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30 July 2020 (30.07.2020)

(54) Title: PRE-ACTIVATED NUCLEOSIDE IMPDH INHIBITORS AS ANTI-INFECTIVE DRUGS

(57) Abstract: The present disclosure provides inosine-5'-monophosphate dehydrogenase (IMPDH)-inhibiting nucleoside derivatives having anti-infective activities, and methods of their synthesis and use.

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INTERNATIONAL SEARCH REPORT

International application No.
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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(s).

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, 5-10

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/US2019/054742

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/4164; A61P 31/12; C07H 15/203; C07H 19/052 (2020.01)
CPC - A61K 31/4164; A61P 31/12; C07H 15/203; C07H 19/052 (2020.01)

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	US 2005/0004144 A1 (CARSON et al) 06 January 2005 (06.01.2005) entire document	1-3, 5-10
A	US 2005/0009737 A1 (CLARK) 13 January 2005 (13.01.2005) entire document	1-3, 5-10
A	US 2005/0049204 A1 (OTTO et al) 03 March 2005 (03.03.2005) entire document	1-3, 5-10

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier 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
07 January 2020	27 JAN 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
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Continued from Box No. III Observations where unity of invention is lacking

Claims 1-3 and 5-10 have been analyzed subject to the restrction that the claims read on a formulation comprising: a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH); and a pharmaceutically acceptable carrier, wherein the nucleoside analog inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein: base is the first shown structure; A is –CH-; W is –C-; X is –OH; Z is O; R1 is –PA1O2(R3)2; R2 is independently at each occurrence, selected as –OH; R3 is, independently at each occurrence, selected as –H; and dashed bond is absent.

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 need to be paid.

Group I+: claims 1-10 are drawn to formulations, methods of treating an infection in a mammal, and methods of inhibiting the growth and/or proliferation of an infective organism.

The first invention of Group I+ is restricted based on the proviso the derivative is not one of the structures shown; and is restricted to a formulation comprising: a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH); and a pharmaceutically acceptable carrier, wherein the nucleoside analog inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein: base is the first shown structure; A is –CH-; W is –C-; X is –OH; Z is O; R1 is –PA1O2(R3)2; R2 is independently at each occurrence, selected as –OH; R3 is, independently at each occurrence, selected as –H; and dashed bond is absent; methods of treating an infection in a mammal thereof; and methods of inhibiting the growth and/or proliferation of an infective organism thereof. It is believed that claims 1-3 and 5-10 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a formulation comprising: a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH); and a pharmaceutically acceptable carrier, wherein the nucleoside analog inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein: base is the first shown structure; A is –CH-; W is –C-; X is –OH; Z is S; R1 is –PA1O2(R3)2; R2 is independently at each occurrence, selected as –OH; R3 is, independently at each occurrence, selected as –H; and dashed bond is absent; methods of treating an infection in a mammal thereof; and methods of inhibiting the growth and/or proliferation of an infective organism thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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.

The inventions listed in Groups I+ 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:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH) and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a formulation comprising: a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH); and a pharmaceutically acceptable carrier; a method of treating an infection in a mammal, comprising administering to the mammal a therapeutically effective amount of an anti-infective formulation such that the infection is reduced, the anti-infective formulation comprising a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH) and a pharmaceutically acceptable carrier; and a method of inhibiting the growth and/or proliferation of an infective organism, comprising contacting the organism with a growth and/or proliferation-inhibiting amount of an anti-infective formulation, the anti-infective formulation comprising a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH) and a pharmaceutically acceptable carrier, these shared technical features do not represent a contribution over the prior art as disclosed by US 2005/0004144 A1 to Carson et al.

US 2005/0004144 A1 to Carson et al. teach a formulation (Para. [0011],... pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of Formula I possessing a ring System according to Formula II.) comprising: a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH) (Para. [0023], FIG. 1 depicts the chemical structures of guanosine; the guanosine inhibitors 7-deazoguanosine and 7-thia-8-oxoguanosine (TOG); and the IMPDH inhibitors ribavirin, misoribine, and mizoribine base.; Fig. 1, see first shown structure); and a pharmaceutically acceptable carrier (Para. [0011]); a method of treating an infection in a mammal (Para. [0014],... a method of treating a viral infection in a mammal by administering a TLR ligand in combination with an IMPDH inhibitor; Claim 52), comprising administering to the mammal a therapeutically effective amount of an anti-infective formulation (Para. [0014]; Claim 52) such that the infection is reduced (Para. [0014]; Claim 52), the anti-infective formulation comprising a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH) (Paras. [0011] and [0014]; Claim 52) and a pharmaceutically acceptable carrier (Paras. [0011] and [0014]; Claim 52); and a method of inhibiting the growth and/or proliferation of an infective organism (Para. [0060],... the methods can be used to treat an intracellular bacterial infection; Para. [0013], The present invention can also enhance resistance to a bacterial infection, and in a preferred embodiment enhances resistance to an intracellular bacterial infection.), comprising contacting the organism with a growth and/or proliferation-inhibiting amount of an anti-infective formulation (Claims 32 and 35; Para. [0013]), the anti-infective formulation comprising a nucleoside analog inhibitor of inosine monophosphate dehydrogenase (IMPDH) (Paras. [0011] and [0014]; Claim 52) and a pharmaceutically acceptable carrier (Paras. [0011] and [0014]; Claim 32).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.