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(81) Designated States (unless otherwise indicated, for every kind of national protection available):

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(54) Title: NOVEL UNIVERSAL ANTI-RNA VIRUS AGENTS

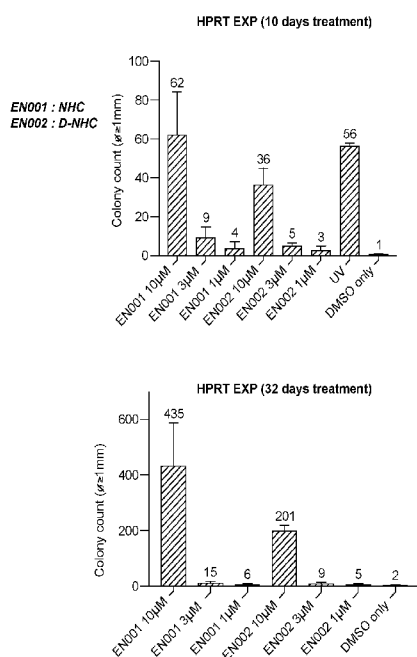


FIG. 3

(57) Abstract: Deuterated and/or methylated N⁴-hydroxycytidine (NHC) analogs, with deuteration at one or both of the 2'- and 3'-positions on the ribo-sugar moiety and/or methylation of the 3'- positions on the ribo-sugar moiety, pharmaceutical compositions comprising one or more of these compounds, and, optionally, at least one additional therapeutic agent, and methods of treating or preventing infections caused by RNA viruses, curing an infection by an RNA virus, or reducing the biological activity of an RNA virus, are disclosed. Representative RNA viruses include, but are not limited to, Coronaviridae, such as MERSr-CoV, SARS-CoV-1, SARSCoV- 2, HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1, Picornaviridae, Hepeviridae, Noroviruses, Zika, Dengue, Mayaro, Influenza A and B, Parainfluenza, HCV, Rinovirus, tick-borne viruses, Ebola, Lassa, RSV, adenoviruses, enteroviruses, metapneumoviruses, Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively), and Chikungunya fever (CHIK).



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- *with international search report (Art. 21(3))*
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/31381

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/7052, A61K 31/33, A61K 31/34, C07H 19/04; ADD. A61K 31/00 (2022.01)

CPC - INV. A61K 31/7052, A61K 31/33, A61K 31/34, C07H 19/04; ADD. A61K 31/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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.
A	WO 2016/106050 A1 (EMORY UNIVERSITY) 30 June 2016 (30.06.2016), especially: pg 55, ln 15-19, scheme, formula EIDD-1931.	1-2,5,9-11,13,16,110-117
A	US 6,943,249 B2 (IONESCU et al.) 13 September 2005 (13.09.2005), especially: col 1, ln 45-59, formula.	1-2,5,9-11,13,16,110-117
A	VASUDEVAN et al. "A concise route to MK-4482 (EIDD-2801) from cytidine", Chem. Commun., 2020. 56, pp 13363-13364, especially: pg 13363, Fig. 1, MX-4482.	1-2,5,9-11,13,16,110-117
A	TIMMINS "Deuterated drugs; where are we now", Expert Opin Ther Pat. 2014. 24(10): pp 1067-1075, especially: pg 4, para 2.	1-2,5,9-11,13,16,110-117

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document delining 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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/31381

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see 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.:
1-2,5,9-11,13,16,110-117

- 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.

--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 1-17, 108-109 and 110-117 (in part) directed to a compound of Formula (A) or a pharmaceutically acceptable salt or prodrug thereof. The compound of Formula (A) will be searched to the extent that it encompasses the first species of claim 1, wherein X is CH₂; Y is N; Z is N; R₁ is OH; R₂ is H; R₃ is H; R₄ is O; R₅ is H; R₈ and R_{8'} are H; R₉ is H; R₁₀ is deuterium. It is believed that claims 1-2, 5, 9-11, 13, 16 and 110-117 (in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. This first named invention has been selected 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 of Formula (A), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein X is -CH(CH₃)-; Y is N; Z is N; R₁ is OH; R₂ is H; R₃ is H; R₄ is O; R₅ is H; R₈ and R_{8'} are H; R₉ is H; R₁₀ is deuterium (i.e. claims 1, 5, 9-11, 13, 16 and 110-117 (in part)).

Group II: Claims 18-31 and 110-117 (in part), directed to a compound of Formula (B) or a pharmaceutically acceptable salt or prodrug thereof.

Group III: Claims 32-44 and 110-117 (in part), directed to a compound of Formula (C) or a pharmaceutically acceptable salt or prodrug thereof.

Group IV: Claims 45-53 and 110-117 (in part), directed to a compound of Formula (D) or a pharmaceutically acceptable salt or prodrug thereof.

Group V: Claims 54-68 and 110-117 (in part), directed to a compound having the following formula: Formula E.

Group VI: Claims 69-83 and 110-117 (in part), directed to a compound having the following formula: Formula F.

Group VII: Claims 84-95 and 110-117 (in part), directed to a compound having the following formula: Formula G.

Group VIII: Claims 96-107 and 110-117 (in part), directed to a compound having the following formula: Formula H.

Group IX: Claims 118-134, directed to a method for treating a host infected with an RNA virus, preventing an infection by an RNA virus, curing an infection caused by an RNA virus, or reducing the biological activity of an infection caused by an RNA virus, comprising administering an effective amount of a compound of any of Formulas A-H to a patient in need of treatment thereof.

The groups of inventions listed above 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+ includes the technical feature of a unique compound of Formula (A), which is not required by any other invention of Group I+.

Group I+ requires a compound of Formula (A), which is not required by Groups II-VIII.

Group II requires a compound of Formula (B), which is not required by Groups I+ or III-VIII.

Group III requires a compound of Formula (C), which is not required by Groups I+, II or IV-VIII.

Group IV requires a compound of Formula (D), which is not required by Groups I+, II-III or V-VIII.

Group V requires a compound of Formula E, which is not required by Groups I+, II-IV or VI-VIII.

Group VI requires a compound of Formula F, which is not required by Groups I+, II-V or VII-VIII.

Group VII requires a compound of Formula G, which is not required by Groups I+, II-VI or VIII.

Group VIII requires a compound of Formula H, which is not required by Groups I+, II-VII.

Group IX requires a method for treating a host infected with an RNA virus, preventing an infection by an RNA virus, curing an infection caused by an RNA virus, or reducing the biological activity of an infection caused by an RNA virus, which is not required by Groups I+, II-VIII.

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Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of Formula (A).

The inventions of Group I+ and Group IX share the technical feature of a compound having the structure of Formula (A).

The inventions of Group I+ and Group II-VIII share the technical feature of a compound having the core structure of a nucleoside derivative.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over the article entitled "A concise route to MK-4482 (EIDD-2801) from cytidine" by Vasudevan et al. (hereinafter 'Vasudevan').

Vasudevan teaches a compound having the structure of Formula (A) wherein X is CH₂; Y is CR'; Z is CR"; R' is H; R" is H; R1 is -O-C(O)-C₃ alkyl; R2 is H; R3 is H; R4 is O; R5 is H; R8 and R8' are H; and R9 is H (pg 13363, Fig. 1, MX-4482), but Vasudevan does not teach wherein R10 is deuterium or methyl. However, it would have been obvious to a person having ordinary skill in the art to know that replacement of a hydrogen atom with a deuterium atom is predicted to enhance the metabolic stability of an existing compound (as evidenced by separately attached supporting document entitled "Deuterated drugs; where are we now" by Timmins; see abstract, Deuterated versions of existing drugs can exhibit improved pharmacokinetic or toxicological properties due the stronger deuterium-carbon bond modifying their metabolism; see also pg 4, para 2, a person of ordinary skill in the art would have motivation to prepare the deuterated version with reasonable expectation of success. Since there is always a desire to modify a compounds pharmacological effects (exemplified by deuteration improvements in half-life) without significant structure modification, or the need to improve pharmacokinetic studies, yet there being only a limited number of strategies to achieve this, obviousness of these solutions is found. Finally, these branches are integrated so that deuteration per se is shown to be a well-known way to improve a pharmaceutical and again obviousness of the approach ensues). Thus it would also have been obvious to prepare the derivative of the compound of Vasudevan wherein one of the hydrogen atoms has been replaced by a deuterium atom in order to enhance the pharmacological profile of the compound. It would have been further obvious to prepare the compound wherein R10 is deuterium by routine experimentation in order to optimize the activity of the compound in the course of development and commercialization.

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+ and II-IX.

The inventions of Group I+ and II-IX thus lack unity under PCT Rule 13.