



(51) International Patent Classification:

C07F 9/24 (2006.01) C07F 9/6506 (2006.01)
A61K 31/7072 (2006.01) C07F 9/6518 (2006.01)
A61K 31/716 (2006.01) C07F 9/6521 (2006.01)
C07H 19/10 (2006.01) C07F 9/653 (2006.01)
C07F 9/58 (2006.01) C07F 9/6558 (2006.01)

(21) International Application Number:

PCT/IB2015/055828

(22) International Filing Date:

31 July 2015 (31.07.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2479/MUM/2014 1 August 2014 (01.08.2014) IN

(71) Applicant: LUPIN LIMITED [IN/IN]; 159 CST Road, Kalina, Santacruz (East), State of Maharashtra, Mumbai 400 098 (IN).

(72) Inventors: ROY, Bhairab, Nath; Lupin Limited (Research Park), 46A / 47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). SINGH, Girij, Pal; Lupin Limited (Research Park), 46A / 47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). SHRIVASTAVA, Dhananjai; Lupin Limited (Research Park), 46A / 47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). MEHARE, Kishor, Gulabrao; Lupin Limited (Research Park), 46A / 47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). MALIK, Vineet; Lupin Limited (Research Park), 46A / 47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). DEOKAR, Sharad, Chandrabhan; Lupin Limited (Research Park), 46A / 47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). DANGE, Abhijeet, Avinash; Lupin Limited (Research Park), 46A /

47A, Nande Village, Taluka Mulshi, Maharashtra, Pune 412 115 (IN).

(74) Agents: MAJUMDAR, Subhatosh et al.; S. Majumdar & Co., 5 Harish Mukherjee Road, State of West Bengal, Kolkata 700 025 (IN).

(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).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

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

(54) Title: A PROCESS FOR THE PREPARATION OF NUCLEOSIDE PHOSPHORAMIDATE

(57) Abstract: The present invention pertains to process for preparing nucleoside phosphoramidate and its intermediate. The present invention provides novel intermediate, its process for preparation and its use for the preparation of Sofosbuvir.



WO 2016/016865 A1

A PROCESS FOR THE PREPARATION OF NUCLEOSIDE PHOSPHORAMIDATE

Field of the Invention:

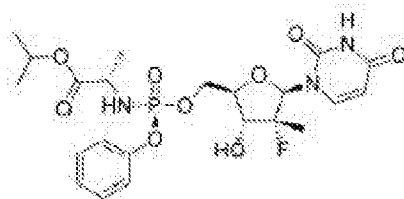
The present invention pertains to process for preparing nucleoside phosphoramidates and their intermediates. Phosphoramidates are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals. One of the recently approved phosphoramidate by USFDA is Sofosbuvir [1190307-88-0]. Sofosbuvir is a component of the first all-oral, interferon-free regimen approved for treating chronic hepatitis C. The present invention provides novel intermediate, its process for preparation and use for the preparation of Sofosbuvir. The present invention also gives one pot process for preparation of Sofosbuvir.

Background of the Invention:

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. There are limited treatment options for individuals infected with hepatitis C virus. The current approved therapeutic option is the use of immunotherapy with recombinant interferon-[alpha] alone or in combination with the nucleoside analog ribavirin.

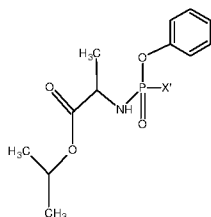
US 7964580 ('580) is directed towards novel nucleoside phosphoramidate prodrug for the treatment of hepatitis C virus infection.

US '580 patent claims Sofosbuvir and process for preparation of Sofosbuvir of Formula 1.

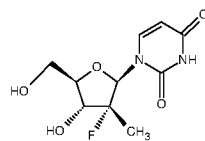


Formula 1

Process for preparation of Sofosbuvir as per US '580 patent involve reaction of compound of Formula 4'' with a nucleoside 5'



Compound 4''

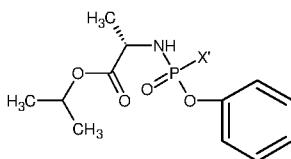


nucleoside 5'

- 5 Wherein X' is a leaving group, such as Cl, Br, I, tosylate, mesylate, trifluoroacetate, trifluoromethanesulfonate, pentafluorophenoxide, p-nitro-phenoxide.

Objects of the invention

The object of the present invention is to provide a novel intermediate of Formula 2



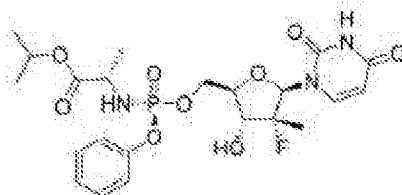
Formula 2

10

- wherein X' is a leaving group selected from 1-hydroxybenzotriazole, 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol, 2-Mercapto-5-methoxybenzimidazole, cyanuric acid, 2-oxazolidinone, 2-Hydroxy Pyridine. The above leaving group can be optionally substituted with n-alkyl, branched alkyl, substituted alkyl; cycloalkyl; halogen; nitro; or aryl, which includes, but not limited to, phenyl or naphthyl, where phenyl or naphthyl are further optionally substituted with at least one of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, F, Cl, Br, I, nitro, cyano, C₁-C₆ haloalkyl, --N(R^{1'})₂, C₁-C₆ acylamino, --NHSO₂C₁-C₆ alkyl, --SO₂N(R^{1'})₂, COR^{1''}, and --SO₂C₁-C₆ alkyl; (R^{1'} is independently hydrogen or alkyl, which includes, but is not limited to, C₁-C₂₀ alkyl, C₁-C₁₀ alkyl, or C₁-C₆ alkyl, R^{1''} is --OR¹ or --N(R^{1'})₂).
- 15
- 20

Another object of the present invention is to provide a process to prepare the intermediate of Formula 2.

Another object of the present invention is use of the intermediate of Formula 2 in the preparation of Sofosbuvir of Formula 1.

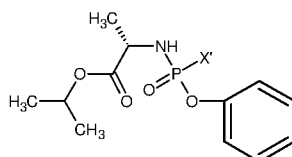


5

Formula 1

Summary of Invention:

One of the embodiments of the present invention is the novel intermediate of Formula 2.



10

Formula 2

wherein X' is a leaving group selected from 1-hydroxybenzotriazole, 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol, 2-Mercapto-5-methoxybenzimidazole, cyanuric acid, 2-oxazolidinone, 2-Hydroxy Pyridine. The above leaving group can be optionally substituted with n-alkyl, branched alkyl, substituted alkyl; cycloalkyl; halogen; nitro; or aryl, which includes, but not limited to, phenyl or naphthyl, where phenyl or naphthyl are further optionally substituted with at least one of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, F, Cl, Br, I, nitro, cyano, C₁-C₆ haloalkyl, --N(R¹)₂, C₁-C₆ acylamino, --NHSO₂C₁-C₆ alkyl, --SO₂N(R¹)₂, COR^{1'}, and --SO₂C₁-C₆ alkyl; (R¹ is independently hydrogen or alkyl,

15

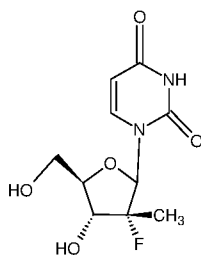
which includes, but is not limited to, C₁-C₂₀ alkyl, C₁-C₁₀ alkyl, or C₁-C₆ alkyl, R^{1a} is -OR¹ or -N(R^{1'})₂.

It is contemplated that compound of the Formula 2 is racemic because of the chirality at phosphorous. The phosphorous atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which has their accepted plain meanings. It is understood that the chirality at phosphorous atom is present unless the substituents bound to the phosphorous exclude the possibility of chirality at phosphorous. Applicants contemplate use of the racemate and/or the resolved enantiomers.

Although the above structure of Formula 2 does not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible. Therefore, the compound of Formula 2 includes all possible stereochemical configurations possible for phosphorus.

In another embodiment of the invention Formula 2 can be prepared by reacting phosphorochloridate with S-oxazolidinone, R-oxazolidinone, benzimidazole, benzotriazole, triazine or 2-hydroxy pyridine or their derivatives.

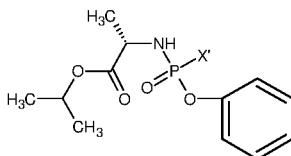
In another embodiment of the present invention is disclosed a novel process for preparation of Sofosbuvir comprising reaction of novel intermediate of Formula 2 with 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydro furan-2-yl) pyrimidine-2,4(1H,3H)-dione (Formula 3).



Formula 3

Detail Description of the Invention:

According to the one embodiment of present invention, there is provided a novel intermediate of Formula 2



Formula 2

wherein X' is a leaving group selected from 1-hydroxybenzotriazole, 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol, 2-Mercapto-5-methoxybenzimidazole, cyanuric acid, 2-oxazolidinone, 2-Hydroxy Pyridine. The above leaving group can be optionally substituted with n-alkyl, branched alkyl, substituted alkyl; cycloalkyl; halogen; nitro; or aryl, which includes, but not limited to, phenyl or naphthyl, where phenyl or naphthyl are further optionally substituted with at least one of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, F, Cl, Br, I, nitro, cyano, C₁-C₆ haloalkyl, --N(R¹)₂, C₁-C₆ acylamino, --NHSO₂C₁-C₆ alkyl, --SO₂N(R¹)₂, COR^{1'}, and --SO₂C₁-C₆ alkyl; (R¹ is independently hydrogen or alkyl, which includes, but is not limited to, C₁-C₂₀ alkyl, C₁-C₁₀ alkyl, or C₁-C₆ alkyl, R^{1'} is --OR¹ or --N(R¹)₂).

It is contemplated that compound of the Formula 2 is racemic because of the chirality at phosphorous. The phosphorous atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which has their accepted plain meanings. It is understood that the chirality at phosphorous atom is present unless the substituents bound to the phosphorous exclude the possibility of chirality at phosphorous. Applicants contemplate use of the racemate and/or the resolved enantiomers.

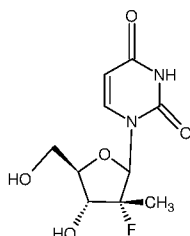
Although the above structure of Formula 2 does not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible.

Therefore, the compound of Formula 2 includes all possible stereochemical configurations possible for phosphorus.

According to yet another embodiment of present invention there is provided a process
Formula 2 by reacting phosphorochloridate with S-oxazolidinone, R-oxazolidinone,
5 benzimidazole, benzotriazole, triazine or 2-hydroxy pyridine or their derivatives such as 1-
hydroxybenzotriazole, 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol, 2-Mercapto-5-
methoxybenzimidazole, cyanuric acid, 2-oxazolidinone, 2-hydroxy-3-nitro-5-
(trifluoromethyl) pyridine, 2-Hydroxy-5-fluoropyridine 2-Hydroxy-5-nitropyridine 2-
Hydroxy-3, 5-dinitropyridine.

10 According to yet another embodiment of present invention there is provided a process for
preparation of Sofosbuvir comprising reaction of novel intermediate of Formula 2 with 1-
((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydro furan-2-yl)
pyrimidine-2,4(1H,3H)-dione (Formula 3).

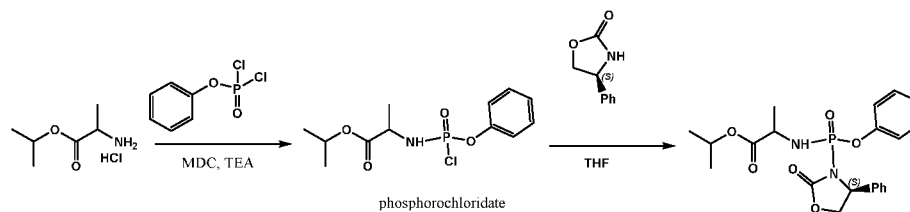
Compound of Formula 3 can be prepared by methods known in the literature



Formula 3

Example 1:

Process for the preparation of S-oxazolidinone derivative of Formula 2



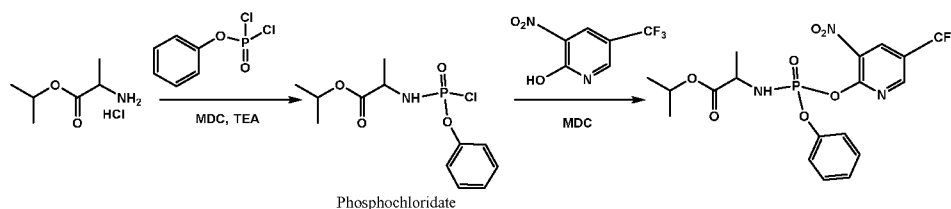
Step-1 Preparation of phosphorochloridate solution:

Dichloromethane (DCM 400ml) was charged in round bottom flask flushed with nitrogen. Phenyl phosphodichloridate (18.30ml) was added in one portion in the flask. The flask was cooled to -60° - -70°C with a dry ice-acetone bath. Solution of L-alanine isopropyl ester hydrochloride (20.6gm) in DCM (50ml) was added to the reaction flask. To this was added a solution of triethylamine (11.20ml) in MDC (100 ml) was added over a course of 60 minutes, while maintaining internal temperature below -70°C throughout the addition. After completion of reaction, temperature of reaction mass was raised to room temperature.

100ml THF was charged in another round bottom flask flushed with nitrogen followed by the addition of S-4-phenyloxazolidinone (10gm). Triethyl-amine (11.2ml) & LiCl (2.85gm) were added to the above flask. The reaction mass was stirred for 15-30 min at room temperature and was cooled to 0 - 5°C . Phosphorochloridate solution from step-1 was added drop-wise to the reaction flask in 15-45 min maintaining reaction temperature at 0 - 5°C . The reaction mass was stirred for 30-60min at 0° - 5°C . The reaction progress was monitored on thin layer chromatography. After completion of the reaction, the reaction temperature was raised to room temperature. Agitation was resumed for an additional 30min. The reaction mass was filtered and concentrated under reduced pressure. To this was added diisopropyl ether (400ml) and aqueous saturated ammonium chloride solution and reaction mass was stirred for 10-15 minutes. Organic layer was separated and was washed with water (100ml) & dried over sodium sulfate and concentrated under vacuum. Cyclohexane (50ml) was charged to the obtained oily mass and reaction mass was stirred till solid precipitated out. Solid was filtered and washed with cyclohexane and dried under vacuum (8.80gm MP 56.5° - 56.6°C). The obtained product was characterized by mass, NMR & IR. ^1H NMR ($\text{DMSO}-d_6$) δ 1.142 -1.18

(m, 9H), 3.85-3.92 (m, 1H), 4.72-4.89(m, 2H), 5.31-5.32(d, 1H), 6.25-6.3 (m, 1H), 6.95-7.31 (m, 10H); MS, m/e 433 (M+1)⁺

Example 2: Process for the preparation of 2-hydroxy pyridine derivatives of formula 2:



5

Anhydrous dichloromethane (DCM) 700ml was charged in round bottom flask flushed with nitrogen. The flask was cooled to -60° to -70°C in a dry ice acetone bath. Phenyl phosphodichloridate (76.04 gm) was added in one portion in the flask at -65°C. Solution of L-alanine isopropyl ester hydrochloride (60.56 gm) in DCM (50 ml) was added to the reaction mass. Solution of triethylamine (72.44gm) in DCM (50ml) was added to the reaction mass over a course of 60 minutes, while maintaining internal temperature below -70°C throughout the addition. The resulting white slurry was agitated for additional 60 minutes. Then the temperature of reaction mass was raised to room temperature. Reaction mass was stirred for 60 min & TLC was checked. Reaction mass was filtered and rinsed with anhydrous dichloromethane (2 X100 mL). The filtrate was concentrate under vacuum to 20 V and reaction mass was filtered, washed with DCM (15ml). The filtrate was transferred to RBF. The reaction mass was cooled to 0°-10°C. A solution of 2-hydroxy-3-nitro-5-(trifluoromethyl) pyridine (15.gm) in DCM (100ml) & triethyl amine (21.89gm) was added to the reaction mass. Temperature of reaction mass was raised to 20-30°C. Reaction mass was stirred overnight. Reaction was monitored using TLC. After completion, the reaction mass was filtered and washed with DCM (30ml). Filtrate was washed with water (150 ml x 2). Organic layer was concentrated under vacuum and degased. Diisopropyl ether (200ml) was charged to reaction mass and reaction mass was stirred for 15 minutes , filtered and washed with methyl ter-butyl ether (MTBE 30ml). Filtrate was concentrated under vacuum

10

15

20

and dried. (8.68gm, MP-125.5°-131.5°C). Obtained compound was characterized by Mass, NMR & IR. ^1H NMR (DMSO- d_6) δ 1.07 -1.27 (m, 9H), 4.04-4.11(m, 1H), 4.73-4.79(m, 1H), 6.76-7.43 (m, 5H), 9.00-9.02 (d, 2H); MS, m/e 478 (M+1) $^+$; FTIR, 1203, 1409, 1580, 1732, 3217.

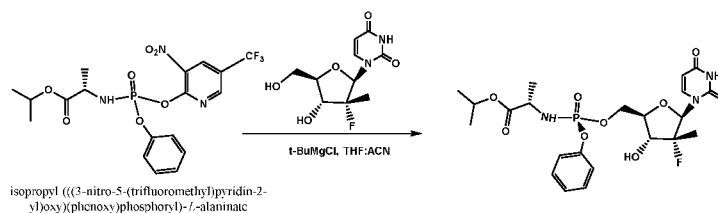
- 5 Other 2-hydroxy pyridine derivatives of Formula 2 were prepared by following the process disclosed in example 2-

2-Hydroxy-5-fluoropyridine derivative of Formula 2;- ^1H NMR (DMSO- d_6) δ 1.09 -1.23 (m, 9H), 3.02-3.06 (m,1H), 3.85-4.01 (m,1H), 4.79-4.87(m, 1H), 6.4-6.52 (m,1H), 7.10-7.89 (m,6H); MS, m/e 383 (M+1) $^+$,

- 10 2-Hydroxy-5-nitropyridine derivative of Formula 2:- ^1H NMR (DMSO- d_6) δ 1.06 -1.22 (m, 9H),4.0-4.02 (m,1H), 4.7-4.8(m,1H), 6.5-6.6 (m,1H),7.12-7.42 (m,6H),8.66-8.68 (d,1H),9.07-9.13(d,1H); MS, m/e 410 (M+1) $^+$

2-Hydroxy-3, 5-dinitropyridine derivative of Formula 2:- ^1H NMR (DMSO- d_6) δ 1.11 -1.24 (m, 9H), 3.04-3.09(m,1H), 4.8-4.86(m,1H), 7.09-7.39 (m,5H),8.97-9.06 (d,2H)

- 15 **Example 3: Process for the preparation of Sofosbuvir by coupling of isopropyl(((3-nitro-5-(trifluoromethyl)pyridin-2-yl)oxy)phenoxy)phosphoryl-L-alaninate with 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione :**



- 20 To a solution of 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (0.2gm) in THF (4 ml), tert-

butylmagnesium chloride (0.80ml, 1.7 M solution in THF) was added dropwise at room temperature and reaction mass was stirred for 30 minutes. A solution of pyridine derivative from example 2 (0.36gm) in THF (4ml) was added dropwise to the reaction mass at room temperature. Completion of reaction was monitored using TLC. After completion of reaction, reaction mass was quenched by using saturated ammonium chloride solution (10ml). Reaction mass was extracted with ethyl acetate (50ml). Organic layer was separated, dried over magnesium sulfate and concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel & obtained solid product was characterized. MS, m/e 530.2 (M+1)⁺.

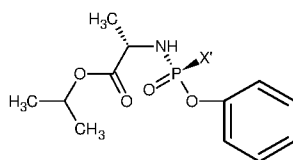
10

15

20

CLAIMS

1. A compound of Formula 2

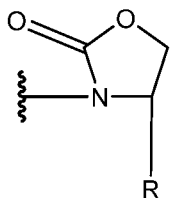


5

Formula 2

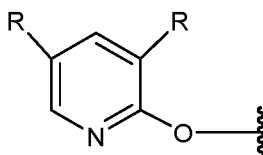
wherein X' is selected from the group consisting of:

a)



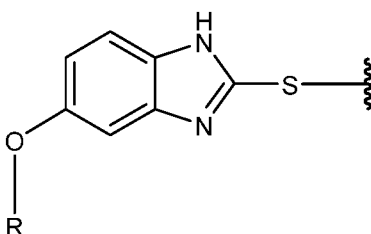
10 wherein R is substituted or un-substituted n-alkyl, branched alkyl, cycloalkyl; halogen; nitro; or aryl, wherein said aryl is optionally substituted with at least one of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, F, Cl, Br, I, nitro, cyano, C₁-C₆ haloalkyl, --N(R^{1'})₂, C₁-C₆ acylamino, --NH-SO₂-C₁-C₆ alkyl, --SO₂-N(R^{1'})₂, COR^{1''}, and --SO₂-C₁-C₆ alkyl; wherein R^{1'} is independently hydrogen or C₁-C₁₀ alkyl; and R^{1''} is --OR^{1'} or --N(R^{1'})₂;

15 b)



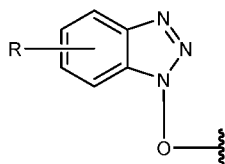
wherein R is substituted or un-substituted n-alkyl, branched alkyl, cycloalkyl; halogen; nitro or aryl, wherein said aryl is optionally substituted with at least one of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, F, Cl, Br, I, nitro, cyano, C₁-C₆ haloalkyl, --N(R^{1'})₂, C₁-C₆ acylamino, --NHSO₂C₁-C₆ alkyl, --SO₂N(R^{1'})₂, COR^{1''}, and --SO₂C₁-C₆ alkyl; wherein
 5 R^{1'} is independently hydrogen or C₁-C₂₀ alkyl; and R^{1''} is --OR^{1'} or --N(R^{1'})₂;

c)



wherein R is H, NO₂, Cl, CHF₂, or CF₃;

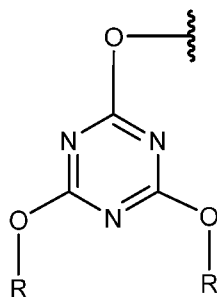
10 d)



wherein R is H, NO₂, Cl, or CF₃;

and

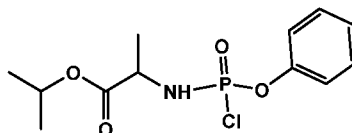
e)



wherein R is hydrogen, substituted or un-substituted alkyl, or alkylaryl.

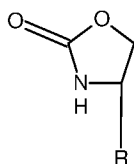
2. The compound according to claim 1, wherein said aryl is an optionally substituted phenyl
5 or naphthyl.

3. A process for preparing the compound of Formula 2 as claimed in claim 1 comprising
reacting a phosphorochloridate of following Formula



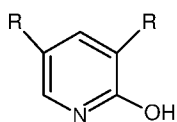
with

10 a)



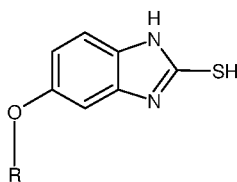
Wherein R is as defined in claim 1;

b)



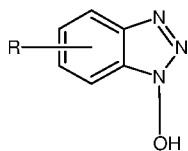
wherein R is as defined in claim 1;

c)



5 wherein R is as defined in claim 1;

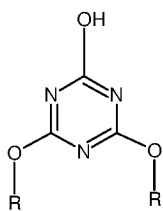
d)



wherein R is as defined in claim 1; or

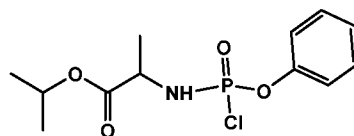
10

e)



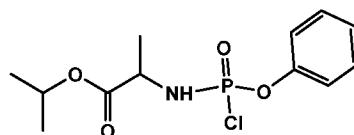
wherein R is as defined in claim 1.

4. The process of claim 3 wherein the phosphorochloridate of the Formula



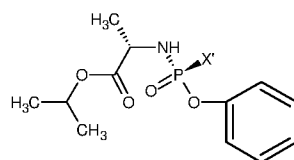
is reacted with 1-hydroxybenzotriazole or 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol,
 5 2-Mercapto-5-methoxybenzimidazole; cyanuric acid; 2-oxazolidinone; 2-Hydroxy Pyridine;
 or a derivative thereof.

5. The process of claim 4 wherein the phosphorochloridate of the Formula



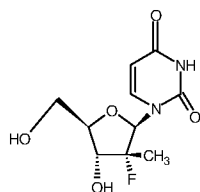
is reacted with S-4-phenyloxazolidine; 2-hydroxy-3-nitro-5-(trifluoromethyl)pyridine; 2-
 10 Hydroxy-5-fluoropyridine; 2-Hydroxy-5-nitropyridine; or 2-Hydroxy-3, 5-dinitropyridine.

6. A process for the preparation of Sofosbuvir comprising reacting a compound of Formula 2



Formula 2

with a compound of Formula 3



Formula 3

7. Use of compound of Formula 2 for the preparation of Sofosbuvir.

5

10

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055828

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07F9/24 A61K31/7072 A61K31/716 C07H19/10 C07F9/58
C07F9/6506 C07F9/6518 C07F9/6521 C07F9/653 C07F9/6558

ADD.

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)

C07F A61K C07H

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)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/251152 A1 (ROSS BRUCE S [US] ET AL) 13 October 2011 (2011-10-13) paragraph [0273] page 23; paragraph [305] page 29 -----	1-7

☐ 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

9 October 2015

Date of mailing of the international search report

20/10/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bourghida, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/055828

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011251152 A1	13-10-2011	US 2011251152 A1	13-10-2011
		US 2013288997 A1	31-10-2013
		US 2013310551 A1	21-11-2013
