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 HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
 a patent (Rule 4.17(ii))

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))

(88) Date of publication of the international search report:

25 February 2010

(54) Title: SPIRO AND DISPIRO 1,2,4-TRIOXOLANE ANTIMALARIALS

(57) Abstract: A means and method for treating malaria, schistosomiasis, and cancer using a spiro or dispiro 1,2,4-trioxolane is described. The preferred 1,2,4-trioxolanes include a spiroadamantane group on one side of the trioxolane group, and a spirocyclohexyl on the other side of the trioxolane group, whereby the spirocyclohexyl ring is preferably substituted at the 4-position. In comparison to artemisinin semisynthetic derivatives, the compounds of this invention are structurally simple, easy to synthesize, non-toxic, and potent against malarial parasites.



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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/081750

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D323/02 C07D405/12 A61K31/335 A61P33/06 A61P33/10

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 practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, 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	US 2004/186168 A1 (VENNERSTROM JONATHAN L [US] ET AL) 23 September 2004 (2004-09-23) claims 14,15,18 compounds 0Z84, 0Z85 -----	1,3-6
X	WO 03/000676 A (MEDICINES FOR MALARIA VENTURE [CH]; VENNERSTROM JONATHAN L [US]; CHOLL) 3 January 2003 (2003-01-03) claims 2,12,13,35,46 compounds 0Z03,0Z48,0Z164,0Z178,0Z208,0Z229 -----	1,3-6
X	US 2005/256185 A1 (VENNERSTROM JONATHAN L [US] ET AL VENNERSTROM JONATHAN L [US] ET AL) 17 November 2005 (2005-11-17) compounds 0Z375,0Z376,0Z4010Z388, page 2, paragraph 30 page 8, paragraphs 55-59,64 page 7, paragraph 53 -----	1,3-6



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 SEARCH REPORT

International application No.
PCT/US2008/081750

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 additional 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 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.:

see annex

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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 3-6 (part)

compound OZ406

2. claims: 1, 3-6 (part)

compounds OZ407, OZ410, OZ456, OZ467, OZ468, OZ471

3. claims: 1, 3-6 (part)

compounds OZ408, OZ409, OZ416, OZ419, OZ420, OZ421, OZ422,
OZ423, OZ426, OZ427, OZ428, OZ430, OZ431, OZ432, OZ441,
OZ442, OZ451, OZ469, OZ470, OZ477, OZ484, OZ514 and OZ515

4. claims: 1, 3-6 (part)

compounds OZ411, OZ412, OZ415 and OZ516

5. claims: 1-6 (part)

compounds OZ413, OZ414, OZ417, OZ418, OZ424, OZ425, OZ440,
OZ447, OZ448, OZ450, OZ452, OZ496, OZ506, OZ507, OZ511 and
OZ554

6. claims: 1-6 (part)

compounds OZ433, OZ434 and OZ435

7. claims: 1-6 (part)

compounds OZ436, OZ437, OZ438, OZ443, OZ444, OZ445, OZ446,
OZ449, OZ457, OZ458, OZ459, OZ463, OZ465, OZ481, OZ487,
OZ488, OZ489, OZ494, OZ497, OZ501, OZ502, OZ503, OZ504,
OZ512, OZ515, OZ517, OZ518, OZ519, OZ520, OZ521,
OZ522-OZ526, OZ528, OZ529, OZ530, OZ531, OZ532, OZ533,
OZ536, OZ538, OZ548, OZ552, OZ553, OZ564, OZ565, OZ566,
OZ567, OZ569, OZ570 and OZ576

8. claims: 1-6 (part)

compounds OZ454, OZ455 and OZ480

9. claims: 1, 3-6 (part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compounds 0Z472, 0Z473, 0Z474, 0Z475 and 0Z476

10. claims: 1, 3-6 (part)

compounds 0Z478 and 0Z479

11. claims: 1, 3-6 (part)

compounds 0Z483 and 0Z492

12. claims: 1, 3-6 (part)

compounds 0Z486, 0Z490 and 0Z491

13. claims: 1, 3-6 (part)

compound 0Z500

14. claims: 1, 3-6 (part)

compounds 0Z509, 0Z510, 0Z546, 0Z550 and 0Z551

15. claims: 1, 3-6 (part)

compound 0Z573

16. claims: 1, 3-6 (part)

compound 0Z574

17. claims: 7-10

medical use of 1,2,4-trioxolanes for the treatment of
fascioliasis

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/081750

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2004186168	A1	23-09-2004	US 2005256185	A1	17-11-2005
WO 03000676	A	03-01-2003	AT 339411	T	15-10-2006
			AU 2002327183	B2	09-03-2006
			BR 0210549	A	11-01-2005
			CA 2451006	A1	03-01-2003
			CN 1545508	A	10-11-2004
			DE 60214733	T2	13-09-2007
			DK 1414813	T3	02-01-2007
			EP 1414813	A1	06-05-2004
			ES 2271323	T3	16-04-2007
			HU 0400246	A2	30-08-2004
			JP 4303585	B2	29-07-2009
			JP 2004535436	T	25-11-2004
			MX PA03011915	A	21-05-2004
			PL 367158	A1	21-02-2005
			PT 1414813	E	29-12-2006
			UA 78709	C2	25-04-2007
			US 6486199	B1	26-11-2002
			YU 100703	A	03-03-2006
US 2005256185	A1	17-11-2005	US 2004186168	A1	23-09-2004