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5 June 2008

(54) Title: TRIAZOLE-CONTAINING RELEASABLE LINKERS AND CONJUGATES COMPRISING THE SAME

(57) Abstract: This invention relates to compounds comprising one or more therapeutic and/or diagnostic moieties and one or more functional moieties linked together via one or more triazole-containing linkers and to their intermediates and methods of their preparation. The triazole-containing linker may optionally contain one or more conditionally-cleavable or conditionally-transformable moieties and one or more spacer systems in between said moiety/moieties and the one or more therapeutic and/or diagnostic moieties.



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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 C07D249/04 A61P43/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D 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 practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOLB HARTMUTH C ET AL: "The growing impact of click chemistry on drug discovery." DRUG DISCOVERY TODAY. 15 DEC 2003, vol. 8, no. 24, 15 December 2003 (2003-12-15), pages 1128-1137, XP002377521 ISSN: 1359-6446	1, 19, 20, 22-26, 28-31, 33-43
Y	page 1132 page 1134, section "Click chemistry ad bioconjugation" figures 3,4	1-43
Y	WO 2004/043493 A (SYNTARGA B.V; DE GROOT, FRANCISCUS, MARINUS, HENDRIKUS; BEUSKER, PATRI) 27 May 2004 (2004-05-27) cited in the application claims	1-43

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 document 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

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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/025512 A (MANTICORE PHARMACEUTICALS, INC; WEINSHENKER, NED, M; WEST, FREDERICK,) 24 March 2005 (2005-03-24) claims figure 1a	1-43
Y	EP 1 243 276 A (DE GROOT, FRANCISCUS MARINUS HENDRIKUS; BEUSKER, PATRICK HENRY; SCHEER) 25 September 2002 (2002-09-25) cited in the application figures & WO 02/083180 A (DE GROOT FRANCISCUS MARINUS HE [NL]; BEUSKER PATRICK HENRY [NL]; SCHEE) 24 October 2002 (2002-10-24) cited in the application	1-43
X	WANG QIAN ET AL: "Bioconjugation by copper(I)-catalyzed azide-alkyne [3 + 2] cycloaddition." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. 19 MAR 2003, vol. 125, no. 11, 19 March 2003 (2003-03-19), pages 3192-3193, XP002377520 ISSN: 0002-7863	1,19,20, 22-26, 28-31, 33-43
Y	Scheme 1 compounds 1-5 page 3193, column 1, last paragraph	1-43
X	SPEERS ANNA E ET AL: "Profiling enzyme activities in vivo using click chemistry methods." CHEMISTRY & BIOLOGY. APR 2004; vol. 11, no. 4, April 2004 (2004-04), pages 535-546, XP002377550 ISSN: 1074-5521	1,2,19, 20, 22-26, 28-31, 33-43
Y	figures 1B,2 page 544	1-43
X	LINK A JAMES ET AL: "Cell surface labeling of Escherichia coli via copper(I)-catalyzed (3+2) cycloaddition" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 125, no. 37, 17 September 2003 (2003-09-17), pages 11164-11165, XP002329889 ISSN: 0002-7863	1,2,19, 20, 22-26, 28-31, 33-43
Y	scheme 1 figure 1 page 11165, column 2, paragraph 2	1-43
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INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2006/050192

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHITTABOINA S ET AL: "One-pot synthesis of triazole-linked glycoconjugates" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 46, no. 13, 28 March 2005 (2005-03-28), pages 2331-2336, XP004846740 ISSN: 0040-4039	1-4, 6-17, 19-26, 28-31, 33-43
Y	tables 1-3 page 2234, column 2, paragraph 2 - page 2235, column 1, paragraph 1 page 2235, column 1, paragraph 5	1-43
X	WU P ET AL: "Efficiency and Fidelity in a Click-Chemistry Route to Triazole Dendrimers by the Copper(I)-Catalyzed Ligation of Azides and Alkynes" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, WILEY VCH VERLAG, WEINHEIM, DE, vol. 43, 2004, pages 3928-3932, XP002351095 ISSN: 1433-7851 schemes 2 and 3 figures 1,2	1-4, 6-26,28, 30,31, 33,35-38
X	WO 03/101972 A (SCRIPPS RESEARCH INST [US]; SHARPLESS BARRY K [US]; FOKIN VALERY [US];) 11 December 2003 (2003-12-11) figures	1,19-26, 28,30, 31,33, 35-38, 40-43
X	DAMEN ERIC W P ET AL: "Synthesis of novel paclitaxel prodrugs designed for bioreductive activation in hypoxic tumour tissue." BIOORGANIC & MEDICINAL CHEMISTRY. JAN 2002, vol. 10, no. 1, January 2002 (2002-01), pages 71-77, XP002377551 ISSN: 0968-0896 abstract schemes 1 and 3;compounds 1B,1J,1K	35,37-43
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2006/050192

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TORNOE C W ET AL: "Peptidotriazoles on solid phase; [1,2,3]-triazoles by regiospecific copper (I) catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 67, no. 9, 2002, pages 3057-3064, XP002234501 ISSN: 0022-3263 schemes 2 and 3 table 1</p>	1, 19-26, 28-31, 33-39
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X	<p>KHANETSKYY BOGDAN ET AL: "Combining Biginelli multicomponent and click chemistry: generation of 6-(1,2,3-triazol-1-yl)-dihydropyrimidone libraries." JOURNAL OF COMBINATORIAL CHEMISTRY 2004 NOV-DEC, vol. 6, no. 6, November 2004 (2004-11), pages 884-892, XP002472172 ISSN: 1520-4766 scheme 2 tables 1,2</p>	1, 19, 20, 22-26, 28, 30, 31, 33, 35-38
E	<p>EP 1 733 742 A (UNIVERSITEIT UTRECHT HOLDING B [NL]) 20 December 2006 (2006-12-20) paragraphs [0044] - [0048] figures</p> <p style="text-align: center;">----- -/--</p>	1, 19, 20, 22-26, 28-31, 33-43

INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2006/050192

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2006/116736 A (SIEMENS MEDICAL SOLUTIONS [US]; KOLB HARTMUTH C [US]; MOCHARLA VANI P) 2 November 2006 (2006-11-02) schemes on page 31,35,40,41,43 pages 36,37	1-4, 6-10, 14-16, 19,20, 22-26, 28,30, 31,33, 35-38, 40-43
E	WO 2007/011696 A (SCRIPPS RESEARCH INST [US]; FINN M G [US]; GUPTA SAYAM SEN [US]; SHARP) 25 January 2007 (2007-01-25) paragraphs [0011] - [0013] figures 1,3,5,6 examples 1-6,9-12	1-4,6-39

INTERNATIONAL SEARCH REPORT

International application No.
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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:

Although claim 43 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 additional search fees were timely paid by the applicant, this international search report covers allsearchable 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2006/050192

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