}F] ;

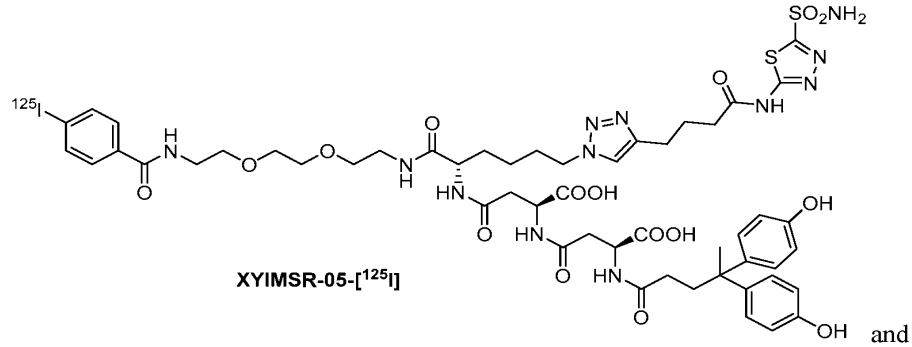


XYIMSR-03-[^{18}F] ;;

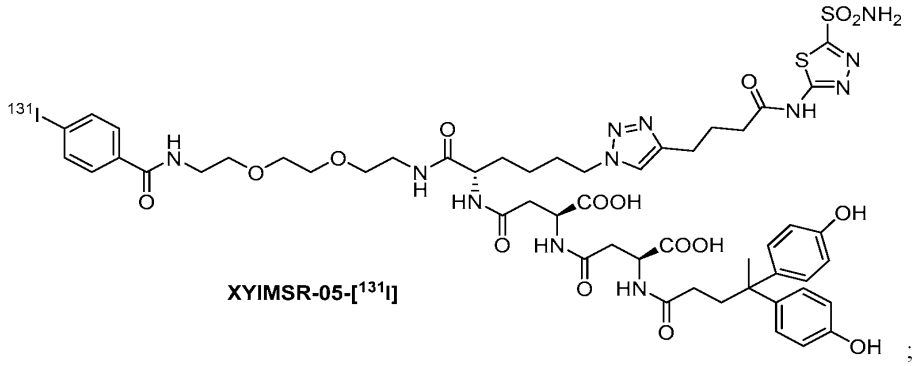
ITM Exhibit 1004, Page 1418 of 1652



XYIMSR-05-[^{124}I] ;



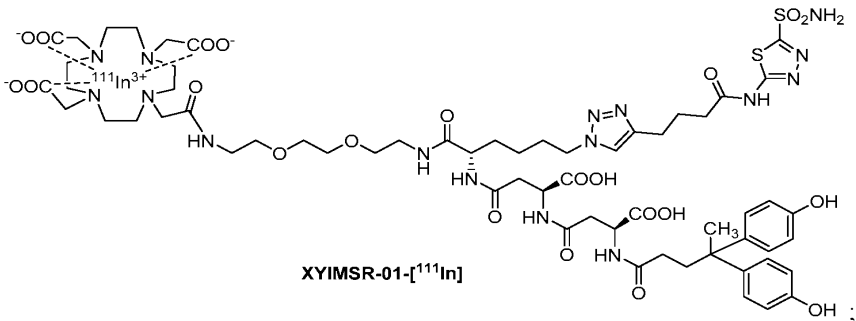
XYIMSR-05-[^{125}I] and



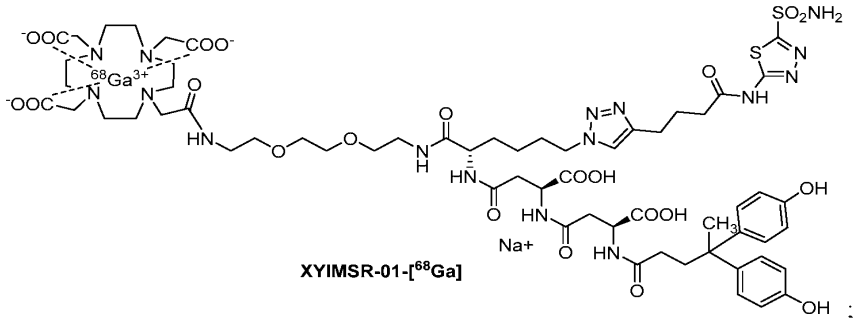
XYIMSR-05-[^{131}I] ;

or a pharmaceutically acceptable salt thereof.

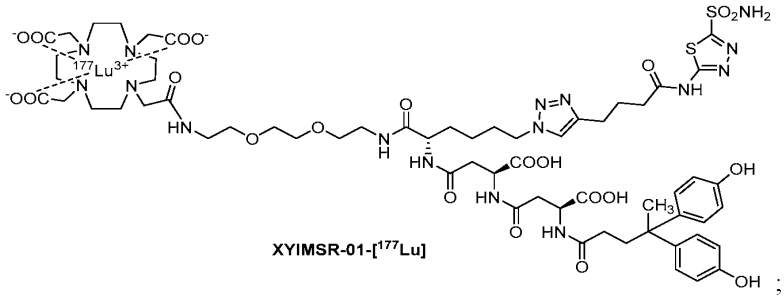
20. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:



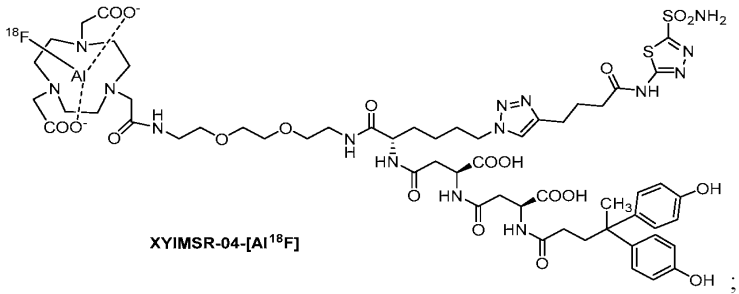
XYIMSR-01-[^{111}In] ;



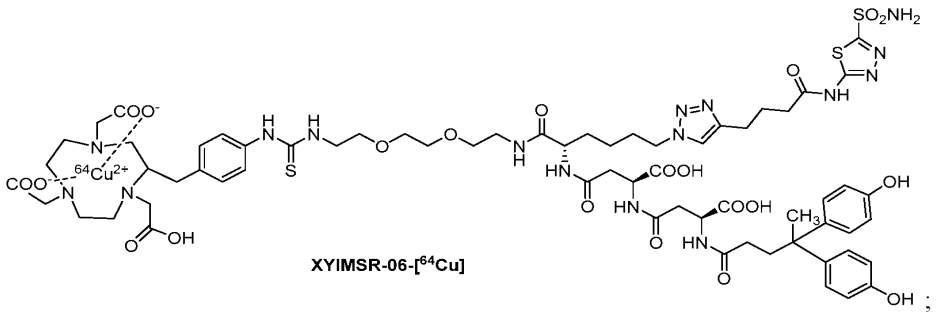
XYIMSR-01-[^{68}Ga] ;



XYIMSR-01-[^{177}Lu] ;



XYIMSR-04-[Al^{18}F] ; and



XYIMSR-06-[^{64}Cu]

or a pharmaceutically acceptable salt thereof.

21. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is selected from the group consisting of: a renal cell carcinoma, a prostate tumor or cell, a metastasized prostate tumor or cell, a lung tumor or cell, a renal tumor or cell, a glioblastoma, a pancreatic tumor or cell, a bladder tumor or cell, a sarcoma, a melanoma, a breast tumor or cell, a colon tumor or cell, a germ cell, a pheochromocytoma, an esophageal tumor or cell, a stomach tumor or cell, and combinations thereof.

22. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is a renal cell carcinoma.

23. The method of claim 13, wherein the imaging comprises positron emission tomography (PET) imaging or single photon emission computed tomography (SPECT) imaging.

24. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is *in vitro*, *in vivo*, or *ex vivo*.

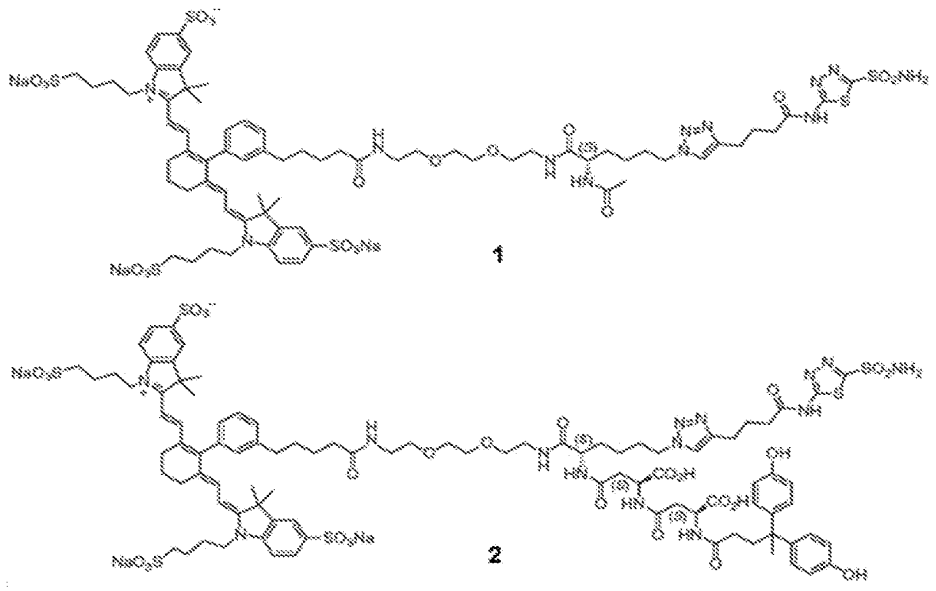
25. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is present in a subject.

26. The method of claim 25, wherein the compound comprising the imaging agent is cleared from the tumor or cell in the subject.

27. The method of claim 25, wherein the compound comprising the imaging agent is cleared more rapidly from a subject's kidneys than from a tumor in the subject.

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ITM Exhibit 1004, Page 1422 of 1652



1

2

Fig. 1A

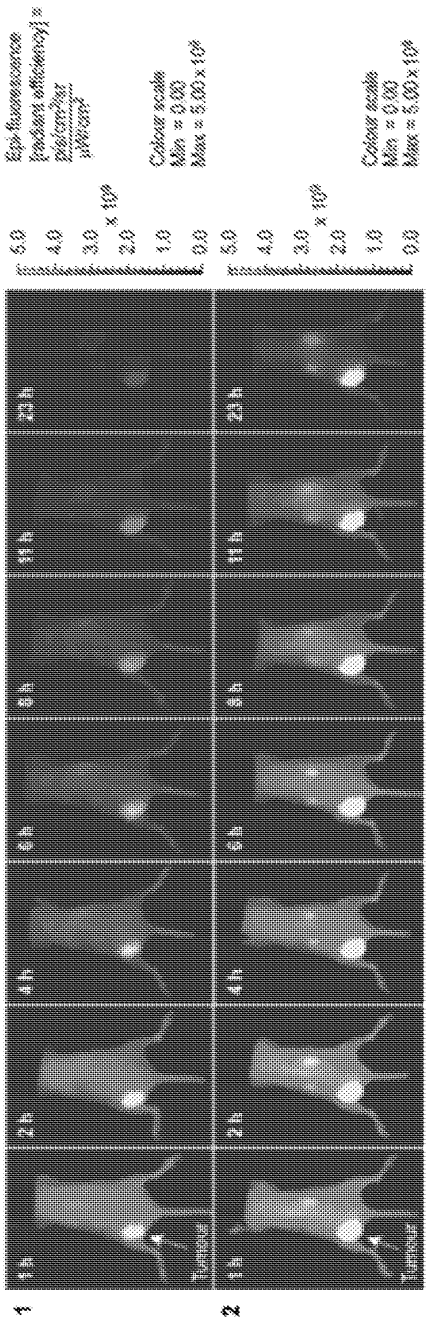

Epi-fluorescence
(Photons s-1cm-2sr-1
/μWcm-2)
Colour scale
Min = 0.00
Max = 5.00 x 10^6
5.0
4.0
3.0
x 10^6
2.0
1.0
0.0
1 h
2 h
4 h
6 h
8 h
11 h
23 h
Tumour
1
2

Fig. 1B

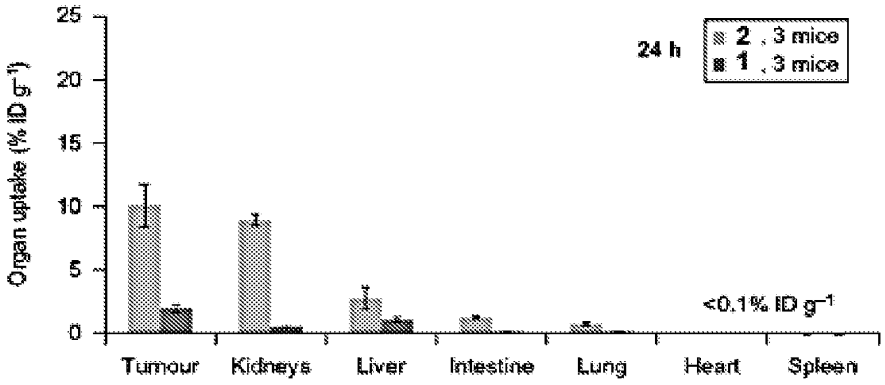

25
20
15
10
5
0
Organ uptake (% ID g⁻¹)
24 h
2 , 3 mice
1 , 3 mice
<0.1% ID g⁻¹
Tumour
Kidneys
Liver
Intestine
Lung
Heart
Spleen

Fig. 1C

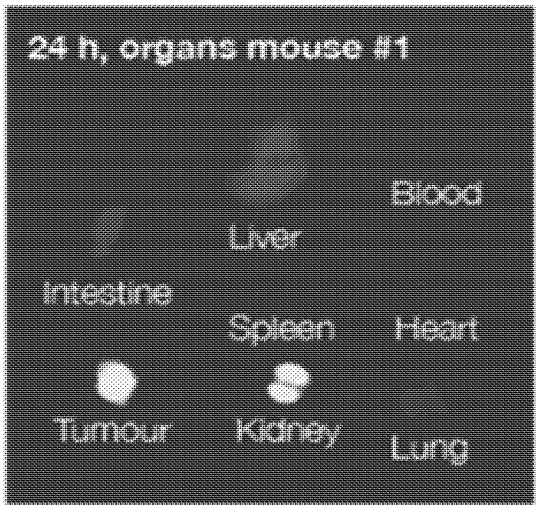
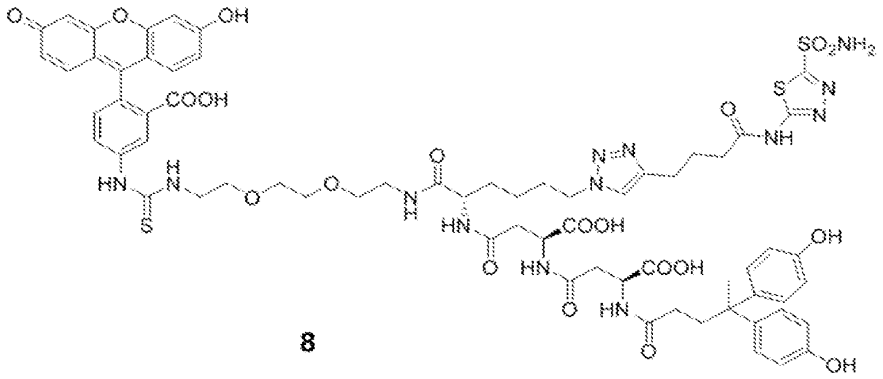

24 h, organs mouse #1
Blood
Liver
Intestine
Spleen
Heart
Tumour
Kidney
Lung

Fig. 1D



8

Fig. 2A

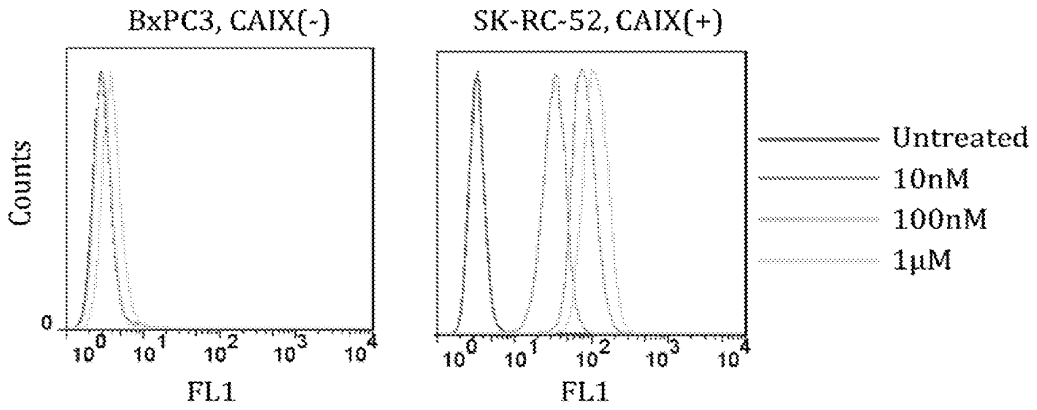


Fig. 2B *Fig. 2C*

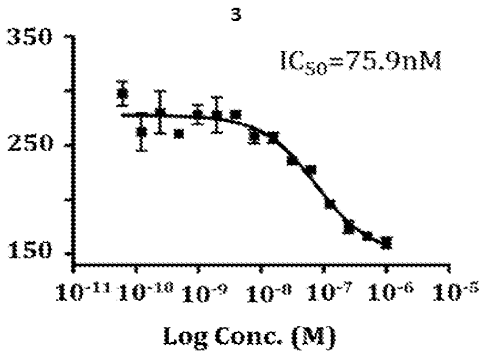


Fig. 3A

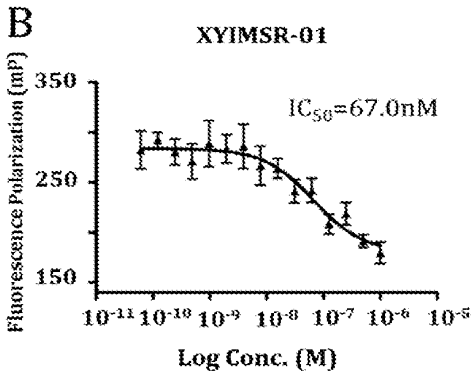


Fig. 3B

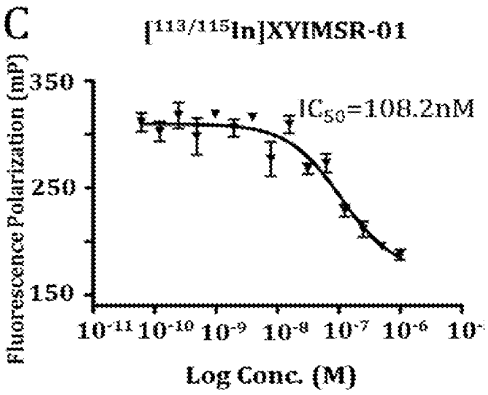


Fig. 3C

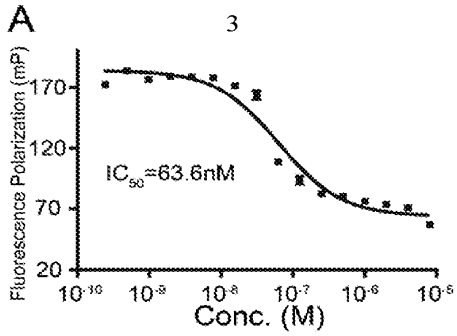


Fig. 4A

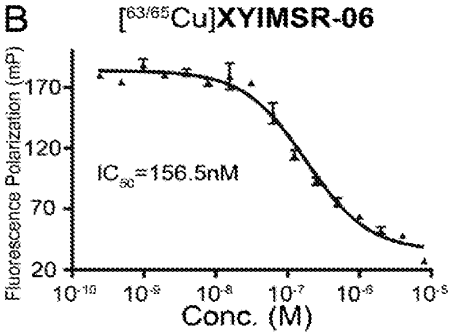


Fig. 4B

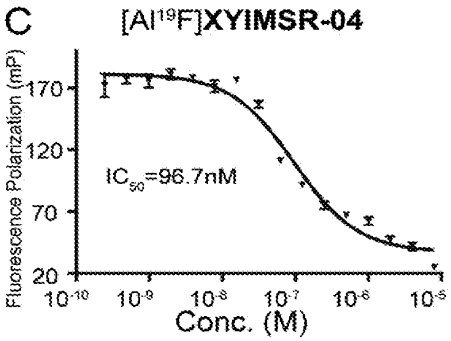


Fig. 4C

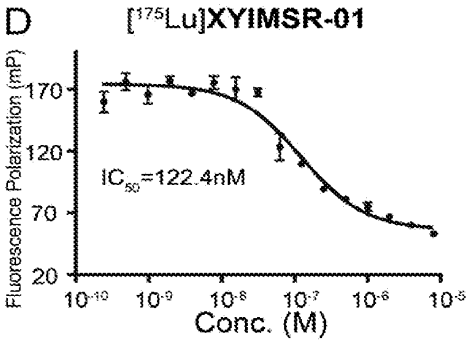


Fig. 4D

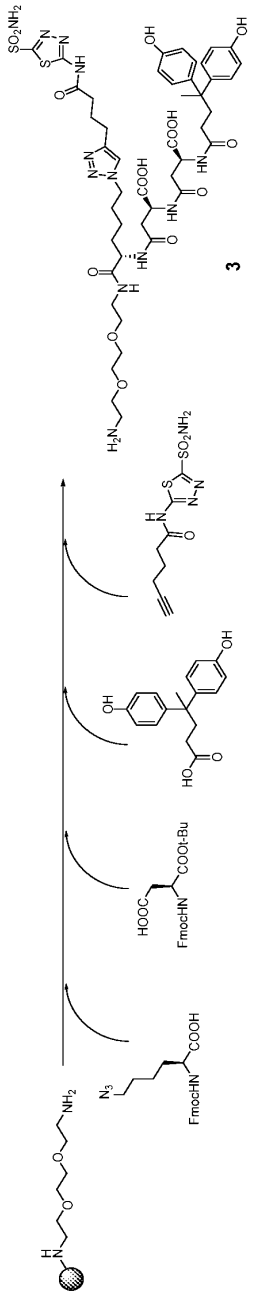


Fig. 5

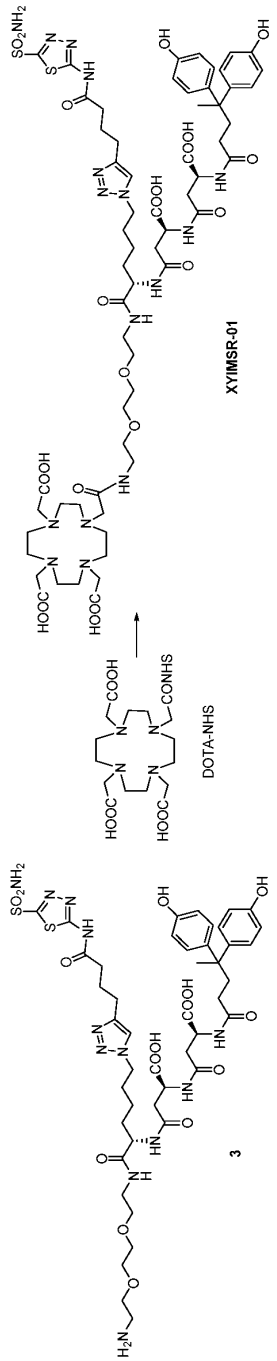


Fig. 6

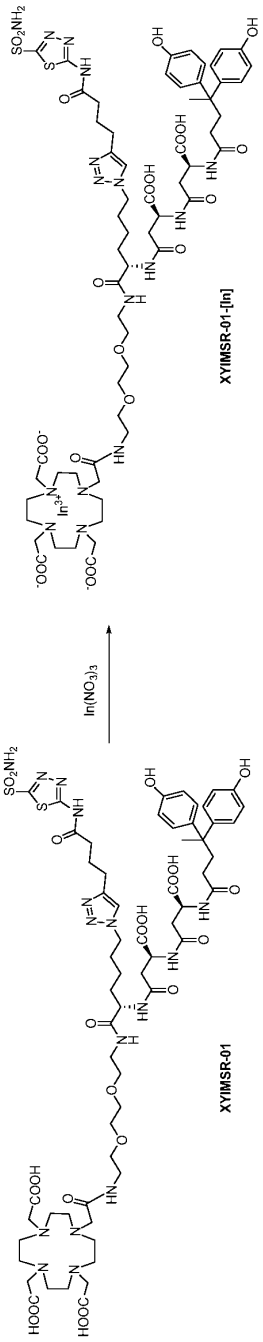


Fig. 7

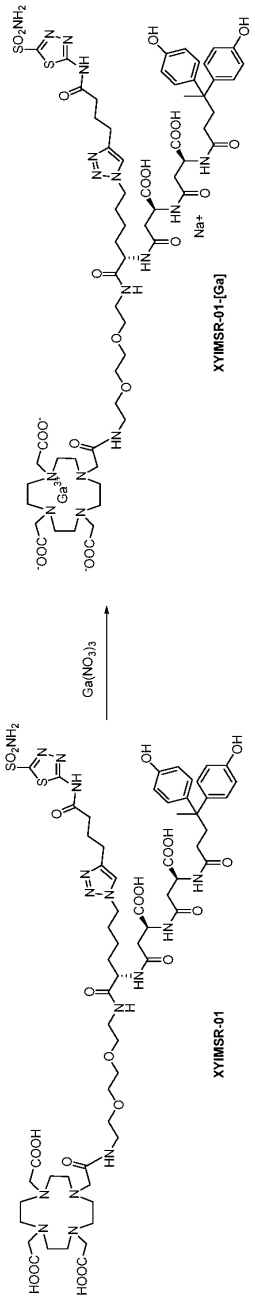


Fig. 8

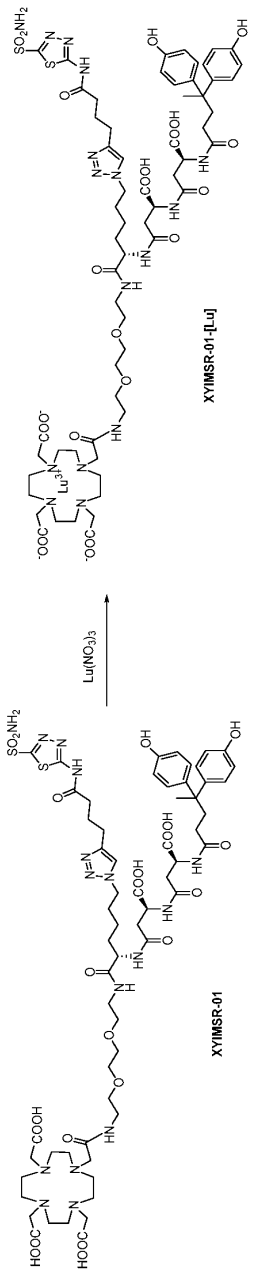


Fig. 9

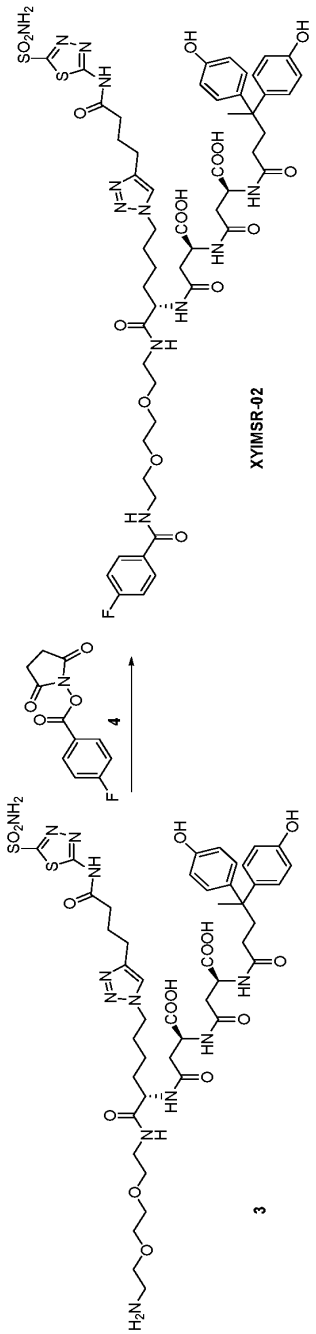


Fig. 10

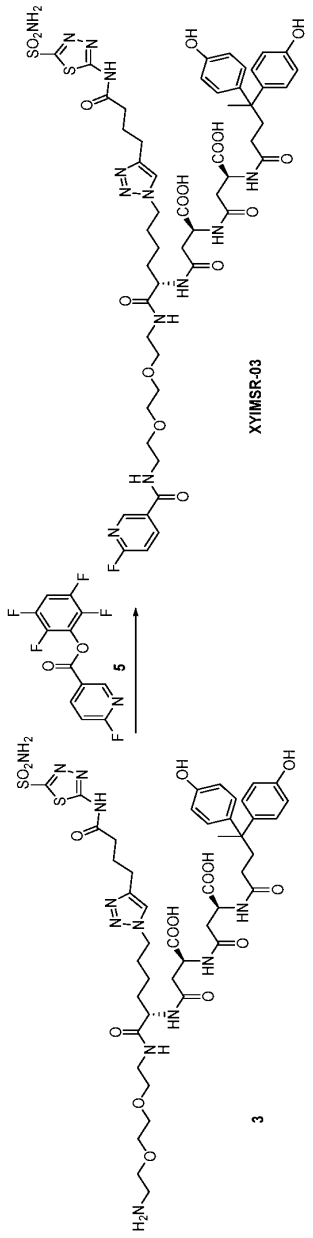


Fig. 11

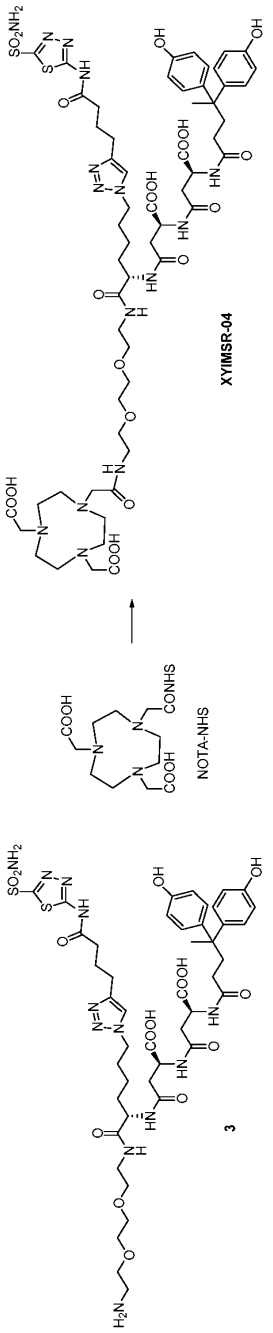


Fig. 12

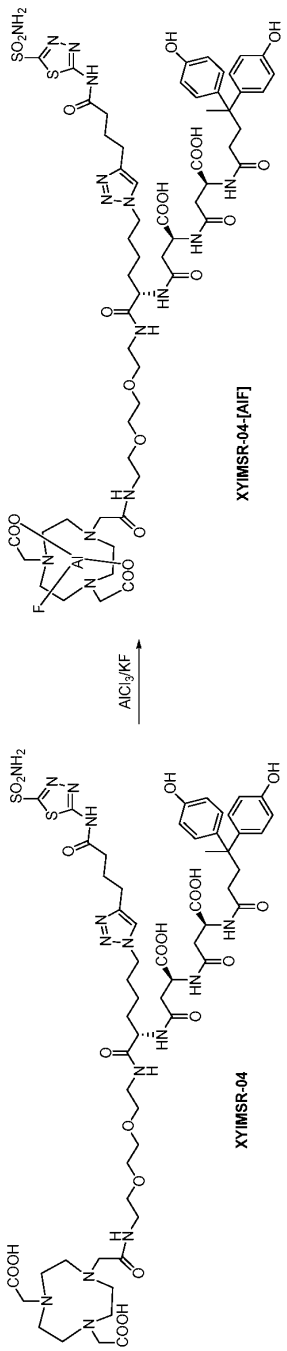


Fig. 13

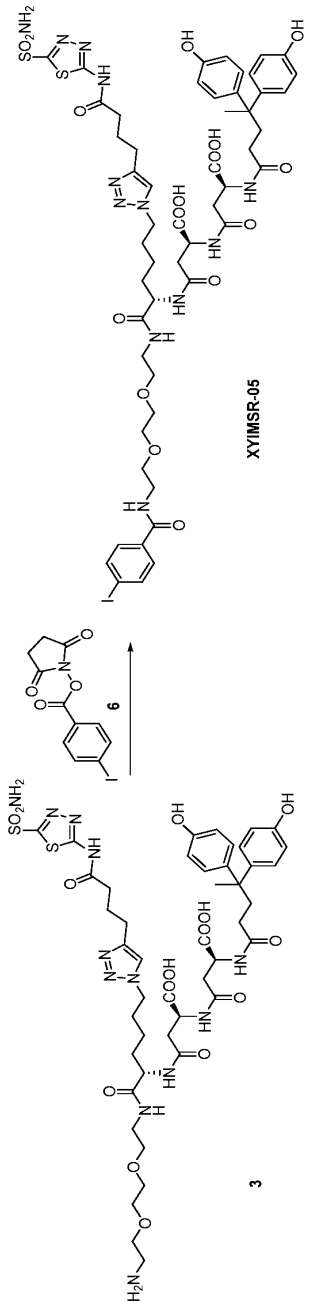


Fig. 14

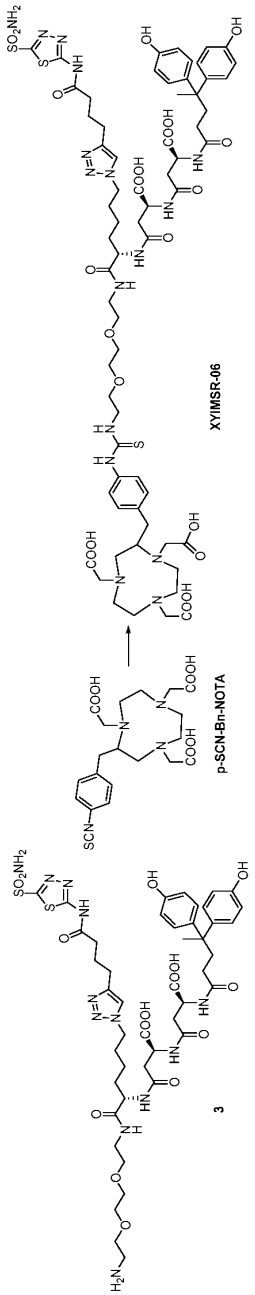


Fig. 15

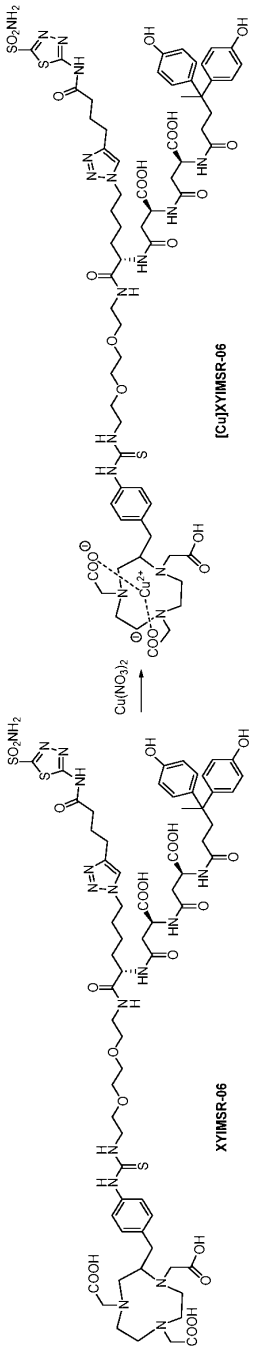


Fig. 16

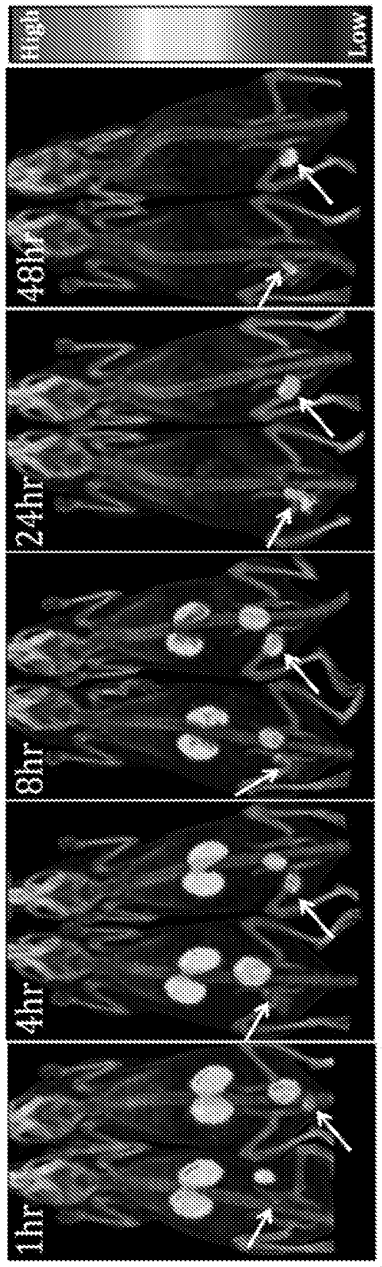


Fig. 17

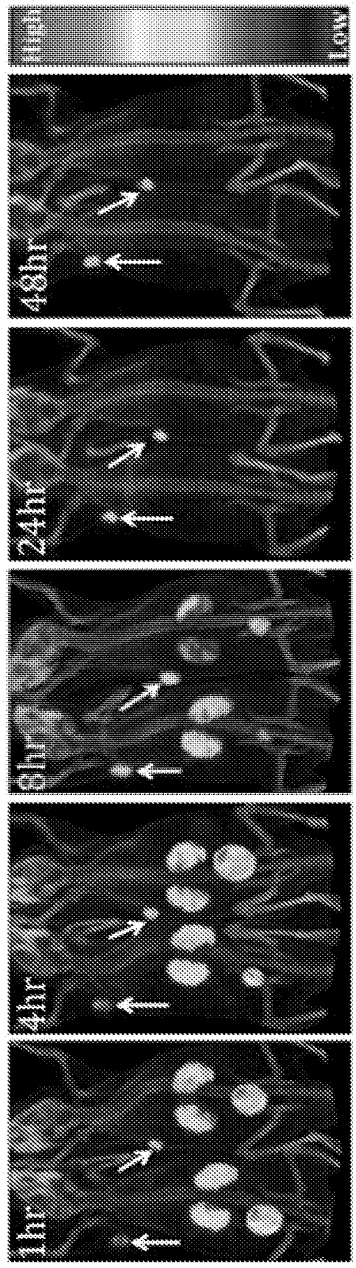


Fig. 18



Fig. 19

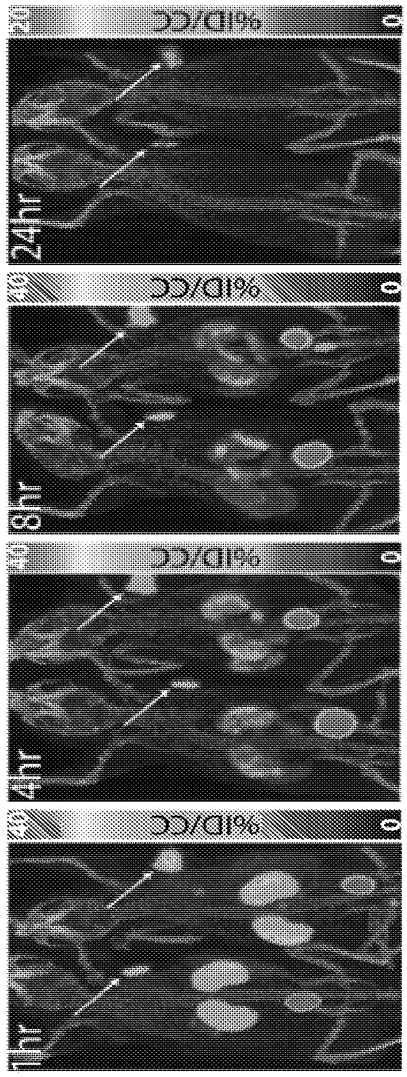


Fig. 20

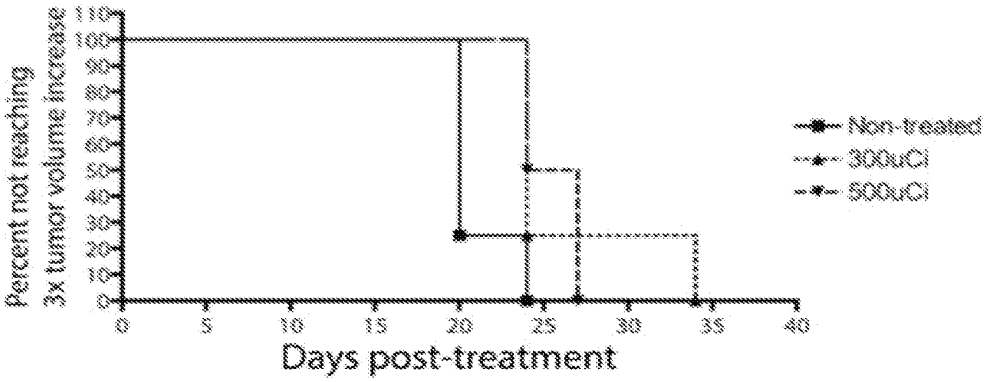

Percent not reaching
3x tumor volume increase
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Days post-treatment
Non-treated
300uCi
500uCi

Fig. 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035259

A. CLASSIFICATION OF SUBJECT MATTER

C07D 417/12(2006.01)i, C07D 417/14(2006.01)i, A61K 51/04(2006.01)i

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)
C07D 417/12; A61K 49/00; C07F 15/00; C07D 417/14; A61K 51/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(Kipo internal), STN (Registry, Caplus), Google & Keywords: imaging, radiolabel, carbonic anhydrase IX, metal-chelate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WICHERT, M. et al., "Dual-display of small molecules enables the discovery of ligand pairs and facilitates affinity maturation", Nature Chemistry, March 2015, Vol. 7, pp. 241-249 See abstract; and figures 5, 6.	1-12
Y	US 2009-0175794 A1 (ZIMMERMAN, C. et al.) 09 July 2009 See abstract; formulas (I), (III), (IV); paragraph [0273]; and claims 1-38.	1-12
A	KRALL, N. et al., "A Small-Molecule Drug Conjugate for the Treatment of Carbonic Anhydrase IX Expressing Tumors", Angewandte Chemie International Edition, 2014, Vol. 53, pp. 4231-4235 See the whole document.	1-12
A	RAMI, M. et al., "Carbonic Anhydrase Inhibitors: Design of Membrane-Impermeant Copper (II) Complexes of DTPA-, DOTA-, and TETA-Tailed Sulfonamides Targeting the Tumor-Associated Transmembrane Isoform IX", ChemMedChem, 2008, Vol.3, pp. 1780-1788 See the whole document.	1-12

☒ 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
18 October 2016 (18.10.2016)	**18 October 2016 (18.10.2016)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
PARK, Jung Min
Telephone No. +82-42-481-3516

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035259

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	YANG, X. et al., "Imaging of carbonic anhydrase IX with an 111In-labeled dual-motif inhibitor", Oncotarget, [Epub.] 16 September 2015, Vol. 6, No. 32, pp. 33733-33742 See the whole document.	1-12

Form PCT/ISA/210 (continuation of second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035259

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-27
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 13-27 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2016/035259

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009-0175794 A1	09/07/2009	AU 2009-204133 A1	16/07/2009
		AU 2009-204133 B2	10/04/2014
		AU 2014-202811 A1	12/06/2014
		BR PI0906797 A2	14/07/2015
		CA 2711678 A1	16/07/2009
		CN 102083427 A	01/06/2011
		CN 102083427 B	10/12/2014
		EP 2240171 A2	20/10/2010
		EP 2240171 B1	13/08/2014
		JP 2011-509304 A	24/03/2011
		RU 2010132910 A	20/02/2012
		RU 2498798 C2	20/11/2013
		US 8877970 B2	04/11/2014
		WO 2009-089383 A2	16/07/2009
		WO 2009-089383 A3	03/09/2009

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Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**01/16/2024 05:15:59 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968554	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
WO2016196628A1.pdf	135	Foreign Reference	5262 KB
2024-01-16 - JHu-36631.303 - Supp IDS.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	39 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
Third Party Observations.pdf	553	Non Patent Literature	9605 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
WO2016196628A1.pdf	515E343648E2878B7A59FC35ECD8E7564DDC2D9AF7A6E4943 ED650ABB977B3C0CCF2B3E57D934968296ED6542E71229439 04B0013C234888C773A934472A23C9
2024-01-16 - JHu-36631.303 - Supp IDS.pdf	91A5DF33719D461247F422010D6C4620CC167D3FB4C8B575C B5C14834F5D1FF57A921C469D75C560C30C4BFEFC83896F9A 3A16ADE638DE1A916D89C64AA059B6
Third Party Observations.pdf	9D1A24255E793F435B294816D357B4D479584A3CF45672812C 46E3D0990121E8D082B3C39584A6CE8DEF76F42207F9DAC07 46F58D55F3C30EBB28133A63F0084

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 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.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

101943 7590 01/10/2024
The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

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 the USPTO patent electronic filing system 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.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

TITLE OF INVENTION: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/10/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
PERREIRA, MELISSA JEAN	1618	424-001890

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/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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 Casimir Jones, SC
2 Jeffrey W. Childers
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: The Johns Hopkins University

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Baltimore, MD

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)

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

☒ Electronic Payment via the USPTO patent electronic filing system ❑ 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. 504302

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

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.

❑ Applicant asserting small entity status. See 37 CFR 1.27

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.

❑ Applicant changing to regular undiscounted fee 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 /Jeffrey W. Childers/ Date January 16, 2024

Typed or printed name Jeffrey W. Childers Registration No. 58126

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	01/16/2024 05:18:26 PM Z ET	JHU-36631.303

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968988	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0636	E20241FH19045329	Van Nguyen

PRE-AUTHORIZED ACCOUNT
504302

PRE-AUTHORIZED CATEGORY
37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	$480.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for 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

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**01/16/2024 05:18:26 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968988	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-01-16 - JHU-36631.303 - Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	143 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for 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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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**01/22/2024 01:37:02 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Aaron Bottjen
PATENT CENTER #	64032495	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-01-22_36631-303_SUPPL_IDS_SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	37 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-01-22_36631-303_SUPPL_IDS_SB08.pdf	52AC7B410E60580F35A2549C9975CA6DE0CDEBE91092F6D89CCF86F79E045BE686845BE62033CFC445D59F1A75D624E8CC

537D9928DBF1740DE72B838D154640

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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18 Jul 2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	Melissa Jean Perreira
Sheet	1	of	2	*Attorney Docket Number*	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2020/0237936	2020-07-30	LOW et al.	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] *(if known)*	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18 Jul 2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	Melissa Jean Perreira
Sheet	2	of	2	*Attorney Docket Number*	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-01-22
Name/Print	Jeffrey W. Childers	Registration Number	58,126

.

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.
[5] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[6] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[7] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[8] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.97 and 1.98. 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 CFR 1.14. This collection is estimated to take 2 hours 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**.

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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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 01/23/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
01/23/2024	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

The Johns Hopkins University c/o Casimir Jones
2275 Deming Way Suite 310
Middleton, WI 53562

In re Application of	:
Yang et al.	: **DECISION ON PETITION**
Application No. 18/354,282	: **UNDER 37 CFR 1.84(a)(2)**
Filed: 07/18/2023	:
Attorney Docket No. JHU-36631.303	:

This is a decision on the Petition to Accept Color Drawings under 37 CFR 1.84(a)(2), received in the United States Patent and Trademark Office (USPTO) on December 13, 2023.

37 CFR 1.84(a)(2) in relevant part states:

> On rare occasions, color drawings may be necessary as the only practical medium by which to disclose the subject matter sought to be patented in a utility patent application. … The Office will accept color drawings in utility patent applications only after granting a petition filed under this paragraph explaining why the color drawings are necessary. Any such petition must include the following:
>
> (i) Payment of the fee set forth under 37 CFR 1.17(h),
> (ii) Submission of three (3) sets of color drawings, or one (1) set of color drawings if filed by EFS-Web, and
> (iii) An amendment to the specification to insert (unless the specification contains or has been previously amended to contain) the following language as the first paragraph of the brief description of the drawings:
>
> > The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the office upon request and payment of the necessary fee.

MPEP § 608.02(VIII) COLOR DRAWINGS OR COLOR PHOTOGRAPHS states in relevant part:

> It is anticipated that such a petition will be granted only when the U.S. Patent and Trademark Office has determined that a color drawing or color photograph is the only practical medium by which to disclose in a printed utility patent the subject matter to be patented.

A review of U.S. Patent and Trademark records indicates that all the criteria set forth in 37 CFR 1.84(a)(2) and MPEP § 608.02(VIII) have been satisfied. Accordingly, the petition under 37 CFR 1.84(a)(2) is **GRANTED**.

Petitioner is advised that this decision grants the petition to accept color drawing(s) or photograph(s) because the requirements of 37 CFR 1.84(a)(2) or (b)(2) have been met. The initial review undertaken for purposes of the petition did not identify new matter in the color drawing(s) or photograph(s). However, the grant of this

petition should not be construed as a determination that should the color drawing(s) be entered the application would be free of statutory and/or formal defects. See MPEP § 608.02(VIII) and 608.02(b). The examiner is charged with determining whether applicant's nonprovisional application as amended to include the replacement drawings complies with all statutory requirements (e.g., enablement under 35 U.S.C. 112) and other applicable requirements (e.g., other formal requirements under 37 CFR 1.84). Further, the determination of whether a petition establishes a sufficient basis to accept color drawings or photographs is separate from the examiner's ultimate determination as to whether an amendment to the drawings should be entered (e.g., based on the prohibition under 35 U.S.C. 132 against introducing new matter). See MPEP § 608.04(a), 608.02 (h), and 2163.06(I).

Should there be any questions about this decision, please contact BENNETT M CELSA, by letter addressed to Director, TC 1600, at the address listed above, or by telephone at (571)272-0807, or by facsimile sent to the general Office facsimile number, 571-273-8300.

/Zachariah Lucas/
Supervisory Patent Examiner, Technology Center 1600

/BENNETT M CELSA/
Quality Assurance Specialist , Technology Center 1600

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

7590 01/30/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	
NOTIFICATION DATE	DELIVERY MODE
01/30/2024	ELECTRONIC

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement (IDS) filed 1.16.2024 in the above-identified application fails to meet the requirements of 37 CFR 1.97(d) for the reason(s) specified below. Accordingly, the IDS will be placed in the file, but the information referred to therein has not been considered.

The IDS is not compliant with 37 CFR 1.97(d) because:

☒ The IDS lacks a statement as specified in 37 CFR 1.97(e).

☐ The IDS lacks the fee set forth in 37 CFR 1.17(p).

☐ The IDS was filed after the issue fee was paid. Applicant may wish to consider filing a petition to withdraw the application from issue under 37 CFR 1.313(c) to have the IDS considered. See MPEP 1308.

N. Horne, for

571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

FORM PTOM327-B (Rev. 02/08)

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

7590 01/30/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	
NOTIFICATION DATE	DELIVERY MODE
01/30/2024	ELECTRONIC

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

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N. Horne, for

571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

FORM PTOM327-B (Rev. 02/08)

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**02/02/2024 05:07:17 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Jeffrey Childers
PATENT CENTER #	64194803	AUTHORIZED BY	-
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	**E202422H07588108**	**Jeffrey Childers**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
504302	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	56.00	1	56.00
2801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	544.00	1	544.00
			TOTAL AMOUNT:	**$600.00**

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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(if known)*	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2020/0237936	2020-07-30	LOW et al.	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] *(if known)*	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
	2.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY		

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
	3.	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages.	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	*Attorney Docket Number*	JHU-36631.303

CERTIFICATION STATEMENT

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OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-02-02
Name/Print	Jeffrey W. Childers	Registration Number	58,126

.

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.
[5] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[6] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[7] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[8] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.97 and 1.98. 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 CFR 1.14. This collection is estimated to take 2 hours 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**.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.	Confirmation No.: 7536
Serial No.: 18/354,282	Art Unit: 1618
Filed: July 18, 2023	Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

INFORMATION DISCLOSURE STATEMENT CERTIFICATION STATEMENT

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Examiner Perreira:

I hereby certify that that the following items of information contained in the information disclosure statement were cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. 37 C.F.R. §1.97(e)(1).

WO 2016/196628 for The Johns Hopkins University (ref. no. 2)
Third Pary Observations for application number EP 18871298.8 (ref. no. 3)

I hereby certify that the following item of information contained in the information disclosure statement was not cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

US Publication 2020/0237936 for LOW et al. (ref. no. 1)

Respectfully submitted,

Date: February 2, 2024

/Jeffrey W. Childers/

Jeffrey W. Childers
Casimir Jones S.C.
Registration No. 58126
2275 Deming Way, Suite 310
Middleton, WI 53562
Office: 919-724-8699
Fax: 608-662-1276

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2016 (08.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/196628 A1

(51) International Patent Classification:
C07D 417/12 (2006.01) *A61K 51/04* (2006.01)
C07D 417/14 (2006.01)

(21) International Application Number:
PCT/US2016/035259

(22) International Filing Date:
1 June 2016 (01.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/169,338 1 June 2015 (01.06.2015) US
62/336,043 13 May 2016 (13.05.2016) US

(71) Applicant: **THE JOHNS HOPKINS UNIVERSITY** [US/US]; 3400 North Charles Street, Baltimore, Maryland 21218 (US).

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(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, 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.

(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, 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).

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(54) **Title**: NUCLEAR IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING CARBONIC ANHYDRASE IX AND USES THEREOF

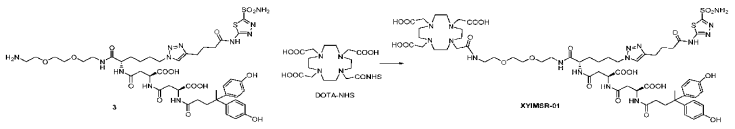


Fig. 6

(57) **Abstract**: Highly potent and selective radionuclide-based imaging and therapy agents targeting carbonic anhydrase IX with minimum non-specific organ uptake are disclosed. Methods of imaging and/or treating carbonic anhydrase IX-expressing cells or tumors also are disclosed.

WO 2016/196628 A1

NUCLEAR IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING CARBONIC ANHYDRASE IX AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 62/169,338, filed June 1, 2015, and 62/336,043 filed May 13, 2016, which are incorporated herein by reference in their entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under CA183031, CA197470, CA184228, and CA134675 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

BACKGROUND

Renal cell carcinoma (RCC) is the most common neoplasm of the kidney (Srigley et al., 2013), with an estimated 60,000 patients diagnosed annually in the United States (Siegel et al., 2015). Among cases of RCC, the clear cell subtype (ccRCC) is the most prevalent, accounting for up to 70 % of RCCs (Pichler et al., 2010; Lipworth et al., 2014; Umbreit et al., 2012). Common to ccRCC is loss of the Von Hippel-Lindau (VHL) tumor suppressor gene (Shuch et al., 2015). Loss of VHL in turn leads to over-expression of carbonic anhydrase IX (CAIX) (Bragmaier et al., 2004), a membrane-associated enzyme responsible for catalyzing the reversible hydration of carbon dioxide to a bicarbonate anion and a proton (Supuran, 2008; Alterio et al., 2012). Over-expression of CAIX has been demonstrated in approximately 95 % of ccRCC tumor specimens (Bui et al., 2003; Atkins et al., 2005; Leibovitch et al., 2007), making it a useful biomarker for this disease.

CAIX has limited expression in normal tissues and organs with the exception of the gastrointestinal tract, gallbladder and pancreatic ducts (Alterio et al., 2012; Clare and Supuran, 2006; Ivanov et al., 2001; Potter and Harris, 2004). No report has demonstrated CAIX expression in normal renal parenchyma or benign renal masses (Supuran, 2008; Alterio et al., 2012; Clare and Supuran, 2006; Ivanov et al., 2001; Potter and Harris, 2004). Feasibility for the non-invasive diagnosis of ccRCC based on CAIX expression has been proved with the radiolabeled antibody G250 (Oosterwijk et al., 1986) and its clinical potential has been reviewed (Smaldone et al.,

2012). However, antibodies as molecular imaging agents suffer from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low-molecular-weight (LMW) agents demonstrate faster pharmacokinetics and higher specific signal within clinically convenient times after administration. They also offer site specific radiolabeling often by a wider range of chemical methods and radionuclides, and may offer a shorter path to regulatory approval (Coenen et al., 2010; Cho et al., 2012; Reilly et al., 2015).

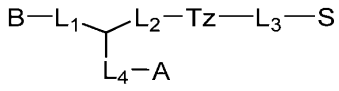
Targeting CAIX with LMW inhibitors has proved challenging in part because fifteen human isoforms of carbonic anhydrase, with high sequence homology, have been identified. Those isoforms share common structural features, including a zinc-containing catalytic site, a central twisted β-sheet surrounded by helical connections, and additional β-strands. The isoforms, however, do vary widely in terms of intracellular location, expression levels, and tissue and organ distribution (Supuran, 2008; Alterio et al., 2012). Significant effort has been expended on development of sulfonamides and other LMW CAIX ligands for nuclear imaging of CAIX, but most reported agents have been fraught with low tumor uptake and significant off-target accumulation (Pan et al., 2014; Akurathi et al., 2010; Lu et al., 2013; Doss et al., 2014; Rana et al., 2012; Peeters et al., 2015).

A new LMW CAIX targeting agent has recently been reported that is composed of two binding motifs, one accessing the CAIX active site and the other binding to an as yet unidentified site (Wichert et al., 2015). Conjugated with the infrared dye IRDye®750, the dual-motif inhibitor showed 10 % injected dose per gram of tumor (ID/g) tumor uptake. In comparison, agents targeting only the active site show 2 % ID/g tumor uptake (Wichert et al., 2015). However, this optical agent also demonstrated high kidney as well as other non-specific organ uptake at 24 h post-administration. Additionally, utility of this agent for *in vivo* studies is somewhat limited due to the substantial attenuation of light emission through tissue inherent to optical agents. Such limitations call for an agent that retains affinity for CAIX, but clears rapidly from non-target tissues and can be detected with existing clinical instrumentation.

ITM Exhibit 1004, Page 1475 of 1652

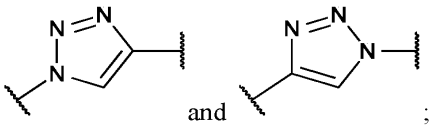
SUMMARY

In some aspects, the presently disclosed subject matter provides compounds of Formula (I):



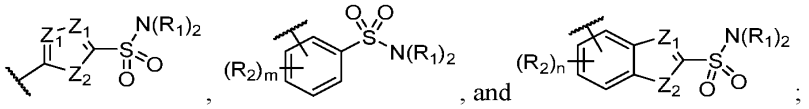
(I);

wherein: B is a metal chelating moiety optionally comprising a metal or a radiometal, or a halogenated or radio-halogenated prosthetic group; L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-; each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl; Tz is a triazole group selected from the group consisting of



and ;

S is a sulfonamide selected from the group consisting of:

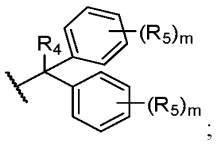


, , and ;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; m is an integer selected from the group consisting of 1, 2, 3, and 4; n is an integer selected from the group consisting of 1, 2, and 3; each Z_1 is independently selected from the group consisting of CR_3, and N; each Z_2 is

ITM Exhibit 1004, Page 1476 of 1652

independently selected from the group consisting of CR_3, and S; each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; A is



;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; R_5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In other aspects, the presently disclosed subject matter provides a method for imaging or treating one or more Carbonic Anhydrase IX-expressing tumors or cells, the method comprising contacting the one or more tumors or cells with an effective amount of a compound of formula (I), and making an image.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Figures as best described herein below.

ITM Exhibit 1004, Page 1477 of 1652

BRIEF DESCRIPTION OF THE FIGURES

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying Figures, which are not necessarily drawn to scale, and wherein:

FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D show (A) optical imaging agents **1** and **2** reported with dual-targeting moiety to CAIX (Wichert et al., 2015); (B) the epi-fluorescence imaging of two mice harboring CAIX expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1, 2, 4, 6, 8, 11 and 23h after injection of 3 nmol of compounds **1** and **2** via the tail vein; (C) quantitative biodistribution analysis of compounds **1** and **2**; compound accumulations in organs are reported as the percentage of injected dose per gram of tissue (% ID g−1) 24 h after intravenous administration of 3 nmol of **1** and of **2**; data points are averages of three mice; error bars indicate standard deviations; and (D) the epi-fluorescence imaging of various organs in a mouse; images were obtained at 24h after injection of 3 nmol of compound **1** via the tail vein;

FIG. 2A, FIG. 2B, and FIG. 2C show (A) the structure of FITC conjugated fluorescent ligand **8**; (B) FACS analysis of **8** for binding to CAIX-negative BxPC3 cells; and (C) FACS analysis of **8** for binding to CAIX-expressing SK-RC-52 cells; flow cytometry was done with **8** at 10 nM, 100 nM and 1μM with 30 min incubation;

FIG. 3A, FIG. 3B, and FIG. 3C show IC_{50} values of (A) positive control CAIX targeting agent **3**; (B) **XYIMSR-01**; and (C) [$^{113/115}$In]**XYIMSR-01**; the IC_{50} values were determined relative to the inhibition of fluorescence polarization of FITC labeled **8** with a known K_d of 0.2 nM for CAIX ; Compounds **3**, **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** demonstrate high binding affinity to CAIX;

FIG. 4A, FIG. 4B, FIG. 4C, and FIG. 4D show binding affinity of (A) **3**, (B) [$^{63/65}$Cu]**XYIMSR-06**, (C) [Al^{19}F]**XYIMSR-04**, and (D) [^{175}Lu]**XYIMSR-01**;

FIG.5 shows the synthesis scheme for compound **3**;

FIG.6 shows the synthesis scheme for compound **XYIMSR-01**;

FIG.7 shows the synthesis scheme for compound **XYIMSR-01**-[In];

FIG.8 shows the synthesis scheme for compound **XYIMSR-01**-[Ga];

FIG.9 shows the synthesis scheme for compound **XYIMSR-01**-[Lu];

FIG.10 shows the synthesis scheme for compound **XYIMSR-02**;

FIG.11 shows the synthesis scheme for compound **XYIMSR-03**;

FIG.12 shows the synthesis scheme for compound **XYIMSR-04**;

ITM Exhibit 1004, Page 1478 of 1652

FIG.13 shows the synthesis scheme for compound **XYIMSR-04**-[AlF];

FIG.14 shows the synthesis scheme for compound **XYIMSR-05**;

FIG.15 shows the synthesis scheme for compound **XYIMSR-06**;

FIG.16 shows the synthesis scheme for compound **XYIMSR-06**-Cu;

FIG.17 shows the SPECT/CT imaging of two mice harboring CAIX-expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1, 4, 8, 24 and 48 h after injection of 14.8 MBq (400 μCi) of [^{111}In]**XYIMSR-01** via the tail vein; arrows indicate tumors; [^{111}In]**XYIMSR-01** enabled specific imaging of CAIX-expressing SK-RC-52 tumors;

FIG.18 shows the SPECT/CT imaging of two mice harboring CAIX-expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1, 4, 8, 24 and 48 h after injection of 740 kBq (20 μCi) of [^{177}Lu]**XYIMSR-01** via the tail vein; arrows indicate tumors;

FIG.19 shows the PET/CT imaging of [Al^{18}F]**XYIMSR-04** in mice harboring CAIX-expressing SK-RC-52 tumors within the lower left flank; images were obtained at 1h after injection of 7.4 MBq (200 μCi) of [Al^{18}F]**XYIMSR-04** via the tail vein;

FIG. 20 shows PET/CT imaging of [^{64}Cu]**XYIMSR-06** in mice harboring CAIX-expressing SK-RC-52 tumors within the upper right flank; images were obtained at 1h after injection of 22.2 MBq (600 μCi) of[^{64}Cu]**XYIMSR-06** via the tail vein; arrows indicate tumors; and

FIG. 21 shows the treatment response of [^{177}Lu]**XYIMSR-01** in SK-RC-52 tumor mice.

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

DETAILED DESCRIPTION

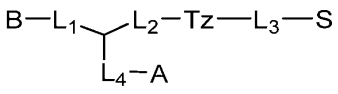
The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Figures, in which some, but not all embodiments of the inventions are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of

the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated Figures. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

I. NUCLEAR IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING CARBONIC ANHYDRASE IX AND USES THEREOF

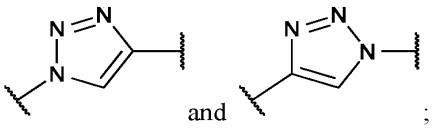
A. Compounds of Formula (I)

Accordingly, in some embodiments, the presently disclosed subject matter provides a compound of formula (I):



(I);

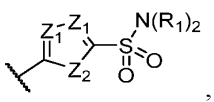
wherein: B is a metal chelating moiety optionally comprising a metal or a radiometal, or a halogenated or radio-halogenated prosthetic group; L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by -O-, -S-, or -(NR')-; each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl; Tz is a triazole group selected from the group consisting of



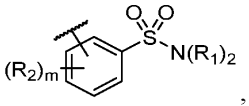
and

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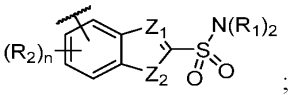
S is a sulfonamide selected from the group consisting of:



,



, and

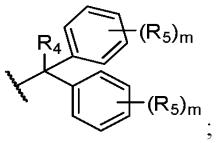


;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;each R_2 is selected from the group consisting of

ITM Exhibit 1004, Page 1480 of 1652

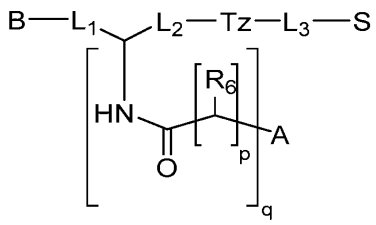
hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; m is an integer selected from the group consisting of 1, 2, 3, and 4; n is an integer selected from the group consisting of 1, 2, and 3;each Z_1 is independently selected from the group consisting of CR_3, and N; each Z_2 is independently selected from the group consisting of CR_3, and S; each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; A is



;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; R_5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

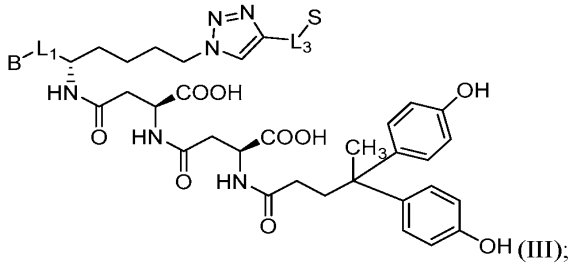
In particular embodiments, the compound of formula (I) is a compound of formula (II):



(II);

wherein: p is an integer selected from the group consisting of 0, 1, 2, 3, and 4; q is an integer selected from the group consisting of 1, 2, 3, and 4; each R_6 is independently selected from the group consisting of H and –COOR; or a pharmaceutically acceptable salt thereof.

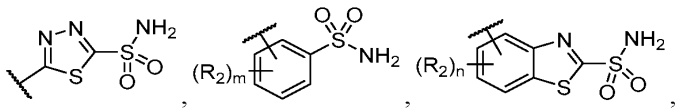
In further embodiments, the compound of formula (II) is a compound of formula (III):

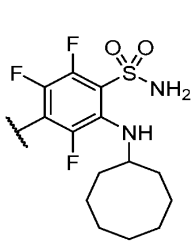


(III);

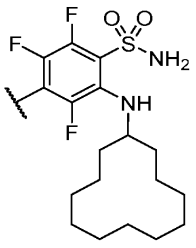
or a pharmaceutically acceptable salt thereof.

In yet further embodiments, S is selected from the group consisting of:



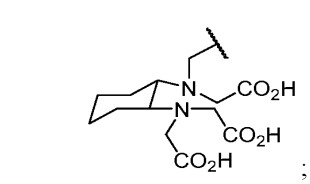
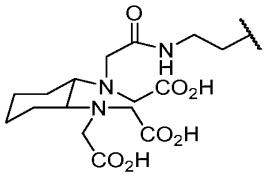
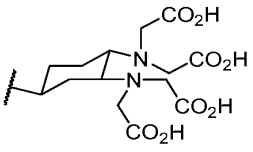
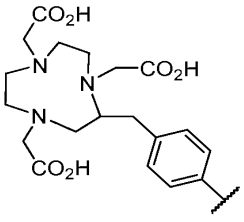
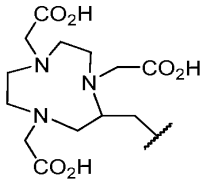
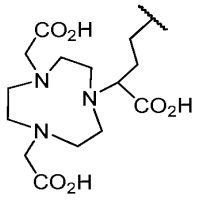
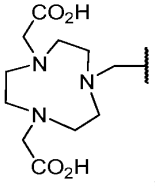
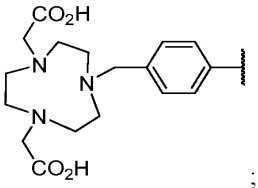
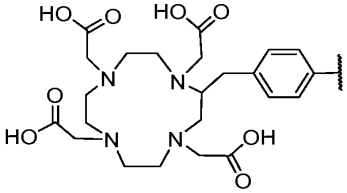
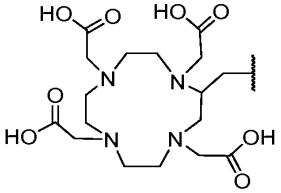
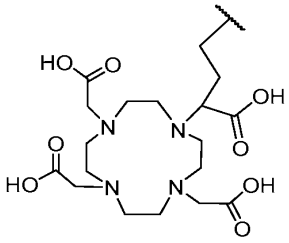
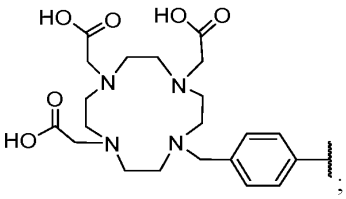
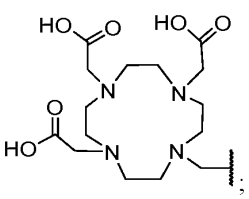
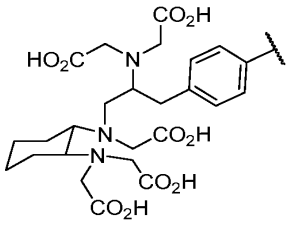
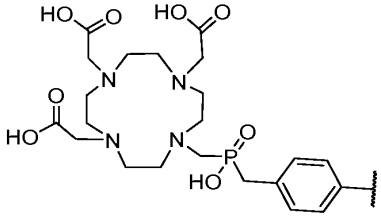


, and



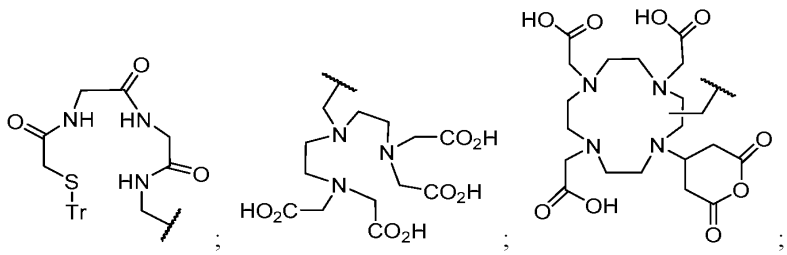
; or a pharmaceutically acceptable salt thereof.

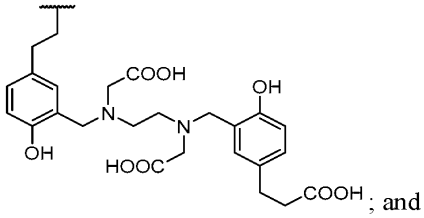
In particular embodiments, B is a metal chelating moiety optionally comprising a metal or a radiometal selected from the group of:

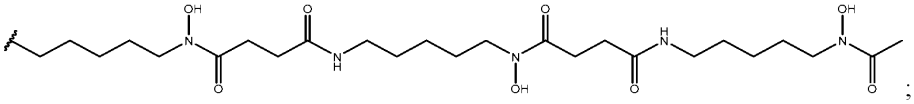

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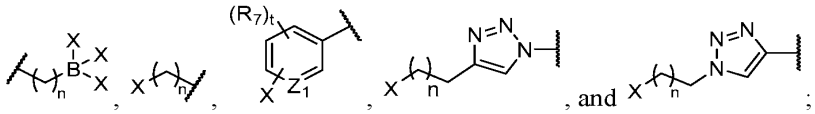
10


;


; and


;

or B is a halogenated or radio-halogenated prosthetic group selected from the group consisting of:


; and ;

wherein: X is a halogen or a radio-halogen; n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6; t is an integer selected from the group consisting of 1, 2, and 3; each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

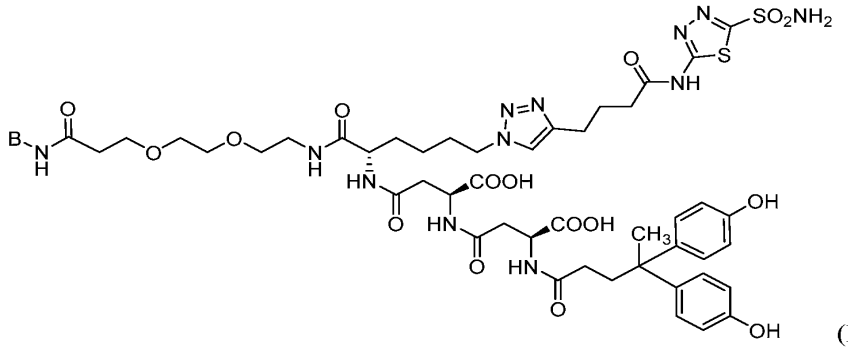
In certain embodiments, the metal chelating agent comprises a metal selected from the group consisting of: Y, Lu, Tc, Zr, In, Sm, Re, Cu, Pb, Ac, Bi, Al, Ga, Re, Ho and Sc. In other embodiments, the metal is a radiometal and is selected from the

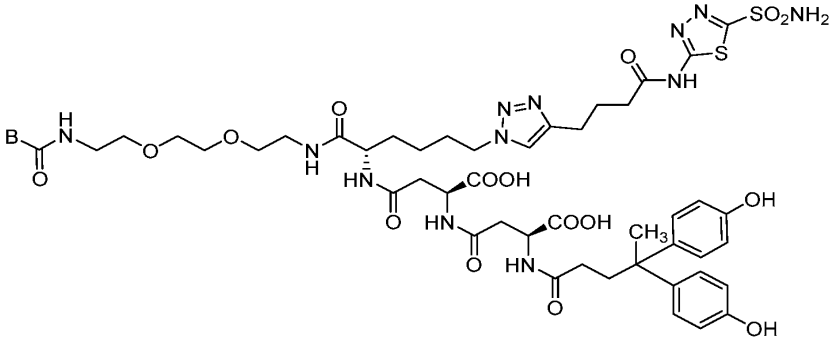
ITM Exhibit 1004, Page 1484 of 1652

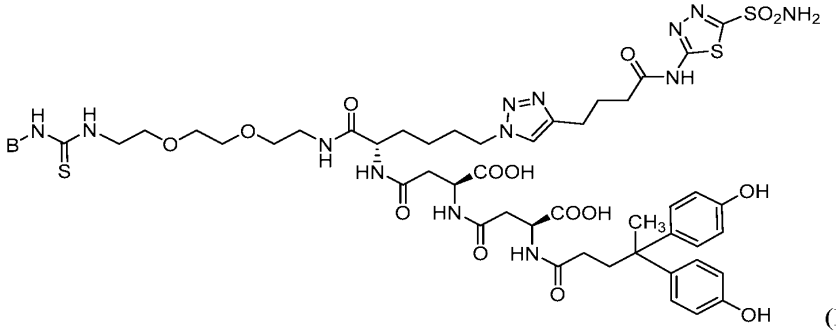
group consisting of ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho.

In further embodiments, halogen is selected from the group consisting of: F, Br, I, and At. In yet further embodiments, the radio-halogen is selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At.

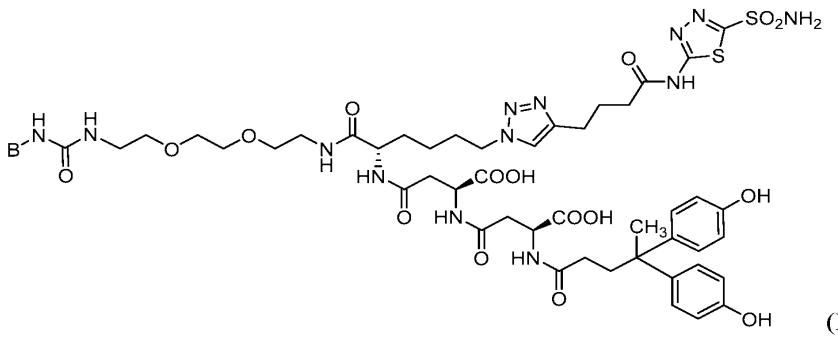
In certain embodiments, the compound of Formula (I) is selected from the group consisting of:


(IVa);


(IVb);


(IVc); and

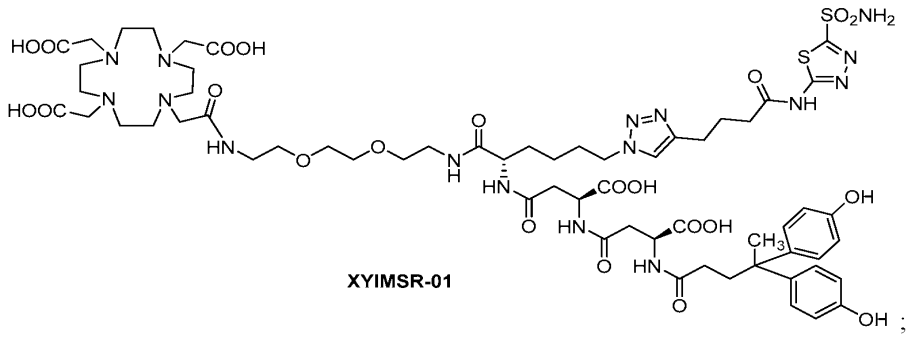
ITM Exhibit 1004, Page 1485 of 1652



(IVd);

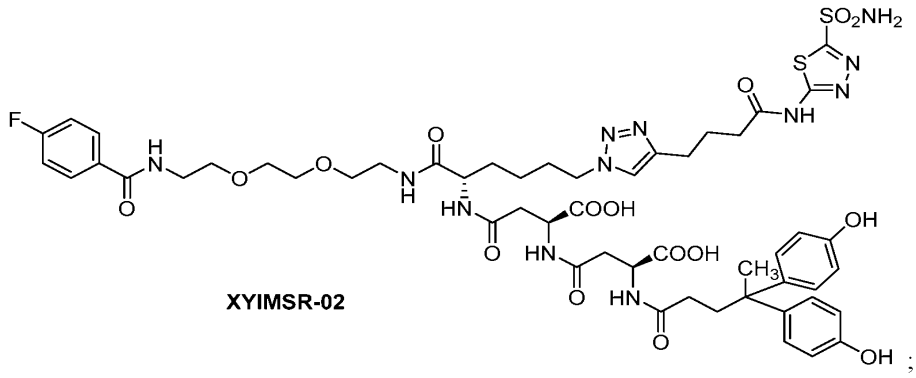
or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of Formula (I) is selected from the group consisting of:



XYIMSR-01

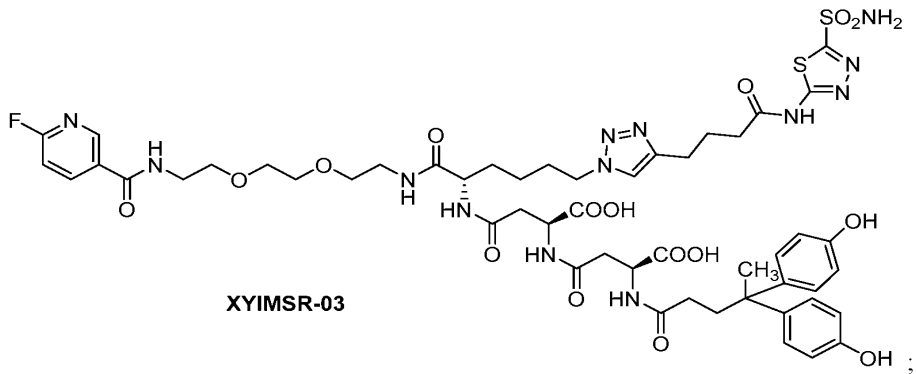
;



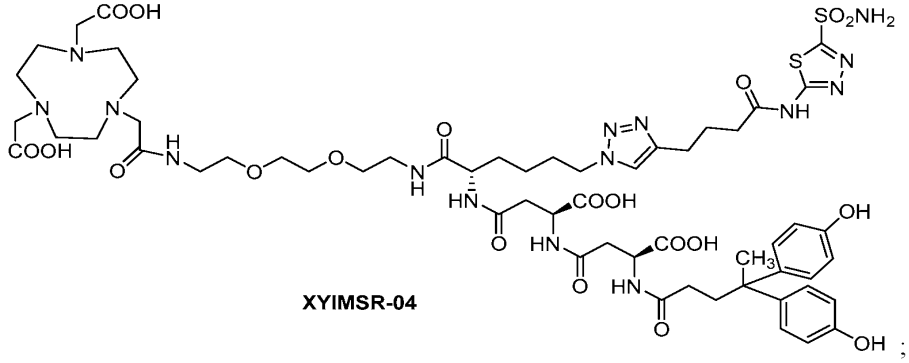
XYIMSR-02

;

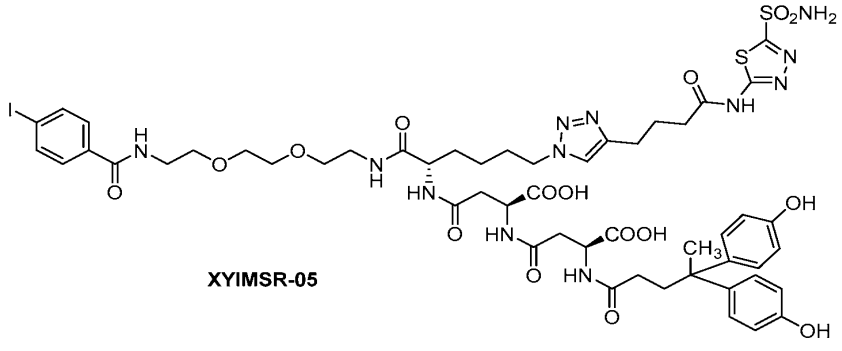
ITM Exhibit 1004, Page 1486 of 1652



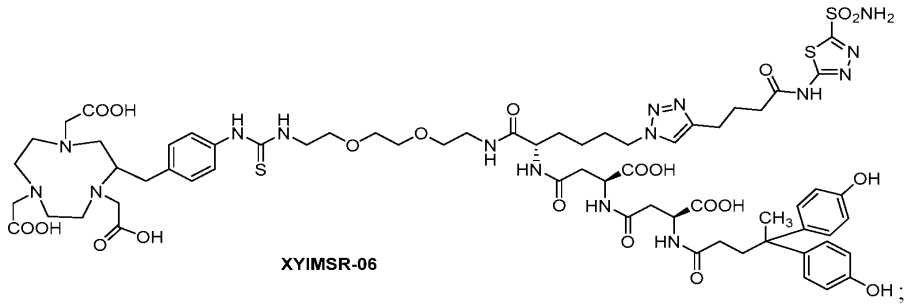
XYIMSR-03 ;



XYIMSR-04 ;



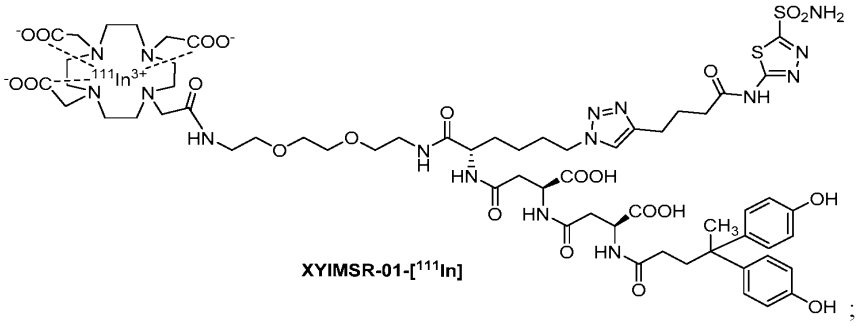
XYIMSR-05 ; and



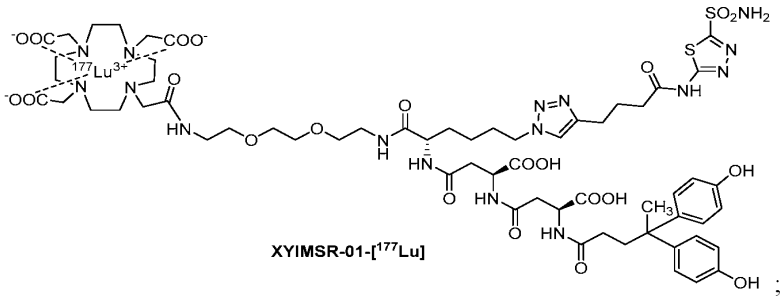
XYIMSR-06 ;

or a pharmaceutically acceptable salt thereof.

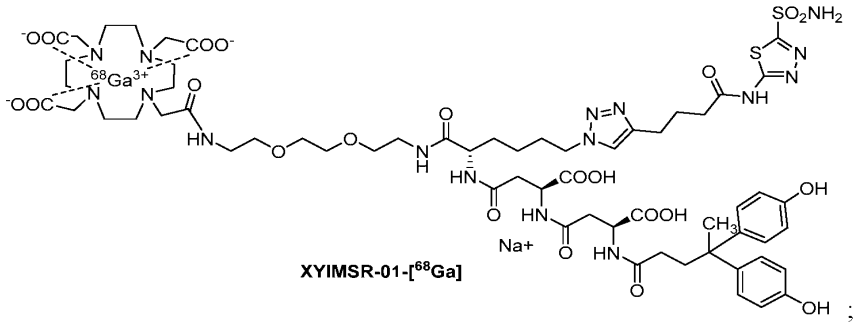
In other particular embodiments, the compound of formula (I) is selected from the group consisting of:



XYIMSR-01-[^{111}In] ;

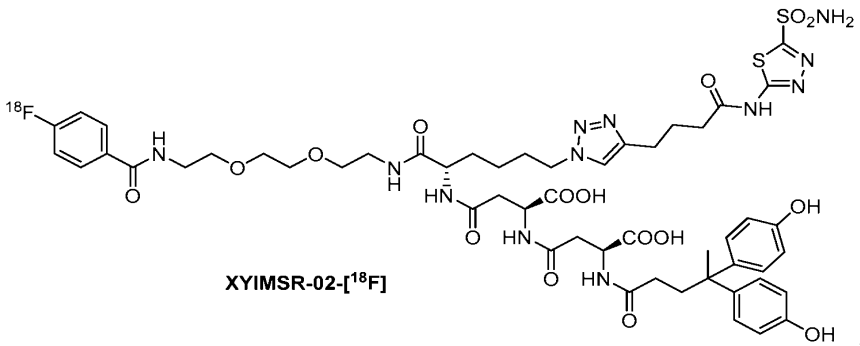


XYIMSR-01-[^{177}Lu] ;

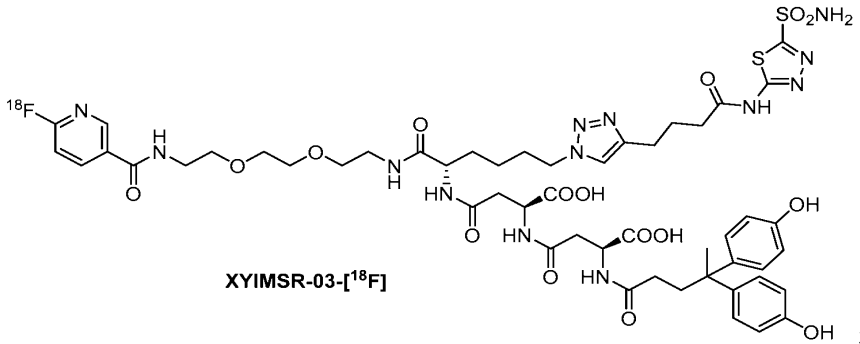


XYIMSR-01-[^{68}Ga] ;

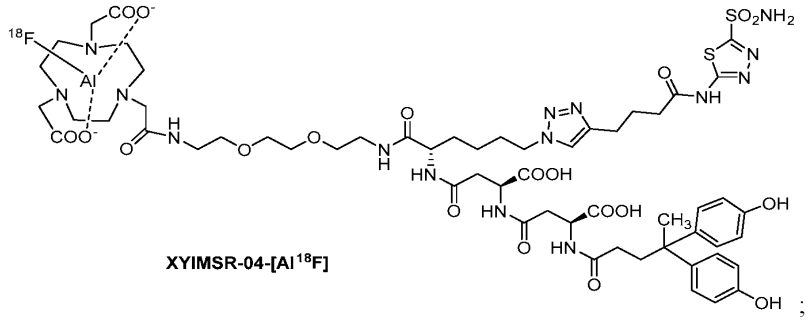
ITM Exhibit 1004, Page 1488 of 1652



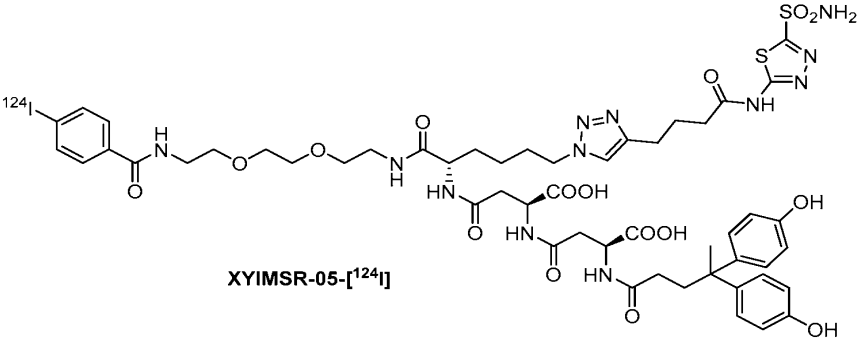
XYIMSR-02-[^{18}F] ;



XYIMSR-03-[^{18}F] ;

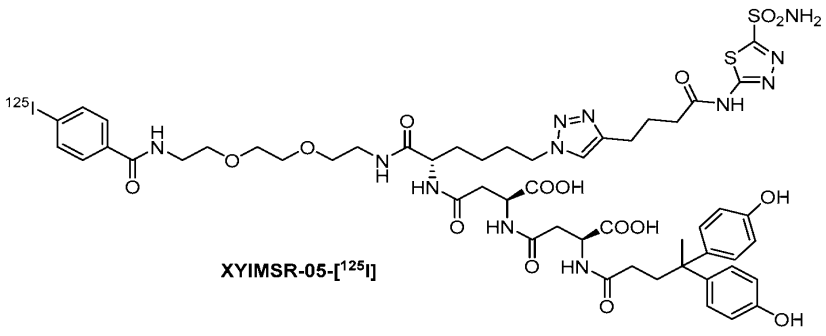


XYIMSR-04-[Al^{18}F] ;

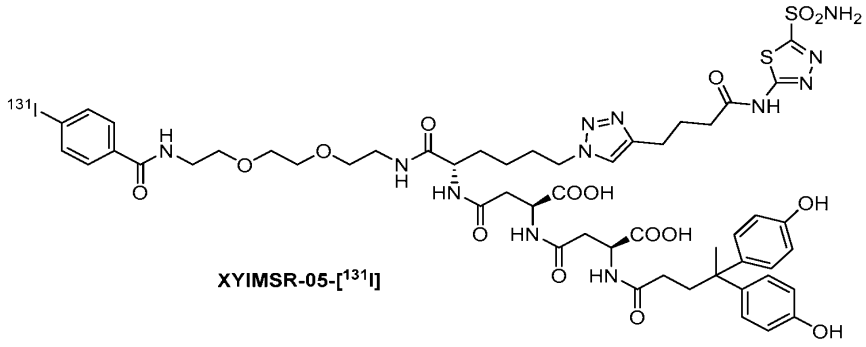


XYIMSR-05-[^{124}I] ;

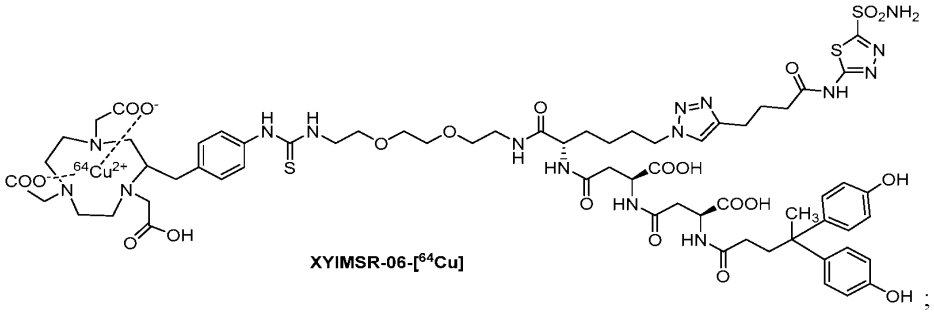
ITM Exhibit 1004, Page 1489 of 1652



XYIMSR-05-[^{125}I] ;



XYIMSR-05-[^{131}I] ; and

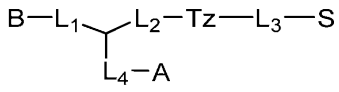


XYIMSR-06-[^{64}Cu] ;

or a pharmaceutically acceptable salt thereof.

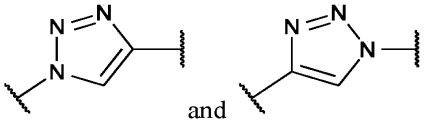
B. Methods of Using Compounds of Formula (I) for Imaging or Treating a Carbonic Anhydrase IX-Expressing Tumor or Cell

Accordingly, in some embodiments, the presently disclosed subject matter provides a method for imaging or treating one or more Carbonic Anhydrase IX expressing tumors or cells, the method comprising contacting the one or more tumors or cells with an effective amount of a compound of formula (I) and making an image, the compound of formula (I) comprising:



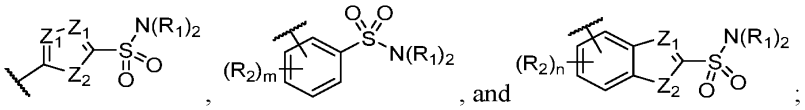
(I);

wherein: B is a metal chelating moiety comprising a radiometal, or a radio-halogenated prosthetic group; L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-; each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl; Tz is a triazole group selected from the group consisting of



and ;

S is a sulfonamide targeting a catalytic pocket of CAIX selected from the group consisting of:

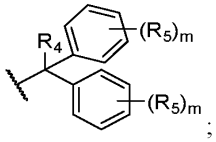


, , and ;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl; each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; m is an integer selected from the group consisting of 1, 2, 3, and 4; n is an integer selected from the group consisting of 1, 2, and 3; each Z_1 is independently selected from the group consisting of CR_3, and N; each Z_2 is independently selected from the group consisting of CR_3, and S; each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl,

ITM Exhibit 1004, Page 1491 of 1652

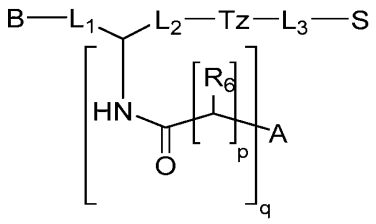
substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; A is



;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; R_5 is independently selected from the group consisting hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of formula (I) is a compound of formula (II):

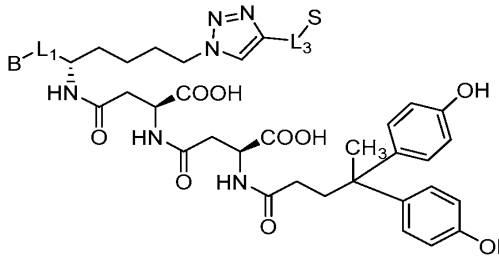


(II);

wherein: p is an integer selected from the group consisting of 0, 1, 2, 3, and 4; q is an integer selected from the group consisting of 1, 2, 3, and 4; each R_6 is independently selected from the group consisting of H and –COOR; or a pharmaceutically acceptable salt thereof.

In further embodiments, the compound of formula (II) is a compound of formula (III):

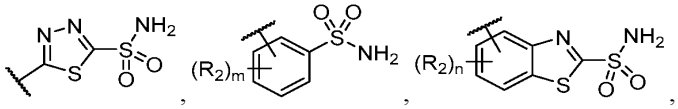
ITM Exhibit 1004, Page 1492 of 1652

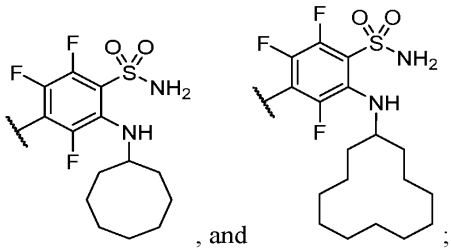


(III);

or a pharmaceutically acceptable salt thereof.

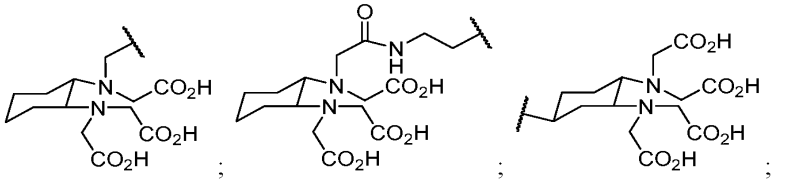
In yet further embodiments, S is selected from the group consisting of:

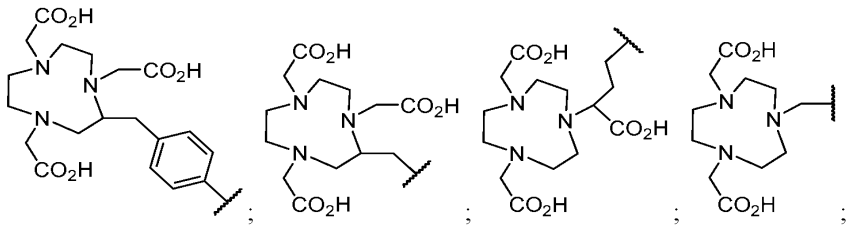




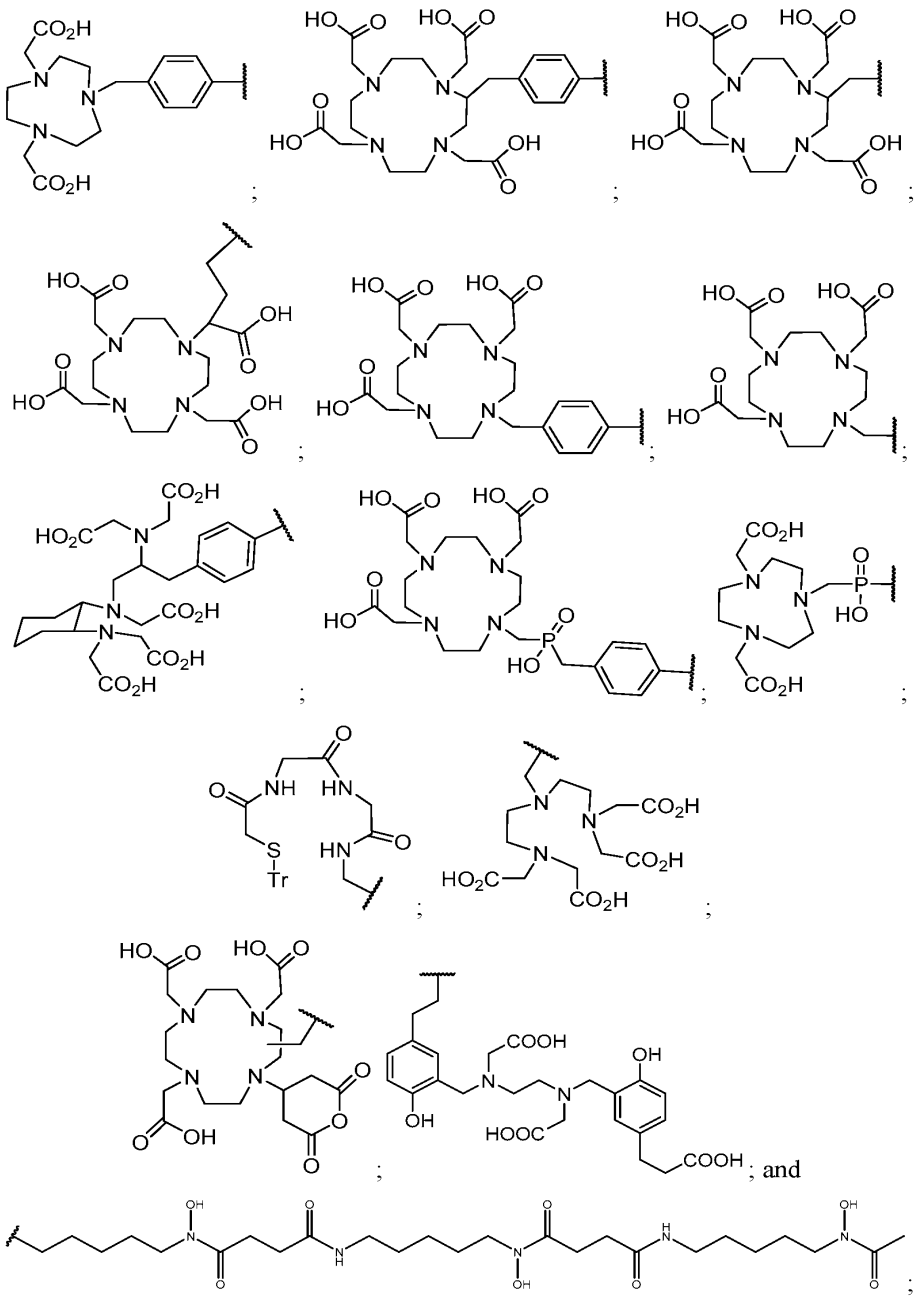
, and ; or a pharmaceutically acceptable salt thereof.

In particular embodiments, B is a metal chelating moiety comprising a radiometal selected from the group of:

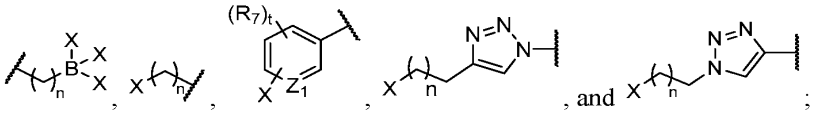




ITM Exhibit 1004, Page 1493 of 1652



or B is a radio-halogenated prosthetic group selected from the group consisting of:

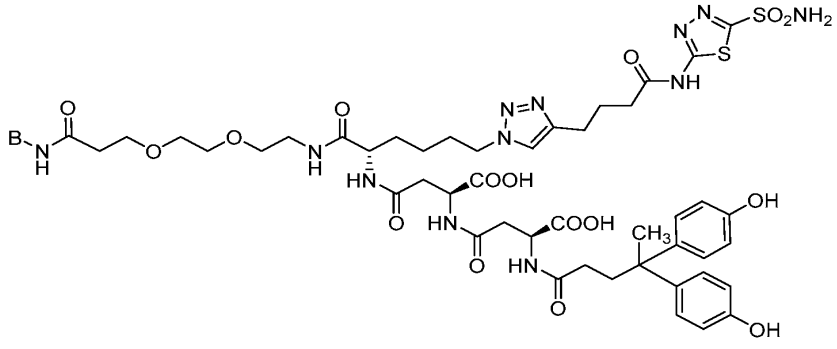


wherein: X is a radio-halogen; n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6; t is an integer selected from the group consisting of 1, 2, and 3; each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the radiometal is selected from the group consisting of ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho.

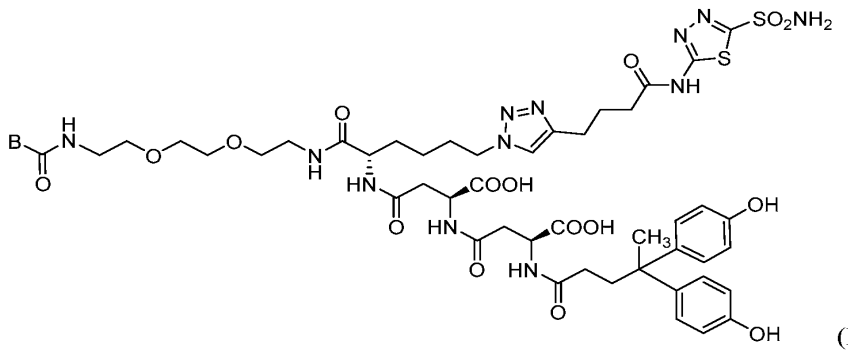
In other embodiments, the radio-halogen is selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At.

In certain embodiments, the compound of Formula (I) is selected from the group consisting of:

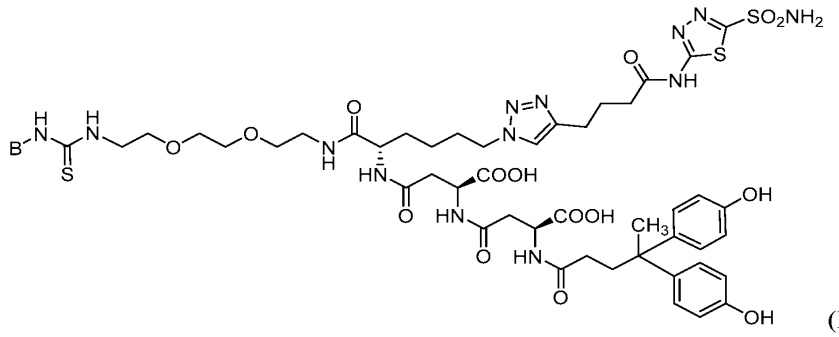


(IVa);

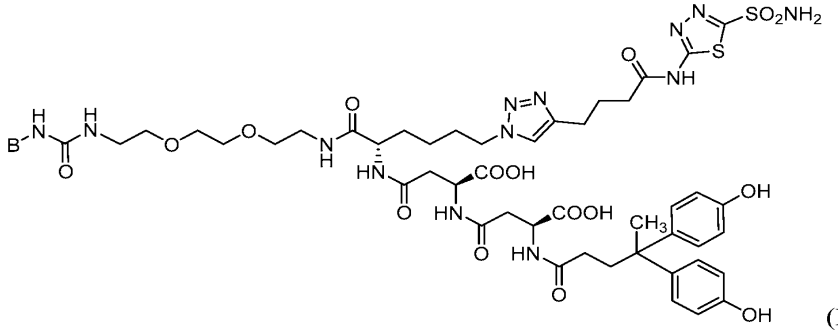
ITM Exhibit 1004, Page 1495 of 1652



(IVb);



(IVc); and

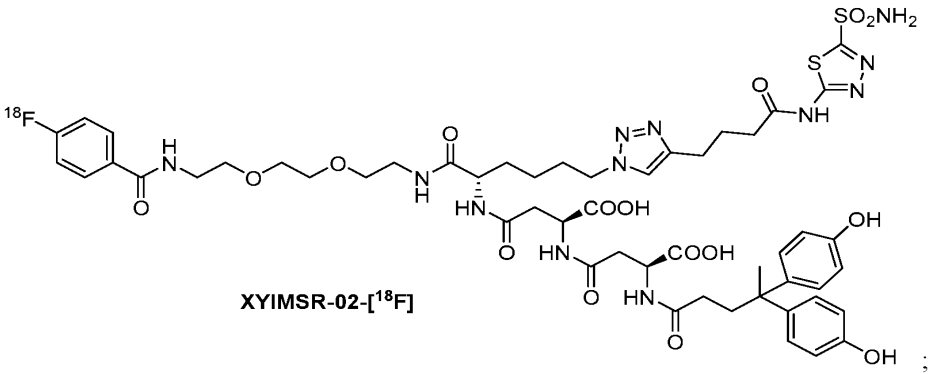


(IVd);

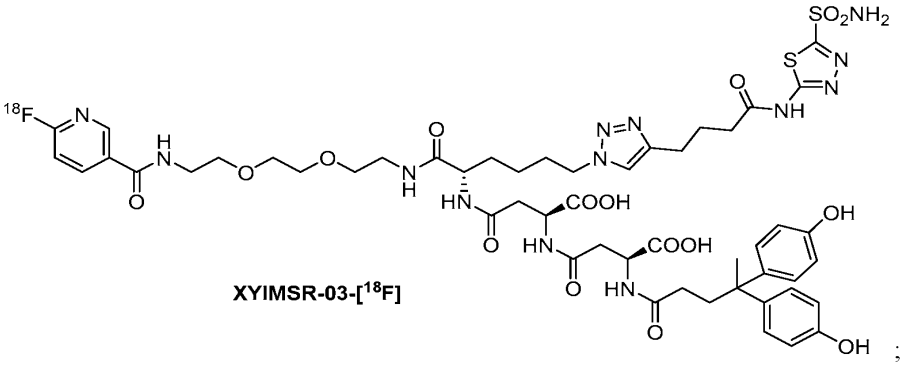
or a pharmaceutically acceptable salt thereof.

In particular embodiments, the compound of Formula (I) is selected from the group consisting of:

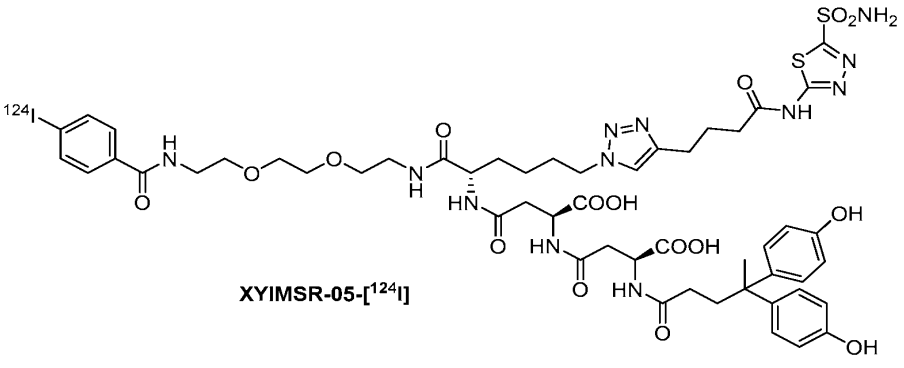
ITM Exhibit 1004, Page 1496 of 1652



XYIMSR-02-[^{18}F] ;

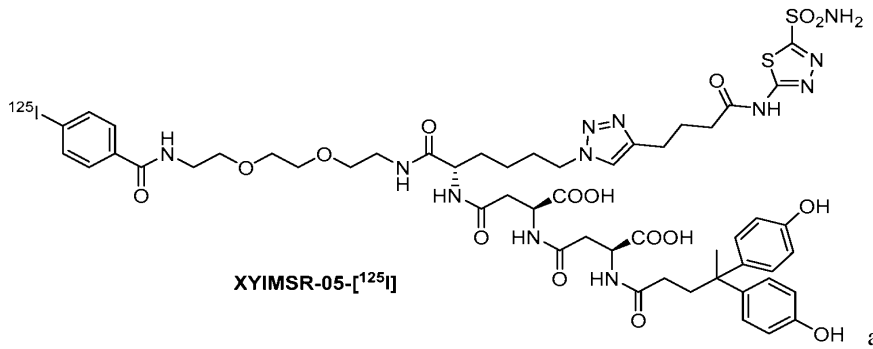


XYIMSR-03-[^{18}F] ;



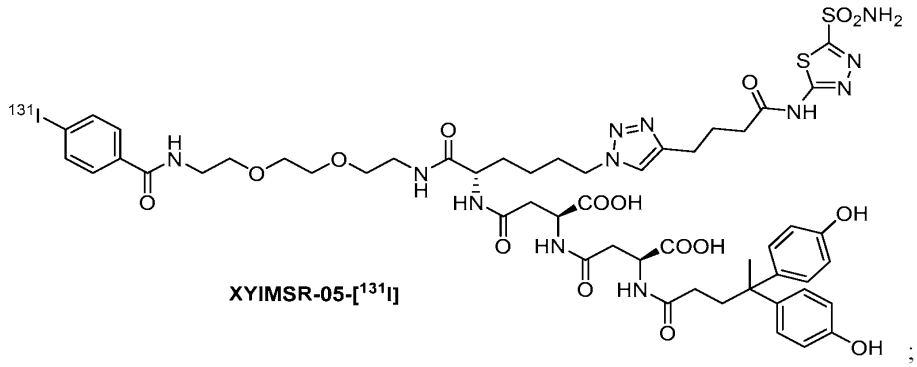
XYIMSR-05-[^{124}I] ;

ITM Exhibit 1004, Page 1497 of 1652



XYIMSR-05-[^{125}I]

and

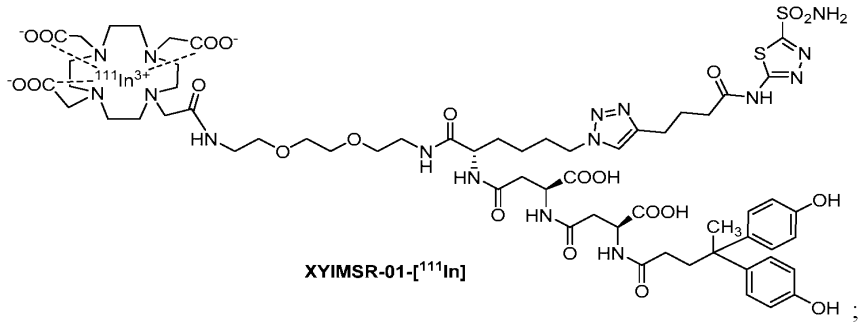


XYIMSR-05-[^{131}I]

;

or a pharmaceutically acceptable salt thereof.

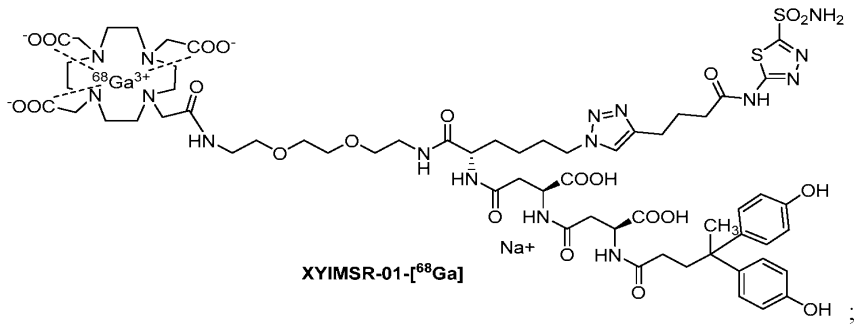
In other particular embodiments, the compound of formula (I) is selected from the group consisting of:



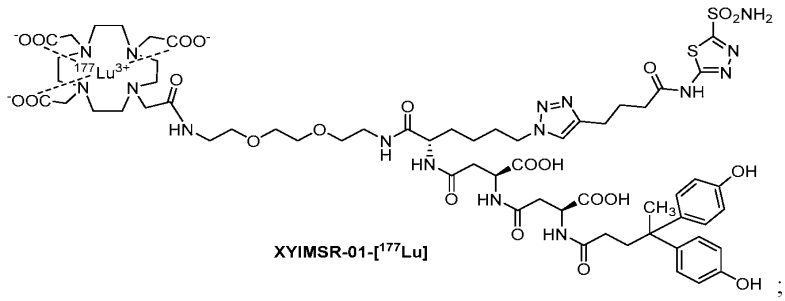
XYIMSR-01-[^{111}In]

;

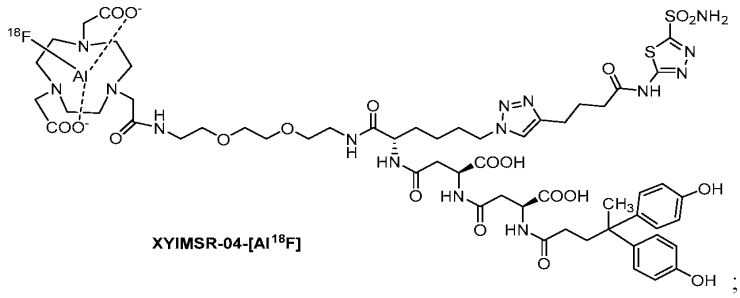
ITM Exhibit 1004, Page 1498 of 1652



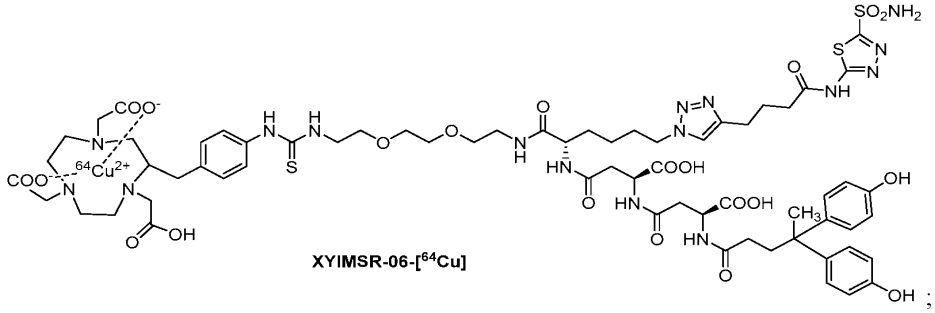
XYIMSR-01-[^{68}Ga] ;



XYIMSR-01-[^{177}Lu] ;



XYIMSR-04-[Al^{18}F] ; and



XYIMSR-06-[^{64}Cu] ;

or a pharmaceutically acceptable salt thereof.

"Contacting" means any action which results in at least one compound comprising the imaging agent of the presently disclosed subject matter physically contacting at least one CAIX-expressing tumor or cell. Contacting can include

exposing the cell(s) or tumor(s) to the compound in an amount sufficient to result in contact of at least one compound with at least one cell or tumor. The method can be practiced *in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube. The method can be practiced *in vivo*, in which case contacting means exposing at least one cell or tumor in a subject to at least one compound of the presently disclosed subject matter, such as administering the compound to a subject via any suitable route. According to the presently disclosed subject matter, contacting may comprise introducing, exposing, and the like, the compound at a site distant to the cells to be contacted, and allowing the bodily functions of the subject, or natural (e.g., diffusion) or man-induced (e.g., swirling) movements of fluids to result in contact of the compound and cell(s) or tumor(s).

By "making an image," it is meant using PET or SPECT to form an image of a cell, tissue, tumor, part of body, and the like.

As used herein, the term "treating" can include reversing, alleviating, inhibiting the progression of, preventing or reducing the likelihood of the cancer to which such term applies, or one or more symptoms or manifestations of such disease, disorder or condition, including killing or eliminating an infectious agent. Preventing refers to causing a disease, disorder, condition, or symptom or manifestation of such, or worsening of the severity of such, not to occur.

In other embodiments, the one or more Carbonic Anhydrase IX-expressing tumors or cells is selected from the group consisting of: a renal cell carcinoma, a prostate tumor or cell, a metastasized prostate tumor or cell, a lung tumor or cell, a renal tumor or cell, a glioblastoma, a pancreatic tumor or cell, a bladder tumor or cell, a sarcoma, a melanoma, a breast tumor or cell, a colon tumor or cell, a germ cell, a pheochromocytoma, an esophageal tumor or cell, a stomach tumor or cell, and combinations thereof. In specific embodiments, the one or more Carbonic Anhydrase IX-expressing tumors or cells is a renal cell carcinoma. In other embodiments, the one or more Carbonic Anhydrase IX expressing tumors or cells is *in vitro*, *in vivo*, or *ex vivo*. In particular embodiments, the one or more Carbonic Anhydrase IX-expressing tumors or cells is present in a subject.

The subject treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which

are intended to be included in the term "subject." Accordingly, a "subject" can include a human subject for medical purposes, such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal (non-human) subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but not limited to, primates, e.g., humans, monkeys, apes, and the like; bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a "subject" can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms "subject" and "patient" are used interchangeably herein.

In some embodiments, a detectably effective amount of the imaging agent of the presently disclosed methods is administered to a subject. In accordance with the presently disclosed subject matter, "a detectably effective amount" of the imaging agent is defined as an amount sufficient to yield an acceptable image using equipment which is available for clinical use. A detectably effective amount of the imaging agent may be administered in more than one injection. The detectably effective amount of the imaging agent can vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual, the dosimetry, and instrument and film-related factors. Optimization of such factors is well within the level of skill in the art.

It is preferable that the compounds of the presently disclosed subject matter are excreted from tissues of the body quickly. Typically compounds of the presently disclosed subject matter are eliminated from the body in less than about 48 hours. More preferably, compounds of the presently disclosed subject matter are eliminated from the body in less than about 24 hours, 16 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 90 minutes, or 60 minutes.

In some embodiments, the presently disclosed methods comprise clearance of the compound comprising the imaging agent from the tumor or cell in the subject. In

ITM Exhibit 1004, Page 1501 of 1652

some other embodiment, the imaging agent is cleared more rapidly from a subject's kidneys than from a tumor in the subject.

In some embodiments, the presently disclosed methods use compounds that are stable *in vivo* such that substantially all, e.g., more than about 50%, 60%, 70%, 80%, or more preferably 90% of the injected compound is not metabolized by the body prior to excretion. In other embodiments, the compound comprising the imaging agent is stable *in vivo*.

In general, the "effective amount" of an active agent refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent or device may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target tissue, and the like.

In some embodiments, the disease or condition is a cancer. Accordingly, the presently disclosed compounds can be administered prophylactically to prevent or reduce the incidence or recurrence of the cancer.

A "cancer" in a subject refers to the presence of cells possessing characteristics typical of cancer-causing cells, for example, uncontrolled proliferation, loss of specialized functions, immortality, significant metastatic potential, significant increase in anti-apoptotic activity, rapid growth and proliferation rate, and certain characteristic morphology and cellular markers. In some circumstances, cancer cells will be in the form of a tumor; such cells may exist locally within a subject, or circulate in the blood stream as independent cells, for example, leukemic cells.

A cancer can include, but is not limited to, renal cancer, head cancer, neck cancer, head and neck cancer, lung cancer, breast cancer, prostate cancer, colorectal cancer, esophageal cancer, stomach cancer, leukemia/lymphoma, uterine cancer, skin cancer, endocrine cancer, urinary cancer, pancreatic cancer, gastrointestinal cancer, ovarian cancer, cervical cancer, and adenomas. In some embodiments, a detectably effective amount of the therapeutic agent of the presently disclosed methods is administered to a subject.

In any of the above-described methods, the administering of a compound can result in at least about a 10% , 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100% decrease in the amount of Carbonic Anhydrase IX released.

C. Pharmaceutical Compositions and Administration

In another aspect, the present disclosure provides a pharmaceutical composition including one compounds of formula (I), formula (II), formula (III) formula (IVa), formula (IVb), formula (IVc), and/or formula (IVd), alone or in combination with one or more additional therapeutic agents in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the compounds described above. Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

The term "combination" is used in its broadest sense and means that a subject is administered at least two agents, more particularly a compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and optionally, one or more therapeutic agents. More particularly, the term "in combination" refers to the concomitant administration of two (or more) active agents for the treatment of a, e.g., single disease state. As used herein, the active agents may be combined and administered in a single dosage form, may be administered as separate dosage forms at the same time, or may be administered as separate dosage forms that are administered alternately or sequentially on the same or separate days. In one embodiment of the presently disclosed subject matter, the active agents are combined and administered in a single dosage form. In another embodiment, the active agents are administered in separate dosage forms (e.g., wherein it is desirable to vary the amount of one but not the other). The single dosage form may include additional active agents for the treatment of the disease state.

Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

The timing of administration of a compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent can be varied so long as the beneficial effects of the combination of these agents are achieved. Accordingly, the phrase "in combination with" refers to the administration of a compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent either simultaneously, sequentially, or a combination thereof. Therefore, a subject administered a combination of a compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent can receive compound of Formula (I) including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent at the same time (i.e., simultaneously) or at different times (i.e., sequentially, in either order, on the same day or on different days), so long as the effect of the combination of both agents is achieved in the subject.

When administered sequentially, the agents can be administered within 1, 5, 10, 30, 60, 120, 180, 240 minutes or longer of one another. In other embodiments, agents administered sequentially, can be administered within 1, 5, 10, 15, 20 or more days of one another. Where the compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd),), and at least one additional therapeutic agent are administered simultaneously, they can be administered to the subject as separate pharmaceutical compositions, each comprising either a compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), or at least one additional therapeutic agent, or they can be administered to a subject as a single pharmaceutical composition comprising both agents.

When administered in combination, the effective concentration of each of the agents to elicit a particular biological response may be less than the effective concentration of each agent when administered alone, thereby allowing a reduction in the dose of one or more of the agents relative to the dose that would be needed if the agent was administered as a single agent. The effects of multiple agents may, but need not be, additive or synergistic. The agents may be administered multiple times.

ITM Exhibit 1004, Page 1504 of 1652

In some embodiments, when administered in combination, the two or more agents can have a synergistic effect. As used herein, the terms "synergy," "synergistic," "synergistically" and derivations thereof, such as in a "synergistic effect" or a "synergistic combination" or a "synergistic composition" refer to circumstances under which the biological activity of a combination of a compound of Formula (I), including compounds of formula (II), (III), (IVa), (IVb), (IVc), and/or (IVd), and at least one additional therapeutic agent is greater than the sum of the biological activities of the respective agents when administered individually.

Synergy can be expressed in terms of a "Synergy Index (SI)," which generally can be determined by the method described by F. C. Kull et al., Applied Microbiology 9, 538 (1961), from the ratio determined by:

$$Q_a/Q_A + Q_b/Q_B = \text{Synergy Index (SI)}$$

wherein:

Q_A is the concentration of a component A, acting alone, which produced an end point in relation to component A;

Q_a is the concentration of component A, in a mixture, which produced an end point;

Q_B is the concentration of a component B, acting alone, which produced an end point in relation to component B; and

Q_b is the concentration of component B, in a mixture, which produced an end point.

Generally, when the sum of Q_a/Q_A and Q_b/Q_B is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated. When the sum is less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. Thus, a "synergistic combination" has an activity higher that what can be expected based on the observed activities of the individual components when used alone. Further, a "synergistically effective amount" of a component refers to the amount of the component necessary to elicit a synergistic effect in, for example, another therapeutic agent present in the composition.

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable

ITM Exhibit 1004, Page 1505 of 1652

acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-toluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by

ITM Exhibit 1004, Page 1506 of 1652

inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra -sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption promoters; and fluorocarbons.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the

ITM Exhibit 1004, Page 1507 of 1652

form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl- cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

D. Kits

In yet other embodiments, the presently disclosed subject matter provides a kit comprising a compound of formula (I), formula (II), formula (III), formula (IVa), formula (IVb), formula (IVc), and/or formula (IVd). In certain embodiments, the kit provides packaged pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent, or excipient, and a presently disclosed compound. In certain embodiments the packaged pharmaceutical composition will comprise the reaction precursors necessary to generate the compound of the invention upon combination with a radio labeled precursor. Other packaged pharmaceutical compositions provided by the present invention further comprise indicia comprising at least one of: instructions for preparing compounds according to the invention from supplied precursors, instructions for using the composition to image cells or tissues expressing Carbonic Anhydrase IX, or instructions for using the composition to image glutamatergic neurotransmission in a patient suffering from a stress-related disorder, or instructions for using the composition to image prostate cancer.

II. Definitions

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of Formula (I) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term "optionally" or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art, to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position.

ITM Exhibit 1004, Page 1509 of 1652

The substituents also may be further substituted (e.g., an aryl group substituent may have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$; $-C(=O)O-$ is equivalent to $-OC(=O)-$; $-OC(=O)NR-$ is equivalent to $-NRC(=O)O-$, and the like.

When the term "independently selected" is used, the substituents being referred to (e.g., R groups, such as groups R_1, R_2, and the like, or variables, such as "m" and "n"), can be identical or different. For example, both R_1 and R_2 can be substituted alkyls, or R_1 can be hydrogen and R_2 can be a substituted alkyl, and the like.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named "R" or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise herein. For the purposes of illustration, certain representative "R" groups as set forth above are defined below.

Description of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

Unless otherwise explicitly defined, a "substituent group," as used herein, includes a functional group selected from one or more of the following moieties, which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions. The hydrocarbon may be unsaturated, saturated, branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term "alkyl" refers to C_{1-20} inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., "straight-chain"), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers thereof.

"Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. "Lower alkyl" refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C_{1-8} alkyl), e.g., 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "Higher alkyl" refers to an alkyl group having about 10 to about 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, "alkyl" refers, in particular, to C_{1-8} straight-chain alkyls. In other embodiments, "alkyl" refers, in particular, to C_{1-8} branched-chain alkyls.

ITM Exhibit 1004, Page 1511 of 1652

Alkyl groups can optionally be substituted (a "substituted alkyl") with one or more alkyl group substituents, which can be the same or different. The term "alkyl group substituent" includes but is not limited to alkyl, substituted alkyl, halo, arylamino, acyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, lower alkyl (also referred to herein as "alkylaminoalkyl"), or aryl.

Thus, as used herein, the term "substituted alkyl" includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_{25}-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)NR', -NR'R", -OR', -SR, -S(O)R, and/or $-S(O_2)R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific

ITM Exhibit 1004, Page 1512 of 1652

heteroalkyl groups, such as -NR'R" or the like.

"Cyclic" and "cycloalkyl" refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The cycloalkyl group can be optionally partially unsaturated. The cycloalkyl group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor, camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

The term "cycloalkylalkyl," as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkyl group, also as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "cycloheteroalkyl" or "heterocycloalkyl" refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10-member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from the group consisting of nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocylic refers to a non-aromatic 5-, 6-, or 7-membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has

0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4- morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C_{1-20} inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadiene, cyclohexenyl, 1,3-cyclohexadiene, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

ITM Exhibit 1004, Page 1514 of 1652

The term "alkynyl" as used herein refers to a monovalent group derived from a straight or branched C_{1-20} hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term "alkylene" by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene ($–CH_2–$); ethylene ($–CH_2–CH_2–$); propylene ($–(CH_2)_3–$); cyclohexylene ($–C_6H_{10}–$); –CH=CH–CH=CH–; –CH=CH–CH_2–; -$CH_2CH_2CH_2CH_2$-, -CH_2CH=$CHCH_2$-, -CH_2CsCCH_2-, -$CH_2CH_2CH(CH_2CH_2CH_3)CH_2$-, -$(CH_2)_q$-N(R)-$(CH_2)_r$–, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxyl (–O–CH_2–O–); and ethylenedioxyl (-O-$(CH_2)_2$–O–). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- and –R'OC(O)-.

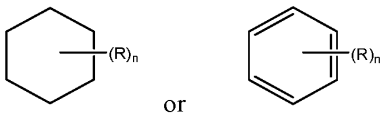
ITM Exhibit 1004, Page 1515 of 1652

The term "aryl" means, unless otherwise stated, an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4- oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4- pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5- isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl" and "heteroarylalkyl" are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

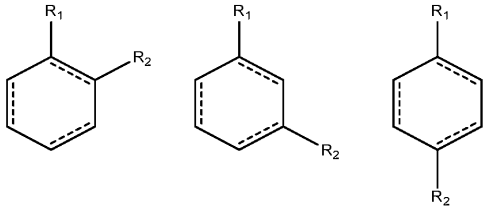
Further, a structure represented generally by the formula:



or

ITM Exhibit 1004, Page 1516 of 1652

as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable "n," which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from the group consisting of a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

The symbol (~~~~~) denotes the point of attachment of a moiety to the remainder of the molecule.

When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being "absent," the named atom is replaced by a direct bond.

Each of above terms (e.g. , "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl," "phosphonate," and "sulfonate" as well as their divalent derivatives) are meant to include both substituted and unsubstituted forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent

ITM Exhibit 1004, Page 1517 of 1652

and divalent derivative groups (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R',-C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"C(O)OR', -NR-C(NR'R")=NR'", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 in a number ranging from zero to (2m'+l), where m' is the total number of carbon atoms in such groups. R', R", R'" and R"" each may independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'" and R"" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7- membered ring. For example, -NR'R" is meant to include, but not be limited to, 1- pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF_3 and -CH_2CF_3) and acyl (e.g., -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"C(O)OR', -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'" -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxo, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R'" and R"" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'" and R"" groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R'")_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R" and R'" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term "acyl" refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula RC(=O)-, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocylic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term "acyl" specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl)- and a 2-phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, -RC(=O)NR', esters, -RC(=O)OR', ketones, -RC(=O)R', and aldehydes, -RC(=O)H.

The terms "alkoxyl" or "alkoxy" are used interchangeably herein and refer to a saturated (i.e., alkyl–O–) or unsaturated (i.e., alkenyl–O– and alkynyl–O–) group attached to the parent molecular moiety through an oxygen atom, wherein the terms "alkyl," "alkenyl," and "alkynyl" are as previously described and can include C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

"Aryloxyl" refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term "aryloxyl" as used herein can refer to phenyloxyl or hexyloxyl, and alkyl, substituted alkyl, halo, or alkoxyl substituted phenyloxyl or hexyloxyl.

"Aralkyl" refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described, and included substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

"Aralkyloxyl" refers to an aralkyl-O– group wherein the aralkyl group is as previously described. An exemplary aralkyloxyl group is benzyloxyl, i.e., C_6H_5-CH_2-O-. An aralkyloxyl group can optionally be substituted.

"Alkoxycarbonyl" refers to an alkyl-O-C(=O)– group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl, and *tert*-butyloxycarbonyl.

"Aryloxycarbonyl" refers to an aryl-O-C(=O)– group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxy-carbonyl.

"Aralkoxycarbonyl" refers to an aralkyl-O-C(=O)– group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" refers to an amide group of the formula –C(=O)NH_2. "Alkylcarbamoyl" refers to a R'RN–C(=O)– group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described. "Dialkylcarbamoyl" refers to a R'RN–C(=O)– group wherein each of R and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxyl, as used herein, refers to a carbonate group of the formula -O-C(=O)-OR.

"Acyloxyl" refers to an acyl-O- group wherein acyl is as previously described.

The term "amino" refers to the –NH_2 group and also refers to a nitrogen containing group as is known in the art derived from ammonia by the replacement of one or more hydrogen radicals by organic radicals. For example, the terms "acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups respectively.

An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and

trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure –NHR' wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group having the structure –NR'R", wherein R' and R" are each independently selected from the group consisting of alkyl groups. The term trialkylamino refers to a group having the structure –NR'R"R"', wherein R', R", and R"' are each independently selected from the group consisting of alkyl groups. Additionally, R', R", and/or R"' taken together may optionally be $–(CH_2)_k–$ where k is an integer from 2 to 6. Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl–S–) or unsaturated (i.e., alkenyl–S– and alkynyl–S–) group attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

"Acylamino" refers to an acyl-NH– group wherein acyl is as previously described. "Aroylamino" refers to an aroyl-NH– group wherein aroyl is as previously described.

The term "carbonyl" refers to the –C(=O)– group, and can include an aldehyde group represented by the general formula R-C(=O)H.

The term "carboxyl" refers to the –COOH group. Such groups also are referred to herein as a "carboxylic acid" moiety.

The terms "halo," "halide," or "halogen" as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "hydroxyl" refers to the –OH group.

The term "hydroxyalkyl" refers to an alkyl group substituted with an –OH group.

The term "mercapto" refers to the –SH group.

The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term "nitro" refers to the $–NO_2$ group.

The term "thio" refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term "sulfate" refers to the $–SO_4$ group.

The term thiohydroxyl or thiol, as used herein, refers to a group of the formula –SH.

More particularly, the term "sulfide" refers to compound having a group of the formula –SR.

The term "sulfone" refers to compound having a sulfonyl group $–S(O_2)R$.

The term "sulfoxide" refers to a compound having a sulfinyl group –S(O)R

The term ureido refers to a urea group of the formula $–NH—CO—NH_2$.

Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms. Optically active (R)- and (S)-, or D- and L-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefenic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each

asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures with the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

The compounds of the present disclosure may exist as salts. The present disclosure includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous

acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Following long-standing patent law convention, the terms “a,” “an,” and “the” refer to “one or more” when used in this application, including the claims. Thus, for example, reference to “a subject” includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

Throughout this specification and the claims, the terms “comprise,” “comprises,” and “comprising” are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term “include” and its grammatical variants

are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about" even though the term "about" may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some embodiments, ± 100% in some embodiments ± 50%, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ±1%, in some embodiments ± 0.5%, and in some embodiments ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term "about" when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can

be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

EXAMPLE 1

Carbonic Anhydrase IX and Applications Thereof

Carbonic Anhydrase IX. Carbonic anhydrase IX (CAIX) is a membrane-associated member of the carbonic anhydrase (CA) family (Krishnamurthy et al., 2008; Supuran, 2008; Alterio et al., 2012). These enzymes catalyze the reversible hydration of carbon dioxide to a bicarbonate anion and a proton. Fifteen human isoforms of CA have been identified. These isoforms show high sequence homology and share common structural features, including a zinc-containing catalytic site, a central twisted β-sheet surrounded by helical connections and additional β-strands (Altero et al., 2006; Lindskog et al., 1997; Hakansson et al., 1992; Christianson and Fierke, 1996). At the same time they are differ widely in molecular features, cellular localization, expression levels and tissue distribution (Clare and Supuran, 2006). CAIX is one of the transmembrane isoforms (along with CAIV, CAXII and CAXIV) and has limited expression in normal tissues with the exception of the gastrointestinal tract, gallbladder and pancreatic ducts (Supuran, 2008; Alterio et al., 2012; Christianson and Fierke, 1996).

CAIX as a Biomarker of Clear Cell RCC. RCC is a primary epithelial malignancy of the renal paryncyma. To date, a number of different histologic variants of RCC have been described (Srigley et al., 2013). Most common among these is the clear cell (ccRCC) subtype. CcRCC is characterized by loss of the Von Hippel-Lindau (VHL) gene located at 3p25 (Cancer Genome Atlas Research Network, 2013). Under normoxic conditions, the VHL protein is responsible for ubiquitination of the hypoxia-inducible factor (HIF) (Gossage, 2015). Upon sensing hypoxia, the VHL gene releases its control over HIF leading to its localization to the nucleus where it up regulates the expression of a number of genes including CAIX and vascular endothelial growth factor (VEGF). Over-expression of CAIX has been demonstrated in approximately 95 % of ccRCC specimens (Bui et al., 2003; Atkins et al., 2005; Leibovich et al., 2007). Given the ubiquitous overexpression of CAIX in cases of ccRCC, CAIX represents a rationale imaging and therapeutic target of this

disease. Moreover, CAIX is unregulated in a number of other cancer types, both due to VHL loss and tissue hypoxia (include citations). Thus, ligands capable of selectively binding CAIX would have widespread utility in cancer imaging and therapeutics.

Significance for CAIX imaging with low-molecular-weight (LMW) agents. Feasibility for the non-invasive diagnosis of ccRCC via CAIX expression level has been extensively studied with the radiolabeled antibody G250, a murine monoclonal antibody (mAbG250) developed by immunization of mice with human ccRCC homogenates in 1986 (Oosterwijk et al., 1986). The clinical applications of this agent have been reviewed (Smaldone et al., 2012) and it was reported to identify ccRCC with 86 % sensitivity, 87 % specificity and 95 % positive predictive value (Uzzo et al., 2010). However, antibodies as molecular imaging agents suffer from certain pharmacokinetic limitations, including slow blood/tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. LMW imaging agents, especially ^{18}F-labeled LMW agents, in principle, could provide superior imaging quality within 2 hours (Alauddin et al., 2012; Coenen et al., 2010; Cho et al., 2012). LMW agents are also more convenient to synthesize and to distribute to imaging centers. Although significant effort has been spent on sulfonamides and other CAIX ligands (Supuran, 2008; Alterio et al., 2012; Askoxylakis et al., 2010), no successful radionuclide-based molecular imaging agent has been reported (Pan et al., 2014; Akurathi et al., 2010; Lu et al., 2013; Doss et al., 2014; Rana et al., 2012). Most imaging results were reported with optical agents (Cecchi et al., 2005; Groves et al., 2012; Bao et al., 2012; Krall et al., 2014), but suffer from low tumor uptake (<2% ID/g) and highly variable imaging quality. Recently, significant progress in the field of CAIX imaging was reported by Wichert and coworkers with the identification of an additional surface binding pocket (Wichert et al., 2015). This dramatically reinforced the binding affinity of common sulfonamides over CAIX up to 0.2 nM and improved the tumor uptake by more than five times in ccRCC xenografts model as disclosed in FIG. 1A through FIG 1D. In addition, the amino-containing western part of the molecule, was prove to expose to water and suitable for various modification. However, there are still two issues with this new generation dual-targeting agents: (1) the limited tissue penetration of optical agents and (2) the high kidney uptake precluding the use of this agent for imaging primary renal tumors apart from kidney background.

ITM Exhibit 1004, Page 1527 of 1652

Fueled by the recent success of optical imaging of CAIX, PET/SPECT radioisotope labeled ligands have been investigated. As shown in FIG. 2A, the molecule contains an acetazolamide analog, 4,4-bis(4-hydroxyphenyl)valeric acid, an optimized linker and a modifiable amino group. FITC conjugated fluorescent ligand 1 has been synthetized, which reported with 0.2 nM Ki and excellent cellular uptake property on CAIX+ SK-RC-52 cells have been demonstrated, which is consistent with the earlier report (Wichert et al., 2015).

Significance for nuclear imaging and radiotherapy. Radionuclide molecular imaging including PET is the most mature molecular imaging technique without tissue penetration limitations. Due to its advantages of high sensitivity and quantifiability, radionuclide molecular imaging plays an important role in clinical and preclinical research (Youn and Honk, 2012; Chen et al., 2014). Many radionuclides, primarily β- and alpha emitters, have been investigated for targeted radioimmunotherapy and include both radiohalogens and radiometals (Table 1). The highly potent and specific binding moiety targeting CAIX enables its nuclear imaging and radiotherapy.

Table 1. Therapeutic Radionucleotides

β-particle emitters	^{90}Y, ^{131}I, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{212}Pb, ^{166}Ho, ^{47}Sc
α-particle emitters	^{225}Ac, ^{213}Bi, ^{212}Bi, ^{211}At, ^{212}Pb
Auger electron emitters	^{125}I, ^{123}I, ^{67}Ga, ^{111}In, ^{80m}Br

Herein, the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to CAIX is described. A new scaffold for radionuclide-based imaging and therapy of clear cell renal cell carcinoma (ccRCC) targeting carbonic anhydrase IX (CAIX) has been developed. The bivalent and low-molecular-weight ligands **XYIMSR-01**, a DOTA-conjugated, **XYIMSR-04**, a NOTA-conjugated, and **XYIMSR-06**, a Bz-NOTA-conjugated, have two moieties that target two separate sites on CAIX, imparting high affinity.

[^{111}In]**XYIMSR-01** in 73.8-75.8 % (n = 3) yield has been synthetized with specific radioactivities ranging from 118 – 1,021 GBq/μmol (3,200 – 27,600 Ci/mmol). Single photon emission computed tomography of [^{111}In]**XYIMSR-01** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 h post-injection. Rapid clearance from non-

ITM Exhibit 1004, Page 1528 of 1652

target tissues, including kidneys, allowed for high and specific signal by 24 h. Biodistribution studies demonstrated 26 % injected dose per gram of radioactivity within tumor at 1 h. Tumor-to- blood, muscle and kidney ratios were 178.1± 145.4, 68.4 ± 29.0 and 1.7 ± 1.2, respectively, at 24 h post-injection. Retention of radioactivity was exclusively observed in tumors by 48 h, the latest time point evaluated.

[^{177}Lu]**XYIMSR-01** in 69.0% yield has been synthetized with specific radioactivity of 2,340 Ci/mmol; 73.0% with specific radioactivity of 2239 Ci/mmol, and in average yield of 60% (n=12), with average specific activity of 1,900 Ci/mmol (ranging from 1,200 Ci/mmol to 2,500 Ci/mmol). Single photon emission computed tomography of [^{177}Lu]**XYIMSR-01** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 h post-injection. Rapid clearance from non-target tissues, including kidneys, allowed for high and specific signal by 24 h. Biodistribution studies confirmed the SPECT/CT data. Tumor-to-blood, muscle, and kidney ratios were 607.4 ± 200.7, 128.4 ± 25.4 and 4.5 ± 1.4, respectively, at 24 h post-injection.

[Al^{18}F]**XYIMSR-04** in 4.3% (n = 3) yield has been synthetized with specific radioactivities of 2.1 – 3.4 GBq/μM (57-92 Ci/mmol). Positron emission tomography of [Al^{18}F]**XYIMSR-04** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor at 1 h post-injection. Biodistribution studies demonstrated 14.40% injected dose per gram of radioactivity within tumor at 1 h. Tumor-to –blood, -muscle and –kidney ratio were 22.1, 9.74 and 0.28 respectively, at 1h post-injection.

[^{64}Cu]**XYIMSR-06**, in 51.0 ± 4.5% (n=5) yield has been synthetized with specific radioactivities of 4.1 – 8.9 GBq/μM (110-240 Ci/mmol). Positron emission tomography of [^{64}Cu]**XYIMSR-06** in immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 h post-injection. By 24 h radioactivity within the tumors dropped to 6.2 % injected dose per gram of radioactivity. Within 24 h, no significant radiotracer uptake within liver was observed, indicative of the *in vivo* stability of NOTA-^{64}Cu chelation.

The dual targeting strategy to engage CAIX enabled specific detection of ccRCC in this xenograft model, with pharmacokinetics surpassing those of previously described radionuclide-based probes against CAIX.

EXAMPLE 2

Material and Methods

General Procedures. Solvents and chemicals obtained from commercial sources were of analytical grade or better and used without further purification. Fmoc-protected azidolysine, HBTU, and N-α-fmoc-L-aspartic acid α-tert-butyl ester were purchased from Chem Impex International, Inc. (Wooddale, IL). Carrier-free [^{111}In]$InCl_3$ was purchased from MDS Nordion (Ottawa, ON, Canada). DOTA-NHS-ester (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid mono N-hydroxysuccinimide ester) was purchased from Macrocyclics, Inc. (Dallas, TX). Indium (III) nitrate, triethylsilane (Et_3SiH), N,N-diisopropylethylamine (DIEA), triethylamine (TEA), piperidine, 4,4-bis(4-hydroxyphenyl)valeric acid, copper iodide (CuI), and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA) were purchased from Sigma-Aldrich (Saint Louis, MO). Pre-loaded O-bis-(aminoethyl)ethylene glycol on trityl resin was purchased from EMD Millipore (Billerica, MA). Flash chromatography was performed using MP SiliTech 32-63 D 60Å silica gel purchased from Bodman (Aston, PA). Recombinant human CAIX was purchased from R&D Systems (Minneapolis, MN). 1H NMR spectra were recorded on a Bruker Ultrashield 500 MHz spectrometer. Chemical shifts (δ) were reported in ppm downfield by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. ESI mass spectra were obtained on a Bruker Daltonics Esquire 3000 Plus spectrometer (Billerica, MA).

HPLC purification of non-labeled compounds were performed using a Phenomenex C18 Luna 10 × 250 mm column on a Agilent 1260 infinity LC system (Santa Clara, CA). HPLC purification of radiolabeled (^{111}In) ligand was performed on another Phenomenex C18 Luna 10 × 250 mm and a Varian Prostar System (Palo Alto, CA), equipped with a Varian ProStar 325 UV-Vis variable wavelength detector and a Bioscan (Poway, CA) Flow-count in-line radioactivity detector, all controlled by Galaxie software. The specific radioactivity was calculated as the ratio of the radioactivity eluting at the retention time of product during the preparative HPLC purification to the mass corresponding to the area under the curve of the UV absorption. The purity of tested compounds as determined by analytical HPLC with absorbance at 254 nm was > 95%.

Synthesis of N^4-((S)-1-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-1-oxo-6-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-

*yl)hexan-2-yl)-N^2-((S)-3-(4,4-bis(4-hydroxyphenyl)pentanamido)-3-carboxypropanoyl)-L-asparagine (**3**).* Referring to FIG. 5, **3** was synthesized through an established solid phase based procedure (Wichert et al., 2015).

*Synthesis of 2,2',2''-(10-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**XYIMSR-01**).* Referring to FIG. 6, N^4-((S)-1-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-1-oxo-6-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)hexan-2-yl)-N^2-((S)-3-(4,4-bis(4-hydroxyphenyl)pentanamido)-3-carboxypropanoyl)-L-asparagine (**3**) 19 mg (0.017 mmol), DOTA-NHS **7** 16 mg (0.021 mmol) and N,N-diisopropylethylamine 150 µL were mixed in 2 mL DMSO. The reaction was stirred at room temperature for 2 h. Solvent was removed under vacuum. 21 mg (0.014 mmol) of product **XYIMSR-01** was obtained as a white powder after purification by HPLC in 82 % yield. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 10/90/0.1 to 50/50/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product eluted at 6.3 min. ^{1}H-NMR (500 MHz, DMSO-d6): δ 13.01 (s, 1H), 12.77 (br. 2H), 9.17 (br. s, 2H), 8.53 (br, 1H), 8.33 (s, 2H), 8.19 (d, J = 8.0, 1H), 8.09 (d, J =7.9, 1H), 7.91 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.84 (s, 1H), 7.45 (br. 2H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J =8.4, 4H), 4.54 – 4.44 (m, 2H), 4.24 (t, J = 7.2, 2H), 4.17 (td, J = 8.3, 5.5, 1H), 4.0-3.0 (36H, overlap with water signal), 2.65 (t, J = 7.5, 2H), 2.64 – 2.55 (m, 4H), 2.51 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H) 1.94 (m, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.75 (m, J = 7.5, 2H), 1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{61}H_{88}N_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1483.6; Found: 1483.4.

*Synthesis of DOTA-In conjugated compound [In]-**XYIMSR-01**.* Referring to FIG. 7, **XYIMSR-01** 2 mg (0.0013 mmol) was dissolved in 1 mL of 0.2 M NaOAc. Then, 20 µL of $In(NO_3)_3$ solution was added (containing 0.6 mg of $In(NO_3)_3$). The solution was kept at 60°C for 30 min. 2.0 mg [In]-**XYIMSR-01**was obtained as white crystal, after HPLC purification. Yield is 98 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/TFA MeCN/H_2O/TFA, flow 10 mL/min. Product was eluded at 10.6 min. MS, calculated for $C_{61}H_{85}InN_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1595.4; Found: 1595.3.

ITM Exhibit 1004, Page 1531 of 1652

*Synthesis of DOTA-Ga conjugated compound [Ga]-**XYIMSR-01***. Referring to FIG. 8, **XYIMSR-01** 2 mg (0.0013 mmol) was dissolved in 1 mL of pure water. Then, 20 µL of $Ga(NO_3)_3$ solution was added (containing 0.5 mg of $Ga(NO_3)_3$). The solution was kept at 60 °C for 30 min. 1.8 mg [Ga]-**XYIMSR-01**was obtained as white crystal, after HPLC purification. Yield is 90 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/TFA MeCN/H_2O/TFA, flow 10 mL/min. Product was eluded at 10.2 min. MS, calculated for $C_{61}H_{85}GaN_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1549.5; Found: 1549.7.

*Synthesis of DOTA-Lu conjugated compound [^{175}Lu]2,2',2''-(10-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid ([Lu]**XYIMSR-01**)* Synthesis of DOTA-Lu conjugated compound [^{175}Lu]**XYIMSR-01**. Referring to FIG. 9, **XYIMSR-01** 1 mg (0.0007 mmol) was dissolved in 1 mL of 0.2 M NaOAc. Then, 10 µL of $Lu(NO_3)_3$ solution was added (containing 0.4 mg of $Lu(NO_3)_3$). The solution was kept at 60°C for 30 min. 1.0 mg [^{175}Lu]**XYIMSR-01** was obtained as white crystal, after HPLC purification. Yield is 90 %. MS, calculated for $C_{61}H_{85}LuN_{16}NaO_{22}S_2^+$ $[M+Na]^+$: 1655.4766; Found: 1655.4787. HPLC, Column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/0.1 MeCN/H_2O/TFA, flow 10 mL/min. Product was eluded at 14.1 min, with free ligand eluted first at 13.1. It is applied to preparative runs.

*Synthesis of SFB conjugated compound **XYIMSR-02***. Referring to FIG. 10, compound **3** 10 mg (0.009 mmol), **4** 5 mg (0.021 mmol) and di-isopropylethylamine 10 µL were dissolved in 1 mL DMF. The reaction was kept at room temperature for 1.5 hour. The solvent was removed under vacuum. 9 mg **XYIMSR-02** was obtained after HPLC as white powder. Yield is 81 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 15/85/0.1 to 60/40/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 7.1 min. ^{1}H-NMR (500 MHz, DMSO-d6): δ 13.01 (s, 1H), 12.62(br, 1H), 12.49(br, 1H), 9.16 (br. s, 2H), 8.55(br, 1H), 8.32 (s, 2H), 8.17 (d, J = 8.0, 1H), 8.09 (d, J = 7.9, 1H) 7.91 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.84 (s, 1H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J = 8.4, 4H), 6.54(br, 2H), 4.51 – 4.45 (m, 2H), 4.26 (t, J = 7.2, 2H), 4.21 (td, J = 8.3, 5.5, 1H), 3.53 (t, J = 5.3, 2H), 3.56 – 3.50 (m, 4H), 3.38 (t, J = 6.1, 2H), 3.24 – 3.15 (m, 2H), 2.65 (t, J = 7.5, 2H),

2.64 – 2.55 (m, 4H), 2.51 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H) 1.95 (quin, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.76 (quin, J = 7.5, 2H),1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{52}H_{65}FN_{12}NaO_{16}S_2^+$ $[M+Na]^+$: 1219.4; Found: 1219.3.

*Synthesis of 6-fluoro-pyridine-3-carbonyl conjugated compound (**XYIMSR-03**).* Referring to FIG. 11, compound **3** 5 mg (0.0045 mmol), **5** 4 mg and di-isopropylethylamine 20 µL were dissolved in 1 mL DMF. The reaction was kept at room temperature for 2 hour. The solvent was removed under vacuum. 2.8 mg **XYIMSR-03** was obtained after HPLC as white powder. Yield is 52 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 15/85/0.1 to 60/40/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 6.9 min. MS, calculated for $C_{51}H_{63}FN_{13}O_{15}S_2^+$ $[M+H-H_2O]^+$: 1180.4; Found: 1180.4.

Synthesis of NOTA conjugated compound 2,2'-(7-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (***XYIMSR-04***). Referring to FIG. 12, **3** 14 mg (0.0126 mmol), NOTA-NHS 10 mg (0.0151 mmol) and triethylamine 50 µL were mixed in 2 mL DMF. The reaction was stirred at room temperature for 2 hours. All the solvent was removed under vacuum. 9.0 mg product **XYIMSR-04** was obtained as white powder, after HPLC purification. Yield is 52%. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 10/90/0.1 to 50/50/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 6.9 min. ^{1}H-NMR (500 MHz, DMSO-d6): δ 12.99 (s, 1H), 12.25(br. 2H), 9.15 (br. s, 2H), 8.31 (s, 2H), 8.24(m, 1H), 8.16 (d, J = 8.0, 1H), 8.05 (d, J =7.9, 1H), 7.90 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.83 (s, 1H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J =8.4, 4H), 6.50(br, 2H), 4.52 – 4.46 (m, 2H), 4.24 (t, J = 7.2, 2H), 4.17 (td, J = 8.3, 5.5, 1H), 4.0-2.84(overlap with water signal), 2.65 (t, J = 7.5, 2H), 2.64 – 2.55 (m, 4H), 2.47 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H), 1.94 (m, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.75 (m, J = 7.5, 2H), 1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{57}H_{81}N_{15}NaO_{20}S_2^+$ $[M+Na]^+$: 1382.5; Found: 1382.8.

Synthesis of NOTA-Al-F conjugated compound [Al^{19}F] 2,2'-(7-((14S,18S,22S)-18,22-dicarboxy-27,27-bis(4-hydroxyphenyl)-2,13,16,20,24-pentaoxo-14-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-

*6,9-dioxa-3,12,15,19,23-pentaazaoctacosyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (**[Al^{19}F]XYIMSR-04**)*. Referring to FIG. 13, **XYIMSR-04** 1 mg (0.0007 mmol) was dissolved in 1 mL water/Ethanol 1:1. To the solution, 500 µL of $AlCl_3$ 2 mmol/NaOAc 2 mmol water solution (pH = 4) was added. Then, 500 µL of 10 mmol KF solution was added, together with 1 mL of ethanol. The resulting solution was heated at 110 °C for 30 min. 0.6 mg of [Al^{19}F]**XYIMSR-04** was obtained as white crystal, after HPLC purification. Yield is 61 %. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. 20/80/TFA MeCN/H_2O/TFA, flow 4 mL/min. Product was eluded at 35.5 min. MS, calculated for $C_{57}H_{79}AlFN_{15}NaO_{20}S_2^+$ $[M+Na]^+$: 1426.4759; Found: 1426.4777.

*Synthesis of conjugated compound **XYIMSR-05**.* Referring to FIG. 14, compound **3** 4 mg (0.0036 mmol), **6** 4 mg and di-isopropylethylamine 20 µL were dissolved in 1 mL DMF. The reaction was kept at room temperature for 2 hour. The solvent was removed under vacuum. 2.9 mg **XYIMSR-05** was obtained after HPLC as white powder. Yield is 62%. HPLC condition: column Phenomenex, Luna 10 × 250 mm, 10 µm. Gradient 15/85/0.1 to 60/40/0.1 MeCN/H_2O/TFA, 0 – 10 min, flow 10 mL/min. Product was eluded at 7.6 min. MS, calculated for $C_{52}H_{66}IN_{12}O_{16}S_2^+$ [M+H]+: 1305.3; Found: 1305.2.

*Synthesis of NOTA conjugated compound 2,2',2''-(2-(4-(3-((11S,15S,19S)-15,19-dicarboxy-24,24-bis(4-hydroxyphenyl)-10,13,17,21-tetraoxo-11-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-3,6-dioxa-9,12,16,20-tetraazapentacosyl)thioureido)benzyl)-1,4,7-triazonane-1,4,7-triyl)triacetic acid (**XYIMSR-06**)*. Referring to FIG. 15, compound **3** (Wichert et al., 2015) 12 mg (0.0111 mmol), p-SCN-Bn-NOTA 8 mg (0.0143 mmol) and *N,N*-diisopropylethylamine 50 µL were mixed in 2 mL DMF. The reaction was stirred at room temperature for 2 h. Solvent was removed under vacuum. 14.0 mg of product **XYIMSR-06** was obtained as a white powder after HPLC purification. Yield was 83%. HPLC conditions: column Phenomenex, Luna 10 × 250 mm, 10 µm. 25/75/0.1 MeCN/H_2O/TFA, flow 10 mL/min. Product eluted at 12.0 min. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.98 (s, 1H), 12.63 (br. 2H), 9.60 (m, 1H), 9.15 (br. s, 2H), 8.31 (s, 2H), 8.16 (d, J = 8.0, 1H), 8.05 (d, J =7.9, 1H), 7.90 (d, J = 8.1, 1H), 7.88 (t, J = 6.0, 1H), 7.83 (s, 1H), 7.69(br, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.4, 4H), 6.64 (d, J =8.4, 4H), 6.50 (br, 2H), 4.52 – 4.46 (m, 2H), 4.24 (t, J = 7.2, 2H), 4.17 (td, J = 8.3, 5.5, 1H), 4.0-2.90 (overlaps with water signal), 2.65 (t, J =

7.5, 2H), 2.64 – 2.55 (m, 4H), 2.47 – 2.41 (m, 2H), 2.17 (t, J = 8.2, 2H), 1.94 (m, J = 7.5, 2H), 1.88 – 1.82 (m, 2H), 1.75 (m, J = 7.5, 2H), 1.66 – 1.60 (m, 1H), 1.53 – 1.46 (m, 1H), 1.45 (s, 3H), 1.28 – 1.17 (m, 2H). MS, calculated for $C_{65}H_{89}N_{16}O_{21}S_3^+$ $[M+H]^+$: 1525.5545; Found: 1525.5527.

*Synthesis of [$^{63/65}$Cu]2,2',2''-(2-(4-(3-((11S,15S,19S)-15,19-dicarboxy-24,24-bis(4-hydroxyphenyl)-10,13,17,21-tetraoxo-11-(4-(4-(4-oxo-4-((5-sulfamoyl-1,3,4-thiadiazol-2-yl)amino)butyl)-1H-1,2,3-triazol-1-yl)butyl)-3,6-dioxa-9,12,16,20-tetraazapentacosyl)thioureido)benzyl)-1,4,7-triazonane-1,4,7-triyl)triacetic acid([$^{63/65}$Cu]**XYIMSR-06**).* Referring to FIG. 16, **XYIMSR-06** 1 mg (0.0007mmol) was dissolved in 0.5 mL 0.2 M NaOAc solution. To the solution 0.2 mg $Cu(NO_3)_23H_2O$ was added in 0.1 mL of water. The reaction was heated at 100°C for 10 min and then loaded onto HPLC for purification. 0.5 mg of product was obtained as blue crystals. Yield was 48%. HPLC conditions: column Phenomenex, Luna 10 × 250 mm, 10 µm. 25/75/TFA MeCN/H_2O/TFA, flow 10 mL/min. Product eluted at 8.3 min with the starting material eluting at 12.6 min. MS, calculated for $C_{65}H_{87}CuN_{16}O_{21}S_3^+$ [M+H]+: 1586.4684; Found: 1586.4683.

Radiolabeling of [^{111}In]XYIMSR-01. 20 µg **XYIMSR-01** was dissolved in 10 µL of 0.2 M NaOAc followed by addition of 3.3 mCi of $^{111}InCl_3$ solution to provide a final pH = 5.5-6. The mixture was heated in a water bath at 65°C for 30 min. Radiolabeling was monitored by HPLC. At completion, the reaction mixture was diluted with 1 mL of water then loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, [^{111}In]**XYIMSR-01**, and starting material, **XYIMSR-01**, were optimized to the point of baseline separation, with [^{111}In]**XYIMSR-01** eluting first. 2.5 mCi of [^{111}In]**XYIMSR-01** was obtained at a radiochemical yield of 75.8 % in specific radioactivities of 118.4 GBq/µmol (3,200 Ci/mmol). The identity of the radiolabeled product was confirmed by co-injection with [$^{113/115}$In]**XYIMSR-01** and co-elution on HPLC with the same condition. Another two syntheses were performed under similar conditions. The average yield was 74 % (n = 3). The specific activities ranged from 118 to 1021.2 GBq/µmol (3,200 to 27,600 Ci/mmol). For preparative runs, the HPLC solvent was removed under vacuum. [^{111}In]**XYIMSR-01** was formulated in phosphate-buffered saline (PBS) for the imaging study. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10µm. 19/81/0.1 MeCN/H_2O/TFA, flow 4 mL/min. Product eluted at 28.3 min, while starting material eluted at 30.2 min.

ITM Exhibit 1004, Page 1535 of 1652

*Radiolabeling of **XYIMSR-01**-[^{177}Lu].* 20 μg **XYIMSR-01** was dissolved in 10 μL of 0.2M NaOAc followed by addition of 10.1 mCi of $^{177}LuCl_3$ solution to provide a final pH = 5.5-6. The mixture was heated in a water bath at 65°C for 30 min. Radiolabeling was monitored by HPLC. At completion, the reaction mixture was diluted with 0.2 mL of water then loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, [^{177}Lu]**XYIMSR-01**, and starting material, **XYIMSR-01**, were optimized to the point of baseline separation, with **XYIMSR-01**-[^{177}Lu] eluting first. 6.97 mCi of **XYIMSR-01**-[^{177}Lu] was obtained at a radiochemical yield of 69.0% in specific radioactivities of 2,340 Ci/mmol. The identity of the radiolabeled product was confirmed by co-injection with **XYIMSR-01**-[Lu] and co-elution on HPLC with the same condition. Another one syntheses were performed under similar conditions, starting with 10.2 mCi and obtaining 7.30 mCi at yield of 73.0% and specific radioactivity of 2239 Ci/mmol. The product was diluted with water, loaded onto Sep-Pak and eluded with 2 mL pure ethanol. After the concentrated under nitrogen gas, **XYIMSR-01**-[^{177}Lu] was formulated in phosphate-buffered saline (PBS) for the study. HPLC conditions: Phenomenex, Luna 4.6 × 250 mm, 5μm. 22/78/0.1 MeCN/H2O/TFA, flow 0.5 mL/min. Product eluted at 24.5 min, while starting material eluted at 29.0 min.

Yet other syntheses were performed under similar conditions, starting with 8.4-20.7 mCi. At completion, the reaction mixture was diluted with 200 μL of water, loaded onto a HPLC column for purification. With Method B, [^{177}Lu]**XYIMSR-01** got eluted first and collected. Base line separation between radiolabel product and starting material was achieved. The average radiochemical yield is 60% (n=12), with average specific activity of 1,900 Ci/mmol (ranging from 1,200 Ci/mmol to 2,500 Ci/mmol). HPLC column Phenomenex, Luna 4.6 × 250 mm, 5 μm. 21/79/0.1 MeCN/H2O/TFA, flow 0.5 mL/min. Product was eluded at 30.5 min, with free ligand eluted second at 36.1 min.

*Radiolabeling of **XYIMSR-04**-[Al^{18}F].* 20μL of 1 mM **XYIMSR-04** in water/EtOH 1/1 was added to 200 μL of Na^{18}F in 0.9% saline containing 1.3 mCi activity. To this mixture, 1 μL of 2 mM $AlCl_3$/NaOAc solution and 200 μL of ethanol were added. The reaction was kept at 105 °C for 20 min, then diluted with 1.5 mL of water and loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, **XYIMSR-04**-[Al^{18}F], and starting material,

XYIMSR-04, were optimized to the point of baseline separation, with **XYIMSR-04**-[$Al^{18}F$] eluting first. 180 μCi of **XYIMSR-04**-[$Al^{18}F$] was obtained a radiochemical yield of 13.8% in specific radioactivity of >1000 Ci/mmol in 1 hour. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10μm. 20/80/0.1 MeCN/H2O/TFA, flow 0.5 mL/min. Product eluted at 35.5 min, while starting material eluted at 39.0 min.

Another radiosynthesis of ***XYIMSR-04***-*[$Al^{18}F$]* was performed. $Na^{18}F$ in saline was purchased from PETNET (Hackensack, NJ) and was directly used in the synthesis 400 μg of **XYIMSR-04** in 200 μL water/ethanol 1:1 was added to 1 mL of $Na^{18}F$ in 0.9% saline containing 0.17 – 0.52 GBq (4.6-14.0 mCi) of radioactivity. To this mixture 20 μL of 2 mM $AlCl_3$/NaOAc solution and 200 μL of ethanol were added. The reaction was kept at 105°C for 20 min, then diluted to 2.0 mL with water and loaded onto a preparative HPLC column for purification. Retention times for the radiolabeled compound, [$Al^{18}F$]**XYIMSR-04**, and starting material, **XYIMSR-04**, were optimized to the point of baseline separation, with [$Al^{18}F$]**XYIMSR-04** eluting first. [$Al^{18}F$]**XYIMSR-04** was obtained in a radiochemical yield of 4.3% (n=3) in specific radioactivity of 2.1 – 3.4 GBq/μmol (57-92 Ci/mmol) in 1.5 h. HPLC conditions: Phenomenex, Luna 10 × 250 mm, 10 μm. 20/80/0.1 MeCN/H_2O/TFA, flow 4 mL/min. Product eluted at 35.5 min, while starting material eluted at 39.0 min. The collected activity was diluted with 20 mL of water and loaded onto an activated Sep-Pak column (WAT020515, Waters, Milford MA). After the Sep-Pak was washed with 10 mL of water, [$Al^{18}F$]**XYIMSR-04** was eluted with 2 mL of ethanol. The ethanol was evaporated under a gentle stream of N_2 (to a total volume of < 50 μL). The resulting solution was formulated in saline for the imaging and biodistribution studies.

*Radiolabeling of [^{64}Cu]**XYIMSR-06***. 40 μg of **XYIMSR-06** in 20 μL 0.2 M NaOAc solution was added to 60 μL $^{64}CuCl_2$ with 0.16 – 0.26 GBq (4.2 – 6.9 mCi) of radioactivity. The reaction was heated in a water bath at 65°C and pH 5.5−6 for 0.5 h. The reaction was then diluted with 1.5 mL of water and injected onto the HPLC for purification. Baseline separation was achieved between [^{64}Cu]**XYIMSR-06** and **XYIMSR-06** with [^{64}Cu]**XYIMSR-06** eluting first. The average non-decay corrected radiochemical yield was 51.0 ± 4.5% (n=5) and specific activities were 4.1 – 8.9 GBq/μmol (110-240 Ci/mmol). HPLC conditions: column Phenomenex, Luna 10 × 250 mm, 10 μm. 23/77/TFA MeCN/H_2O/TFA, flow 4 mL/min. Product eluted at

ITM Exhibit 1004, Page 1537 of 1652

29.2 min. The collected radioactivity was diluted with 20 mL of water and loaded onto activated Sep-Pak (WAT020515, Waters, Milford MA). After the Sep-Pak was washed with 10 mL of water, [^{64}Cu]**XYIMSR-06** was eluted with 2 mL of ethanol. The ethanol was evaporated under a gentle stream of N_2 (to a total volume of < 50 μL). The resulting solution was formulated in saline for the imaging and biodistribution studies.

Cell Lines and Mouse Models. Animal experiments were performed in accordance with protocols approved by the Johns Hopkins Animal Care and Use Committee (ACUC). Six-week-old female NOD/SCID mice were purchased from the Animal Resource Core of the Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins and were subcutaneously injected in the lower left flank or upper right flank with 1 x 10^6 SK-RC-52 cells in RPMI 1640 GlutaMAX™ media (Life Technologies, Frederick, MD) supplemented with 1% fetal bovine serum (FBS). Mice were monitored for tumor size and used for SPECT/CT imaging when the size of the tumor reached 100 mm^3.

FACS Analysis. CAIX-positive SK-RC-52 and CAIX-negative BxPC3 cells were maintained in RPMI 1640 media supplemented with 10% FBS and 1 x penicillin-streptomycin in a 37°C humidified incubator. Cells were detached from the flask with trypsin and reconstituted in RPMI 1640 media supplemented with 1% FBS at a density of 1 x 10^6 cells per mL. FITC-labeled **8** was added to the cells at the indicated concentration and incubated at room temperature for 30 min. Cells were washed twice with the same media for staining and analyzed using the FACSCalibur (BD Bioscience, San Jose, CA) instrument.

*Competitive Fluorescence Polarization Assay for [$^{113/115}$In]**XYIMSR-01.*** Fluorescence polarization (FP) experiments were performed in 21 μL of the assay buffer (12.5 mM Tris-HCl, pH 7.5, 75 mM NaCl) in black flat bottom 384-well microplates (Corning, Inc., New York, NY) The FP reaction employed 100 nM of purified CAIX (R&D systems, Minneapolis, MN) and 80 nM FITC-labeled **8** (Wichert, et al., 2015) within the assay buffer. The FP values were measured as mP units using the Victor3 multi-label plate reader equipped with excitation (485 nm) and emission (535 nm) filters (Perkin Elmer, Waltham, MA). 100 nM CAIX was incubated with serially diluted (from 1 μM to 61 fM) concentrations of the three targeting molecules, **2**, **XYIMSR-01**, and [$^{113/115}$In]**XYIMSR-01** for 30 min at room temperature in 384-well plates. 80 nM **8** was added to each well and the reaction was

incubated for 30 min at room temperature followed by FP measurement. Experiments were carried out in triplicate and the concentration resulting in 50% response (IC_{50}) was calculated in GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using the sigmoidal dose-response regression function.

*Competitive Fluorescence Polarization Assay for [$Al^{19}F$]**XYIMSR-04**, [$^{63/65}Cu$]**XYIMSR-06**, and [^{175}Lu]**XYIMSR-01***. Fluorescence polarization (FP) experiments were performed in 21 µL of the assay buffer (12.5 mM Tris-HCl, pH 7.5, 75 mM NaCl) in transparent flat bottom 384 well Small Volume™ LoBase Microplates (Greiner Bio-One, Frickenhausen Germany). The FP reaction employed 100 nM of purified CAIX (R&D systems, Minneapolis, MN) and 80 nM FITC-labeled ligand within the assay buffer. The FP values were measured as mP units using the Safire2™ plate reader (Tecan, Morrisville, NC) with excitation at 475 nm and emission at 532 nm emission. 100 nM CAIX was incubated with serially diluted (from 8 µM to 488.2 fM) concentrations of the three targeting molecules, [$Al^{19}F$]**XYIMSR-04**, [$^{63/65}Cu$]**XYIMSR-06** and [^{175}Lu]**XYIMSR-01** for 30 min at room temperature in 384 well plates. 80 nM FITC-labeled ligand was added to each well and the reaction was incubated for 30 min at room temperature followed by FP measurements. Experiments were carried out in triplicate and the concentration resulting in 50% response (IC_{50}) was calculated in GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using the sigmoidal dose-response regression function.

*SPECT/CT imaging of [^{111}In]**XYIMSR-01***. Mice harboring subcutaneous SK-RC-52 tumors with the lower left flank were injected with 14.8 MBq (400 µCi) of [^{111}In]**XYIMSR-01** in 250 µL of PBS (pH = 7.0) intravenously (tail vein). Anesthesia was then induced with 3% isofluorane and maintained at 2% isoflurane. Physiologic temperature was maintained with an external light source while the mouse was on the gantry. Imaging employed a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA). SPECT data were acquired in 64 projections at 65 s per projection using medium energy pinhole collimators. A CT scan was performed in 512 projections at the end of each SPECT scan for anatomic co-registration. CT and SPECT scans were performed at 1, 4, 8, 24, and 48 h post-injection of [^{111}In]**XYIMSR-01**. Imaging data sets were reconstructed using the manufacturer's software. Display of images utilized Amide software (Dice Holdings, Inc. NY).

*SPECT/CT imaging of [^{177}Lu]**XYIMSR-01***. Mice were injected with 1.7 mCi of **[^{177}Lu]XYIMSR-01** in 250uL of PBS (pH7.0) intravenously, anesthetized under

ITM Exhibit 1004, Page 1539 of 1652

3% isofluorane prior to being placed on the scanner bed and kept warm with an external light source while being scanned. Isofluorane levels were decreased to 1% throughout the scanning process in order to ensure mouse survival. Imaging of mice was then carried out using a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA). A CT scan was performed at the end of each SPECT scan for anatomical co-registration. CT and SPECT scans were performed at 1, 4, 8, 24, and 48 hrs post injection of the **[^{177}Lu]XYIMSR-01**. Obtained data sets were subsequently reconstructed using the provided Gamma Medica-Ideas software. Final data visualization and image generation was accomplished using Amide software (Dice Holdings, Inc. NY).

*PET/CT imaging of [Al^{18}F]**XYIMSR-04***. Mice harboring subcutaneous SK-RC-52 tumors with the lower left flank were injected with 7.4 MBq (200 μCi) of [Al^{18}F]**XYIMSR-04** in 250 μL of PBS (pH = 7.0) intravenously (tail vein). Anesthesia was then induced with 3% isofluorane and maintained at 2% isoflurane. Physiologic temperature was maintained with an external light source while the mouse was on the gantry. Imaging employed a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA). Whole body 2-bed PET scan was performed using ARGUS small-animal PET/CT scanner (Sedecal, Madrid, Spain) at 250-700 keV energy window. PET acquisition times were: 5 min/bed (1 h) post-injection of [Al^{18}F]**XYIMSR-04**. PET images were co-registered with the corresponding 360-slice CT images. Imaging datasets were reconstructed using the 3D-FORE/2D-OSEM iterative algorithm with 2 iterations and 16 subsets, using the manufacturer's software. Display of images utilized Amide software (Dice Holdings, Inc. NY).

*PET/CT imaging of [^{64}Cu]**XYIMSR-06***. Mice harboring subcutaneous SK-RC-52 tumors within the upper right flank were injected intravenously (tail vein) with 22.2 MBq (600 μCi) of [^{64}Cu]**XYIMSR-06** in 250 μL of PBS (pH = 7.0). Anesthesia was then induced with 3% isoflurane and maintained with 2% isoflurane. Physiologic temperature was maintained with an external light source while the mouse was on the gantry. Whole body, 2-bed PET/CT imaging was performed using the SuperArgus small animal PET/CT scanner (Sedecal, Madrid, Spain), CT employing a 250-700 keV energy window. PET acquisition times were: 5 min/bed position (1 h post-injection of [^{64}Cu]**XYIMSR-06**); 10 min/bed position (4 and 8 h) and 20 min/bed position (24 h). PET images were co-registered with the corresponding 360-slice CT images. Imaging datasets were reconstructed using the 3D-FORE/2D-OSEM iterative

algorithm with 2 iterations and 16 subsets, using the manufacturer's software. Imaging data sets were reconstructed using the manufacturer's software. Display of images utilized the software package PMOD (v3.3, PMOD Technologies Ltd, Zurich, Switzerland).

*Biodistribution of [^{111}In]**XYIMSR-01** and [^{177}Lu]**XYIMSR-01***. Mice bearing SK-RC-52 xenografts at lower left flank were injected intravenously with 740 kBq (20 μCi) of [^{111}In]**XYIMSR-01**, or [^{177}Lu]**XYIMSR-01** in 200 μL of PBS. For competitive blocking, same tumor bearing mice were injected with 740 kBq (20 μCi) of [^{111}In]**XYIMSR-01** and 200 nmole of **8** in 200 μL of PBS. At 1 h, 4 h, 8 h, 24 h and 48 h post-injection, mice were sacrificed by cervical dislocation and the blood was immediately collected by cardiac puncture. Heart, lungs, pancreas, spleen, fat, brain, muscle, small intestines, liver, stomach, kidney, urinary bladder, and tumor were collected. Each organ was weighed and the tissue radioactivity was measured with an automated gamma counter (1282 Compugamma CS, Pharmacia/ LKBNuclear, Inc., Mt. Waverly, Vic. Australia). The percentage of injected dose per gram of tissue (% ID/g) was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for radioactive decay.

Data were expressed as mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, California) was used to determine statistical significance. Statistical significance was calculated using a paired t test. *P*-values < 0.0001 were considered significant.

*Biodistribution of [Al^{18}F]**XYIMSR-04***. Mice bearing SK-RC-52 xenografts within the lower left flank were injected intravenously with 740 kBq (20 μCi) of [Al^{18}F]**XYIMSR-04** in 200 μL of PBS. At specific 1 hour time point mentioned in the paper, mice (n = 5) were sacrificed by cervical dislocation and the blood was immediately collected by cardiac puncture. Heart, lungs, pancreas, spleen, fat, brain, muscle, small intestines, liver, bone, stomach, kidney, urinary bladder, and tumor were collected. Each organ was weighed and the tissue radioactivity was measured with an automated gamma counter (1282 Compugamma CS, Pharmacia/ LKBNuclear, Inc., Mt. Waverly, Vic. Australia). The percentage of injected dose per gram of tissue (% ID/g) was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for radioactive decay. Data were expressed as mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, California) was used to determine statistical significance. Statistical

ITM Exhibit 1004, Page 1541 of 1652

significance was calculated using a paired t test. *P*-values < 0.0001 were considered significant.

*Biodistribution of [^{64}Cu]**XYIMSR-06***. Mice bearing SK-RC-52 xenografts within the upper right flank were injected intravenously with 740 kBq (20 μCi) of [^{64}Cu]**XYIMSR-06** in 200 μL of PBS. For *in vivo* competition (binding specificity) studies, tumor-bearing mice were injected with 740 kBq (20 μCi) of [^{64}Cu]**XYIMSR-06** and 200 nmole of **8** in 200 μL of PBS concurrently. At specific times after injection (1 h, 4 h, 8 h and 24 h), mice (n = 5) were sacrificed by cervical dislocation with blood immediately collected by cardiac puncture. Heart, lungs, pancreas, spleen, fat, brain, muscle, small intestines, liver, stomach, kidney, urinary bladder, and tumor were also collected. Each organ was weighed and the tissue radioactivity was measured with an automated gamma counter (1282 Compugamma CS, Pharmacia/ LKBNuclear, Inc., Mt. Waverly, Vic. Australia). The percentage of injected dose per gram of tissue (%ID/g) was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for radioactive decay. Data were expressed as mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, California) was used to determine statistical significance. Statistical significance was calculated using a paired t test. *P*-values < 0.0001 were considered significant.

*Radio-therapy of [^{177}Lu]**XYIMSR-01***. Mice bearing SK-RC-52 xenografts at lower left flank were injected intravenously with PBS, 11.1 MBq (300 μCi) and 18.5 MBq (500 μCi) of [^{177}Lu]**XYIMSR-01** in 200 μL of PBS (n=4). Size of the tumors was measured twice a week after the injection. Delays in tumor growth were observed from mice injected with [^{177}Lu]**XYIMSR-01** in compared with control non-treated mice. The *P*-values were 0.042 and 0.031 for the 11.1 and 18/5 MBq doses, respectively.

EXAMPLE 3

Results

Chemical synthesis of **XYIMSR-01**, **XYIMSR-04**, and **XYIMSR-06** were achieved as in FIG. 5, FIG. 6, FIG.12 and FIG.15 respectively. Following a reported procedure, key intermediate **3** was obtained *via* solid support synthetic methods (Wichert et al., 2015). **XYIMSR-01** has been generated by conjugating the commercially available DOTA-NHS ester with **3** in 82 % yield. In(III) was

ITM Exhibit 1004, Page 1542 of 1652

incorporated into DOTA in nearly quantitative yield in 0.2 M NaOAc buffer at 60°C, providing the non-radiolabeled standard, [$^{113/115}$In]**XYIMSR-01** (FIG. 7). After optimization, baseline separation between **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** could be achieved by high performance liquid chromatography (HPLC). Lu(III) was incorporated into DOTA in excellent yield in 0.2 M NaOAc buffer at 60 °C, providing the non-radiolabeled standard, [^{175}Lu]**XYIMSR-01** (FIG. 9). After optimization, baseline separation between **XYIMSR-01** and [^{175}Lu]**XYIMSR-01** could be achieved by high performance liquid chromatography (HPLC). **XYIMSR-04** has been generated by conjugating the commercially available NOTA-NHS ester with **3** in 52 % yield. Al(III) was incorporated into NOTA in fair yield in 0.2 M NaOAc buffer at 60°C, providing the non-radiolabeled standard, [Al^{19}F]**XYIMSR-04** (FIG. 13). After optimization, baseline separation between **XYIMSR-04** and [Al^{19}F]**XYIMSR-04** could be achieved by high performance liquid chromatography (HPLC). **XYIMSR-06** has been generated by conjugating the commercially available p-SCN-Bn-NOTA with **3** in 83 % yield. Cu(II) was incorporated into Bn-NOTA in fair yield in 0.2 M NaOAc buffer at 60°C, providing the non-radiolabeled standard, [$^{63/65}$Cu]**XYIMSR-06** (FIG. 16). After optimization, baseline separation between **XYIMSR-06** and [$^{63/65}$Cu]**XYIMSR-06** could be achieved by high performance liquid chromatography (HPLC).

Fluorescein isothiocyanate (FITC)-labeled **8**, as shown on FIG. 2A, has been synthesized as a standard to measure CAIX binding affinities of the corresponding radiotracers. Compound **8** bound specifically to CAIX-expressing SK-RC-52 cells, but not to CAIX-negative BxPC3 cells (FIG. 2B and FIG. 2C) (Rana et al., 2012; Wichert et al., 2015). In order to test the relative binding of **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** to CAIX a competitive fluorescence polarization assay (Alquicer et al., 2012) for use with **8** has been modified. For the competitive binding assay, after optimization for background fluorescence, concentrations of 80 nM and 100 nM have been chosen for **8** and CAIX, respectively. As a positive control, non-fluorescent **3** has been employed, which has a reported K_d value of 2.6 nM (Wichert et al., 2015). Increasing concentrations of **3**, **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** were incubated with CAIX for 30 min at room temperature. After **8** was added, fluorescence polarization signal was recorded. The IC_{50} values determined for **3**, **XYIMSR-01** and [$^{113/115}$In]**XYIMSR-01** were 75.9, 67.0, and 108.2 nM, respectively (FIG. 3A, FIG. 3B, and FIG. 3C). Using a similar method, the IC_{50} value determined

for **3**, [$^{63/65}$Cu]**XYIMSR-06,** [Al^{19}F]**XYIMSR-04**, and [^{175}Lu]**XYIMSR-01** were 63.6 ± 2.8, 156.5 ± 4.3 nM, 96.7±3.3 nM, and 122.4 ± 3.8 nM (FIG. 4A, FIG. 4B, FIG. 4C and FIG. 3D). These findings suggest that the DOTA/NOTA-modified adducts were capable of binding CAIX with high affinity, on the order of positive control **3**.

The capacity for [^{111}In]**XYIMSR-01,** [^{177}Lu]**XYIMSR-01**], [Al^{18}F] **XYIMSR-04**, and [^{64}Cu]**XYIMSR-06**, to detect CAIX-expressing tumors *in vivo* using PET or SPECT imaging was further investigated. The synthesis and purification of [^{111}In]**XYIMSR-01** were achieved within 1.5 h in yield of 73.8-75.8% (n = 3) and with specific radioactivities of 118.4 – 1021.2 GBq/μM (3,200 -27,600 Ci/mmol). The synthesis and purification of [^{177}Lu]**XYIMSR-01** was achieved within 1.5 h in yield of 69.0% with specific radioactivity of 2,340 Ci/mmol; 73.0% with specific radioactivity of 2239 Ci/mmol, and in average yield of 60% (n=12), with average specific activity of 1,900 Ci/mmol (ranging from 1,200 Ci/mmol to 2,500 Ci/mmol). The synthesis and purification of [Al^{18}F]**XYIMSR-04,** were achieved within 1.5 h in yield of 4.3% (n = 3) and with specific radioactivity of 2.1 – 3.4 GBq/μM (57-92 Ci/mmol).The synthesis and purification of [^{64}Cu]**XYIMSR-06,** were achieved within 1.5 h in yield of 51.0 ± 4.5% (n=5) and with specific radioactivities of 4.1 – 8.9 GBq/μM (110-240 Ci/mmol).

*SPECT/CT imaging of [^{111}In]**XYIMSR-01***. [^{111}In]**XYIMSR-01** was administered intravenously to two mice with SK-RC-52 flank tumors, followed by SPECT/CT. As shown in FIG. 17, radiotracer uptake was observed within the tumors at 1 h post-injection. By 24 h post-injection, nearly all the radioactivity in the kidneys and other organs had been eliminated, with tumor still retaining significant amounts of radiotracer. Image contrast improved even further by 48 h post-injection.

*SPECT/CT imaging of [^{177}Lu]**XYIMSR-01***. [^{177}Lu]**XYIMSR-01**was administered intravenously to mice with SK-RC-52 flank tumors, followed by SPECT/CT. [^{177}Lu]**XYIMSR-01** exhibited CAIX specific uptake in vitro. As shown in FIG. 18, SPECT/CT imaging demonstrated tumor visualization by 1 h post-injection and achieved high signal contrast by 24 h.

*PET/CT imaging of [Al^{18}F]**XYIMSR-04***. [Al^{18}F]**XYIMSR-04**was administered intravenously to mice with SK-RC-52 flank tumors, followed by PET/CT. As shown in FIG 19, PET/CT imaging demonstrated tumor visualization by 1 h post-injection.

*PET/CT imaging of [^{64}Cu]**XYIMSR-06***. As shown in FIG. 20, the imaging findings closely matched the results of the biodistribution study (Table 3). At 1 h, tumor could be observed distinctly with additional visible signal in the kidneys and urinary bladder. Relatively selective tumor imaging could be achieved at 8 h with target selectivity continuing to improve by 24 h, with the SK-RC-52 ccRCC tumor xenografts as the only remaining visible radiotracer-avid structures. There was no significant background signal from blood or muscle. The liver did not retain significant radioactivity at any time.

*Biodistribution of [^{111}In]**XYIMSR-01***. Table 2 shows the biodistribution of [^{111}In]**XYIMSR-01** at 1 h, 4 h, 8h, 24 h and 48 h post-injection; results are expressed as the percentage injected dose per gram (% ID/g) of tissue, n = 5; block was done by simultaneously injecting 200 nmole of non-labeled **1** with **[^{111}In]XYIMSR-01**. Biodistribution confirmed tumor-selective uptake and retention of [^{111}In]**XYIMSR-01** observed in imaging studies (Table 2). At 1 h post-injection, 26.0% ID/g of radiotracer uptake was observed within the tumor. Tumor/blood, and tumor/muscle ratios reached 19.7 and 12.7, respectively. Major non-specific organ uptake was observed in kidney, lung, stomach, small intestine and liver (Table 2).

Biodistribution studies conducted at later time points showed that the radiotracer continued to wash out from those organs while being retained within the tumor. At 24 h post-injection, tumor/blood and tumor/muscle ratios reached 178 and 68, respectively. Importantly, tumor/kidney ratio reached 1.7, suggesting that it might be possible to detect local ccRCC in the kidney at 24 h. The enhanced hydrophilicity of [^{111}In]**XYIMSR-01,** relative to the reported optical analog (Wichert et al., 2015), may have contributed to the low liver uptake. Tumor/liver ratio for [^{111}In]**XYIMSR-01** and optical agent were 8.5 and 4.0 at 24 h, respectively (Wichert et al., 2015). All other organs showed tumor/organ ratio close to or higher than 10, indicating that good image contrast can be expected from these imaging agents. Biodistribution of [^{111}In]**XYIMSR-01** simultaneously injected with non-radioactive competitor **8** at 24h and 48h post injection showed competitive inhibition of the uptake to tumors to 1% level (Table 2). The fast normal tissue clearance and the long lasting tumor retention may enable applications to radiopharmaceutical therapy with appropriately selected therapeutic radiometals.

Table 2. Biodistribution of [^{111}In]**XYIMSR-01** at 1 h, 4 h, 8h, 24 h and 48 h post-injection

Organs	**1hr**	**4hr**	**8hr**	**24hr**	**24hr +Block**	**48hr**	**48hr +Block**
Blood	1.34 ±0.17	0.65 ±0.06	0.48 ±0.02	0.15 ±0.02	0.03 ±0.00	0.06 ±0.02	0.03 ±0.00
Heart	5.98 ±0.53	2.91 ±0.45	2.61 ±0.35	1.16 ±0.20	0.04 ±0.01	0.84 ±0.16	0.04 ±0.01
Lung	45.85 ±19.89	17.85 ±3.55	17.39 ±8.99	11.01 ±3.71	0.12 ±0.02	9.22 ±1.25	0.09 ±0.02
Pancreas	3.81 ±0.72	1.54 ±0.40	1.61 ±0.28	0.69 ±0.18	0.03 ±0.00	0.59 ±0.18	0.03 ±0.01
Spleen	0.52 ±0.04	0.51 ±0.08	0.64 ±0.07	0.69 ±0.39	0.08 ±0.01	0.67 ±0.13	0.11 ±0.03
Fat	1.03 ±0.24	0.42 ±0.22	0.45 ±0.08	0.28 ±0.19	0.02 ±0.01	0.25 ±0.08	0.03 ±0.01
Brain	1.23 ±1.10	0.45 ±0.06	0.59 ±0.09	0.71 ±0.85	0.03 ±0.00	0.41 ±0.05	0.03 ±0.01
Muscle	2.34 ±2.19	1.01 ±0.28	1.09 ±0.15	0.35 ±0.12	0.02 ±0.00	0.39 ±0.28	0.02 ±0.00
Small intestine	9.37 ±1.26	4.27 ±0.69	4.31 ±0.67	2.11 ±0.33	0.08 ±0.01	1.22 ±0.44	0.08 ±0.02
Liver	8.36 ±0.73	4.00 ±0.8	3.65 ±0.65	3.02 ±3.46	0.10 ±0.02	1.65 ±0.26	0.13 ±0.04
Stomach	16.71 ±2.46	7.91 ±1.28	8.74 ±1.26	3.31 ±1.25	0.14 ±0.02	1.82 ±0.43	0.14 ±0.03
Kidney	71.26 ±8.74	41.52 ±6.07	28.79 ±21.35	15.29 ±1.69	0.68 ±0.14	8.78 ±1.89	0.45 ±0.09
Bladder	4.90 ±4.96	2.68 ±1.89	2.28 ±0.51	0.74 ±0.17	0.20 ±0.07	0.38 ±0.18	0.14 ±0.03
Tumor	26.01 ±5.74	20.83 ±6.25	34.00 ±15.16	25.62 ±17.67	1.41 ±0.20	13.92 ±6.67	1.22 ±0.54
Tumor/ Blood	19.7 ±4.8	31.9 ±9.4	77.0 ±32.5	178.1 ±145.4	45.2 ±9.7	212.0 ±41.4	45.4 ±13.8
Tumor/ Muscle	12.7 ±5.8	21.4 ±7.2	34.2 ±16.0	68.4 ±29.0	91.4 ±11.1	52.0 ±21.0	75.1 ±17.7
Tumor/ Kidney	0.36 ±0.06	0.50 ±0.15	3.1 ±3.1	1.7 ±1.2	2.1 ±0.3	1.5 ±0.5	2.7 ±0.8

*Biodistribution of [^{177}Lu]**XYIMSR-01***. Biodistribution studies confirmed the SPECT/CT data. Tumor-to-blood, muscle, and kidney ratios were 607.4 ± 200.7, 128.4 ± 25.4 and 4.5 ± 1.4, respectively, at 24 h post-injection.

Table 3. Biodistribution of [^{177}Lu]**XYIMSR-01**

Organs	**1hr**	**4hr**	**8hr**	**24hr**	**24hr +Block**	**48hr**	**48hr +Block**
Blood	0.55 ±0.06	0.18 ±0.02	0.16 ±0.05	0.02 ±0.01	0.04 ±0.02	0.04 ±0.01	0.04 ±0.07

Heart	3.59 ±0.73	1.52 ±0.54	1.49 ±0.59	0.28 ±0.14	0.08 ±0.04	0.12 ±0.17	0.04 ±0.01
Lung	23.72 ±6.49	10.35 ±1.86	8.87 ±3.30	1.48 ±0.59	0.73 ±0.58	0.90 ±0.05	0.18 ±0.05
Pancreas	2.03 ±0.25	0.99 ±0.19	1.03 ±0.50	0.16 ±0.07	0.05 ±0.03	0.06 ±0.01	0.02 ±0.00
Spleen	0.29 ±0.07	0.15 ±0.03	0.29 ±0.05	0.20 ±0.07	0.38 ±0.32	0.13 ±0.04	0.15 ±0.06
Fat	1.07 ±0.58	0.56 ±0.14	0.46 ±0.17	0.05 ±0.04	0.03 ±0.03	0.03 ±0.01	0.02 ±0.01
Brain	0.49 ±0.08	0.33 ±0.04	0.44 ±0.08	0.28 ±0.10	0.04 ±0.01	0.17 ±0.03	0.02 ±0.00
Muscle (mm)	1.42 ±0.40	0.65 ±0.19	0.47 ±0.18	0.10 ±0.05	0.03 ±0.01	0.04 ±0.01	0.01 ±0.00
Sm. intestine	6.11 ±0.68	2.64 ±0.17	3.67 ±0.93	0.96 ±0.32	0.18 ±0.07	0.20 ±0.05	0.05 ±0.01
Liver	4.15 ±0.39	1.79 ±0.44	1.87 ±0.77	0.47 ±0.21	0.46 ±0.34	0.19 ±0.03	0.23 ±0.04
Stomach	12.20 ±1.66	6.06 ±1.57	6.15 ±2.65	1.02 ±0.56	0.21 ±0.07	0.35 ±0.04	0.09 ±0.02
Kidney (kid)	40.77 ±6.68	19.17 ±2.82	18.99 ±6.14	3.11 ±1.59	1.54 ±1.44	0.76 ±0.11	0.39 ±0.05
Bladder	26.55 ±11.08	6.60 ±3.66	6.00 ±3.52	1.29 ±1.10	0.73 ±0.55	0.20 ±0.01	0.28 ±0.09
Tumor	26.91 ±6.06	26.28 ±4.25	27.48 ±4.32	12.51 ±3.02	1.70 ±0.79	5.82 ±2.14	0.65 ±0.10
Tumor/ Blood	47.9 ±13.4	150.3 ±34.6	178.6 ±36.6	607.4 ±200.7	42.0 ±20.9	200.2 ±101.7	42.7 ±23.7
Tumor/mm	18.8 ±5.0	43.7 ±16.8	65.0 ±19.0	128.4 ±25.4	58.6 ±25.3	141.5 ±71.7	62.5 ±34.5
Tumor/kid	0.6 ±0.2	1.4 ±0.4	1.5 ±0.3	4.5 ±1.4	1.4 ±0.6	7.1 ±1.8	1.7 ±0.3

*Biodistribution of [Al^{18}F]**XYIMSR-04***. The biodistribution data at 1 h is shown in Table 4. The tumor uptake is 14.40%ID/g, with tumor-to –blood, -muscle and –kidney of 22.1, 9.74 and 0.28.

Table 4. Biodistribution of [Al^{18}F]**XYIMSR-04**

Organs	**1 h (%ID/g)**
Blood	0.65 ± 0.11
Heart	5.03 ± 0.51
Lung	34.07 ± 5.85
Pancreas	3.47 ± 0.16
Spleen	0.54 ± 0.18
Fat	1.54 ± 0.25
Brain	0.66 ± 0.04
Muscle (mm)	1.74 ± 0.58
Sm. intestine	9.59 ± 1.04

Liver	5.55 ± 0.91
Stomach	21.62 ± 1.85
Kidney (kid)	50.84 ± 2.65
Bladder	20.12 ± 12.51
Bone	1.91 ± 1.39
Tumor	14.40±2.18
Tumor/Blood	22.1 ± 1.5
Tumor/mm	9.74 ± 2.9
Tumor/kid	0.28 ± 0.03

*Biodistribution of [^{64}Cu]**XYIMSR-06***. Table 5 shows the radiotracer uptake in selected organs. Radiotracer uptake within tumor was 14.5 %ID/g at 1 h with tumor-to-blood and muscle ratios >10. After the radiotracer reached a maximum of 19.3 %ID/g in tumor at 4 h, it began to wash out from tumors slowly. By 24 h radioactivity within the tumors dropped to 6.2 %ID/g. Compared with [^{111}In]**XYIMSR-01** (20.8 %ID/g at 4 h, 34.0 %ID/g at 8 h, 25.6 %ID/g at 24h and 13.9%ID/g at 48 h)[33], [^{64}Cu]**XYIMSR-06** demonstrated faster clearance, likely due to the more hydrophilic nature of NOTA-Cu(II), which has an additional non-coordinated free carboxylate not present for DOTA-In(III). At 8 h post-injection tumor signal was predominant, with kidney, lung and stomach as the only readily visible organs. Tumor-to-blood, muscle and kidney ratios were 129.6 ± 18.8, 84.3 ± 21.0 and 2.1 ± 0.26, respectively. In principle those ratios would allow the detection of localized tumor in kidney. At 24 h, tumor-to-kidney and -lung ratios were further improved to 7.1 and 4.9, with all other tumor-to-organ ratios tested ≥ 10.0. Co-injection of 200 nmole of **8** along with [^{64}Cu]**XYIMSR-06** blocked tumor uptake of the latter (Table 3) indicating specific, CAIX-mediated binding of this radiotracer. Within 24 h, no significant radiotracer uptake within liver was observed, indicative of the *in vivo* stability of NOTA-^{64}Cu chelation.

Table 5. Biodistribution of [^{64}Cu]**XYIMSR-06**

Organs	**1h**	**4h**	**8h**	**8h +block**	**24h**	**24h +block**
Blood	0.66 ±0.05	0.33 ±0.06	0.13 ±0.02	0.08 ±0.01	0.00 ±0.06	0.01 ±0.08
Heart	3.41 ±0.79	1.78 ±0.33	0.65 ±0.10	0.16 ±0.03	0.12 ±0.03	0.08 ±0.01
Lung	25.52 ±3.35	12.03 ±1.61	4.64 ±0.58	0.77 ±0.14	1.27 ±0.38	0.29 ±0.05
Pancreas	2.94 ±0.24	1.36 ±0.19	0.47 ±0.21	0.14 ±0.03	0.21 ±0.29	0.07 ±0.02

Spleen	0.36 ±0.08	0.24 ±0.04	0.18 ±0.02	0.14 ±0.02	0.09 ±0.01	0.11 ±0.04
Fat	0.80 ±0.17	0.52 ±0.29	0.28 ±0.27	0.05 ±0.01	0.03 ±0.01	0.01 ±0.01
Brain	1.46 ±2.23	0.29 ±0.06	0.24 ±0.06	0.04 ±0.01	0.13 ±0.02	0.02 ±0.01
Muscle (mm)	1.28 ±0.27	0.70 ±0.18	0.21 ±0.05	0.05 ±0.02	0.02 ±0.01	0.04 ±0.06
Sm. intestine	7.35 ±0.78	4.15 ±0.69	1.98 ±0.14	0.38 ±0.06	0.47 ±0.03	0.19 ±0.05
Liver	3.25 ±0.97	2.18 ±0.57	0.99 ±0.22	0.55 ±0.08	0.38 ±0.03	0.42 ±0.04
Stomach	14.80 ±2.27	8.19 ±0.97	4.02 ±0.53	0.69 ±0.18	0.65 ±0.04	0.29 ±0.04
Kidney (kid)	33.65 ±3.91	19.99 ±2.88	8.14 ±1.15	1.82 ±0.39	0.90 ±0.12	0.48 ±0.09
Bladder	11.12 ±6.33	17.05 ±8.86	7.43 ±7.72	1.45 ±1.53	0.34 ±0.09	0.45 ±0.50
Tumor	14.47 ±2.69	19.31 ±4.51	16.74 ±1.58	2.39 ±0.24	6.23 ±1.41	1.20 ±0.47
Tumor/ Blood	21.9 ±4.6	57.7 ±9.3	129.6 ±18.8	32.0 ±3.8	142.6 ±115.8	27.1 ±26.7
Tumor/mm	10.8 ±3.7	29.4 ±9.9	84.3 ±21.0	53.0 ±12.6	261.3 ±47.3	49.0 ±28.7
Tumor/kid	0.4 ±0.1	1.0 ±0.1	2.1 ±0.26	1.3 ±10.2	7.1 ±2.5	2.4 ±0.4

*Radio-therapy of [^{177}Lu]**XYIMSR-01***. Delays in tumor growth were observed from mice injected with [^{177}Lu]**XYIMSR-01** in compared with control non-treated mice. The *P*-values were 0.042 and 0.031 for the 11.1 and 18/5 MBq doses, respectively.

EXAMPLE 4

Discussion

Recently, Wichert and co-workers (Wichert et al., 2015) identified 4,4-bis(4-hydroxyphenyl)valeric acid/acetazolamide as a dual-motif CAIX inhibitor, from a DNA-encoded chemical library(Krall et al., 2013; Franzini et al., 2014; Brenner and Lerner, 1992; Dower et al., 1993). The addition of a second binding motif significantly improved the potency of sulfonamide inhibitors (up to 40 times) (Wichert et al., 2015), while also suggesting a solution to the problem of generating an isoform-selective CAIX inhibitor caused by conserved structures at the active site. It has been hypothesized that the slow renal clearance and high liver uptake of the reported optical agent might derive from the hydrophobicity of the molecule. To

ITM Exhibit 1004, Page 1549 of 1652

improve the pharmacokinetics, the IRDye®750 portion of the molecule has been replaced with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), a more hydrophilic species that also enables convenient radiolabeling with metal isotopes for positron emission tomography (PET), single photon emission computed tomography (SPECT), and radiopharmaceutical therapy (Wadas et al., 2010; Cutler et al., 2013). Indium-111 has been chosen as the initial radionuclide for its relatively long half-life (2.8 day) to enable extended monitoring of pharmacokinetics.

Despite intensive effort expended in the development of CAIX inhibitors designed to engage only the active site, nuclear imaging analogs continued to demonstrate limited success, showing < 2% ID/g within tumor and high radiotracer uptake within kidney and liver (Pan et al., 2014; Akurathi et al., 2010; Lu et al., 2013; Doss et al., 2014; Peeters et al., 2015). Peptides that bind to the surface of CAIX may provide an alternative solution to selective targeting, but they are limited by low potency and *in vivo* stability (Rana et al., 2012). Dual-motif ligands that may concurrently engage the CAIX active site and surface binding demonstrated high potency and tumor uptake for [^{111}In]**XYIMSR-01,** [^{177}Lu]**XYIMSR-01**, [Al^{18}F]**XYIMSR-04**, and [^{64}Cu]**XYIMSR-06**, and for the previously reported optical agent (Wichert et al., 2015). The hydrophilicity of these compounds, with multiple carboxylates and heteroatoms, improved non-targeted organ clearance, including that from kidney and liver.

In summary, highly potent and selective low-molecular-weight (LMW) ligands of carbonic anhydrase IX (CAIX) with a dual-targeting moiety were conjugated with metal chelators, metal complexes and fluorine prosthetic groups, enabling radio-labeling with a wide array of PET, SPECT and radiotherapeutic isotopes. As examples, a ^{111}In labeled ligand ([^{111}In]**XYIMSR-01**) a ^{177}Lu labeled ligand ([^{177}Lu]**XYIMSR-01**), a ^{18}F labeled ligand ([Al^{18}F]**XYIMSR-04**), and a ^{64}Cu labeled ligand ([^{64}Cu]**XYIMSR-06**), were successfully synthesized in high yield and purity. These compounds were then injected into mice bearing CA IX+ tumors (SK-RC-52) and allowed for successful imaging with rapid uptake and minimum non-specific organ uptake. In addition, [^{111}In]**XYIMSR-01** showed long lasting tumor residence, and also demonstrates improved pharmacokinetics, with fast clearance from non-targeted tissues, including kidney. Further, PET imaging ligands, such as [^{64}Cu]**XYIMSR-06** and [Al^{18}F]**XYIMSR-04**, enabled detecting CAIX expressing tumor in higher sensitivity and resolution. Moreover, the structure modifications on

[^{64}Cu]**XYIMSR-06** and [^{177}Lu]**XYIMSR-01** enabled significant improvement on *in vivo* pharmacokinetics for both imaging and therapy applications. Finally, [^{177}Lu]**XYIMSR-01** showed significant therapeutic effect in controlling tumor growth.

Radioisotope labeled CA IX targeting agents stand to enable a wide range of imaging and therapeutic applications, including but not limited to renal cell carcinoma (RCC). Based on the structural similarity of the ligands synthesized, kinetic data of these ligands could help to predict the *in vivo* properties of other PET/SPECT/radiotherapeutic isotope labeled ligands. These analogs of [^{111}In]**XYIMSR-01,** [^{177}Lu]**XYIMSR-01**, [Al^{18}F]**XYIMSR-04** and [^{64}Cu]**XYIMSR-06**, with other radiometals should allow for their use in other nuclear imaging modalities and targeted radiopharmaceutical therapy, including but not limited to renal cell carcinoma (RCC).

REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references are herein incorporated by reference to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art. In case of a conflict between the specification and any of the incorporated references, the specification (including any amendments thereof, which may be based on an incorporated reference), shall control. Standard art-accepted meanings of terms are used herein unless indicated otherwise. Standard abbreviations for various terms are used herein.

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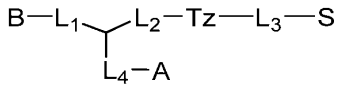
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Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims.

ITM Exhibit 1004, Page 1557 of 1652

THAT WHICH IS CLAIMED:

1. A compound of formula (I):



(I);

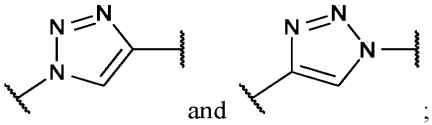
wherein:

B is a metal chelating moiety optionally comprising a metal or a radiometal, or a halogenated or radio-halogenated prosthetic group;

L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-;

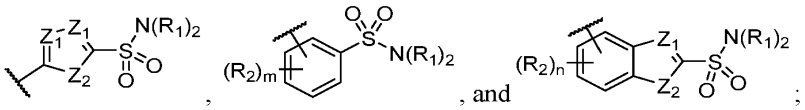
each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl;

Tz is a triazole group selected from the group consisting of



and ;

S is a sulfonamide selected from the group consisting of:



, , and ;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;

each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted

ITM Exhibit 1004, Page 1558 of 1652

heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

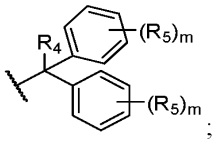
n is an integer selected from the group consisting of 1, 2, and 3;

each Z_1 is independently selected from the group consisting of CR_3, and N;

each Z_2 is independently selected from the group consisting of CR_3, and S;

each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

A is



;

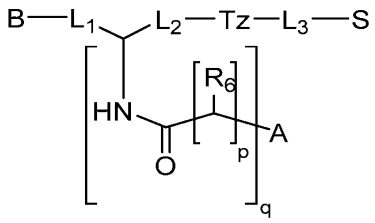
R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl;

R_5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, $-CF_3$, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound of formula (I) is a compound of formula (II):

ITM Exhibit 1004, Page 1559 of 1652



(II);

wherein:

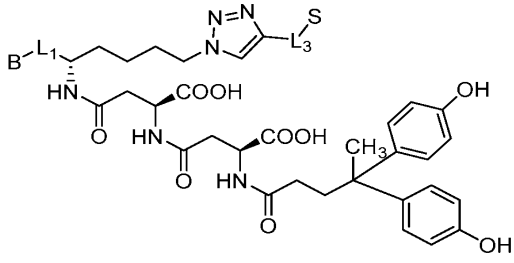
p is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

q is an integer selected from the group consisting of 1, 2, 3, and 4;

each R_6 is independently selected from the group consisting of H and –COOR;

or a pharmaceutically acceptable salt thereof.

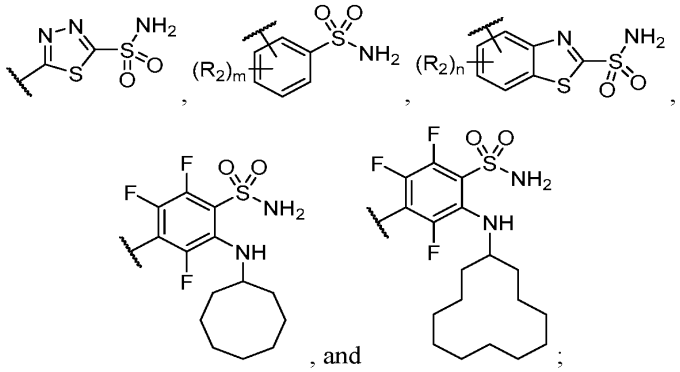
3. The compound of claim 2, wherein the compound of formula (II) is a compound of formula (III):



(III);

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein S is selected from the group consisting of:

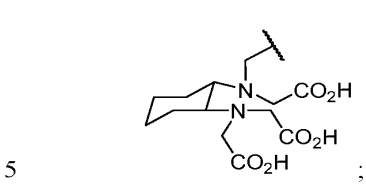
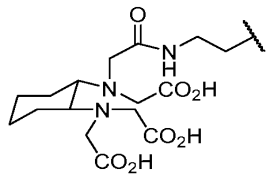
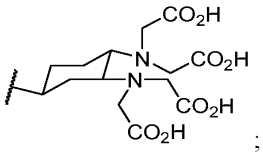
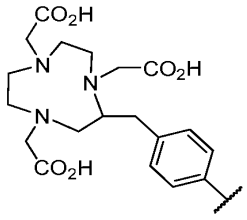
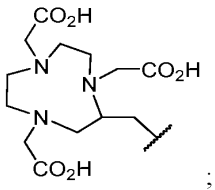
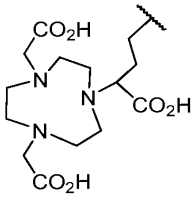
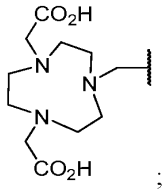
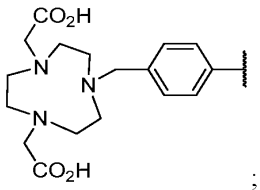
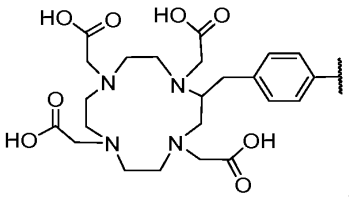
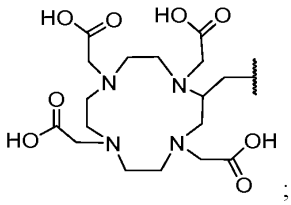
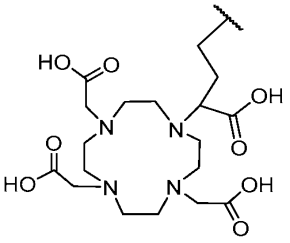
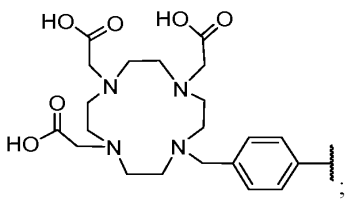
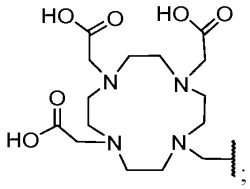
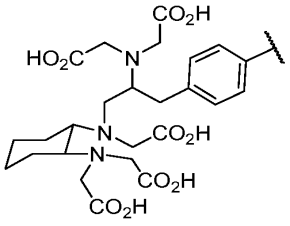
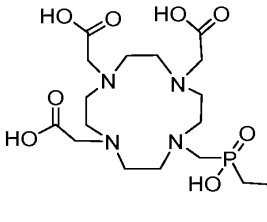
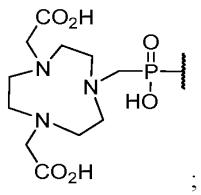


, and ;

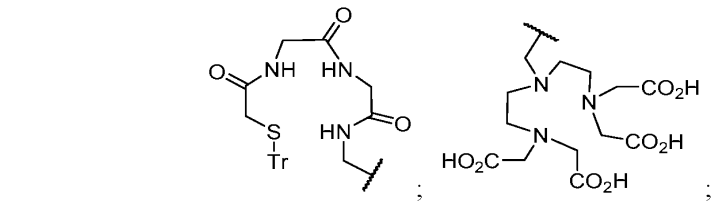
ITM Exhibit 1004, Page 1560 of 1652

or a pharmaceutically acceptable salt thereof.

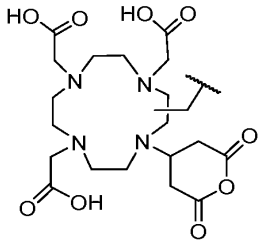
5. The compound of claim 1, wherein B is a metal chelating moiety optionally comprising a metal or a radiometal selected from the group of:

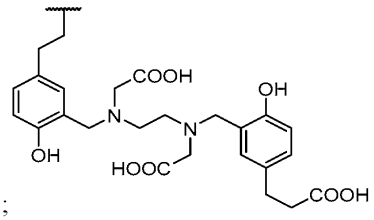

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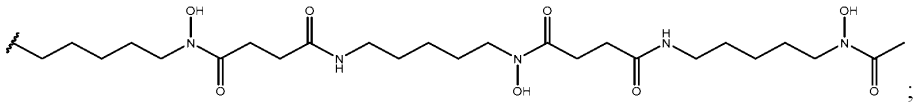
ITM Exhibit 1004, Page 1561 of 1652


;

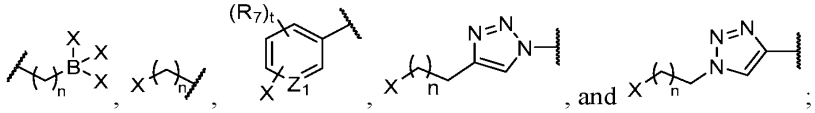
;


;


; and


;

or wherein B is a halogenated or radio-halogenated prosthetic group selected from the group consisting of:


, and ;

wherein:

X is a halogen or a radio-halogen;

n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6;

t is an integer selected from the group consisting of 1, 2, and 3;

each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

ITM Exhibit 1004, Page 1562 of 1652

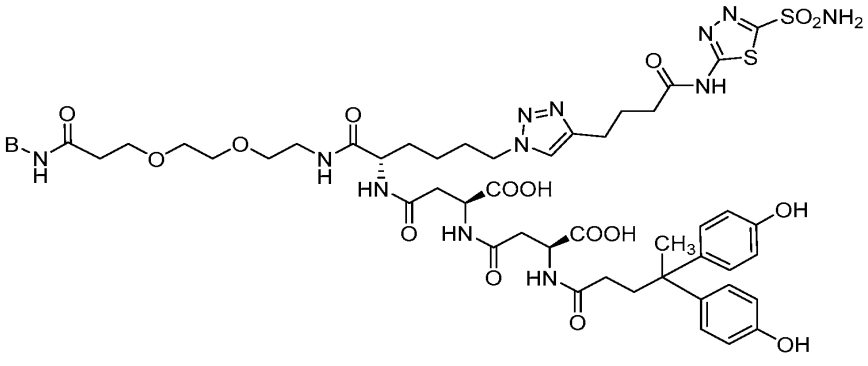
6. The compound of claim 5, wherein the metal chelating agent comprises a metal selected from the group consisting of: Y, Lu, Tc, Zr, In, Sm, Re, Cu, Pb, Ac, Bi, Al, Ga, Re, Ho and Sc.

7. The compound of claim 5, wherein the metal is a radiometal and is selected from the group consisting of: ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho.

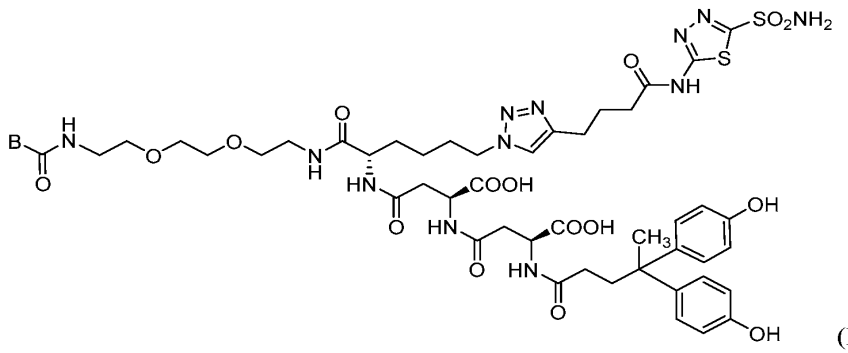
8. The compound of claim 5, wherein the halogen is selected from the group consisting of: F, Br, I, and At.

9. The compound of claim 5, wherein the radio-halogen is selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At.

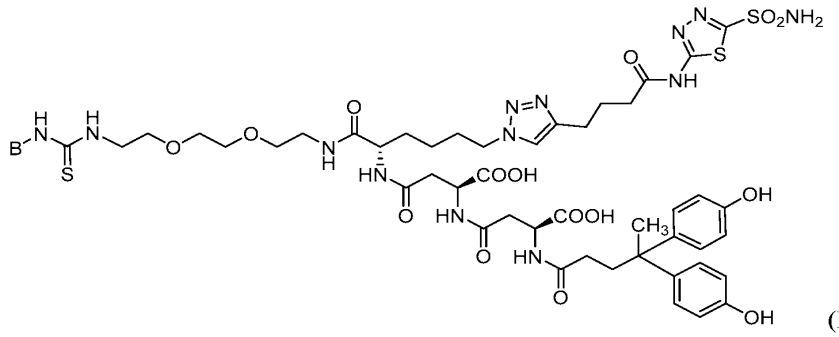
10. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



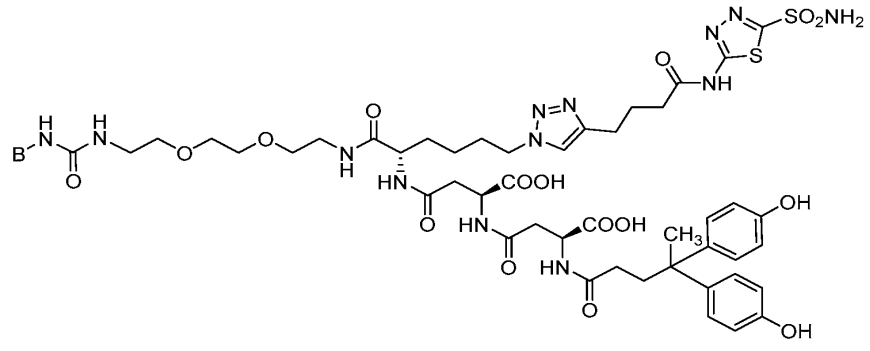
(IVa);



(IVb);



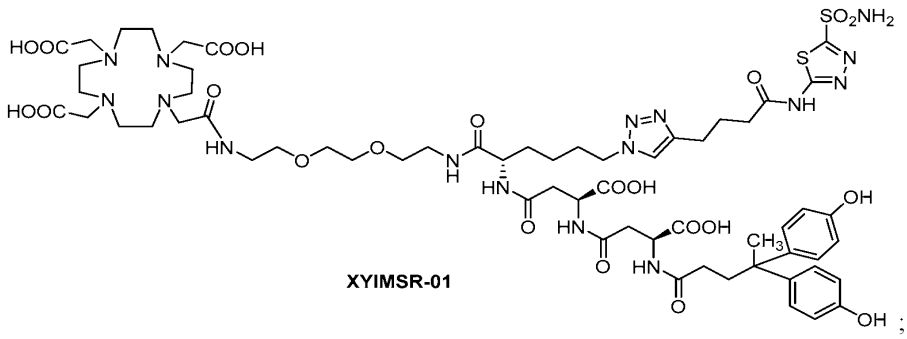
(IVc); and



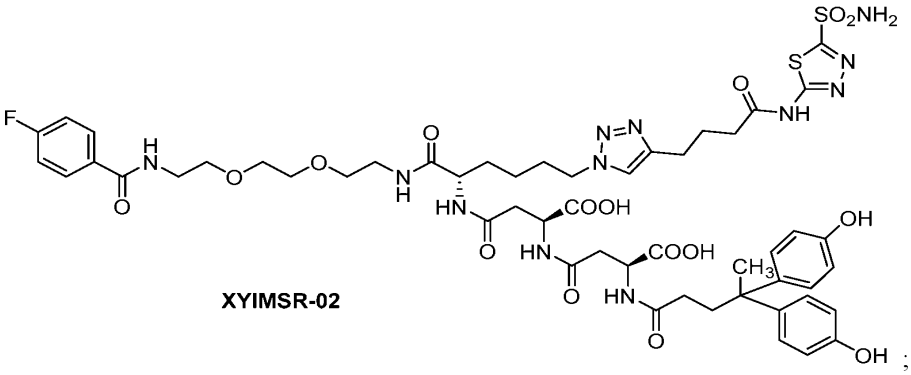
(IVd);

or a pharmaceutically acceptable salt thereof.

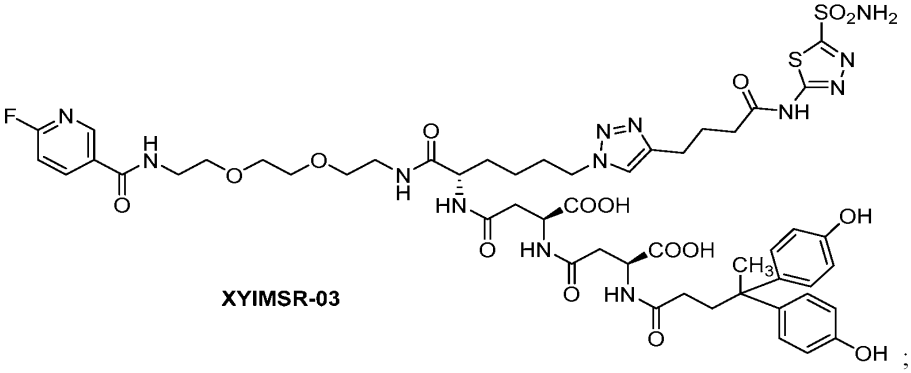
11. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



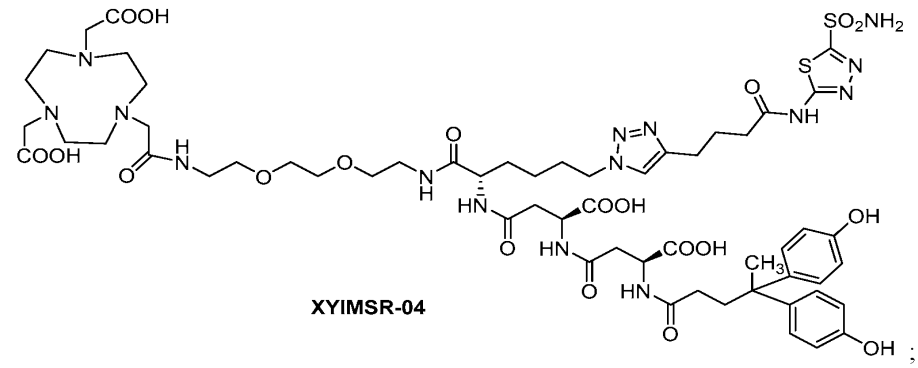
XYIMSR-01 ;



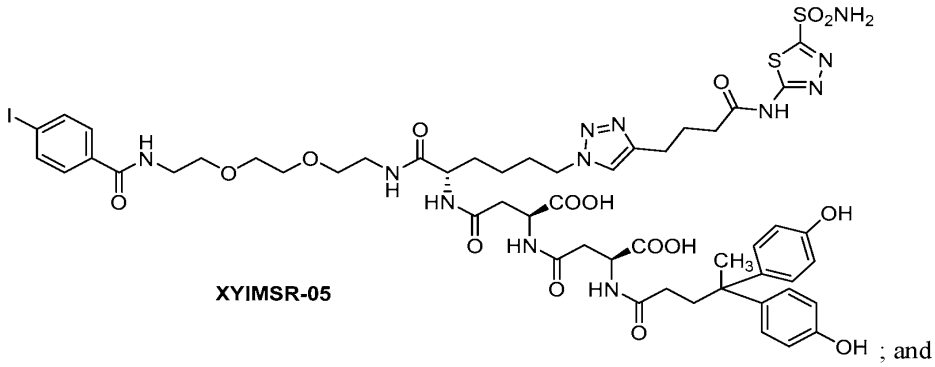
XYIMSR-02 ;



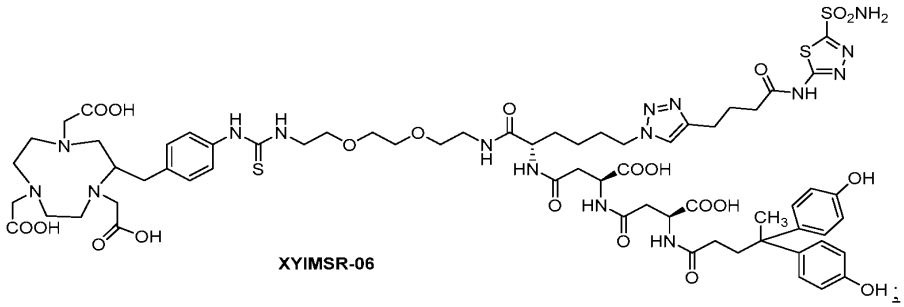
XYIMSR-03 ;



XYIMSR-04 ;



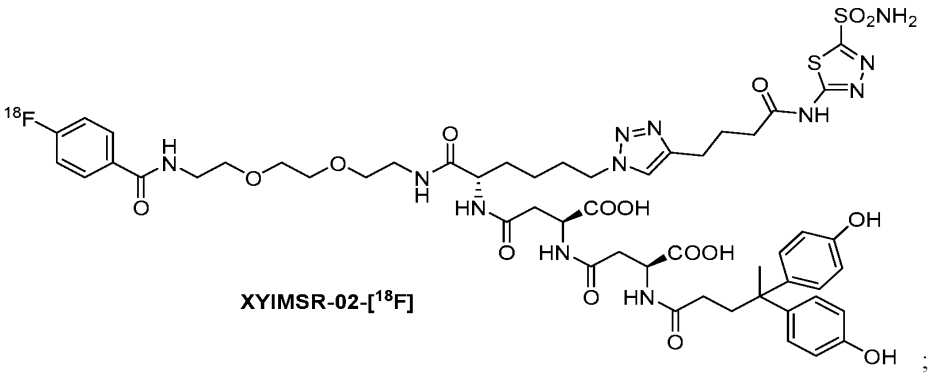
XYIMSR-05 ; and



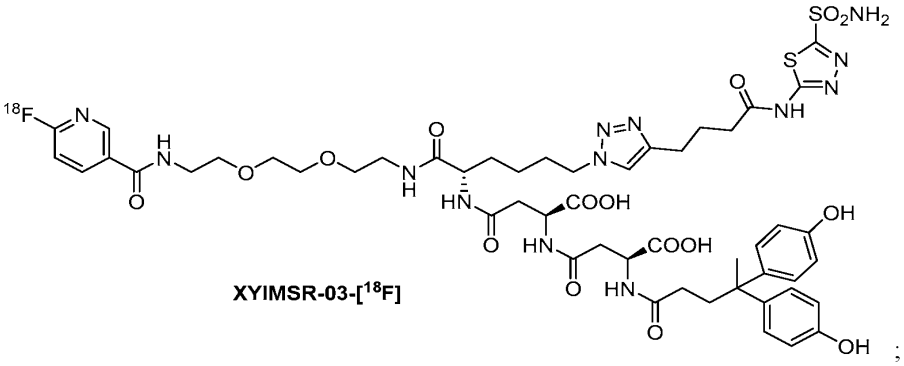
XYIMSR-06 ;

or a pharmaceutically acceptable salt thereof.

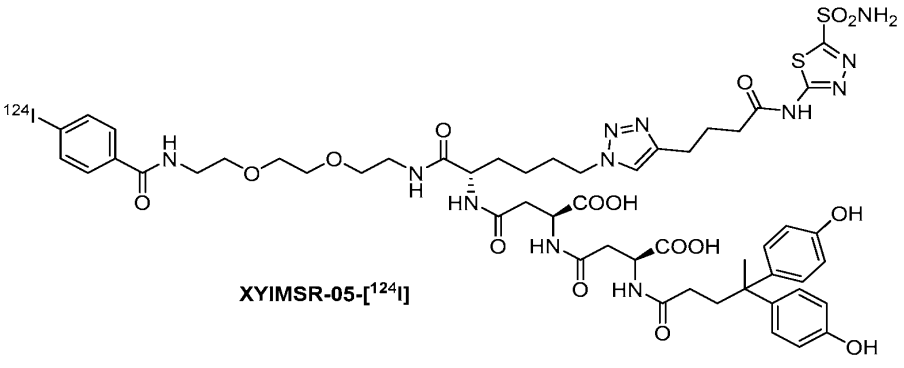
12. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:



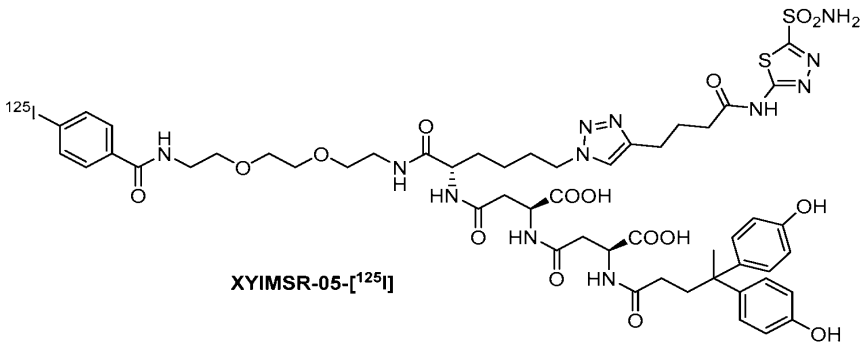
XYIMSR-02-[^{18}F] ;



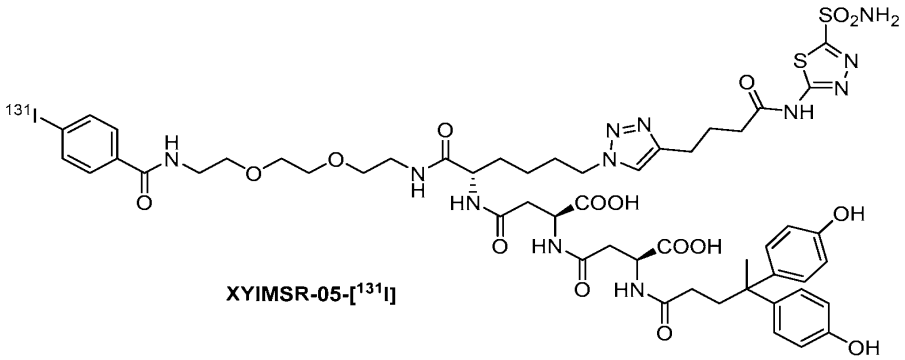
XYIMSR-03-[^{18}F] ;



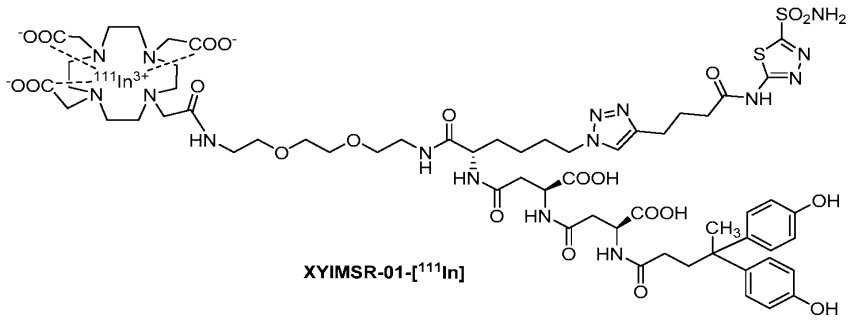
XYIMSR-05-[^{124}I] ;



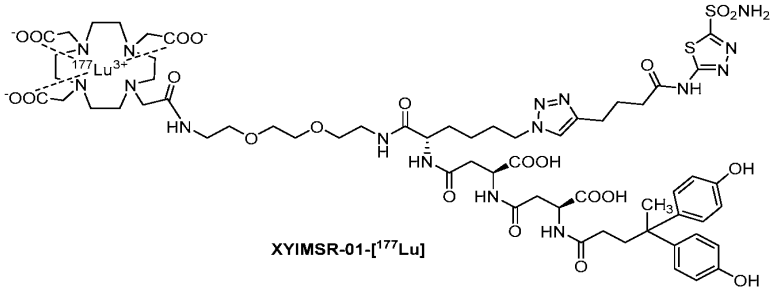
XYIMSR-05-[^{125}I] ;



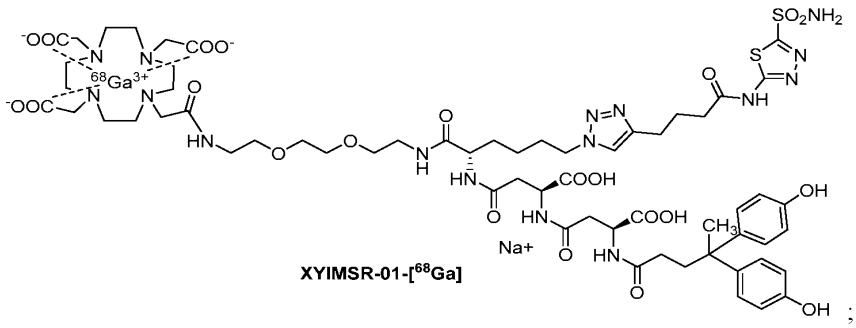
XYIMSR-05-[^{131}I] ;



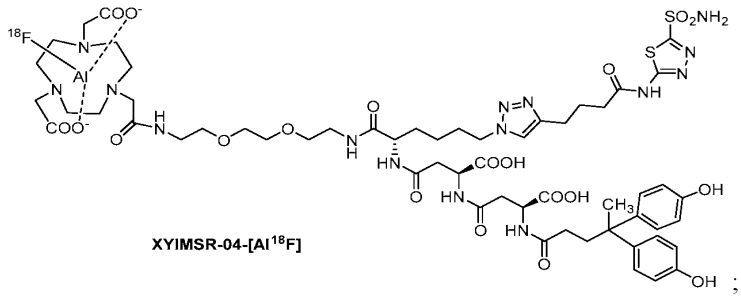
XYIMSR-01-[^{111}In] ;



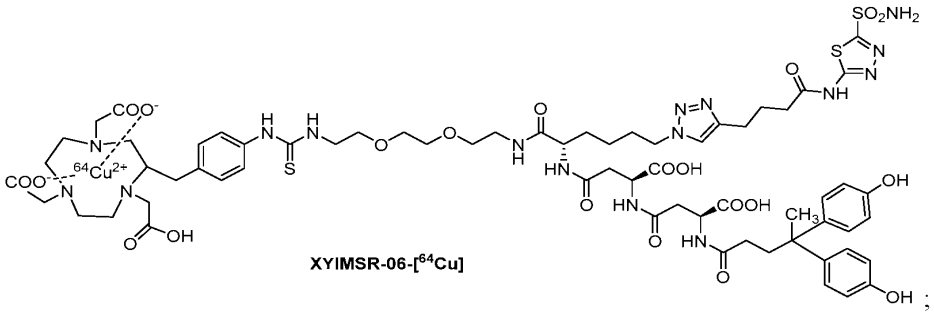
XYIMSR-01-[^{177}Lu] ;



XYIMSR-01-[^{68}Ga] ;



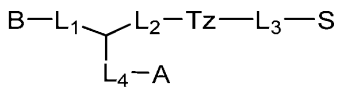
XYIMSR-04-[Al^{18}F] ; and



XYIMSR-06-[^{64}Cu] ;

or a pharmaceutically acceptable salt thereof.

13. A method for imaging or treating one or more Carbonic Anhydrase IX expressing tumors or cells, the method comprising contacting the one or more tumors or cells with an effective amount of a compound of formula (I) and making an image, the compound of formula (I) comprising:



(I);

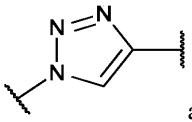
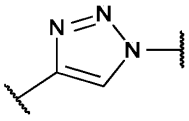
wherein:

B is a metal chelating moiety comprising a radiometal, or a radio-halogenated prosthetic group;

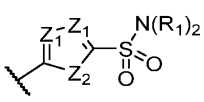
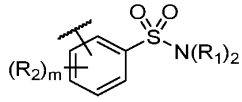
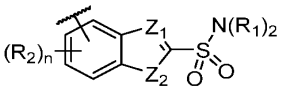
L_1, L_2, L_3, and L_4 are -C_1-C_{24} alkyl-, wherein each alkyl group is optionally substituted with one to four groups selected from the group consisting of =O, =S, and –COOR and one to six of the methylene groups in each alkyl group is optionally replaced by -O-, -S-, or -(NR')-, provided that no two adjacent methylene groups are both replaced by-O-, -S-, or -(NR')-;

each R and R' is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_{12} aryl, and C_4-C_{16} alkyl aryl;

Tz is a triazole group selected from the group consisting of


and

;

S is a sulfonamide targeting a catalytic pocket of CAIX selected from the group consisting of:


,

, and

;

each R_1 is independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted and unsubstituted aryl, and substituted and unsubstituted heteroaryl;

each R_2 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

m is an integer selected from the group consisting of 1, 2, 3, and 4;

n is an integer selected from the group consisting of 1, 2, and 3;

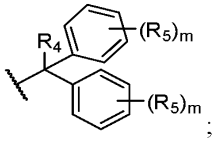
each Z_1 is independently selected from the group consisting of CR_3, and N;

each Z_2 is independently selected from the group consisting of CR_3, and S;

ITM Exhibit 1004, Page 1570 of 1652

each R_3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, amino, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

A is



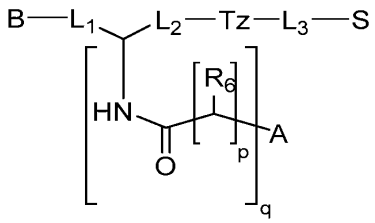
;

R_4 is independently selected from the group consisting of hydrogen, hydroxyl, alkoxyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl;

R_5 is independently selected from the group consisting hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the compound of formula (I) is a compound of formula (II):



(II);

ITM Exhibit 1004, Page 1571 of 1652

wherein:

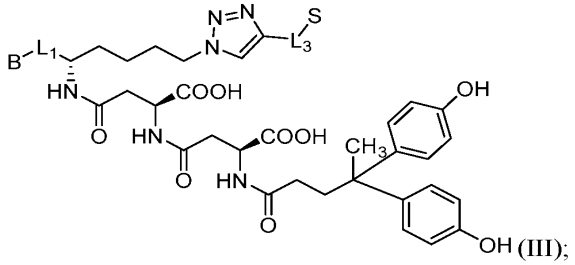
p is an integer selected from the group consisting of 1, 2, 3, and 4;

q is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

each R_6 is independently selected from the group consisting of H and –COOR;

or a pharmaceutically acceptable salt thereof.

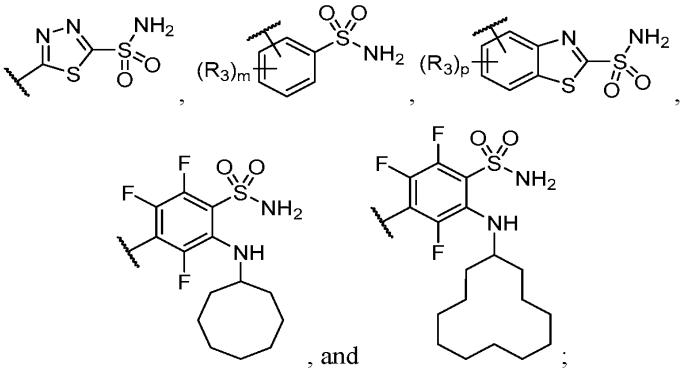
15. The method of claim 14, wherein the compound of formula (II) is a compound of formula (III):



(III);

or a pharmaceutically acceptable salt thereof.

16. The method of claim 13, wherein S is selected from the group of:

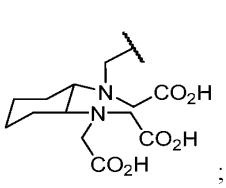
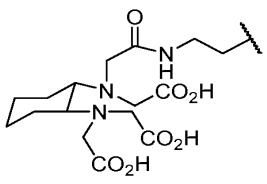
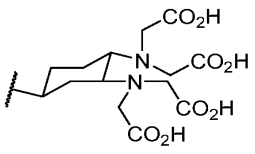
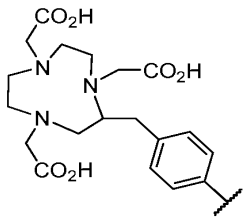
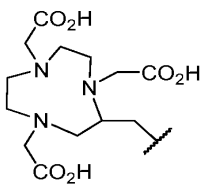
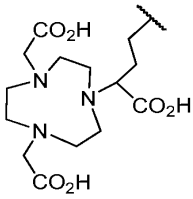
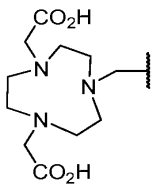
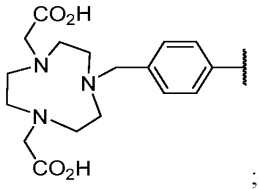
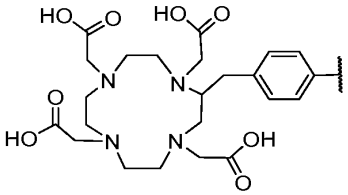
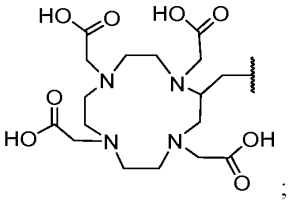
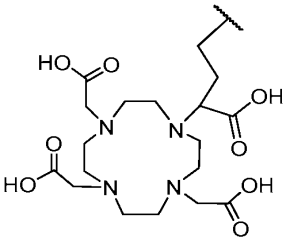
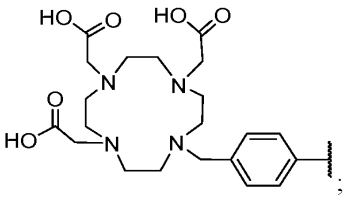
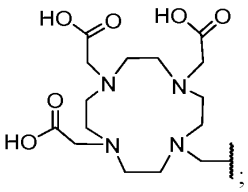
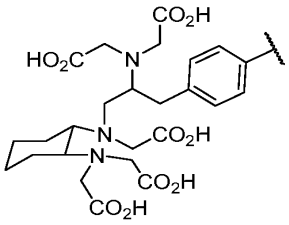
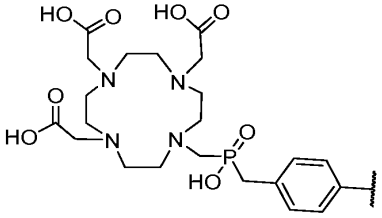
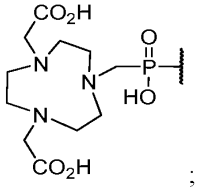


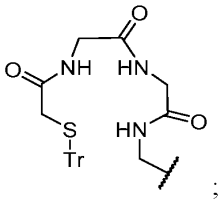
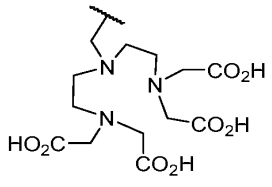
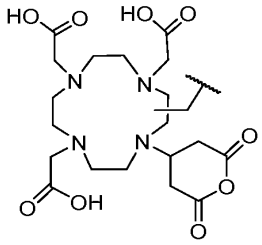
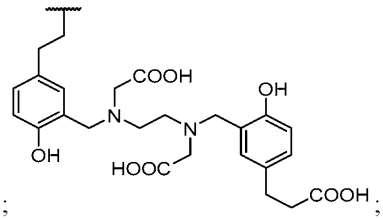
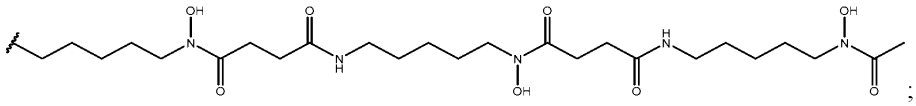
, and ;

or a pharmaceutically acceptable salt thereof.

17. The method of claim 13, wherein B is a metal chelating moiety comprising a radiometal selected from the group of:

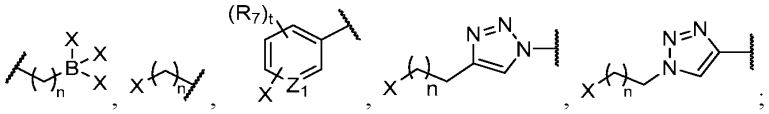
ITM Exhibit 1004, Page 1572 of 1652


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; and

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and the radiometal and is selected from the group consisting of: ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{67}Cu, Al-^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{47}Sc, and ^{166}Ho;

or wherein B is a radio-halogenated prosthetic group selected from the group consisting of:


;

wherein:

X is a radio-halogen selected from the group consisting of: ^{18}F, ^{76}Br, ^{77}Br, ^{80m}Br, ^{125}I, ^{124}I, ^{131}I, and ^{211}At;

n is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6;

t is an integer selected from the group consisting of 1, 2, and 3;

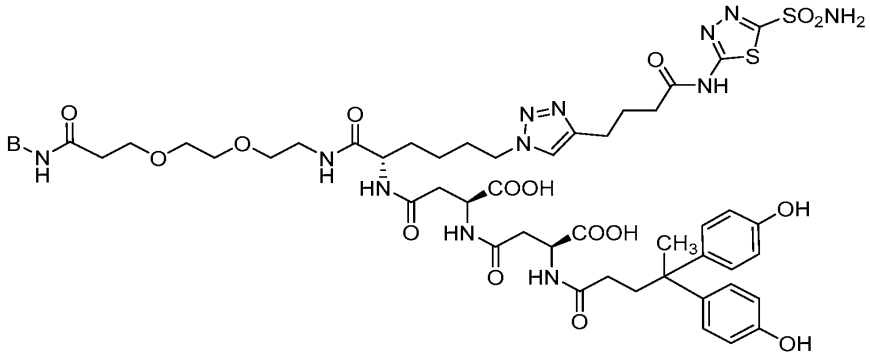
each R_7 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxyl, -CN, -CF_3, substituted or unsubstituted amine, nitro, sulfonyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylaryl substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylheteroaryl, substituted or unsubstituted

ITM Exhibit 1004, Page 1574 of 1652

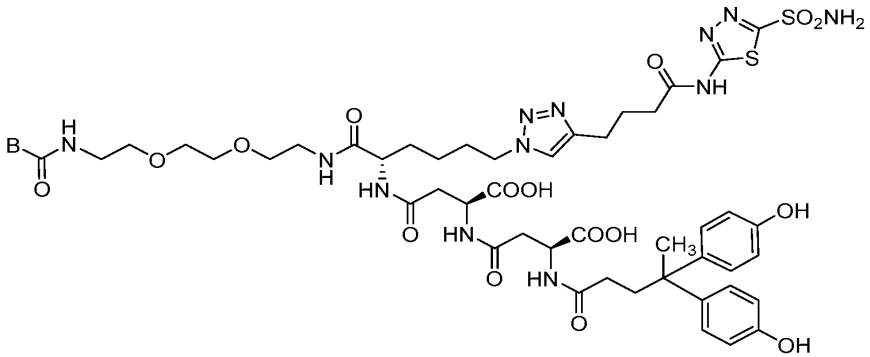
heteroalkylaryl, and substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl;

or a pharmaceutically acceptable salt thereof.

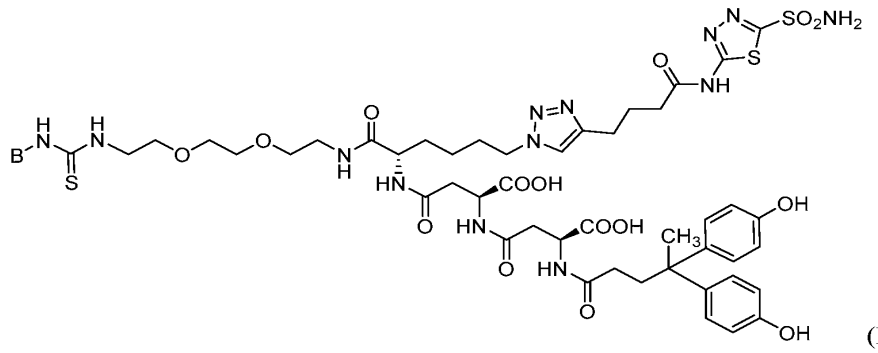
18. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:



(IVa);



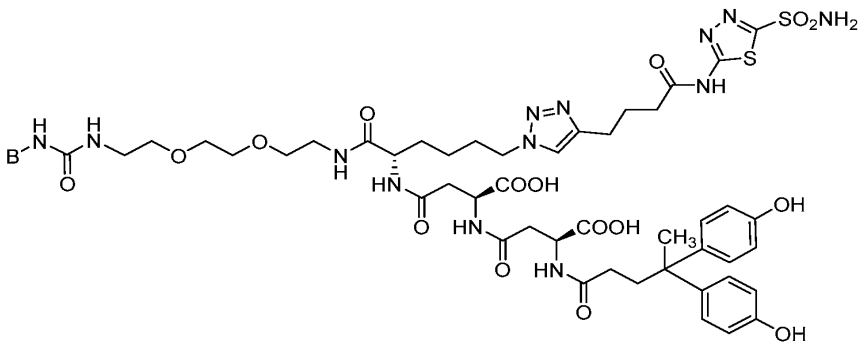
(IVb);



(IVc);

and

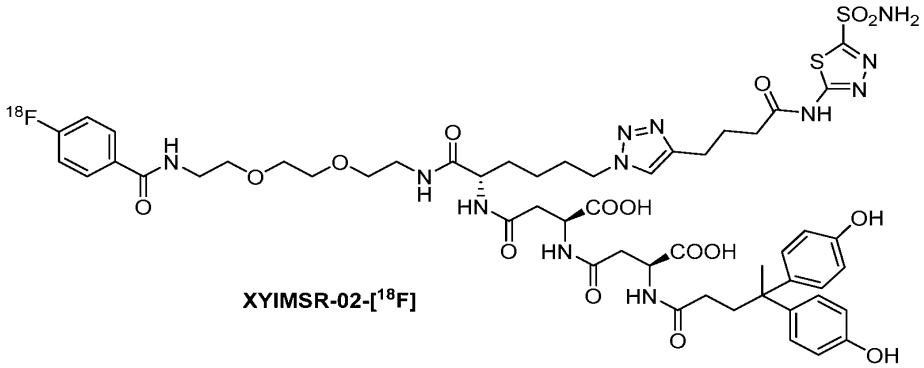
ITM Exhibit 1004, Page 1575 of 1652



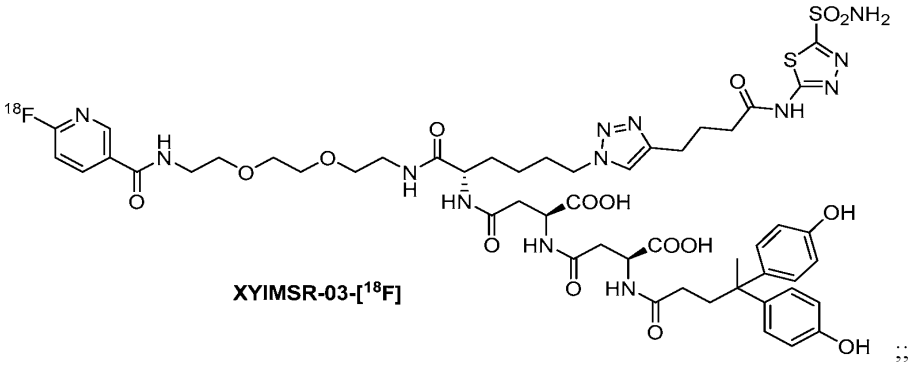
(IVd);

or a pharmaceutically acceptable salt thereof.

19. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:

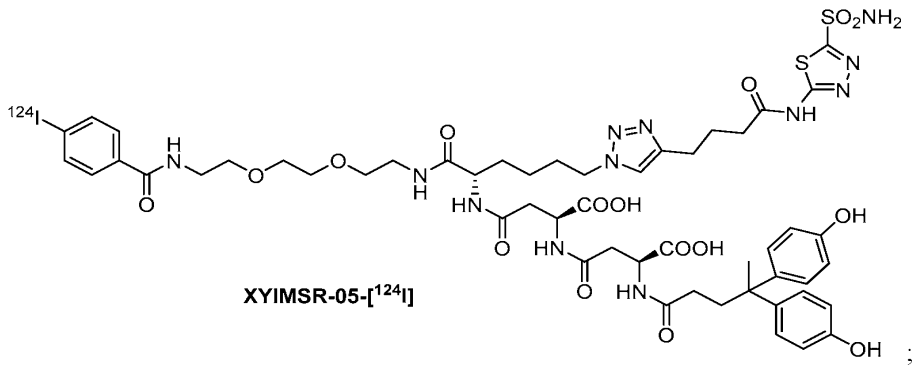


XYIMSR-02-[^{18}F] ;

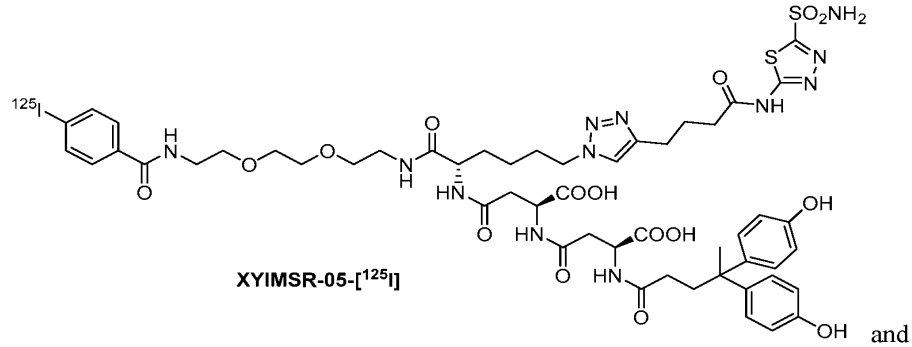


XYIMSR-03-[^{18}F] ;;

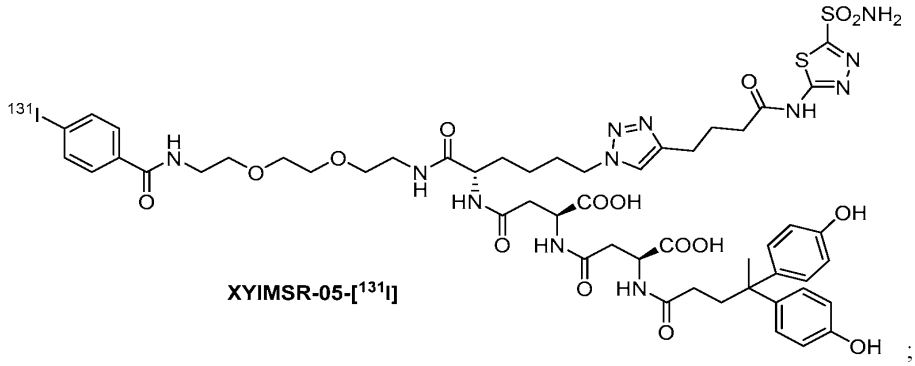
ITM Exhibit 1004, Page 1576 of 1652



XYIMSR-05-[^{124}I] ;



XYIMSR-05-[^{125}I] and

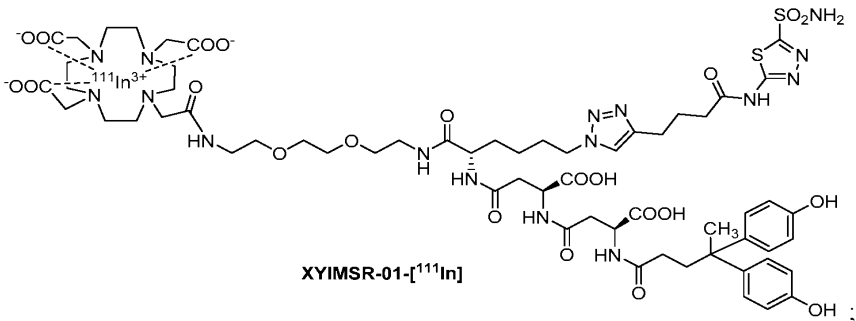


XYIMSR-05-[^{131}I] ;

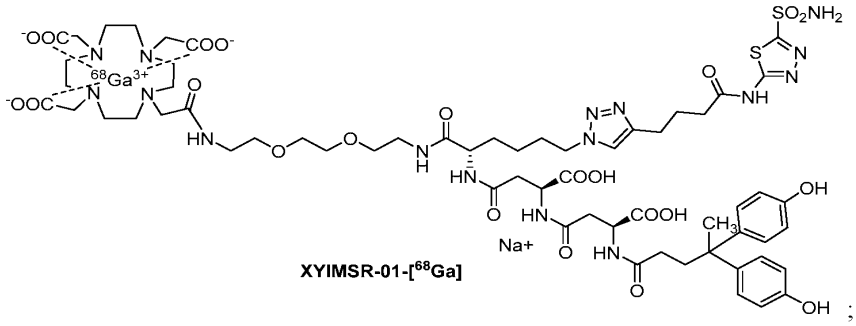
or a pharmaceutically acceptable salt thereof.

20. The method of claim 13, wherein the compound of formula (I) is selected from the group consisting of:

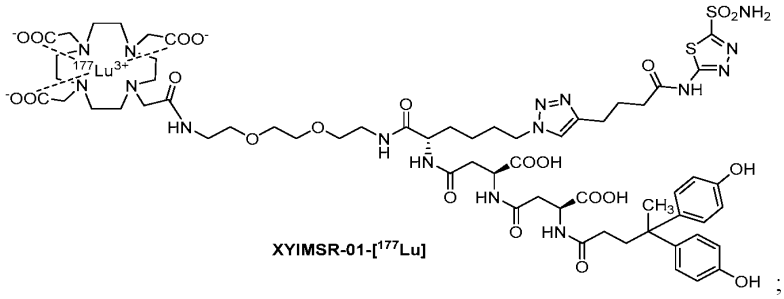
ITM Exhibit 1004, Page 1577 of 1652



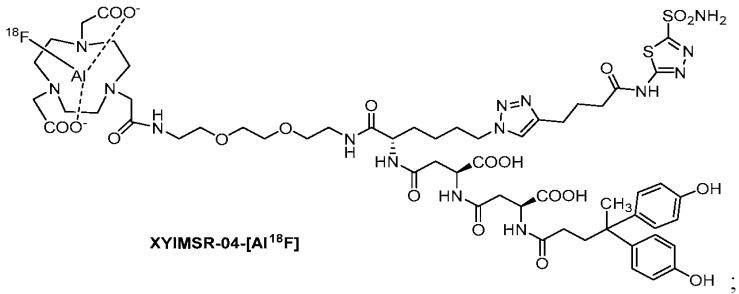
XYIMSR-01-[^{111}In] ;



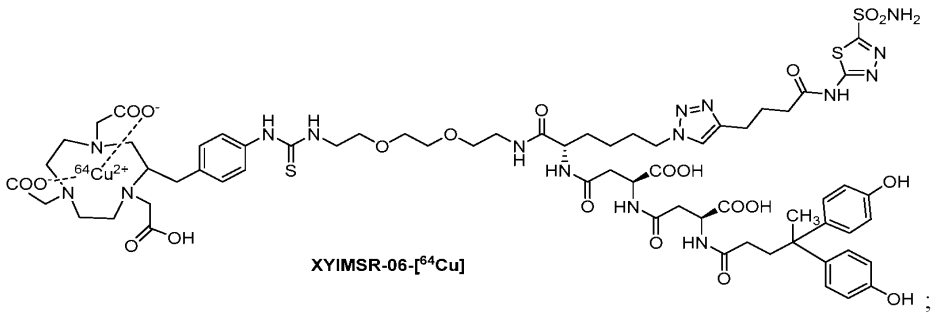
XYIMSR-01-[^{68}Ga] ;



XYIMSR-01-[^{177}Lu] ;



XYIMSR-04-[Al^{18}F] ; and



XYIMSR-06-[^{64}Cu]

or a pharmaceutically acceptable salt thereof.

21. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is selected from the group consisting of: a renal cell carcinoma, a prostate tumor or cell, a metastasized prostate tumor or cell, a lung tumor or cell, a renal tumor or cell, a glioblastoma, a pancreatic tumor or cell, a bladder tumor or cell, a sarcoma, a melanoma, a breast tumor or cell, a colon tumor or cell, a germ cell, a pheochromocytoma, an esophageal tumor or cell, a stomach tumor or cell, and combinations thereof.

22. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is a renal cell carcinoma.

23. The method of claim 13, wherein the imaging comprises positron emission tomography (PET) imaging or single photon emission computed tomography (SPECT) imaging.

24. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is *in vitro*, *in vivo*, or *ex vivo*.

25. The method of claim 13, wherein the one or more Carbonic Anhydrase IX expressing tumors or cells is present in a subject.

26. The method of claim 25, wherein the compound comprising the imaging agent is cleared from the tumor or cell in the subject.

27. The method of claim 25, wherein the compound comprising the imaging agent is cleared more rapidly from a subject's kidneys than from a tumor in the subject.

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ITM Exhibit 1004, Page 1580 of 1652

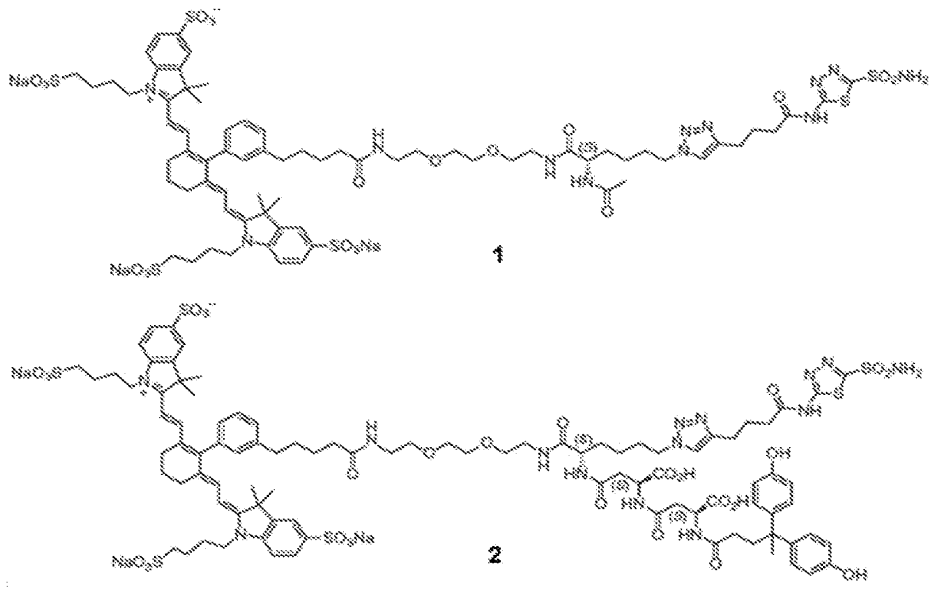


Fig. 1A

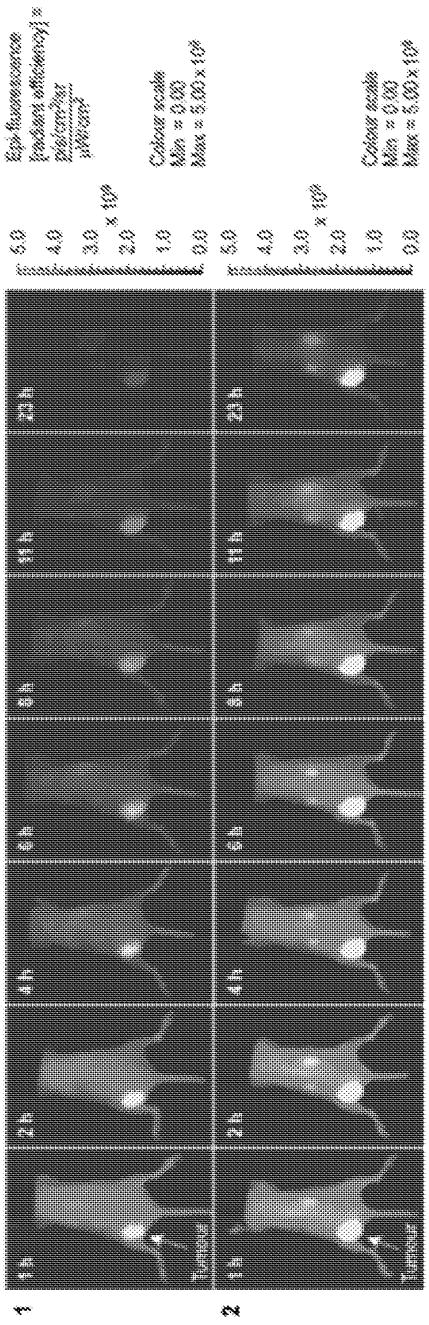

Epi-fluorescence
[Photons s-1cm-2sr-1]
Radiance
Photons
Colour scale
Min = 0.00
Max = 5.00 x 10^6
5.0
4.0
3.0 x 10^6
2.0
1.0
0.0
1 h
2 h
4 h
6 h
8 h
24 h
Tumour
1
2

Fig. 1B

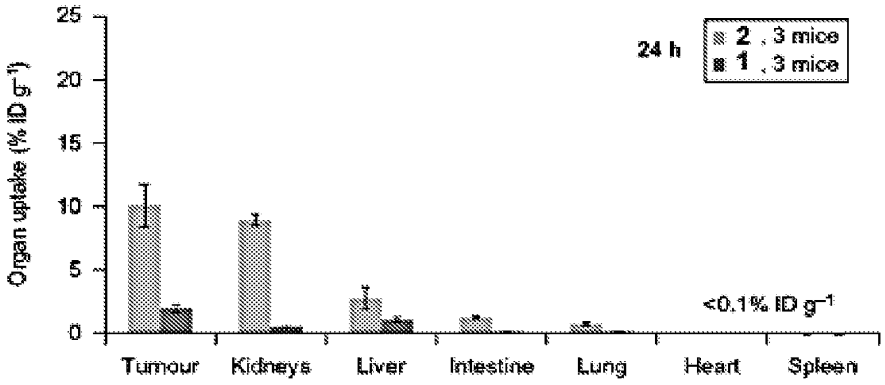

Organ uptake (% ID g⁻¹)
25
20
15
10
5
0
24 h
2 , 3 mice
1 , 3 mice
<0.1% ID g⁻¹
Tumour
Kidneys
Liver
Intestine
Lung
Heart
Spleen

Fig. 1C

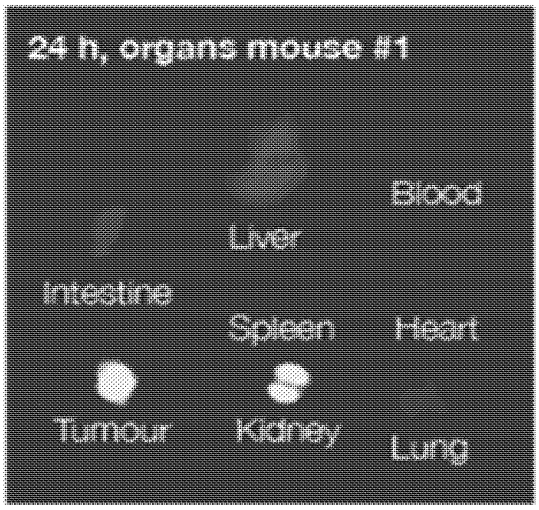
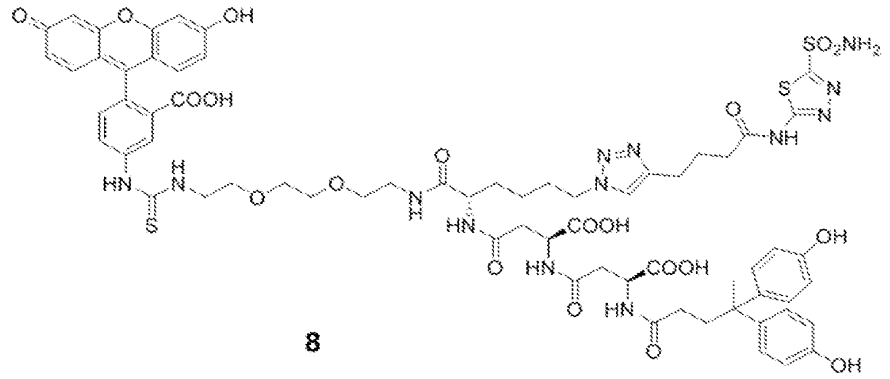

24 h, organs mouse #1
Blood
Liver
Intestine
Spleen
Heart
Tumour
Kidney
Lung

Fig. 1D



8

Fig. 2A

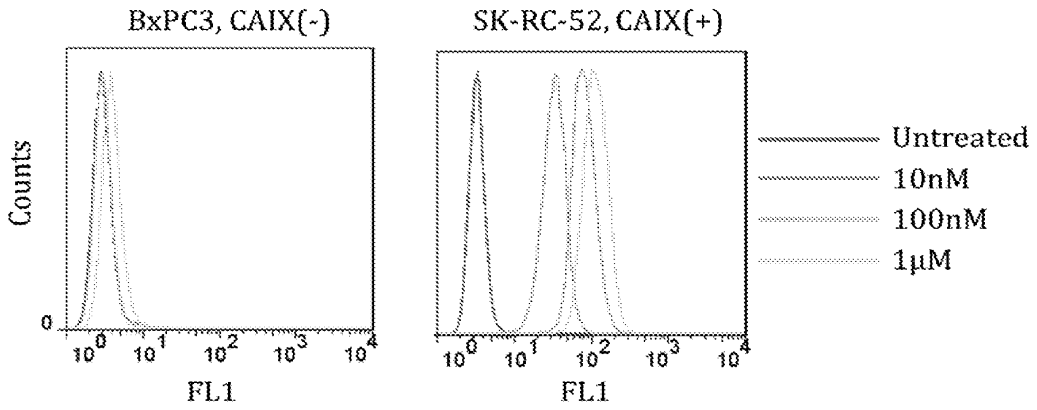


Fig. 2B *Fig. 2C*

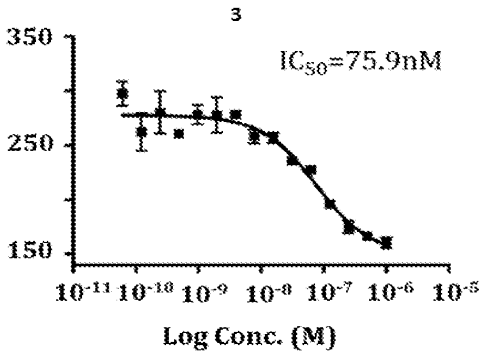


Fig. 3A

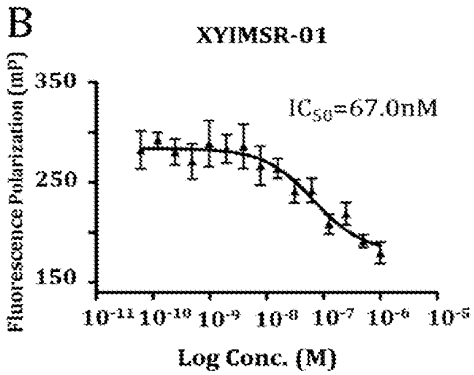


Fig. 3B

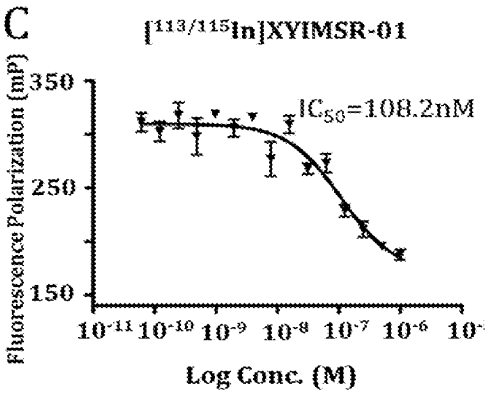


Fig. 3C

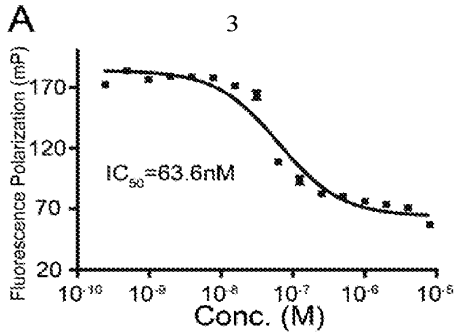


Fig. 4A

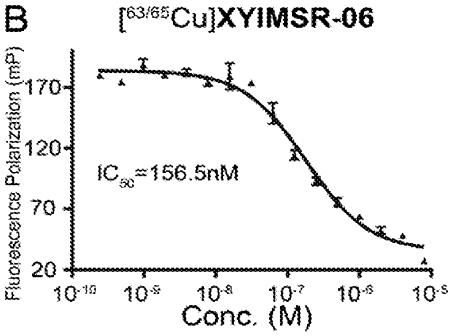


Fig. 4B

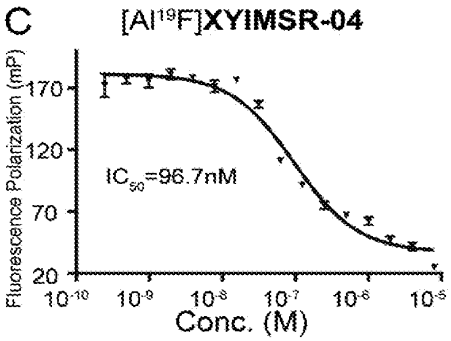


Fig. 4C

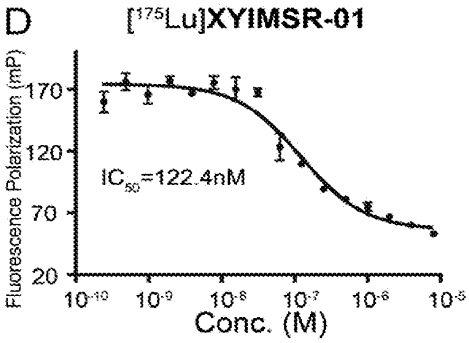


Fig. 4D

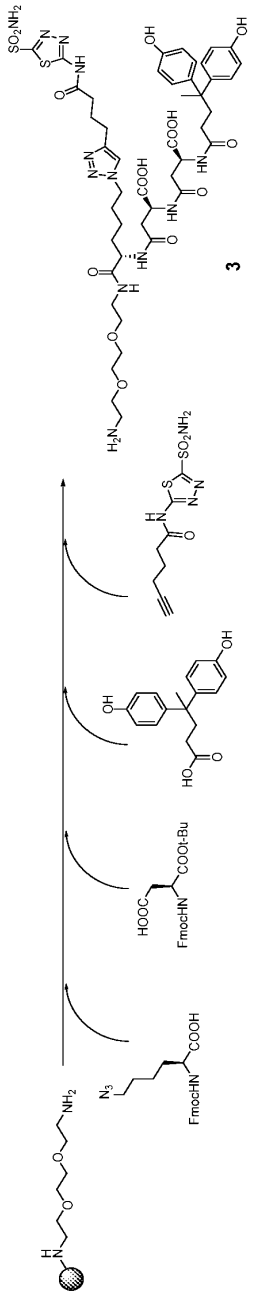


Fig. 5

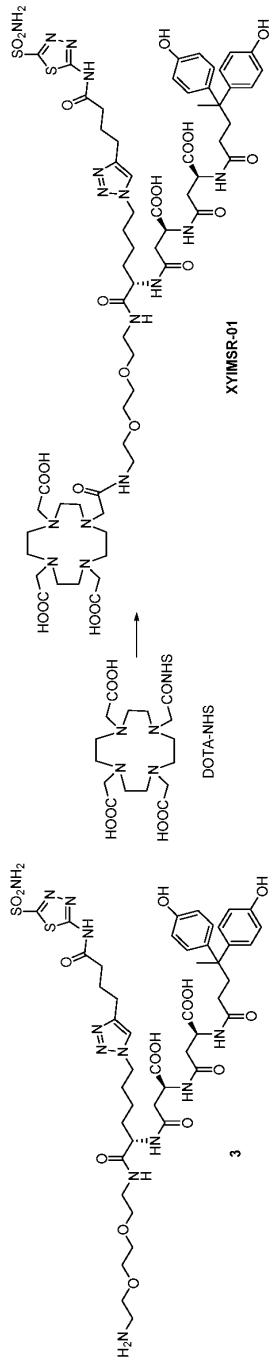


Fig. 6

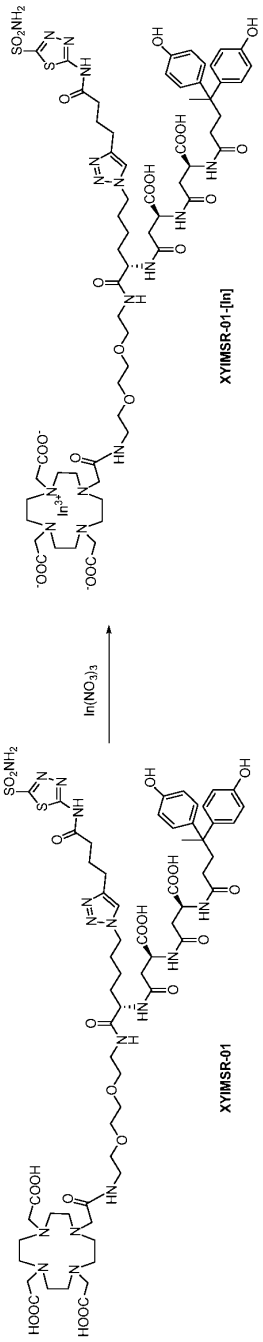


Fig. 7

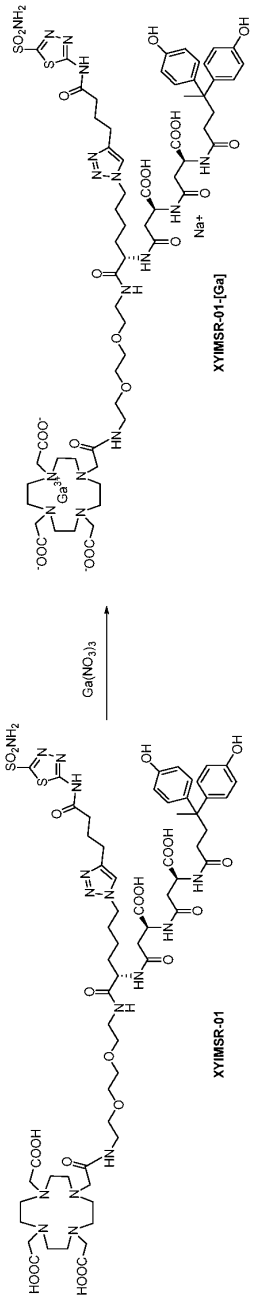


Fig. 8

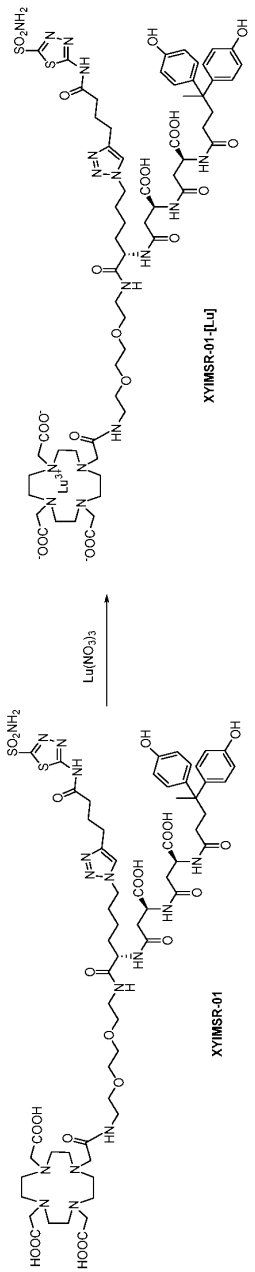


Fig. 9

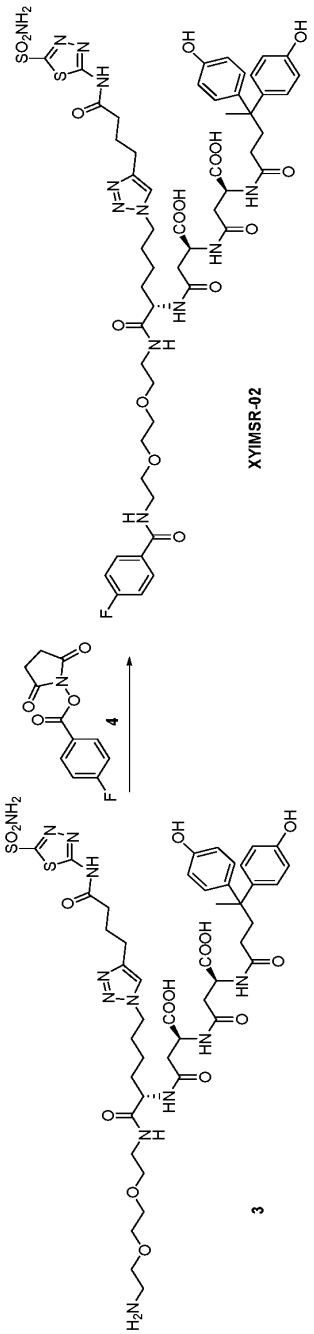


Fig. 10

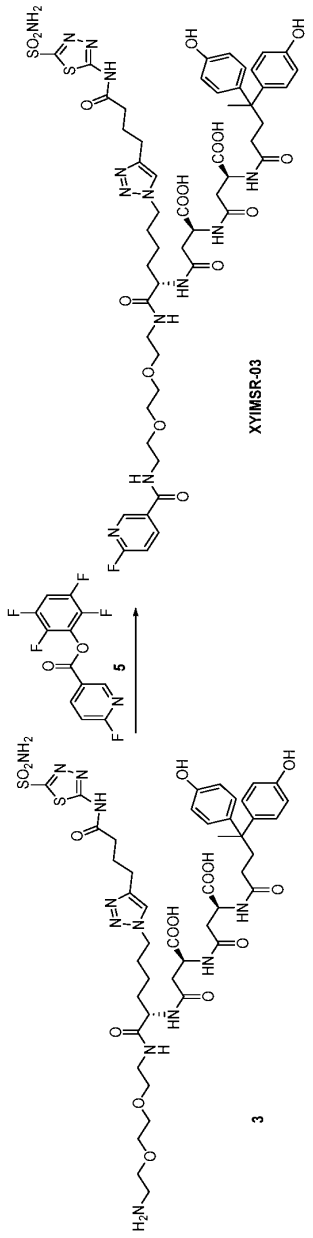


Fig. 11

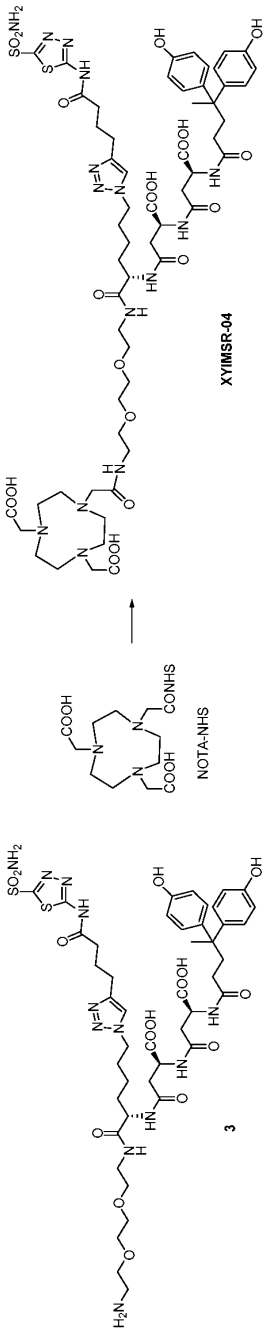


Fig. 12

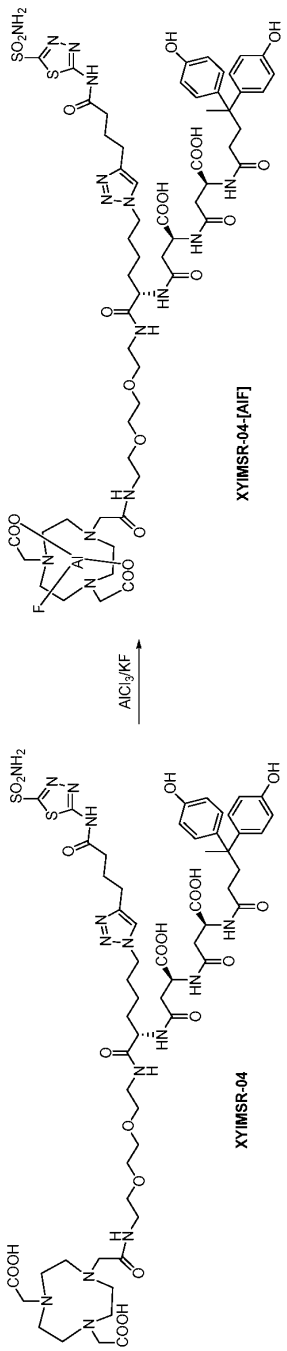


Fig. 13

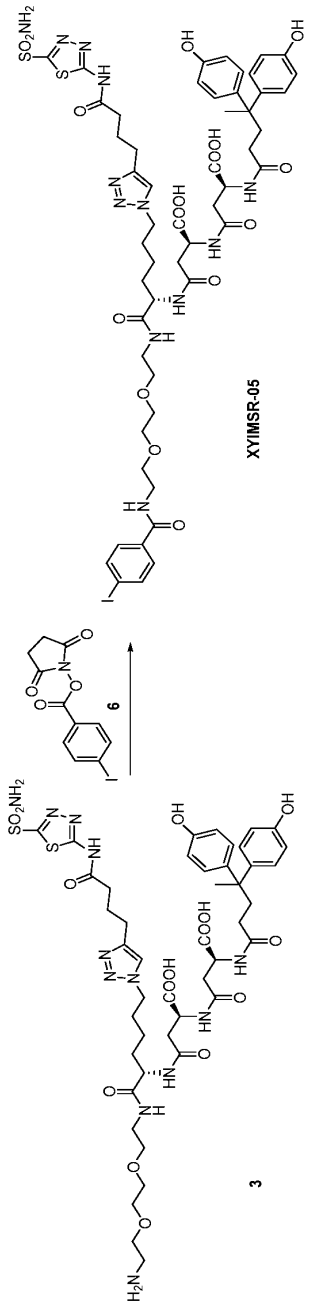


Fig. 14

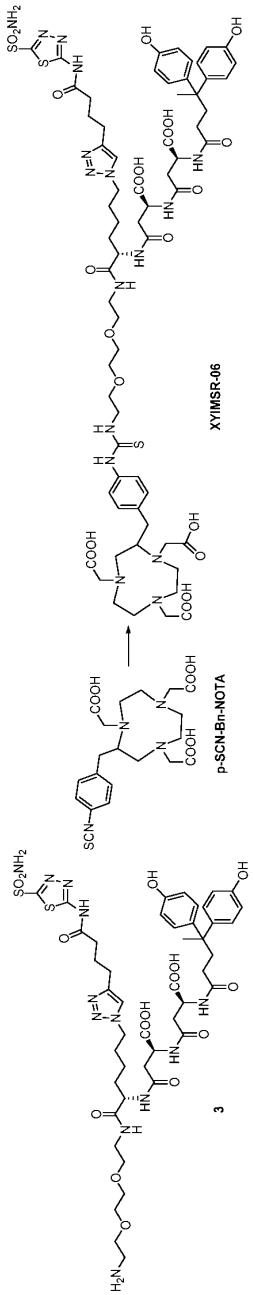


Fig. 15

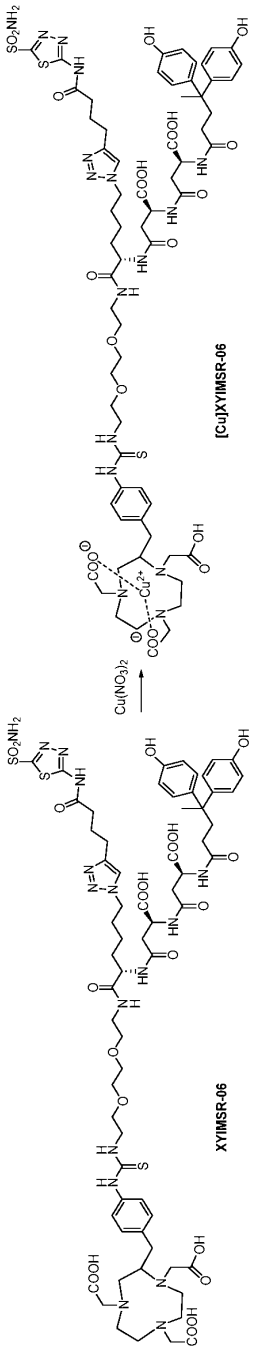


Fig. 16

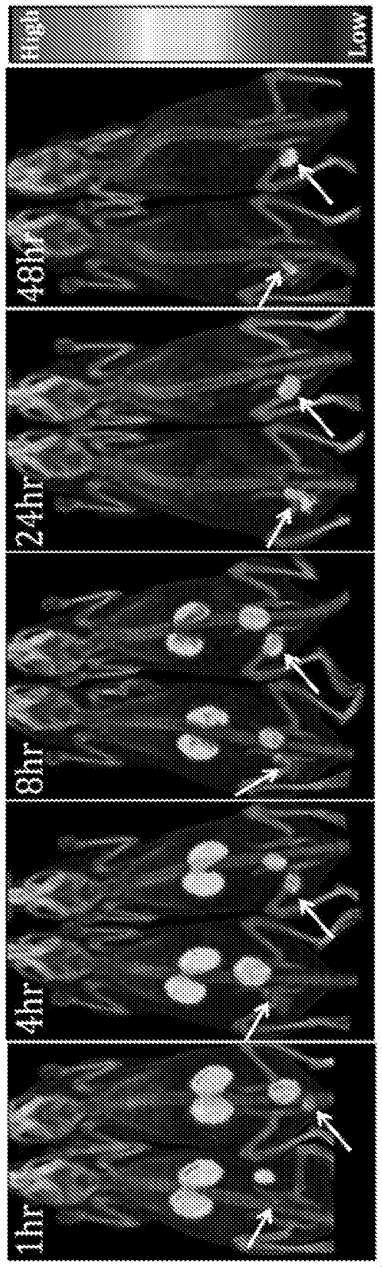


Fig. 17

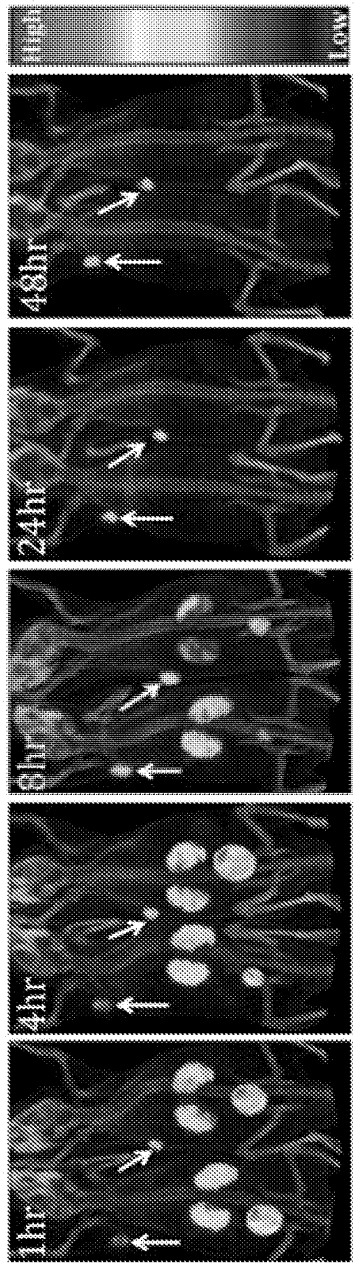


Fig. 18



Fig. 19

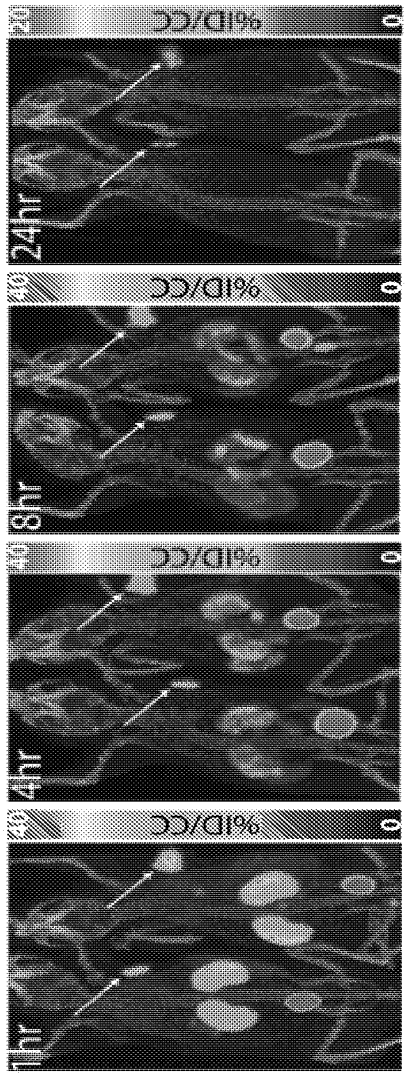


Fig. 20

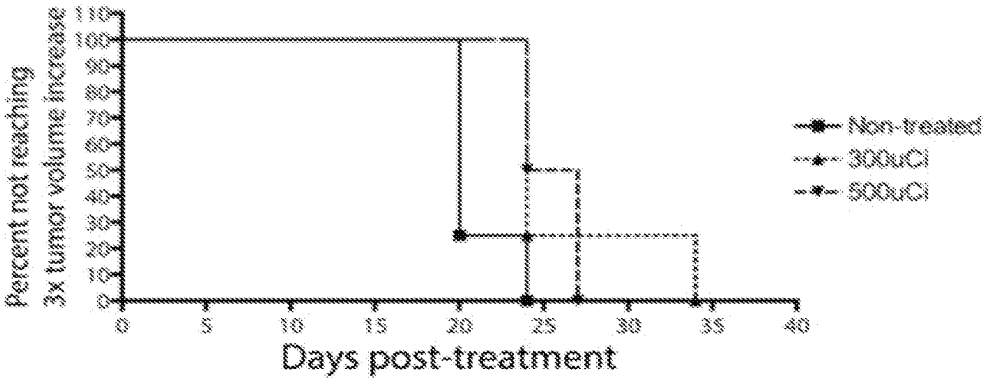

Percent not reaching
3x tumor volume increase
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Days post-treatment
Non-treated
300uCi
500uCi

Fig. 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035259

A. CLASSIFICATION OF SUBJECT MATTER

C07D 417/12(2006.01)i, C07D 417/14(2006.01)i, A61K 51/04(2006.01)i

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)
C07D 417/12; A61K 49/00; C07F 15/00; C07D 417/14; A61K 51/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(Kipo internal), STN (Registry, Caplus), Google & Keywords: imaging, radiolabel, carbonic anhydrase IX, metal-chelate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WICHERT, M. et al., "Dual-display of small molecules enables the discovery of ligand pairs and facilitates affinity maturation", Nature Chemistry, March 2015, Vol. 7, pp. 241-249 See abstract; and figures 5, 6.	1-12
Y	US 2009-0175794 A1 (ZIMMERMAN, C. et al.) 09 July 2009 See abstract; formulas (I), (III), (IV); paragraph [0273]; and claims 1-38.	1-12
A	KRALL, N. et al., "A Small-Molecule Drug Conjugate for the Treatment of Carbonic Anhydrase IX Expressing Tumors", Angewandte Chemie International Edition, 2014, Vol. 53, pp. 4231-4235 See the whole document.	1-12
A	RAMI, M. et al., "Carbonic Anhydrase Inhibitors: Design of Membrane-Impermeant Copper (II) Complexes of DTPA-, DOTA-, and TETA-Tailed Sulfonamides Targeting the Tumor-Associated Transmembrane Isoform IX", ChemMedChem, 2008, Vol.3, pp. 1780-1788 See the whole document.	1-12

☒ 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
18 October 2016 (18.10.2016)	**18 October 2016 (18.10.2016)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
PARK, Jung Min
Telephone No. +82-42-481-3516

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035259

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	YANG, X. et al., "Imaging of carbonic anhydrase IX with an 111In-labeled dual-motif inhibitor", Oncotarget, [Epub.] 16 September 2015, Vol. 6, No. 32, pp. 33733-33742 See the whole document.	1-12

Form PCT/ISA/210 (continuation of second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035259

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-27
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 13-27 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2016/035259

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009-0175794 A1	09/07/2009	AU 2009-204133 A1	16/07/2009
		AU 2009-204133 B2	10/04/2014
		AU 2014-202811 A1	12/06/2014
		BR PI0906797 A2	14/07/2015
		CA 2711678 A1	16/07/2009
		CN 102083427 A	01/06/2011
		CN 102083427 B	10/12/2014
		EP 2240171 A2	20/10/2010
		EP 2240171 B1	13/08/2014
		JP 2011-509304 A	24/03/2011
		RU 2010132910 A	20/02/2012
		RU 2498798 C2	20/11/2013
		US 8877970 B2	04/11/2014
		WO 2009-089383 A2	16/07/2009
		WO 2009-089383 A3	03/09/2009

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**02/02/2024 05:07:17 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Jeffrey Childers
PATENT CENTER #	64194803	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 7

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	2	ePetition Request Form	29 KB
2024-02-02 - JHU-36631.303 - Supp IDSpdf.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	39 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
2024-02-02 - JHU-36631.303 - RCE.pdf	3	Request for Continued Examination (RCE)	131 KB
Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
2024-02-01 - JHU-36631.303 - QPIDS.pdf	2	Quick Path Information Disclosure Statement	151 KB

WO2016196628A1.pdf	135	Foreign Reference	5262 KB
Third Party Observations.pdf	553	Other reference-Patent/Application/Search Documents	9605 KB
2024-02-02 - JHU-36631.303 - IDS Certification Statement.pdf	1	Letter specifying the conditions for filing under 37 CFR 1.97	20 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	24A562B12BC7CF67E5C6722EA0826261D028C88AC39617E8E B3A682E5A1A0DA48402AE7E0947487559C69E462816E3EFDD 74DF1E035F7D3FD596FC159EB63ED0
2024-02-02 - JHU-36631.303 - Supp IDSpdf.pdf	8DD1BB24F49C8A9DADA5B5A745DF6FD51DBD47EE1DD6AC 77F320ADA0C471DB22799B873A9DE73C38311DEC1657DDDE 772C7A82E22C924D6856B7EC460C755CDB
2024-02-02 - JHU-36631.303 - RCE.pdf	3FC1787EC432E484337EA03713EF5FF6BA594D11702F21CBA 7DC15E89F54560B433A2564F6752CE61FCAB1000AAFDA21A6 70EB00EFA2D2D6EF30F77784DDEF57
2024-02-01 - JHU-36631.303 - QPIDS.pdf	F01234071E6EE3FB329DAE476CC39D1A7CB244D0B99A0768 B1BD9574470652397488FBCF72113E283C8184CEEACA897A0 E2F89C07A83C048E88A892E65BAB370
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2024-02-02 - JHU-36631.303 - IDS Certification Statement.pdf	4CB170D87AAB22FCA3F32AC3032D81F30C1172BA26BE1A0C 1C963BB4FCACBB84FDBDD80FA8769827F7FD50D32BA1E345 FE1CCF03FC5AA795E2CD9EB334BDA982

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 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.

Doc Code: QPIDS.REQ
Document Description: QuickPath Information Disclosure Statement

PTO/SB/09 (09-18)

CERTIFICATION AND REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM

Non-Provisional Application Number: 18/354,282	Filing Date: July 18, 2023
First Named Inventor: Xing Yang	Title of Invention: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTE

THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE-IDENTIFIED APPLICATION.

1. Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee.
2. Check the box next to the appropriate selection:

   ☐ Each item of information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(1).

   OR

   ☐ No item of information contained in the IDS was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the IDS was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(2).

   OR

   ☑ See attached certification statement in compliance with 37 CFR 1.97(e).
3. Please charge the IDS fee set forth in 37 CFR 1.17(p) to Deposit Account No. 504302.
4. A Petition to Withdraw from Issue After Payment of the Issue Fee (37 CFR 1.313(c)(2)), including the petition fee set forth in 37 CFR 1.17(h), is submitted herewith as a **Web-based ePetition**. **WARNING:** Do not submit the petition as a follow-on paper via EFS-Web. Submit the petition as a Web-based ePetition by signing on to EFS-Web as a registered user, selecting the radio button next to "Existing application/patent," and then selecting the radio button next to "ePetition (for automatic processing and immediate grant, if all petitions requirements are met)." Failure to use the Web-based ePetition interface will result in automatic entry of the RCE.
5. A request for continued examination (RCE) under 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.
6. The RCE will be treated as a "conditional" RCE. In the event the examiner determines that any item of information contained in the IDS necessitates the reopening of prosecution in the application, the undersigned understands that (i) the RCE will be processed and treated as an RCE under 37 CFR 1.114 and therefore (ii) the IDS fee under 37 CFR 1.17(p) will be returned in accordance with 37 CFR 1.97(b)(4). In the event that no item of information in the IDS necessitates reopening prosecution, the undersigned understands that the RCE will not be processed and the RCE fee under 37 CFR 1.17(e) will be returned.
7. This certification and request is being filed as a **Web-based ePetition** and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE.

Signature /Jeffrey W. Childers/	Date February 2, 2024
Name (Print/Typed) Jeffrey W. Childers	Practitioner Registration Number (If applicable) 58126

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below.**

☑ *Total of 1 forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2)

APPLICATION #	ATTORNEY DOCKET #	FILING DATE
18354282	JHU-36631.303	07/18/2023

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

CONFIRMATION #	**7536**	FILING DATE	**07/18/2023**
ART UNIT	**1618**	FIRST NAMED INVENTOR	**Xing Yang**
EXAMINER	**MELISSA PERREIRA**		

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:

(1) Petition fee; and
(2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination (Quick Path Information Disclosure Statement) - RCE request, submission, and fee are attached

Applicant claims the following entity status

Small

Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:
An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/Jeffrey W. Childers/	Jeffrey Childers	58126

Doc code : PET.DEC.AUTO
Description : ePetition Grant Letter

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

GRANT LETTER

APPLICATION #	DECISION DATE	DECISION ON PETITION #	ATTORNEY DOCKET NUMBER
18/354,282	02/02/2024		JHU-36631.303

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

In re Application of Xing Yang

This is an electronic decision on the petition under , filed February 02, 2024 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED.**

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

The application is being referred to Technology Center AU for

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Juliet McMillan

Sale Accounting Date:02/06/2024

Sale Item Reference Number	Effective Date
18354282	02/02/2024

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202425J43169200	2806	SUBMISSION- INFORMATION DISCLOSURE STMT	$104.00	Deposit Account

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
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 02/14/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
02/14/2024	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

Notice of Allowability	Application No. 18/354,282	Applicant(s) Yang et al.	
	Examiner MELISSA J PERREIRA	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 2/02/24.
   ☐ 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 29-31 . 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 2/2/24.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

U.S. PATENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number / Number-Kind Code[4] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2020/0237936	2020-07-30	LOW et al.	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document — Country Code[5] Number[6] Kind Code[7] (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
	2.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY		

NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), 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.	Translation[6]
	3.	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages.	

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	02/06/2024

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number _____ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-02-02
Name/Print	Jeffrey W. Childers	Registration Number	58,126

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

PTO Notes regarding this form:

[1] Applicant's unique citation designation number (optional).
[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.
[5] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[6] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[7] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[8] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.97 and 1.98. 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 CFR 1.14. This collection is estimated to take 2 hours 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**.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sengpheth Sandara

Refund Accounting Date:02/22/2024

Effective Date	Sale Item Reference Number	Refund Total
02/22/2024	18354282	$544.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20242LE59085803	2801	RCE- 1ST REQUEST	$544.00	Visa	**********0638

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sengpheth Sandara

Sale Adjustment Accounting Date:02/22/2024

Effective Date	Sale Accounting Date	Sale Item Reference Number
02/22/2024	02/22/2024	18354282

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20242LE59085803	2801	RCE- 1ST REQUEST	$544.00	Visa

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	03/26/2024	11938201	JHU-36631.303	7536

101943 7590 03/06/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

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 Center (https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Xing Yang, Baltimore, MD;
Sridhar Nimmagadda, Balimore, MD;
Steven Rowe, Parkville, MA;
Stephanie Slania, Baltimore, MD;
Martin G. Pomper, Baltimore, MD;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

The Johns Hopkins University, Baltimore, MD;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 03/26/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
03/26/2024	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/354,282	26-Mar-2024	11938201

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Middleton, WI 53562

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants

DocCode - PATENT.GRANT

SCORE Placeholder Sheet for IFW Content

Application Number: 18354282 Document Date: 03/26/2024

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Patent Grant with Color/Grayscale Drawings

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	YANG, Xing	Confirmation No.:	7536
Patent No.:	11,938,201		
Issue Date:	26-Mar-2024		
Serial No.:	18/354,282	Group No.:	1618
Filing Date:	18-Jul-2023	Examiner:	PERREIRA
Entitled:	**IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)**		

REQUEST FOR CERTIFICATE OF CORRECTION

VIA EFS WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir or Madam,

Pursuant to 35 U.S.C. §254 and 37 C.F.R. §1.322, applicants respectfully request that the Office issue a Certificate of Correction in the above-referenced patent. Applicant submits herewith Form PTO/SB/ requests a Certificate of Correction for the above-referenced patent and hereby submits form PTO/SB/44 showing the correction that is requested.

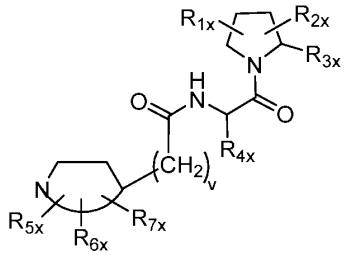
In the Letters Patent, Claim 1, Column 64, lines 47-67, Column 65, lines 1-62:

1. A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

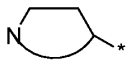
R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

v is 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof. -

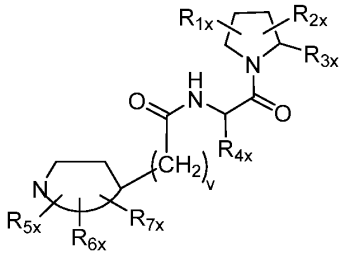
Whereas it should read:

1. A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

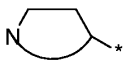
R_{5x}, R_{6x} and R_{7x} are each ~~independently selected from the group consisting of H, OH, oxo, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $NR_{8x}R_{9x}$, OR_{12x}, Het_2 and Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen~~;

~~R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, OH, halo, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and Ar_3;~~

~~R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from $NR_{10x}R_{11x}$, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;~~

~~Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from $NR_{13x}R_{14x}$, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;~~

v is 0~~;~~, ~~1, 2, or 3; and~~



represents a quinolinyl ring~~5 to 10 membered N containing aromatic or non aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S~~;

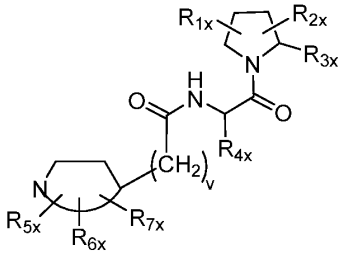
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

In the Letters Patent, Claim 3, Column 66, lines 1-67, and Column 67, lines 1-4:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

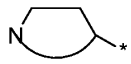
R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;
v is 0, 1, 2, or 3; and

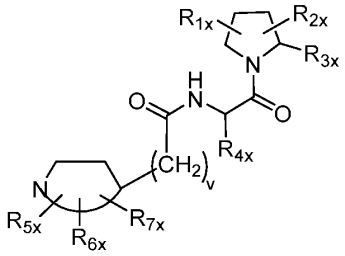


represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or
a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.-

Whereas it should read:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

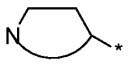
R_{5x}, R_{6x} and R_{7x} are each ~~independently selected from the group consisting of H, -OH, oxo, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $NR_{8x}R_{9x}$, OR_{12x}, Het_2 and Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen~~;

~~R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3;~~

~~R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from $NR_{10x}R_{11x}$, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;~~

~~Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from $NR_{13x}R_{14x}$, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;~~

v is 0~~, 1, 2, or 3; and~~



represents a quinolinyl ring ~~5 to 10 membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S~~;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

Applicant submits herewith a request for certificate of correction. Applicant notes that the Supplemental Amendment to Non-Final Office Action filed December 18, 2023 was entered by the Examiner. However, the amendments were not included in the granted claims.

Because the error in the patent is a result of the Office's mistake, applicant believes that no fee is due. However, in the event a fee is due, the Commissioner is hereby authorized to charge the fee, or credit any overpayment, to Deposit Account 50-4302, referencing Attorney Docket No. **JHU-36631.303.**

Respectfully submitted,

Dated: August 22, 2024

/Jeffrey W. Childers/

Jeffrey W. Childers
Registration No. 58126
CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, WI 53562
Phone: (608) 662-1277

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**08/22/2024 05:18:06 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11938201
CONFIRMATION #	7536	FILED BY	Jeremiah Gile
PATENT CENTER #	66893434	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-08-22_36631.303_Request for Certificate of Correction.pdf	7	Request for Certificate of Correction	68 KB
2024-08-22_36631.303_CoC.pdf	4	Request for Certificate of Correction	65 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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2024-08-22_36631.303_CoC.pdf

F43EFA29A4425069313B778D9162E39E218B14D94D5BA1FAC5AF200E49C0CE90D07D8ACDAC1E976FDE5947CBF8AF5B4D34F1393C3B81B30F95126567C4499A67

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 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.

PTO/SB/44 (09-07)
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 11,938,201
APPLICATION NO.: 18/354,282
ISSUE DATE : 26-Mar-2024
INVENTOR(S) : YANG, Xing, et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

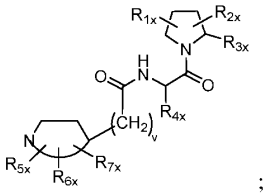
In the Letters Patent, Claim 1, Column 64, lines 47-67, Column 65, lines 1-62:

1. A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

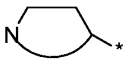
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each H;

v is 0;



represents a quinolinyl ring;

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Casimir Jones, S.C.
2275 Deming Way, Suite 310
Middleton, WI 53562

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. 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 1.0 hour 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: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/44 (09-07)
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UNITED STATES PATENT AND TRADEMARK OFFICE
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PATENT NO. : 11,938,201
APPLICATION NO.: 18/354,282
ISSUE DATE : 26-Mar-2024
INVENTOR(S) : YANG, Xing, et al.

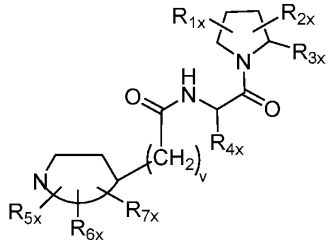
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

In the Letters Patent, Claim 3, Column 66, lines 1-67, Column 67, lines 1-4:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

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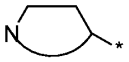
PATENT NO. : 11,938,201
APPLICATION NO.: 18/354,282
ISSUE DATE : 26-Mar-2024
INVENTOR(S) : YANG, Xing, et al

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R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each H;

v is 0;



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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.
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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.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,938,201 B2
APPLICATION NO. : 18/354282
DATED : March 26, 2024
INVENTOR(S) : Xing Yang et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

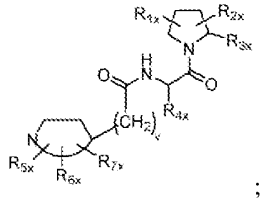
Claim 1, Column 64, Lines 47-67, Column 65, Lines 1-62 should read:

1. A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



;

wherein:

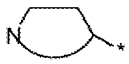
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)$_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each H;

v is 0;



represents a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

Signed and Sealed this
Twenty-fourth Day of September, 2024

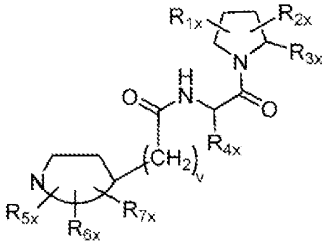
Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

Claim 3, Column 66, Lines 1-67, Column 67, Lines 1-4 should read:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP-α, wherein A has the structure of:



wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each H;

v is 0;



represents a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536

101943 7590 09/24/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
09/24/2024	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):

docketing@casimirjones.com
jwchilders@casimirjones.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/354,282	24-Sep-2024	11938201

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Middleton, WI 53562

ELECTRONIC CERTIFICATE OF CORRECTION NOTIFICATION

Your electronic certificate of correction is now available, and can be accessed via Patent Center at https://patentcenter.uspto.gov.

The electronic certificate of correction is the official certificate of correction under 35 U.S.C. 254 or 255. For more information, please visit https://www.uspto.gov/electronicgrants.

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PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, Virginia 22313-1450
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ACKNOWLEDGEMENT OF LOSS OF ENTITLEMENT TO ENTITY STATUS DISCOUNT

APPLICATION #	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET #	REQUEST ID
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	305750

The entity status change request below filed through Patent Center on 11/19/2024 has been accepted.

Certifications

APPLICANT CHANGING TO REGULAR UNDISCOUNTED FEE STATUS

Signature

I certify, in accordance with 37 CFR 1.4(d)(4), that I am one of the signatories making the entity status change.

Signature	Name	Registration #
/ Jeffrey Childers /	Jeffrey Childers	58126

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application No.:	18/354,282
Filed:	18-July-2023
Applicant:	Xing Yang, et al.
Art Unit:	1618
Examiner:	MELISSA JEAN PERREIRA
Confirmation No.:	7536
Docket No.:	JHU-36631.303
Title:	*IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)*

APPLICANT'S STATEMENT REGARDING OUTSTANDING FEES DUE TO ASSERTION OF LARGE ENTITY STATUS UNDER 37 CFR 1.28(c)

Pursuant to the requirements of MPEP § 509, Applicant hereby submits this Statement Regarding Outstanding Fees in connection with the above-captioned patent application. Based on the USPTO's current fee schedule corresponding to Large Entity fees, Applicant submits the following:

	Large Entity Fee Code	**Large Entity Fee**	**Small Entity Fee Code**	**Small Entity Fee Paid**	**Date of Small Entity Fee Payment**	**Difference (Amount Now Owed)**
Information Disclosure Statement	1806	$260.00	2806	$104.00	02/05/2024	$156.00
Petition 37CFR 1.17 (H)	1464	$ 140.00	2464	$ 56.00	02/02/2024	$84.00
Information Disclosure Statement	1806	$260.00	2806	$104.00	01/17/2024	$156.00
Utility Issue Fee	1501	$1,200.00	2501	$480.00	01/17/2024	$720.00
Petition 37CFR 1.17 (H)	1464	$ 140.00	2464	$ 56.00	12/13/2023	$84.00
Information Disclosure Statement	1806	$260.00	2806	$104.00	12/13/2023	$156.00
Terminal Disclaimer	1814	$170.00	2814	$170.00	12/13/2023	$0.00
Information Disclosure Statement	1806	$260.00	2806	$104.00	10/30/2023	$156.00
Processing Fee, Except Prov. Appls	1830	$140.00	2830	$56.00	07/18/2023	$84.00
Request for Prioritized Exam	1817	$4,200	2817	$1,680	07/18/2023	$2,520
Utility Filing Fee	1011	$ 320.00	4011	$ 64.00	07/18/2023	$256.00
Utility Exam Fee	1311	$ 800.00	2311	$ 320.00	07/18/2023	$480.00
Utility Search Fee	1111	$ 700.00	2111	$ 280.00	07/18/2023	$420.00
TOTALS:		**$ 8,850.00**		**$3,578.00**		**$5,272.00**

Applicant also hereby authorizes the Director to charge all outstanding fees as reflected in the table above, as well as any additional fees associated with the change in Applicant's entity

status, to Deposit Account Number 50-4302, referencing the Attorney Docket No. above.

Respectfully submitted,

CASIMIR JONES S.C.

Date: November 19, 2024

/Jeffrey W. Childers /
Jeffrey W. Childers, Ph.D.
Registration No. 58126

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**11/19/2024 01:47:17 PM Z ET**	**JHU-36631.303**

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11938201
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	68018045	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-11-19 - JHU-36631.303_Petition-Pay-LE-Fee.pdf	3	Petition for review by the Office of Petitions	29 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-11-19 - JHU-36631.303_Petition-Pay-LE-Fee.pdf	D15DC3B7F868E39643787860C1734DD430D761B8F449728936 18A5A0E70DF2D8418F5F5381509BB13C10B62DE1EF65EE57B 330DD8B8B309CD0A16EED6037DAD0

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 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.

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Suad Mohammed

Sale Accounting Date:12/12/2024

Sale Item Reference Number	Effective Date
18354282	11/19/2024

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I2024BBB28079303	1461	1.28(C) SUBMISSIONS - APPLIC FILE FEE	$5,272.00	Deposit Account