A61K 38/44 (2006.01) C12N 1/20 (2006.01)

(21) International Application Number: PCT/US20 16/052409

(22) International Filing Date: 19 September 2016 (19.09.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/222,304 23 September 2015 (23.09.2015) US
62/302,452 2 March 2016 (02.03.2016) US

(71) Applicants (for all designated States except US): MERCK SHARP & DOHME CORP.; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon Hertfordshire EN1 19BU (GB).


(72) Inventors; and

(74) Common Representative: MERCK SHARP & DOHME CORP.; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).


(84) Designated States (unless otherwise indicated, for every kind of regional protection available): AR IPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, ...)

(54) Title: 4'-SUBSTITUTED NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS AND PREPARATIONS THEREOF

(57) Abstract: The present invention is directed to 4'-substituted nucleoside derivatives of Formula (I) and their use in the inhibition of HIV reverse transcriptase, the prophylaxis of infection by HIV, the treatment of infection by HIV, and the prophylaxis, treatment, and delay in the onset or progression of AIDS and/or ARC. The present invention also provides processes for the preparation of 4'-substituted nucleoside derivatives of Formula (I) and derivatives thereof.
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report: 18 May 2017
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC (8) - A61K 38/44, C12N 1/20 (2017.01)
CPC - A61K 38/50, A61K 47/48215

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 38/44, C12N 1/20 (2017.01)
CPC - A61K 38/50, A61K 47/48215

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Pubsearch, Google Patent, Google Web
Search terms used - Reverse transcriptase inhibitors nucleoside 2-fluoro deoxyadenosine synthesis nucleobase lactol ethynyl Pubchem substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Kageyama et al. &quot;Concise Synthesis of the Anti-HIV Nucleoside EFdA&quot; Bioscience, Biotechnology, and Biochemistry. 22 May 2014 (22.05.2014) vol 76, pg. 1219-1225; pg. 1222, table 2, scheme 4, pg. 1223, scheme 5</td>
<td>13-20, 21-34</td>
</tr>
<tr>
<td>Y</td>
<td>Oheui &quot;Development of modified nucleosides that have extremely high anti-HIV activity and low toxicity and prevent the emergence of resistant HIV mutants&quot; Proceedings of the Japan Academy, Series B Physical and Biological Sciences. 11 March 2011 (11.03.2011), vol 87, pg. 53-65; pg. 53, left col, last para - right col, first para, pg. 54, figure 1, pg. 58, scheme 2</td>
<td>1-3, 5, 7-9, 21-34</td>
</tr>
<tr>
<td>Y</td>
<td>US 2014/0309412 A1 (Bhat et al.) 16 October 2014 (16.10.2014); para [0558], [0582], [1088], [1136]</td>
<td>1-3, 5, 7-9, 21-34</td>
</tr>
<tr>
<td>Y</td>
<td>US 2015/0133395 A1 (Clarke et al.) 14 May 2015 (14.05.2015); entire document, especially para [0304], [0316]</td>
<td>1-3, 5, 7-9, 13-34</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Note: 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
G document member of the same patent family

Date of the actual completion of the international search: 23 January 2017
Date of mailing of the international search report: 31 March 2017

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: Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

International application No. PCT/US 16/52409

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:

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.

Group I: Claims 1-9, directed to compounds having the structural formula I and to pharmaceutical compositions containing the same. The compound of formula I will be searched to the extent that it encompasses the first species of claim 1, represented by the first \( \delta \) of formula of claim 1, wherein \( R_1 = H \) and \( R_2 = H \). It is believed that claim 1-3, 5 and 7-9 read on 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. Applicant is invited to elect additional compounds of claim 1, 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.

-see supplemental 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.:

   Group I(a) (claims 1-3, 5 and 7-9) and Group III (claims 13-34)

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.:

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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (January 2015)
Failure to clearly identify how any paid additional invention fees are to be applied to the "x" 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, represented by the first formula of claim 1, wherein R1 is the first structure listed (phosphoric acid) and R2 is H (i.e., claims 1-2, 4 and 7-9 (in part)).

Group II: Claims 10-12, directed to a method for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of the compound of any one of claims 2, 3, or 5 and medicament containing the same.

Group III: Claims 13-34, directed to a process for preparing a compound of Formula (IA).

Group IV: Claims 35-36, directed to compounds of the general formula listed, comprising derivatives of 4'-ethylidino-2-fluor0'-2'-deoxyadenosine wherein the amino and hydroxyl groups are protected.

Group V: Claims 37-38, directed to compounds of the general formula listed comprising an ethynyl-diol-lactone.

The group 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 I and a pharmaceutical composition containing the same, which is not required by any other invention of Group I, IV or V.

Group II includes the technical feature of a method for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of the compound of any one of claims 2, 3, or 5, not required by Group I, III, IV, or V.

Group III includes the technical feature of a process for preparing a compound of Formula (IA), not required by Group I, II, IV, or V.

Group IV includes the technical feature of a compound of claim 35 or 36, comprising derivatives of 4'-ethylidino-2-fluoro-2'-deoxyadenosine wherein the amino and hydroxyl groups are protected, not required by Group I, II, III, or V.

Group V includes the technical feature of a compound of claim 37 or 38 comprising an ethynyl-diol-lactone, not required by Group I, II, V, or IV.

Common technical features:

The inventions of Group I share the technical feature of compound of formula I in claim 1.

Groups I, II, III, IV, and V share the technical feature of a 2-hydroxymethyl-2-ethylidino-3-hydroxy-oxolane substituted at the 5 position and derivatives thereof.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by an article entitled "Development of modified nucleosides that have supremely high anti-HIV activity and low toxicity and prevent the emergence of resistant HIV mutants" to Ohrui who teaches a 2-hydroxymethyl-2-ethylidino-3-hydroxy-oxolane substituted at the 5 position (pp. 54, Figure 1, compound 4'E2CIA).

Groups III and IV share the technical feature of a compound which is protected nucleoside (A) (claim 13).

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over US 8,039,614 B2 to Kohgo et al. (hereinafter Kohgo) who teaches a compound which is protected nucleoside (A) wherein X is F; Y is N; Z1 is NH2 and Rd is C(0)C1 alkyl (col 20, in 25-30: compound 3), but does not disclose wherein Z1 is N(H)PG, and PG is an amino protecting group. It would have been obvious to one with skill in the art to prepare the disclosed compound where the primary amine is bound to an amino protecting group (wherein Z1 is N(H)PG, and PG is an amino protecting group) in order to use the resulting compound in syntheses involving reagents which react with a primary amine.
Groups I+, II and III share the technical feature of a compound having the general formula of claim 1.

These shared technical features, however, do not provide a contribution over the prior art, as being being obvious over Ohrui in view of US 2010/0227833 A1 to Yin et al. (hereinafter Yin). Ohrui discloses a compound similar to the compound of structural Formula I wherein R1 is H and R2 is H (pg. 54, Figure 1, compound 4'Ed2CIA), but does not disclose a compound wherein the bicyclic heterocyclic contains a carbon bound to fluorine in the 5-membered ring. However, Yin discloses a similar compound containing the bicyclic heterocyclic comprising a carbon bound to fluorine in the 5-membered ring (para [0260]). Yin further teaches pharmaceutical compositions containing compound similar to the compound of formula I (para [0035]). It would have been obvious to one with skill in the art to prepare the compound disclosed by Ohrui, wherein a nitrogen in the pyrrole ring is replaced with a carbon bound to fluorine, as disclosed by Yin, preparing derivatives of the disclosed compound which are used as reverse transcriptase inhibitors and varying the substituents of said compounds in order to optimize the compounds pharmacological properties.

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+, II, III, IV and V.