

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: BRENT R. BELLOWES, PH.D., ESQ.
KNOWLES INTELLECTUAL PROPERTY
STRATEGIES, LLC
400 PERIMETER CENTER TERRACE, SUITE
200
ATLANTA, GA 30346

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 12020-049WO1	Date of mailing (day/month/year) NOV 02 2023
International application No. PCT/US 23/23739	International filing date (day/month/year) 26 May 2023 (26.05.2023)
Applicant ATEA PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau preferably through ePCT, or on paper to:
The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland

For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriguez Telephone No. PCT Helpdesk: 571-272-4300
---	---

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 12020-049WO1		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 23/23739	International filing date (day/month/year) 26 May 2023 (26.05.2023)	(Earliest) Priority Date (day/month/year) 26 May 2022 (26.05.2022)	
Applicant ATEA PHARMACEUTICALS, INC.			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 24
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/23739

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.: 10-35, 54-58, 65-69, 76-84, 93-109 and 126
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.:
1-9,36-44,85-92,110-125

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 23/23739

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/395, A61K 31/4164, A61K 31/66, A61K 31/664 (2023.01)

ADD. A61K 31/33 (2023.01)

CPC - INV. A61K 31/395, A61K 31/4164, A61K 31/66, A61K 31/664

ADD. A61K 31/33

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 data base consulted during the international search (name of data base 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.
X	GOOD et al. "Evaluation of AT-752, a Double Prodrug of a Guanosine Nucleotide Analog with In Vitro and In Vivo Activity against Dengue and Other Flaviviruses", Antimicrobial Agents and Chemotherapy. 2021. Volume 65 Issue 11, e00988-21, 15 pages, especially: abstract; pg 1, para 1; pg 2, FIG 1, formula AT-752; pg 3, para 2; pg 7, para 2.	1-9,36-44,85-92,110-125
A	GOOD et al. "Preclinical evaluation of AT-527, a novel guanosine nucleotide prodrug with potent, pan-genotypic activity against hepatitis C virus", PLoS ONE. 2020. 15(1): e0227104, 25 pages, entire document.	1-9,36-44,85-92,110-125
A	DO et al. "A robust SARS-CoV-2 replication model in primary human epithelial cells at the air liquid interface to assess antiviral agents", Antiviral Research. 2021. 192, 105122, 8 pages, entire document.	1-9,36-44,85-92,110-125

☐ 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

22 September 2023

Date of mailing of the international search report

NOV 02 2023

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Kari Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/23739

--Box III - Lack of Unity--

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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-9, 36-44, 85-92 and 110-125, directed to a method of treating a Dengue virus infection in a human host in need thereof comprising administering from about 700 to about 1000 mg of a compound of Formula I: or a pharmaceutically acceptable salt thereof.

Group II: Claims 45-53 and 59-64, directed to a method of treating a Dengue virus infection in a human host in need thereof comprising administering from about 700 to about 1000 mg of a compound of a compound of Formula II, or a pharmaceutically acceptable salt thereof.

Group III: Claims 70-75, directed to a process for the preparation of Compound 1 comprising: a. reacting a compound of the formula Intermediate A with Intermediate B in the presence of an activator and a trialkylamine or pyridine base to form a compound of the formula Intermediate C; and b. reacting a compound of the formula Intermediate C with phenol in the presence of a guanidine base.

The inventions listed as Groups I, II, and III 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:

Special Technical Features

Group I requires a compound of Formula I: or a pharmaceutically acceptable salt thereof, which is not required by Group II.***

Group II requires a compound of Formula II, or a pharmaceutically acceptable salt thereof, which is not required by Group I or Group III.

Group III requires a process for the preparation of Compound 1, which is not required by Group I or Group II.

Shared Common Features

The only feature shared by Groups I and III that would otherwise unify the groups is a compound having the formula of Compound 1. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by the article entitled "Evaluation of AT-752, a Double Prodrug of a Guanosine Nucleotide Analog with In Vitro and In Vivo Activity against Dengue and Other Flaviviruses" by Good et al. (hereinafter "Good").

Good teaches Compound 1 (pg 2, FIG 1, formula AT-281).

The only feature shared by Groups I and II that would otherwise unify the groups is a method of treating a Dengue virus infection in a human host in need thereof comprising administering from about 700 to about 1000 mg of a compound. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is obvious over Good.

Good teaches a method of treating a Dengue virus infection in a host in need thereof comprising administering from about 1000 mg/kg of a compound (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight). However, it would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat humans because Good teaches that the compound was evaluated against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg of the compound by routine experimentation in order to identify the most effective dosage to treat the infection.

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I, II, and III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 continued: Claims 10-35, 54-58, 65-69, 76-84, 93-109 and 126 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

To: BRENT R. BELLWS, PH.D., ESQ.
KNOWLES INTELLECTUAL PROPERTY
STRATEGIES, LLC
400 PERIMETER CENTER TERRACE, SUITE
200
ATLANTA, GA 30346

Date of mailing
(day/month/year)

NOV 02 2023

Applicant's or agent's file reference
12020-049WO1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 23/23739

International filing date (day/month/year)

26 May 2023 (26.05.2023)

Priority date (day/month/year)

26 May 2022 (26.05.2022)

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

IPC - INV. A61K 31/395, A61K 31/4164, A61K 31/66, A61K 31/664 (2023.01)

ADD. A61K 31/33 (2023.01)

CPC - INV. A61K 31/395, A61K 31/4164, A61K 31/66, A61K 31/664

ADD. A61K 31/33

Applicant ATEA PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

22 September 2023

Authorized officer

Kari Rodriguez

PCT Help Desk

Telephone No. 571-272-4300

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

- a. ☐ forming part of the international application as filed.
b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 10-35, 54-58, 65-69, 76-84, 93-109 and 126

because:

- ☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. see below are so unclear that no meaningful opinion could be formed (*specify*):

Claims 10-35, 54-58, 65-69, 76-84, 93-109 and 126 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☒ no international search report has been established for said claims Nos. 10-35, 54-58, 65-69, 76-84, 93-109 and 126

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

- ☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-9, 36-44, 85-92 and 110-125, directed to a method of treating a Dengue virus infection in a human host in need thereof comprising administering from about 700 to about 1000 mg of a compound of Formula I: or a pharmaceutically acceptable salt thereof.

Group II: Claims 45-53 and 59-64, directed to a method of treating a Dengue virus infection in a human host in need thereof comprising administering from about 700 to about 1000 mg of a compound of a compound of Formula II, or a pharmaceutically acceptable salt thereof.

Group III: Claims 70-75, directed to a process for the preparation of Compound 1 comprising: a. reacting a compound of the formula Intermediate A with Intermediate B in the presence of an activator and a trialkylamine or pyridine base to form a compound of the formula Intermediate C; and b. reacting a compound of the formula Intermediate C with phenol in the presence of a guanidine base.

The inventions listed as Groups I, II, and III 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:

Special Technical Features

Group I requires a compound of Formula I: or a pharmaceutically acceptable salt thereof, which is not required by Group II.

Group II requires a compound of Formula II, or a pharmaceutically acceptable salt thereof, which is not required by Group I or Group III.

Group III requires a process for the preparation of Compound 1, which is not required by Group I or Group II.

Shared Common Features

The only feature shared by Groups I and III that would otherwise unify the groups is a compound having the formula of Compound 1. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by the article entitled "Evaluation of AT-752, a Double Prodrug of a Guanosine Nucleotide Analog with In Vitro and In Vivo Activity against Dengue and Other Flaviviruses" by Good et al. (hereinafter 'Good').

Good teaches Compound 1 (pg 2, FIG 1, formula AT-281).

The only feature shared by Groups I and II that would otherwise unify the groups is a method of treating a Dengue virus infection in a human host in need thereof comprising administering from about 700 to about 1000 mg of a compound. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is obvious over Good.

--continued in first Supplemental Box--

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1-9,36-44,85-92,110-125

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 23/23739

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9,36-44,85-92,110-125	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-9,36-44,85-92,110-125	NO
Industrial applicability (IA)	Claims	1-9,36-44,85-92,110-125	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-9, 36-44, 85-92 and 110-125 lack an inventive step under PCT Article 33(3) as being obvious over the article entitled "Evaluation of AT-752, a Double Prodrug of a Guanosine Nucleotide Analog with In Vitro and In Vivo Activity against Dengue and Other Flaviviruses" by Good et al. (hereinafter 'Good').

Regarding claim 1, Good teaches a method of treating a Dengue virus infection in a host in need thereof comprising administering about 1000 mg of a pharmaceutically acceptable salt of Compound 1 (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge; see also pg 2, FIG 1, formula AT-752), and Good further teaches wherein the compound is subsequently administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight and doesn't teach the weight of the individual animals) or wherein the 1000 mg is administered twice (Good teaches 500 mg twice per day). It would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat humans because Good teaches that the compound was evaluated against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg (total dose) of the compound twice per day by routine experimentation in order to identify the most effective dosage to treat the infection.

Regarding claim 2, Good teaches the method of claim 1 (see above discussion). Good further teaches wherein the compound is Compound 2 (pg 2, FIG 1, formula AT-752).

Regarding claim 3, Good teaches the method of claim 1 (see above discussion). Good further teaches wherein a pharmaceutically acceptable salt of Compound 1 is provided (pg 2, FIG 1, formula AT-752 is a hemi H₂SO₄ salt).

Regarding claim 4, Good teaches the method of claim 1 (see above discussion). Good further teaches wherein about 1000 mg of the compound is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a total dose of 700 to 850 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 700 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 5, Good teaches the method of claim 4 (see above discussion). Good further teaches wherein about 1000 mg of the compound is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a total dose of 700 to 800 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 700 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 6, Good teaches the method of claim 2 (see above discussion). Good further teaches wherein about 1000 mg of Compound 2 is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a total dose of 700 to 900 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 700 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization. --continued in second Supplemental Box--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--Box IV - Lack of Unity--

Good teaches a method of treating a Dengue virus infection in a host in need thereof comprising administering from about 1000 mg/kg of a compound (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight). However, it would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat humans because Good teaches that the compound was evaluated against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg of the compound by routine experimentation in order to identify the most effective dosage to treat the infection.

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I, II, and III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 continued: Claims 10-35, 54-58, 65-69, 76-84, 93-109 and 126 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--Box V.2 - Citations and Explanations--

Regarding claim 7, Good teaches the method of claim 3. Good further teaches wherein about 1000 mg of the pharmaceutically acceptable salt of the compound is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge, but Good doesn't teach a total dose of 700 to 900 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 700 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 8, Good teaches the method of claim 7 (see above discussion). Good further teaches wherein about 1000 mg of the pharmaceutically acceptable salt of the compound is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge, but Good doesn't teach a total dose of 700 to 900 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 700 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 9, Good teaches the method of claim 3. Good further teaches wherein about 1000 mg of the pharmaceutically acceptable salt of Compound 1 is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge, but Good doesn't teach a total dose of 700 to 900 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 700 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 36, Good teaches a method of treating a Dengue virus infection in a host in need thereof comprising administering about 1000 mg of a pharmaceutically acceptable salt of a compound of Formula I wherein R2 is aryl which is unsubstituted; R3 is hydrogen; R4a is C1 alkyl; R4b is hydrogen; R5 is C3 alkyl (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge; see also pg 2, FIG 1, formula AT-752), and Good further teaches wherein the compound is subsequently administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight and doesn't teach the weight of the individual animals) or wherein the 1000 mg is administered twice (Good teaches 500 mg twice per day). It would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat humans because Good teaches that the compound was evaluated against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg (total dose) of the compound twice per day by routine experimentation in order to identify the most effective dosage to treat the infection.

Regarding claim 37, Good teaches the compound of claim 36 (see above discussion). Good further teaches wherein the compound is the formula listed in claim 37 (pg 2, FIG 1, formula AT-752).

Regarding claim 38, Good teaches the compound of claim 36 (see above discussion). Good further teaches wherein the compound is similar to the formula listed in claim 38 (pg 2, FIG 1, formula AT-752), but Good doesn't teach the stereoisomer indicated for R2-O- moiety (Good teaches the opposite configuration). However, it would have been obvious to a person having ordinary skill in the art to isolate and test all diastereomers in order to identify the most active compound.

Regarding claim 39, Good teaches the compound of claim 36 (see above discussion). Good further teaches wherein the compound is the formula listed in claim 39 (pg 2, FIG 1, formula AT-752).

Regarding claim 40, Good teaches the compound of claim 37. Good further teaches wherein the compound is the formula listed in claim 40 (pg 2, FIG 1, formula AT-752).

Regarding claim 41, Good teaches the compound of claim 37. Good further teaches wherein the compound is similar to the formula listed in claim 38 (pg 2, FIG 1, formula AT-752), but Good doesn't teach the stereoisomer indicated for CH3- moiety adjacent to the phosphoramidate group (Good teaches the opposite configuration). However, it would have been obvious to a person having ordinary skill in the art to isolate and test all diastereomers in order to identify the most active compound.

--continued in next Supplemental Box--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--previous Supplemental Box--

Regarding claim 42, Good teaches the compound of claim 36 (see above discussion). Good further teaches wherein the compound is similar to the formula listed in claim 42 (pg 2, FIG 1, formula AT-752), but Good doesn't teach the stereoisomer indicated for CH₃- moiety adjacent to the phosphoramidate group (Good teaches the opposite configuration). However, it would have been obvious to a person having ordinary skill in the art to isolate and test all diastereomers in order to identify the most active compound.

Regarding claim 43, Good teaches the compound of claim 38 (see above discussion). Good further teaches wherein the compound is similar to the formula listed in claim 43 (pg 2, FIG 1, formula AT-752), but Good doesn't teach the stereoisomer indicated for phenoxy moiety (Good teaches the opposite configuration). However, it would have been obvious to a person having ordinary skill in the art to isolate and test all diastereomers in order to identify the most active compound.

Regarding claim 44, Good teaches the compound of claim 38 (see above discussion). Good further teaches wherein the compound is similar to the formula listed in claim 43 (pg 2, FIG 1, formula AT-752), but Good doesn't teach the stereoisomer indicated for phenoxy moiety or the CH₃- moiety adjacent to the phosphoramidate group (Good teaches the opposite configuration for both groups). However, it would have been obvious to a person having ordinary skill in the art to isolate and test all diastereomers in order to identify the most active compound.

Regarding claim 85, Good teaches a method of treating a Dengue virus infection in a host in need thereof comprising administering about 1000 mg of a pharmaceutically acceptable salt of Compound 1 (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge; see also pg 2, FIG 1, formula AT-752), and Good further teaches wherein the compound is subsequently administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), and Good further teaches wherein the free base form of the compound which is generated in vivo is effective against Dengue virus serotype 3 in vitro (abstract, Here, we show that AT-281, the free base of AT-752, an orally available double prodrug of a guanosine nucleotide analog, was a potent inhibitor of DENV serotypes 2 and 3 in vitro, requiring concentrations of 0.48 and 0.77 mM, respectively, to inhibit viral replication by 50% (EC₅₀) in Huh-7 cells), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight and doesn't teach the weight of the individual animals) or wherein the 1000 mg is administered twice (Good teaches 500 mg twice per day). It would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat Dengue virus serotype 3 in humans because Good teaches that the compound was effective against Dengue serotype 3 in vitro (abstract, Here, we show that AT-281, the free base of AT-752, an orally available double prodrug of a guanosine nucleotide analog, was a potent inhibitor of DENV serotypes 2 and 3 in vitro, requiring concentrations of 0.48 and 0.77 mM, respectively, to inhibit viral replication by 50% (EC₅₀) in Huh-7 cells) against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg (total dose) of the compound twice per day by routine experimentation in order to identify the most effective dosage to treat the infection.

Regarding claim 86, Good teaches the method of claim 85 (see above discussion). Good further teaches wherein the compound is Compound 2 (pg 2, FIG 1, formula AT-752).

Regarding claim 87, Good teaches the method of claim 85 (see above discussion). Good further teaches wherein the compound is a pharmaceutically acceptable salt of Compound 1 (pg 2, FIG 1, formula AT-752 is the hemi sulfate salt of Compound 1).

Regarding claim 88, Good teaches the method of claim 86. Good further teaches wherein about 1000 mg of the compound is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a total dose of about 750 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 750 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 89, Good teaches the method of claim 87. Good further teaches wherein about 1000 mg of the compound is administered (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge), but Good doesn't teach a total dose of about 750 mg (Good teaches 1000 mg/kg of body weight and doesn't teach the weight of the individual animals). However, it would have been obvious to a person having ordinary skill in the art to administer 750 mg total dose by routine experimentation in order to identify the most effective dosage in the course of development and commercialization.

Regarding claim 90, Good teaches the method of claim 85 (see above discussion). Good further teaches wherein the compound is administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)).

--continued in next Supplemental Box--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--previous Supplemental Box--

Regarding claim 91, Good teaches the method of claim 85 (see above discussion). Good further teaches wherein the compound is administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), but Good doesn't specifically teach wherein the compound is administered three times per day. However, it would have been obvious to a person having ordinary skill in the art to administer the compound three times per day by routine experimentation in order to identify the most effective method in the course of development and commercialization.

Regarding claim 92, Good teaches the method of claim 85 (see above discussion). Good further teaches wherein the compound is administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), but Good doesn't specifically teach wherein the compound is administered four times per day. However, it would have been obvious to a person having ordinary skill in the art to administer the compound four times per day by routine experimentation in order to identify the most effective method in the course of development and commercialization.

Regarding claim 110, Good teaches a pharmaceutically acceptable salt of the compound of the formula listed in claim 110 (pg 2, FIG 1, formula AT-752) for use to treat a Dengue virus infection in a host in need thereof comprising administering about 1000 mg of a pharmaceutically acceptable salt of Compound 1 (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge, and Good further teaches wherein the compound is subsequently administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), and Good further teaches wherein the free base form of the compound which is generated in vivo is effective against Dengue virus serotype 3 in vitro (abstract, Here, we show that AT-281, the free base of AT-752, an orally available double prodrug of a guanosine nucleotide analog, was a potent inhibitor of DENV serotypes 2 and 3 in vitro, requiring concentrations of 0.48 and 0.77 mM, respectively, to inhibit viral replication by 50% (EC50) in Huh-7 cells), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight and doesn't teach the weight of the individual animals) or wherein the 1000 mg is administered twice (Good teaches 500 mg twice per day). It would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat Dengue virus serotype 3 in humans because Good teaches that the compound was effective against Dengue serotype 3 in vitro (abstract, Here, we show that AT-281, the free base of AT-752, an orally available double prodrug of a guanosine nucleotide analog, was a potent inhibitor of DENV serotypes 2 and 3 in vitro, requiring concentrations of 0.48 and 0.77 mM, respectively, to inhibit viral replication by 50% (EC50) in Huh-7 cells) against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg (total dose) of the compound twice per day by routine experimentation in order to identify the most effective dosage to treat the infection.

Regarding claim 111, Good teaches the compound for use of claim 110 (see above discussion). Good further teaches wherein the compound is Compound 2 (pg 2, FIG 1, formula AT-752).

Regarding claim 112, Good teaches the method of claim 110 (see above discussion). Good further teaches wherein the Dengue virus is serotype 1 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 113, Good teaches the method of claim 110 (see above discussion). Good further teaches wherein the Dengue virus is serotype 3 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 114, Good teaches the method of claim 110 (see above discussion). Good further teaches wherein the Dengue virus is serotype 4 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

--continued in next Supplemental Box--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--previous Supplemental Box--

Regarding claim 115, Good teaches the use of a pharmaceutically acceptable salt of the compound of the formula listed in claim 115 (pg 2, FIG 1, formula AT-752) for the treatment of Dengue virus infection in a host in need thereof comprising administering about 1000 mg of a pharmaceutically acceptable salt of Compound 1 (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge, and Good further teaches wherein the compound is subsequently administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), and Good further teaches wherein the free base form of the compound which is generated in vivo is effective against Dengue virus serotype 3 in vitro (abstract, Here, we show that AT-281, the free base of AT-752, an orally available double prodrug of a guanosine nucleotide analog, was a potent inhibitor of DENV serotypes 2 and 3 in vitro, requiring concentrations of 0.48 and 0.77 mM, respectively, to inhibit viral replication by 50% (EC50) in Huh-7 cells), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight and doesn't teach the weight of the individual animals) or wherein the 1000 mg is administered twice (Good teaches 500 mg twice per day). It would have been obvious to a person having ordinary skill in the art to adapt the method of Good to treat Dengue virus serotype 3 in humans because Good teaches that the compound was effective against Dengue serotype 3 in vitro (abstract, Here, we show that AT-281, the free base of AT-752, an orally available double prodrug of a guanosine nucleotide analog, was a potent inhibitor of DENV serotypes 2 and 3 in vitro, requiring concentrations of 0.48 and 0.77 mM, respectively, to inhibit viral replication by 50% (EC50) in Huh-7 cells) against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to human disease. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg (total dose) of the compound twice per day by routine experimentation in order to identify the most effective dosage to treat the infection.

Regarding claim 116, Good teaches the use of claim 115 (see above discussion). Good further teaches wherein the compound is Compound 2 (pg 2, FIG 1, formula AT-752).

Regarding claim 117, Good teaches the compound for use of claim 115 (see above discussion). Good further teaches wherein the Dengue virus is serotype 1 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 118, Good teaches the compound for use of claim 115 (see above discussion). Good further teaches wherein the Dengue virus is serotype 3 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 119, Good teaches the compound for use of claim 115 (see above discussion). Good further teaches wherein the Dengue virus is serotype 4 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 120, Good teaches the use of a pharmaceutically acceptable salt of the compound of the formula listed in claim 120 (pg 2, FIG 1, formula AT-752) for the treatment of Dengue virus infection in a host in need thereof comprising administering about 1000 mg of a pharmaceutically acceptable salt of Compound 1 (pg 7, para 2, AT-752 reduces viremia and improves survival of AG129 mice after DENV2 D2Y98P infection. To test the efficacy of AT-752 against DENV infection, AG129 mice were subcutaneously inoculated with DENV2 D2Y98P, a non-mouse-adapted strain that follows a similar disease kinetic as described in humans (19). The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge, and Good further teaches wherein the compound is subsequently administered twice per day (pg 7, para 2, The prodrug was orally administered as a loading dose (1,000 mg/kg) 4 h prior to viral challenge and afterwards as twice a day (BID) doses (500 mg/kg) for 7 consecutive days, beginning 1 h post-infection (pi)), but Good doesn't teach a human host (Good teaches mice) and Good doesn't specifically teach the total dose (Good teaches mg/kg of body weight and doesn't teach the weight of the individual animals) or wherein the 1000 mg is administered twice (Good teaches 500 mg twice per day), and Good doesn't teach manufacture of a medicament. However, it would have been obvious to a person having ordinary skill in the art to use the compound of Good in the manufacture of a medicament because Good teaches that the compound was effective against the virus in multiple different human derived cell lines (pg 3, para 2, To assess whether AT-281, the free base of AT-752, had antiviral activity against DENV and other flaviviruses, human hepatocarcinoma (Huh-7) cells, baby hamster kidney (BHK-21) cells, or human peripheral blood mononuclear cells (PBMCs) were acutely infected with the different viruses and exposed to serial dilutions of the drug) which suggests the applicability to manufacture of a medicament. It would have been further obvious that humans are much larger than mice, thus it may be necessary to administer a different amount of the compound to treat an infected human. It would therefore have also been obvious to administer 700 mg to about 1000 mg (total dose) of the compound twice per day by routine experimentation in order to identify the most effective dosage to treat the infection.

Regarding claim 121, Good teaches the use of claim 120 (see above discussion). Good further teaches wherein the compound is Compound 2 (pg 2, FIG 1, formula AT-752).

Regarding claim 122, Good teaches the compound for use of claim 120 (see above discussion). Good further teaches wherein the Dengue virus is serotype 1 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 123, Good teaches the compound for use of claim 120 (see above discussion). Good further teaches wherein the Dengue virus is serotype 2 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Regarding claim 124, Good teaches the compound for use of claim 120 (see above discussion). Good further teaches wherein the Dengue virus is serotype 3 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

--continued in next Supplemental Box--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 23/23739

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--previous Supplemental Box--

Regarding claim 125, Good teaches the compound for use of claim 120 (see above discussion). Good further teaches wherein the Dengue virus is serotype 4 (pg 1, para 1, There are four antigenically distinct but closely related DENV serotypes (DENV1 to 4)).

Claims 1-9, 36-44, 85-92 and 110-125 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.