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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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21 December 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED QUINOLINE AND QUINAZOLINE INHIBITORS OF QUINONE REDUCTASE 2

(57) Abstract: The present invention provides composition and methods of inhibiting quinone reductase 2 (QR2). The methods are useful in the treatment of malaria and autoimmune diseases. The compositions of the invention comprise quinoline and quinazoline derivatives. The invention also provides methods for inhibiting the activity of QR2 by contacting the enzyme with one or more compositions of the invention.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D215/42 C07D215/44 C07D215/36 C07D215/22
C07D215/40 C07D215/18 C07D215/60 C07D239/94 A61K31/4706
A61K31/4409 A61K31/517

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

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, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VIPPAGUNTA, SUDHA RANI ET AL: "Structural Specificity of Chloroquine-Hematin Binding Related to Inhibition of Hematin Polymerization and Parasite Growth" JOURNAL OF MEDICINAL CHEMISTRY , 42(22), 4630-4639 CODEN: JMCMAR; ISSN: 0022-2623, 1999, XP002365933 the whole document ----- -/--	1

[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 document but published on or after the international filing date

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2006	17/10/06

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, Stefano

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

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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.
X	EGAN, TIMOTHY J. ET AL: "Structure-Function Relationships in Aminoquinolines: Effect of Amino and Chloro Groups on Quinoline-Hematin Complex Formation, Inhibition of .beta.-Hematin Formation, and Antiplasmodial Activity" JOURNAL OF MEDICINAL CHEMISTRY , 43(2), 283-291 CODEN: JMCMAR; ISSN: 0022-2623, 2000, XP002365934 the whole document	1
X	ISMAIL, F. M. D. ET AL: "An exploration of the structure-activity relationships of 4-aminoquinolines: novel antimalarials with activity in vivo" JOURNAL OF PHARMACY AND PHARMACOLOGY , 48(8), 841-850 CODEN: JPPMAB; ISSN: 0022-3573, 1996, XP009060292 examples 8,9	1
X	TOENNESEN, HANNE HJORTH ET AL: "Photochemical stability of antimalarials . I. Hydroxychloroquine" INTERNATIONAL JOURNAL OF PHARMACEUTICS , 43(3), 215-19 CODEN: IJPHDE; ISSN: 0378-5173, 1988, XP002365935 Figure 2, compound III	1
X	STELL, J. G. P. ET AL: "Effect of chloroquine and its congeners on mitochondrial oxidation" JOURNAL OF PHARMACY AND PHARMACOLOGY , 24(SUPPL.), 163P-164P CODEN: JPPMAB; ISSN: 0022-3573, 1972, XP009060419 table 1	1
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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.
X	MICHNE, WILLIAM F. ET AL: "Novel Inhibitors of Potassium Ion Channels on Human T Lymphocytes" JOURNAL OF MEDICINAL CHEMISTRY , 38(11), 1877-83 CODEN: JMCMAR; ISSN: 0022-2623, 1995, XP002079143 Scheme 1, compounds 14a-i	1
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X	BOLTE, JEAN ET AL: "Synthetic models of deoxyribonucleic acid complexes with antimalarial compounds. Comparative ultraviolet and proton magnetic resonance study of quinoline-base, quinoline-quinoline, and base-base stacking interactions" BIOCHEMISTRY , 18(22), 4928-35 CODEN: BICHAW; ISSN: 0006-2960, 1979, XP002365937 compounds 4a-4b	1
X	RENAULT, SYLVIANE ET AL: "Study of aminoquinolines. XV: Long-chain 4-alkylaminoquinolines and quinaldines with potential amebicide activity. Part 3: Effect of nuclear electron-attracting substituents" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY , 11(6), 555-60 CODEN: EJMCA5; ISSN: 0223-5234, 1976, XP009060324 table 1	1
X	RENAULT, JEAN ET AL: "Aminoquinolines. I. Various methods of synthesis of secondary and tertiary alkyl 4-aminoquinolines" CHIMICA THERAPEUTICA , 66(5-6), 339-46 CODEN: CHTPBA; ISSN: 0009-4374, 1966, XP009060779 table 1	1
X	JAIME-FIGUEROA, SAUL ET AL: "Allyl amines as ammonia equivalents in the preparation of anilines and heteroarylamines" TETRAHEDRON LETTERS , 39(11), 1313-1316 CODEN: TELEAY; ISSN: 0040-4039, 1998, XP002365938 table 1, entry 3	1

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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.
X	DESVIGNES, A. ET AL: "Aminoquinolines. XVIII. In vitro antibacterial and antifungal activity of long chain 4-alkylaminoquinolines" ANNALES PHARMACEUTIQUES FRANCAISES , 35(7-8), 239-47 CODEN: APFRAD; ISSN: 0003-4509, 1977, XP009060311 table II	1
X	EP 1 435 356 A (WARNER-LAMBERT COMPANY LLC) 7 July 2004 (2004-07-07) example 95	1
X	GB 1 496 371 A (SERDEX) 30 December 1977 (1977-12-30) table 1 claims 1-3,6,11	1
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A	FR 2 077 455 A (ARIES ROBERT) 29 October 1971 (1971-10-29) page 1, line 28 - line 30 claim 1	1

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Box 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. [X] Claims Nos.: 10, 12-22, 24-26, 28
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10, 12-22, 24-26, 28 are 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 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 fee, this Authority did not invite payment of any additional fee.

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. [X] 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.

[ ] 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: 1-2(part), 5(part), 10-13(part), 19

   4-aminoquinoline derivatives according to claim 1 or 10 for which R2 is NHR5, where R5 is a unsubstituted alkyl, cycloalkyl, progargyl or allyl moiety

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2. claims: 1-2(part), 5 (part), 10-13(part)

   4-aminoquinoline derivatives according to claim 1 or 10 for which R2 is NHR5, where R5 is unsubstituted aryl

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3. claims: 1-2(part), 5(part), 10-13(part), 19

   4-aminoquinoline derivatives according to claim 1 or 10 for which R2 is NHR5, where R5 is a substituted aryl moiety.

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4. claims: 1-3(part), 5(part), 10-14(part),

   4-aminoquinoline derivatives according to claim 1 or 10 for which R2 is NHR5, where R5 is an heteroaryl moiety.

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5. claims: 1-3,(part), 4, 10-15(part), 16

   4-aminoquinoline derivatives according to claim 1 or 10 for which R2 is NHR5, where R5 is a substituted alkyl or cycloalkyl moiety.

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6. claims: 1 (part), 5(part), 10-12(part), 19

   4-aminoquinoline derivatives according to claim 1 or 10 for which R2 is NR5R6.

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7. claims: 1-2(part), 5(part), 10-13(part)

   Quinoline derivatives according to claim 1 or 10 for which R2 is OR5.

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8. claims: 1-2(part), 5(part), 10-13(part)

   Quinoline derivatives according to claim 1 or 10 for which R2 is SR5.

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9. claims: 6-7, 15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8-aminoquinoline derivatives according to claim 6.

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10. claims: 8-9, 22-28

4-aminopryridine according to claim 8 or 22.

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11. claims: 10(part), 17,

Method encompassing quinazoline derivatives according to claim 10.

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12. claims: 18, 20

Method encompassing quinoline derivatives unsubstituted at positions 4 and 8 ad defined in clains 18 and 20.

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13. claims: 10, 21

Method encompassing quinoline derivatives according to clain 10 for which R7=R8=H.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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