



(43) International Publication Date  
13 August 2015 (13.08.2015)

(51) International Patent Classification:

A61K 31/7052 (2006.01) C07H 19/04 (2006.01)  
A61K 31/7072 (2006.01)

(21) International Application Number:

PCT/US2015/014762

(22) International Filing Date:

6 February 2015 (06.02.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/936,569 6 February 2014 (06.02.2014) US

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

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

— with international search report (Art. 21(3))

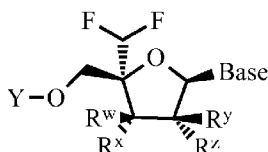
(88) Date of publication of the international search report:

5 November 2015



WO 2015/120237 A3

(54) Title: 4'-DIFLUOROMETHYL SUBSTITUTED NUCLEOSIDE DERIVATIVES AS INHIBITORS OF INFLUENZA RNA REPLICATION



(i)

(57) Abstract: The application discloses nucleoside derivatives of Formula I as inhibitors of Influenza RNA replication. In particular, the application discloses the use of purine and pyrimidine nucleoside derivatives of Formula I as inhibitors of Influenza RNA replication and pharmaceutical compositions containing such compounds.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 15/14762

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(8) - A61K 31/7052; A61K 31/7072; C07H 19/04 (2015.01)

CPC - C07H 19/06; C07H 19/16; C07H 19/04; A61K 31/7052

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)

IPC(8): A61K 31/7052; A61K 31/7072; C07H 19/04 (2015.01)

CPC: C07H 19/06; C07H 19/16; C07H 19/04; A61K 31/7052

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
USPC: 514/43; 536/26.26; 536/22.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Scholar, PubWEST, SureChem

4'-substituted, 4'-modified, nucleoside, 4'-difluoromethyl, antiviral, influenza, treat, 4'-difluoromethyl-2'-deoxyuridine, 4'difluoromethyl cytidine, 4'-difluoromethylcytidine

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,192,749 A (O-YANG et al.) 09 March 1993 (09.03.1993) col 23, ln 4-14; col 23, ln 60 to col 24, ln 12; col 24, ln 18-21; col 46, ln 57	1, 20, 24-29
Y	US 2013/0243725 A1 (CLARKE) 19 September 2013 (19.09.2013) abstract; para [0008], [0089], [0173]	1-2, 19-20, 23-29
Y	US 2010/0003213 A1 (DEVOS et al.) 07 January 2010 (07.01.2010) para [0006], [0017], pg 4, compound 11; pg 7, compound 22; para [0182], [0185]	1-2, 19, 23-29
A	US 2003/0087873 A1 (STUYVER et al.) 08 May 2003 (08.05.2003) Entire Document	1-2, 19-20, 23-29

Further documents are listed in the continuation of Box C.

\* 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

11 July 2015 (11.07.2015)

Date of mailing of the international search report

**30 JUL 2015**

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

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PCT OSP: 571-272-7774

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/14762

**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.: 30  
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 1-29 directed to a compound of Formula I for use in the prophylaxis or treatment of influenza infection. The compound of Formula I will be searched to the extent that it encompasses the first species of claim 1, wherein Y is H; Rw, Ry and Rz are each H; Rx is OH and wherein Base is uracil, wherein the compound meets the proviso that when Rw, Ry and Rz are each H, then Rx is not H. It is believed that claims 1, 20 and 24-29 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 described above.

--Please see attached 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.:  
First invention: claims 1, 20, 24-29; Second invention: claims 1-2, 19, 23-29
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.

Attachment to Box.No.III:

--continued --

Applicant is invited to elect additional compounds of Formula (I), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound of Formula (I). 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. An exemplary election would be a compound of Formula (I), wherein Y is H; R<sub>w</sub> is H; R<sub>y</sub> is H; R<sub>x</sub> is OH and R<sub>z</sub> is OH and wherein the Base is cytosine (i.e. claims 1-2, 19, 23-29).

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:

The special technical feature of each invention of Group I+ is a unique compound of Formula I, which is not required in any other invention in the group.

Common technical features:

The inventions of Group I+ share the technical feature of a compound having the core structure of Formula I. This shared technical feature, however, does not make a contribution over the prior art as follows:

Regarding claims 1, 28 and 29, US 2013/0243725 A1 (Clarke) published on 19 September 2013 teaches a compound of Formula I, wherein Y is H; R<sub>w</sub> is H; R<sub>y</sub> is H; R<sub>x</sub> is OH and R<sub>z</sub> is F and Base is a heterocycloalkyl wherein the compound meets the provisos laid out in claim 1 (para [0089], pg 14, col 1, first structure listed), for use in the treatment or prophylaxis of influenza infection (abstract).

Regarding claim 23, Clarke teaches an analog of 2'-Deoxy-2'-fluoro-4'-difluoromethylcytidine, wherein the cytosine is replaced by a bicyclic heteroaryl (para [0089], compound in col 1, row 3) as an antiviral agent having therapeutic utility in treating influenza infections (abstract). Clarke does not teach the claimed 2'-Deoxy-2'-fluoro-4'-difluoromethylcytidine. However, US 2003/0087873 A1 to Stuyver et al. (hereinafter 'Stuyver') teaches 3-deoxycytidine (para [0228]; Fig 5, Beta-D-AJ) as having antiviral activity (para [1555], Table 23) and therapeutic utility in the treatment of influenza infection (para [0230]).

It would have been obvious to one of ordinary skill in the art to introduce the cytosine base moiety as disclosed in Stuyver in place of the bicyclic heteroaryl of the nucleoside analog disclosed in Clarke, in order to design 2'-Deoxy-2'-fluoro-4'-difluoromethylcytidine as an anti-influenza agent having enhanced therapeutic utility, because both Stuyver and Clarke teach nucleoside analogs having anti-influenza activity.

As said compounds were known/obvious in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Group I+.

The inventions of Groups I+, therefore, lack unity under PCT Rule 13.

Note reg. item 4: Claim 30 has been held unsearchable because it is a dependent claim and is not drafted in accordance with the second and third sentences of Rule 6.4(a). Claim 30 is, therefore, not included in the above analysis.

Note reg second invention: Applicant has elected the species 4'-difluoromethylcytidine (I-46) as the additional invention to be searched. It is believed that claims 1-2, 19 and 23-29 encompass this elected species. Claim 13 specified by the Applicant is not searched because it is drawn to a non-elected species.