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(71) Applicants: **UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.** [US/US]; 210 S. Jackson Street, 110 Terrell Hall, Athens, Georgia 30602 (US). **NORTHEASTERN UNIVERSITY** [US/US]; 360 Huntington Avenue, Boston, Massachusetts 02115 (US).

(72) Inventors: **WAGNER, Alicia N.**; 73 S Huntington Ave, Apt. 5, Jamaica Plain, Massachusetts 02130 (US). **TROMBLEY, Roger**; 375 Commonwealth Ave, #BR, Boston, Massachusetts 02115 (US). **PODGURSKI, Maris E.**; 32 Kayla Drive, Arundel, Maine 04046 (US). **SMITH, Jacqueline R.**; 35 Trefry Lane, Stow, Massachusetts 01775 (US). **CUI, Meng**; 805 Columbus Ave, ISEC 429, Boston, Massachusetts 2118 (US). **MARIN, Adriana A.**; Carrera 4 #16-15, Apt 1108, Bogotá-Colombia, 110311 (CO). **MAHER, Steven P.**; 491 Rapids Dr., Bogart, Georgia 30622 (US). **KYLE, Dennis E.**; 1040 Maple Court, Athens, Georgia 30606 (US). **MANETSCH, Roman**; 360 Huntington Avenue, Boston, Massachusetts 02115 (US). **RUBERTO, Anthony A.**; 270 Barber St., Apt #D3, Athens, Georgia 30601 (US).

(74) Agent: **BUCKLEY, Ragan** et al.; Thomas Horstemeyer LLP, 3200 Windy Hill Road SE, Suite 1600E, Atlanta, Georgia 30339 (US).

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(54) Title: PLASMODIUM FALCIPARUM BLOOD STAGE INHIBITORS

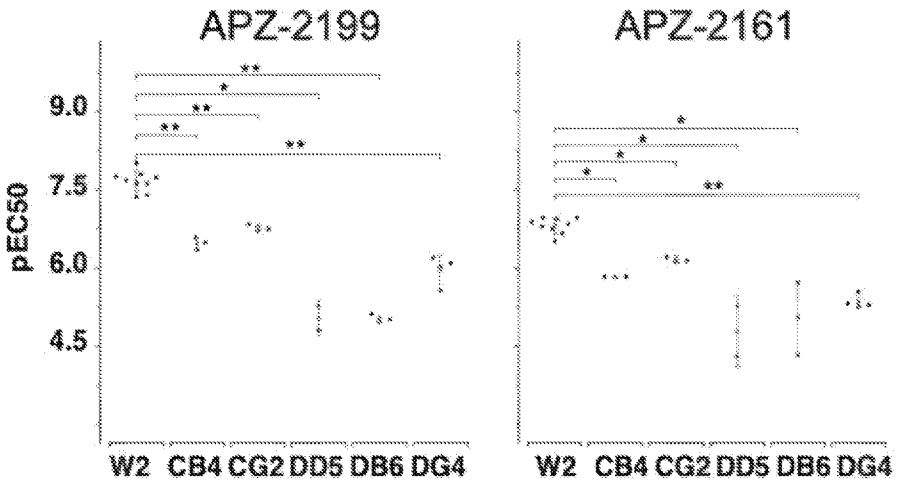


FIG. 1

(57) Abstract: In one aspect, the disclosure relates to compounds that inhibit *Plasmodium falciparum* asexual blood stage parasites (PfABS) In one aspect, the compounds exhibit sub-millimolar potency against the intraerythrocytic stages of *Plasmodium falciparum* and other *Plasmodium* species. In another aspect, the compounds are soluble in aqueous solutions at pH 7.4, making them suitable for oral administration to patients. Also disclosed are methods of making the compounds, pharmaceutical compositions comprising the same, and methods of treating or preventing malaria using the same. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present disclosure.

WO 2024/258900 A3

[Continued on next page]

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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))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

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A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/426; A61K 31/4192; A61K 31/421; A61K 31/4245; A61K 31/4418; A61K 31/50; A61K 31/505 (2024.01)
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ADD. A61P 33/06

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/200934 A1 (UNIVERSITY OF NAGASAKI) 07 October 2021, translation; paragraph [0176], original; paragraph [0175], translation	1-3, 5, 6, 15-16, 31/1-3, 31/5, 31/6, 31/15-16, 32/31/1-3, 32/31/5, 32/31/6, 32/31/15-16, 33/32/31/1-3, 33/32/31/5, 33/32/31/6, 33/32/31/15-16, 34/31/1-3, 34/31/5, 34/31/6, 34/31/15-16, 35/34/31/1-3, 35/34/31/5, 35/34/31/6, 35/34/31/15-16, 36/35/34/31/1-3, 36/35/34/31/5, 36/35/34/31/6, 36/35/34/31/15-16, 37/34/31/1-3, 37/34/31/5, 37/34/31/6, 37/34/31/15-16, 38/37/34/31/1-3, 38/37/34/31/5, 38/37/34/31/6, 38/37/34/31/15-16
A	US 2019/0010148 A1 (HOFFMANN - LA ROCHE INC.) 10 January 2019; paragraphs	1-3, 5, 6, 15-16, 31/1-3,

☒ 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
"D" document cited by the applicant in the international application
"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
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Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

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International application No.
PCT/US2024/033498

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	[0052]-[0053]	31/5, 31/6, 31/15-16, 32/31/1-3, 32/31/5, 32/31/6, 32/31/15-16, 33/32/31/1-3, 33/32/31/5, 33/32/31/6, 33/32/31/15-16, 34/31/1-3, 34/31/5, 34/31/6, 34/31/15-16, 35/34/31/1-3, 35/34/31/5, 35/34/31/6, 35/34/31/15-16, 36/35/34/31/1-3, 36/35/34/31/5, 36/35/34/31/6, 36/35/34/31/15-16, 37/34/31/1-3, 37/34/31/5, 37/34/31/6, 37/34/31/15-16, 38/37/34/31/1-3, 38/37/34/31/5, 38/37/34/31/6, 38/37/34/31/15-16
A	US 2015/0291610 A1 (THE SCRIPPS RESEARCH INSTITUTE) 15 October 2015; paragraph [0106]	1-3, 5, 6, 15-16, 31/1-3, 31/5, 31/6, 31/15-16, 32/31/1-3, 32/31/5, 32/31/6, 32/31/15-16, 33/32/31/1-3, 33/32/31/5, 33/32/31/6, 33/32/31/15-16, 34/31/1-3, 34/31/5, 34/31/6, 34/31/15-16, 35/34/31/1-3, 35/34/31/5, 35/34/31/6, 35/34/31/15-16, 36/35/34/31/1-3, 36/35/34/31/5, 36/35/34/31/6, 36/35/34/31/15-16, 37/34/31/1-3, 37/34/31/5, 37/34/31/6, 37/34/31/15-16, 38/37/34/31/1-3, 38/37/34/31/5, 38/37/34/31/6, 38/37/34/31/15-16
A	US 2005/0182121 A1 (COHEN, FE et al.) 18 August 2005; figure 6	1-3, 5, 6, 15-16, 31/1-3, 31/5, 31/6, 31/15-16, 32/31/1-3, 32/31/5, 32/31/6, 32/31/15-16, 33/32/31/1-3, 33/32/31/5, 33/32/31/6, 33/32/31/15-16, 34/31/1-3, 34/31/5, 34/31/6, 34/31/15-16, 35/34/31/1-3, 35/34/31/5, 35/34/31/6, 35/34/31/15-16, 36/35/34/31/1-3, 36/35/34/31/5, 36/35/34/31/6, 36/35/34/31/15-16, 37/34/31/1-3, 37/34/31/5, 37/34/31/6, 37/34/31/15-16, 38/37/34/31/1-3, 38/37/34/31/5, 38/37/34/31/6, 38/37/34/31/15-16
	-***-Continued Within the Next Supplemental Box-***-	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/033498

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:

-***-Please See Supplemental Page-***-

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.:

1-3, 5-6, 15-16, 31-38

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/US2024/033498

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

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 1-38, Formula I or derivative Formula II, wherein in Formula I, each of R1a-R1e is hydrogen; Ar is a 6-membered aromatic ring; each of R2a-R2c is hydrogen; X is NR8; R8 is C1 linear alkyl; wherein R3 is the first moiety; R4 is deuterated C1 alkyl; R5 is substituted C3 cycloalkyl, provided the compound of Formula I is not as shown (first exemplary compound), and pharmaceutical compositions and methods associated therewith.

The compounds of Claims 1-3, 5, 6, 15-16 and 31-38 (each in-part) are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they encompass a compound comprising Formula I, wherein each of R1a-R1e is hydrogen; Ar is a 6-membered aromatic ring; each of R2a-R2c is hydrogen; X is NR8; R8 is C1 linear alkyl; wherein R3 is the first moiety; R4 is deuterated C1 alkyl; R5 is substituted C3 cycloalkyl, provided the compound of Formula I is not as shown (first exemplary compound), and pharmaceutical compositions and methods associated therewith. This first named invention of Group I+ has been selected to encompass the first species of the genus found in claim 1 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional compounds, with specified substituents for each Rx, and where available as an option within at least one searchable claim, to be searched. Additional compound(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound comprising Formula I, wherein each of R1a-R1e is Cl; Ar is a 5-membered heteroaromatic ring; each of R2a-R2c is C1 alkyl; X is absent; wherein R3 is the second moiety; R6(a-e) is hydrogen, provided the compound of Formula I is not as shown (second exemplary compound), and pharmaceutical compositions and methods associated therewith.

Groups I+ share the technical features including a compound comprising Formula I, a pharmaceutical composition comprising the compound, wherein the pharmaceutical composition has an EC50 against Plasmodium falciparum asexual blood stages W2 of less than or equal to 0.1 mkM, a method for treating or preventing an infection caused by a Plasmodium species in a subject, the method comprising administering a therapeutically effective amount of the pharmaceutical composition to the subject, wherein the infection comprises malaria, wherein the malaria is a drug-resistant strain of malaria, further comprising administering at least one additional anti-malarial treatment to the subject, wherein the at least one additional anti-malarial treatment comprises atovaquone-proguanil, chloroquine, doxycycline, mefloquine, primaquine, tafenoquine, artesunate, clindamycin, hydroxychloroquine, quinidine gluconate-sulfate, quinine dihydrochloride, quinine sulfate, or any combination thereof.

However, these shared technical features are previously disclosed by WO 2021/200934 A1 (UNIVERSITY OF NAGASAKI) (Hereinafter "NAGASAKI").

NAGASAKI discloses a compound comprising Formula I (N- (1H-benzo[d]imidazol-2-yl)-1-methyl-5-phenyl-1H-pyrazole-3-carboxamide, or Compound 24; paragraph [0176], original; paragraph [0175], translation), wherein each of R1a-R1e is hydrogen (the terminal phenyl ring of the Compound 24 is not substituted, each of R1a-R1e is hydrogen; paragraph [0176], original; paragraph [0175], translation); Ar is a 5-membered heteroaromatic ring (the pyrazolyl ring is linked to the terminal phenyl moiety; paragraph [0176], original; paragraph [0175], translation); R2a is C1 alkyl, each of R2b-R2c is absent (the methyl group is linked to N1 nitrogen of the pyrazolyl ring; paragraph [0176], original; paragraph [0175], translation); X is absent (the pyrazolyl ring is attached directly to the carbonyl moiety of the carboxamide core, X is absent; paragraph [0176], original; paragraph [0175], translation); wherein R3 is the first moiety (the 1H-benzo[d] imidazole-NH- terminal moiety is in the compound; paragraph [0176], original; paragraph [0175], translation); R4 is hydrogen (the hydrogen atom is attached to the nitrogen atom in the 1H-benzo[d]imidazole-NH- terminal moiety; paragraph [0176], original; paragraph [0175], translation); R5 is unsubstituted heteroaryl (the benzimidazole heteroaryl is in the terminal 1H-benzo[d]imidazole-NH- moiety; paragraph [0176], original; paragraph [0175], translation), provided the compound of Formula I is not as shown (Compound 24 is not shown; paragraph [0176], original; paragraph [0175], translation), a pharmaceutical composition comprising the compound (the compound is in the form of a pharmaceutical composition containing the compound; paragraph [0144], translation), wherein the pharmaceutical composition has an EC50 against Plasmodium falciparum asexual blood stages W2 of less than or equal to 2 mkM (the life cycle of malaria includes sexual reproduction stage of Plasmodium in mosquito and asexual reproduction stage in inhuman, and the asexual reproduction stage is divided into the intrahepatic stage and the erythrocyte stage, for testing in erythrocyte stage, i.e., asexual blood stage W2, erythrocytes were infected with chloroquine-resistant falciparum malaria strain Dd2, and treated with the compound 24, 50 percent inhibitory concentration IC50 value was calculated and for the compound 24 was found to be Dd2(IC50)= 1580 nM, or 1.5 mkM, as shown on page 90, original; paragraph [0292], original; paragraphs [0002], [0287], [0291], translation), a method for treating or preventing an infection caused by a Plasmodium species in a subject, the method comprising administering a therapeutically effective amount of the pharmaceutical composition to the subject (erythrocytes, i.e., the subject, were infected with chloroquine-resistant Plasmodium falciparum malaria strain, and treated with the compound, IC50 value was calculated, i.e., where the amount of the compound was effective to produce IC50 value, or the therapeutic effect; paragraphs [0002], [0287], translation), wherein the infection comprises malaria, wherein the malaria is a drug-resistant strain of malaria (erythrocytes were infected with chloroquine-resistant Plasmodium falciparum malaria strain, and treated; paragraphs [0002], [0287], translation), further comprising administering at least one additional anti-malarial treatment to the subject (artemisinin combination therapy for preventing resistance is becoming mainstream in treatment of malaria; paragraphs [0002], [0152], translation), wherein the at least one additional anti-malarial treatment comprises atovaquone-proguanil, chloroquine, doxycycline, mefloquine, primaquine, tafenoquine, artesunate, clindamycin, hydroxychloroquine, quinidine gluconate-sulfate, quinine dihydrochloride, quinine sulfate, or any combination thereof (examples of the druigs to be used in combination therapy include artesunate; paragraph [0152], translation), and in a separate embodiment NAGASAKI further discloses wherein the pharmaceutical composition has an EC50 of less than or equal to 0.1 mkM (as shown in table on page 90, original, in treatment of erythrocytes infected with chloroquine-sensitive falciparum malaria strain 3D7A, the IC50 value was found to be 88 nM for the compound 32, which is less than 0.1 mkM; paragraph [0292], original; paragraphs [0002], [0287], [0291], translation). It would have

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from previous Supplemental Box-***-

been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the method, as previously disclosed by NAGASAKI, in order to have provided for wherein the pharmaceutical composition has an EC50 of less than or equal to 0.1 mkM, as previously disclosed by NAGASAKI in a separate embodiment (paragraph [0292], original; paragraphs [0002], [0287], [0291], translation), to indicate that the compound might be more effective in treatment of other strains of the malaria (paragraph [0292], original; paragraphs [0002], [0287], [0291], translation). Further, provided that in both embodiments NAGASAKI discloses the use of compounds for treatment of erythrocytes infected with different strains of malaria (paragraph [0292], original; paragraphs [0002], [0287], [0291], translation), the modification to NAGASAKI's method, of providing for wherein the pharmaceutical composition has an EC50 of less than or equal to 0.1 mkM, would provide the benefit of indicating that the compound might be more effective in treatment of other strains of the malaria (paragraph [0292], original; paragraphs [0002], [0287], [0291], translation).

Since none of the special technical features of the Group I+ is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the NAGASAKI reference, unity of invention is lacking.