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12 February 2009

(54) Title: LABELED INHIBITORS OF PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA), BIOLOGICAL EVALUATION, AND USE AS IMAGING AGENTS

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



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/07947

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 47/28; A61K 31/17 (2008.04)

USPC - 514/588

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)

USPC: 514/588

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/1.53, 1.69; 435/7.71, 69.2 (text search-see search terms below)

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

US WEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Dialog PRO (Engineering)

Prostate specific membrane antigen, PSMA, inhibitor, small molecule inhibitor, urea, thiourea, linker, metal chelator, cysteine, glutamic acid, tyrosine, lysine, radio\$, metal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2007/0031326 A1 (SHIRVAN et al.) 08 February 2007 (08.02.2007) para [0015]-[0026], [0038]-[0039]	1 ----- 2-52
Y	US 2003/0138432 A1 (GLAZIER) 24 July 2003 (24.07.2003) para [0096], [0650], [0694], [0710], [1114]-[1115]	2-52
Y	FOSS et al. Radiolabeled Small-Molecule Ligands for prostate-Specific Membrane Antigen: In vivo Imaging in Experimental Models of Prostate Cancer. Clin Cancer Res, 2005, Vol 11(11), pp 4022-4028, pg 4023, para 4-5	4-52

☐ Further documents are listed in the continuation of Box C.

* 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

03 December 2008 (03.12.2008)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/07947

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.:
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:
see extra sheet

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 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.:
1-52

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

International application No.

PCT/US 08/07947

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-52, drawn to compounds comprising an inhibitor, a linker, and a metal chelator.

Group II, claims 53-61, drawn to methods of imaging in a subject, comprising the steps of: providing a radiolabeled compound according to Formula (IX), etc.

Group III, claims 62-67, drawn to methods for identifying a compound which modulates the activity of a prostate-specific membrane antigen (PSMA), the method comprising, etc.

Group IV, claim 68, drawn to a method of synthesizing a compound of formula II or formula IX.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

US 2007/0031326 A1 to Shrivan et al. (8 February 2007) (see para 0071) teaches the generic formula of claim 1. Thus, the special technical feature of the claims of the various groups is known in the art. It will be appreciated that the methods of the claims of groups II and III are distinct from the compounds of the claims of groups I, as there is no limitation that the compounds of the claims of groups I be limited to the methods of use as specified in the claims of groups II and III. It will also be appreciated that the method of synthesizing compounds of group IV is distinct from the compounds of the claims of groups I, as well as the methods of imaging and identifying compounds of the claims of groups II and III, which are distinct from one another as well, in that methods of imaging in a subject are distinct from methods for identifying a compound.

Thus, the inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

Further, Group I of this application contain claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of Group I are the various species (compounds) of formula (II), represented by formulae (III), (VI), (VII), (VIII), and (IX).

In this instance, the first species that will be searched without payment of additional fees for Group I is formula (III).

In order for more than one species (and subspecies) to be examined, the appropriate additional examination fees must be paid and the desired species (and subspecies) clearly identified.

In this case the first named invention and first named species that will be searched without additional fees is Group I represented by claims 1-52.