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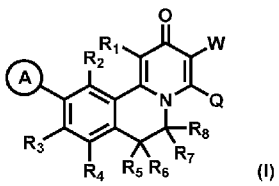
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(54) Title: SUBSTITUTED HETEROCYCLES AS ANTIVIRAL AGENTS



(I)

(57) Abstract: The present invention discloses compounds of Formula (I), and pharmaceutically acceptable salts thereof: which inhibit the protein(s) encoded by hepatitis B virus (HBV) or interfere with the function of the HBV life cycle of the hepatitis B virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HBV infection. The invention also relates to methods of treating an HBV infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/14144

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:

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

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.:

Claims 1, 4-5, 13/1, 13/4-5, 14/1, 14/4-5, 15/14/1, 15/14/4-5, 16/15/14/1, 16/15/14/4-5, 17/15/14/1, 17/15/14/4-5, 18/15/14/1, 18/15/14/4-5, 19/15/14/1, 19/15/14/4-5, 20/15/14/1, 20/15/14/4-5, 21/15/14/1, 21/15/14/4-5

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/US19/14144

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/4745, 31/496, 31/5377; C07D 455/06 (2019.01)

CPC - A61K 31/4745, 31/496, 31/5377; C07D 455/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic 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 -- Y	US 2016/0296515 A1 (HOFFMANN-LA ROCHE INC.) 13 October 2016; paragraphs paragraphs [0010]-[0014], [0022], [0024]-[0025], [0027], [0051], [0586]-[0588]	1, 4-5, 13/1, 13/4-5, 14/1, 14/4-5 --- 15/14/1, 15/14/4-5, 16/15/14/1, 16/15/14/4-5, 17/15/14/1, 17/15/14/4-5, 18/15/14/1, 18/15/14/4-5, 19/15/14/1, 19/15/14/4-5, 20/15/14/1, 20/15/14/4-5, 21/15/14/1, 21/15/14/4-5
Y	US 2017/0253609 A1 (ENANTA PHARMACEUTICALS, INC.) 07 September 2017; paragraphs [0078], [0080]-[0082]	15/14/1, 15/14/4-5, 16/15/14/1, 16/15/14/4-5, 17/15/14/1, 17/15/14/4-5, 18/15/14/1, 18/15/14/4-5, 19/15/14/1, 19/15/14/4-5, 20/15/14/1, 20/15/14/4-5, 21/15/14/1, 21/15/14/4-5

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2019 (21.05.2019)	25 JUL 2019
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 Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid. Groups I+, Claims 1-21; compound of Formula (I), wherein X is -O-; R1 is H; R2 and R3 are H; R4 is H; R5 is H; R6 is (C5-C16)alkyl, unbranched or branched, optionally substituted with R7; R7 is -N3; and R8 is H (compound structure), and methods associated therewith.

The compound, compositions and methods will be searched to the extent the compound encompasses a compound of Formula (I), wherein R1 is hydrogen; R2 is hydrogen; A is optionally substituted C3-C12 cycloalkyl; R3 is R11 wherein R11 is hydrogen; R4 is halo; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; Q is hydrogen; and W is -COOR9 wherein R9 is hydrogen (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 4-5 (each in-part), and 13-21 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), wherein R1 is hydrogen; R2 is hydrogen; A is optionally substituted C3-C12 cycloalkyl; R3 is R11 wherein R11 is hydrogen; R4 is halo; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; Q is hydrogen; and W is -COOR9 wherein R9 is hydrogen (compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), wherein R1 is halo; R2 is hydrogen; A is optionally substituted C3-C12 cycloalkyl; R3 is R11 wherein R11 is hydrogen; R4 is halo; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; Q is hydrogen; and W is -COOR9 wherein R9 is hydrogen (compound structure).

Groups I+ share the technical features including: a compound of Formula (I), wherein R1 is hydrogen; R2 is hydrogen; A is optionally substituted C3-C12 cycloalkyl; R3 is R11 wherein R11 is hydrogen; R4 is halo; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; Q is hydrogen; and W is -COOR9 wherein R9 is hydrogen, for use in treating or preventing an HBV infection comprising administering to a subject a therapeutically effective amount of a compound, a pharmaceutically acceptable carrier or excipient, and an additional therapeutic agent.

However, these shared technical features are previously disclosed by US 2016/0296515 A1 (HOFFMANN-LA ROCHE INC.) (hereinafter 'Hoffmann').

Hoffmann discloses a compound of Formula (I), wherein R1 is hydrogen; R2 is hydrogen; A is optionally substituted C3-C12 cycloalkyl; R3 is R11 wherein R11 is hydrogen; R4 is halo; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; R8 is hydrogen; Q is hydrogen; and W is -COOR9 wherein R9 is hydrogen (compound of formula I (R1, R6, R8, and Q are hydrogen and W is -COOR9 wherein R9 is hydrogen) wherein R1 (R2) is hydrogen, R2 (A) is C3-7cycloalkyl, R3 is hydrogen (R3 is R11 wherein R11 is hydrogen), R4 is halogen, R5 is hydrogen, and R6 (R7) is hydrogen; paragraphs [0010]-[0014], [0022], [0024]-[0025]), for use in treating or preventing an HBV infection comprising administering to a subject a therapeutically effective amount of a compound (method of treating and/or preventing an HBV infection by administering an effective amount of a compound of formula I; paragraphs [0010], [0027], [0586]-[0588]), a pharmaceutically acceptable carrier or excipient (composition comprising a therapeutic carrier or excipient; paragraph [0587]), and an additional therapeutic agent (compound of formula I is combined with additional HBV agents; paragraph [0608]). Hoffmann does not provide a single concise embodiment with each of the selected moieties, from the list of possible moieties. However, provided that Hoffmann discloses the chosen substituents (Hoffmann; paragraphs [0055], [0057]-[0062]), it would have been obvious to one of ordinary skill in the art, at the time of the invention, to have modified the compound of Hoffmann, by narrowing the range of substituents so to as select the chosen substituents for Formula (I), for providing dihydroquinolizinone compounds that are useful as HBV DNA production inhibitors in the treatment of HBV infections (Hoffmann; paragraphs [0002]-[0004]).

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