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(71) Applicant: **GRANULES INDIA LIMITED** [IN/IN]; 2nd Floor; 3rd Block; My Home Hub, Madhapur, Hyderabad 500081 (IN).

(72) Inventors; and
(71) Applicants *(for US only)*: **VETUKURI, Prasada Raju Vnkv** [IN/IN]; 2nd Floor; 3rd Block; My Home Hub, Madhapur, Hyderabad 500081 (IN). **GILLA, Goverdhan** [IN/IN]; 2nd Floor; 3rd Block; My Home Hub, Madhapur, Hyderabad 500081 (IN). **RAPOLU, Rajesh Kumar** [IN/IN]; 2nd Floor; 3rd Block; My Home Hub, Madhapur, Hyderabad 500081 (IN). **CHIGURUPATI, Krishna Prasad** [IN/IN]; 2nd Floor; 3rd Block; My Home Hub, Madhapur; Hyderabad, Hyderabad 500081 (IN).

(74) Agent: **SURAPUREDDY, Padmaja**; iProPAT Intellectual Property Solutions, 2nd Floor, Above Apollo Clinic, Suresh Square, Plot No 1-58/91/SS, Survey No 228 & 229/1, Madinaguda, Miyapur Hyderabad 500 049 (IN).

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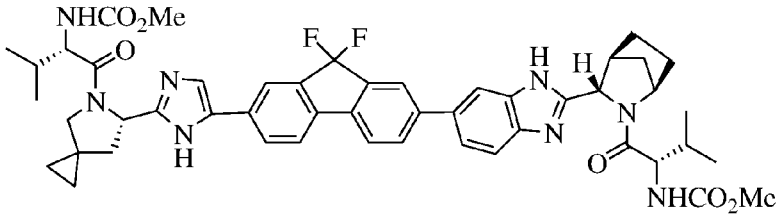
(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF HCV INHIBITOR



Formula I

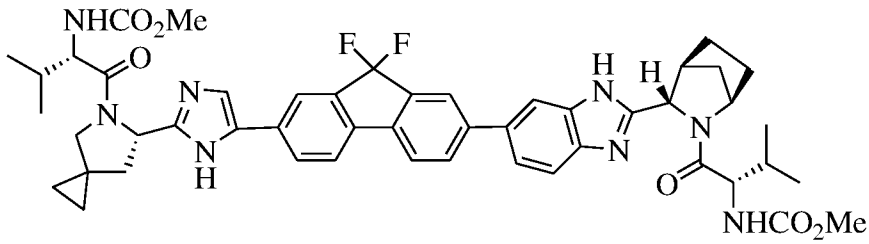
(57) Abstract: The present invention provides a novel process for the preparation of Ledipasvir of Formula (I) and its pharmaceutically acceptable salts.

WO 2016/103232 A1

AN IMPROVED PROCESS FOR THE PREPARATION OF HCV INHIBITOR

FIELD OF INVENTION

The present invention provides a novel process for the preparation of Ledipasvir of Formula I and its pharmaceutically acceptable salts.



Formula I

BACKGROUND OF THE INVENTION

Ledipasvir is an inhibitor of the hepatitis C virus NS5A protein. Ledipasvir (formerly GS-5885) is a drug for the treatment of hepatitis C that was developed by Gilead Sciences. Ledipasvir/Sofosbuvir fixed-dose combination tablet for genotype 1 hepatitis C was approved recently by the USFDA with Harvoni Brand name. The ledipasvir/Sofosbuvir combination is a direct-acting antiviral agent that interferes with HCV replication and can be used to treat patients with genotypes 1a or 1b without PEG-interferon or ribavirin.

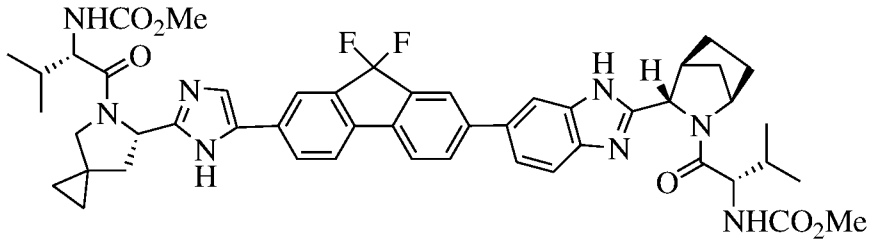
Harvoni is the first combination pill approved to treat chronic HCV genotype 1 infection. It is also the first approved regimen that does not require administration with interferon or ribavirin. Both drugs in Harvoni interfere with the enzymes needed by HCV to multiply. Sofosbuvir is a previously approved HCV drug marketed under the brand name Sovaldi.

Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with HCV have no symptoms of the disease until liver damage becomes apparent, which may take decades. Some people with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections and liver cancer.

Ledipasvir inhibits an important viral phosphoprotein, NS5A, which is involved in viral replication, assembly, and secretion. Sofosbuvir, on the other hand, is metabolized to the

active uridine analog triphosphate, which acts as a RNA chain terminator when incorporated into the RNA via the NS5B polymerase.

Ledipasvir chemically known as (l-{3-[6-(9,9-difuoro-7-{2-[5-(2-methoxycarbonylamino-3-methyl-butyryl)-5-aza-spiro[2.4]hept-6-yl]-3H-imidazol-4-yl}-9H-fluoren-2-yl)-lH-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester, is known to be an effective anti-HCV agent, as described in WO 2010/132601.



Formula I

Though few synthetic methods have been reported in WO 2010/132601, it is desirable to discover new synthetic routes to Ledipasvir that can be executed on a large commercial scale resulting in industrially feasible process.

Also the synthesis of Ledipasvir reported in the literature involves costly, expensive, hazardous reagents which are difficult to handle at commercial scale. This problem needs to be addressed so that large scale manufacturing of Ledipasvir becomes commercially and economically viable.

There are number of cost-limiting raw materials and intermediates involved in the known methods of Ledipasvir synthesis which needs to be optimized in order to make Ledipasvir economically viable.

OBJECTIVE OF THE INVENTION

The first embodiment of the present invention is to provide a novel process for the preparation of Ledipasvir of Formula I.

The second embodiment of the present invention is to provide an improved process for the preparation of various Salts, Solvates, Hydrates of Ledipasvir of Formula I.

The third embodiment of the present invention is to provide an improved process for the preparation of novel intermediates for the preparation of Ledipasvir of Formula I.

The fourth embodiment of the present invention is to provide an improved process for the preparation of Acid addition salts of intermediates of Ledipasvir of Formula I.

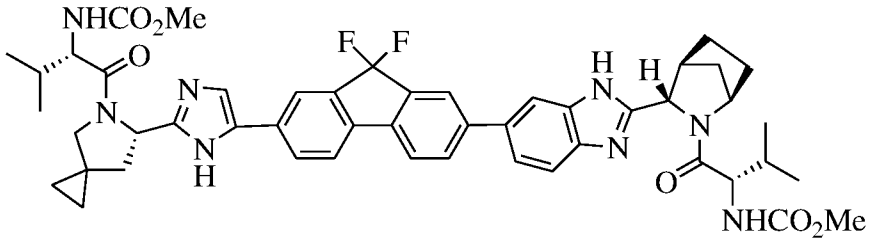
The fifth embodiment of the present invention is to provide an improved process for the purification of intermediates of Ledipasvir of Formula I.

The sixth embodiment of the present invention is to provide an improved process for the preparation of Novel Acid addition salts of Ledipasvir of Formula I.

The seventh embodiment of the present invention is to provide a one pot process without isolation of the intermediates for the preparation of Ledipasvir of Formula I.

SUMMARY OF THE INVENTION

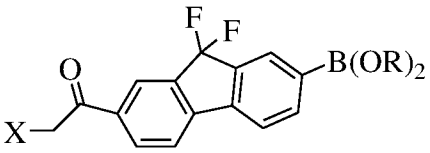
Accordingly, the present invention provides a process for the preparation of a Ledipasvir of Formula I or a pharmaceutically acceptable salt or solvate thereof



Formula I

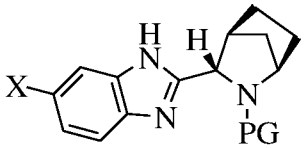
which comprises :

(i) reacting the compound of Formula VIa or its salts



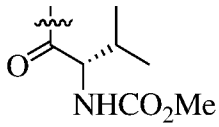
Formula VIa

wherein X is halo or leaving group, R is C_{1-6} alkyl, aryl or R groups combined together to form cycloalkyl group, with the compound of Formula V or its salts

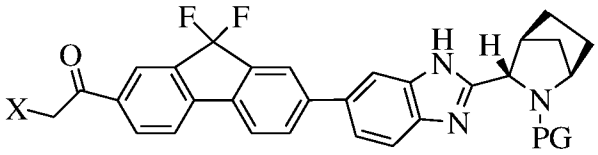


Formula V

wherein X is as defined above, PG represents a protecting group or the group of Formula

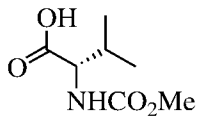


to give a compound of Formula VII,



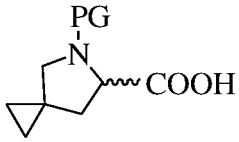
Formula VII

(ii) optional deprotecting the compound of Formula VII when PG represents a protecting group followed by reaction with compound of Formula



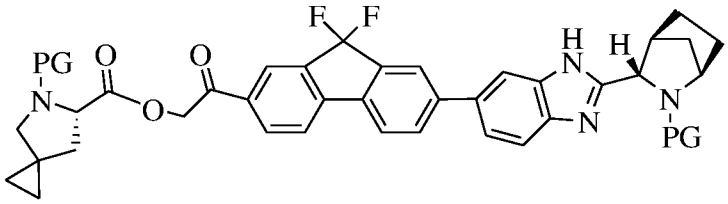
or its reactive derivative,

(iii) coupling the compound of Formula VII with compound of Formula VIh or its salts



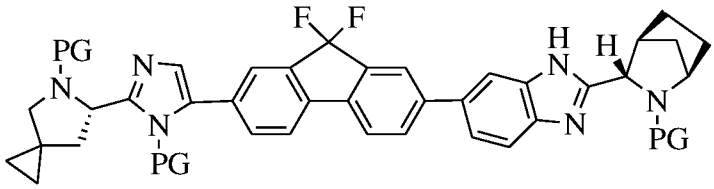
Formula VIh

to give compound of Formula IX,



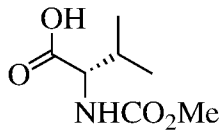
Formula IX

(iv) converting compound of formula IX to compound of formula IXi, and



Formula IXi

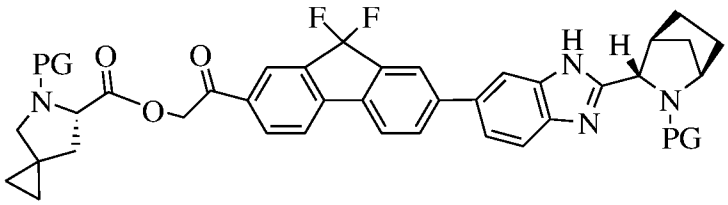
(v) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

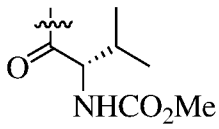
In one aspect, the present invention provides an improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) cyclizing compound of Formula IX

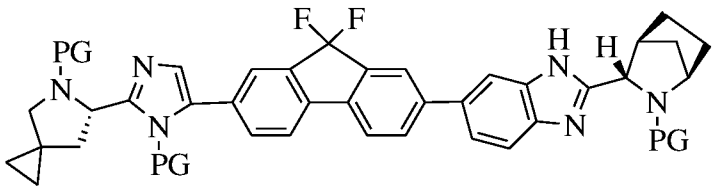


Formula IX

wherein PG represents protecting group or the group of Formula

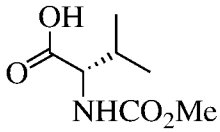


in the presence of a cyclizing agent and a solvent to give compound of formula IXi, and



Formula IXi

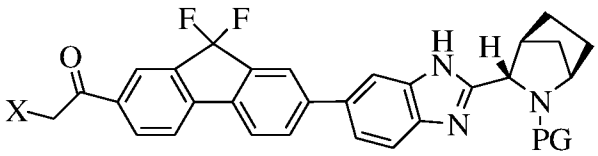
(ii) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

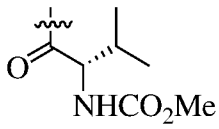
In another aspect, the present invention provides an improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VII

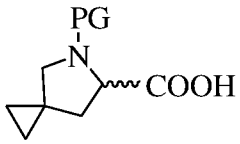


Formula VII

wherein X is halo or leaving group, PG represents N-protecting group or the group of Formula

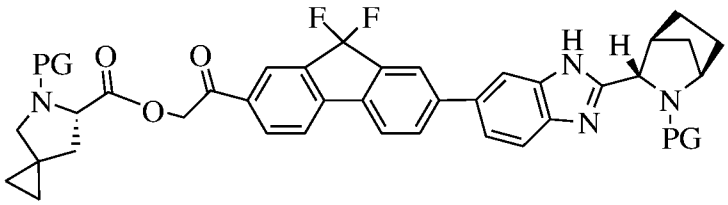


with compound of Formula VIh or its salts



Formula VIh

to give compound of Formula IX,

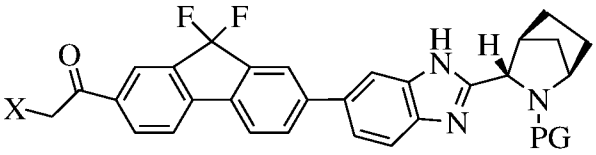


Formula IX

(ii) converting compound of formula IX to Ledipasvir of Formula I.

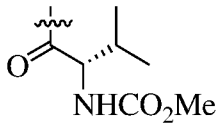
In another aspect, the present invention provides an improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VII

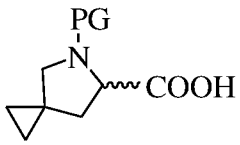


Formula VII

wherein X is halo or leaving group, PG represents N-protecting group or the group of Formula

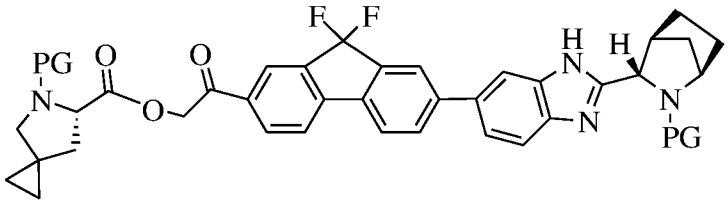


with compound of Formula VIh or its salts



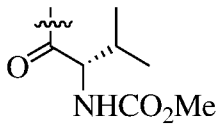
Formula VIh

to give compound of Formula IX,

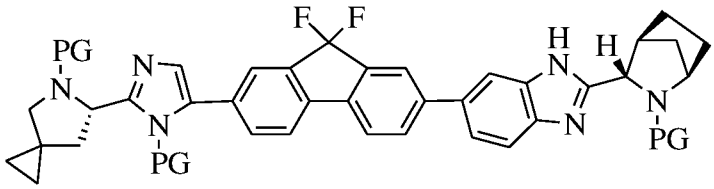


Formula IX

wherein PG represents N-protecting group or the group of Formula



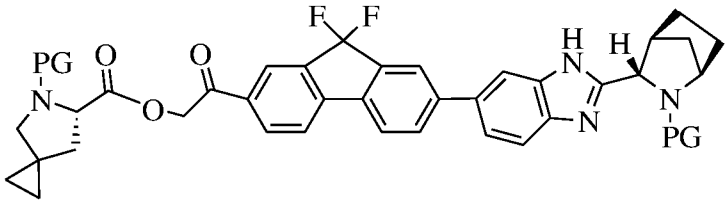
(ii) cyclizing compound of Formula IX in the presence of a cyclizing agent and a solvent to give compound of formula IXi, and



Formula IXi

(iii) converting compound of formula IXi to Ledipasvir of Formula I.

In another aspect, the present invention provides compound of formula IX or its salts, an intermediate of Ledipasvir.

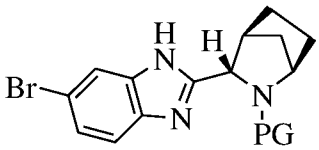


Formula IX

wherein PG represents protecting group

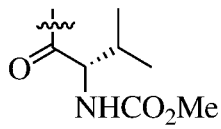
In another aspect, the present invention provides an improved process for the preparation of Ledipasvir of Formula I or a pharmaceutically acceptable salt or solvate thereof which comprises :

(i) coupling the compound of Formula V

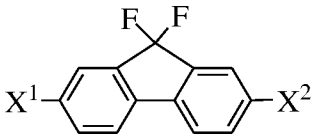


Formula V

wherein PG is conventional protecting group, which can be deprotected using appropriate reagents, or a group of Formula

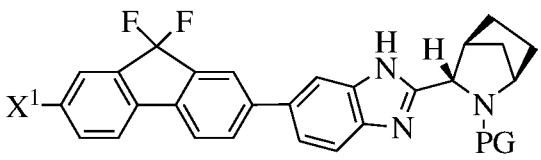


with compound of Formula VI



Formula VI

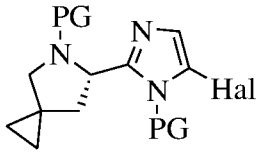
wherein X^1 represents halogen or a leaving group, and X^2 represents halogen or boronate esters by employing metal catalyst in an solvent to give compound of Formula VIIi



Formula VIIi

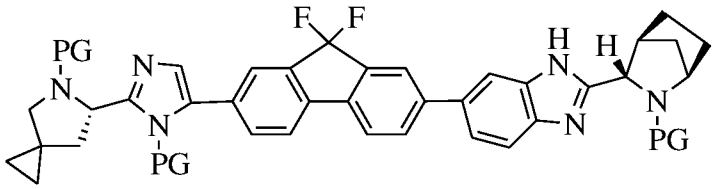
wherein PG, X^1 is as defined above,

(ii) condensation of compound of Formula VIIi with compound of Formula VIII



Formula VIII

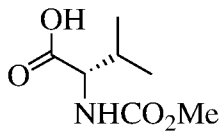
wherein PG is as defined above and Hal means halogen in a solvent to give compound of Formula IXi



Formula IXi

wherein PG is as defined above, and

(iii) deprotecting the compound of Formula IXi when PG represents a conventional protecting group followed by peptide coupling with 2-methoxycarbonylamino-3-methylbutyric acid of the Formula

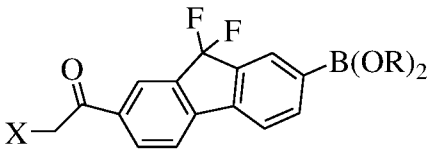


or its reactive derivative to give Ledipasvir of Formula I.

In yet another aspect, the present invention provides an alternative process for the preparation of the Ledipasvir of the Formula I

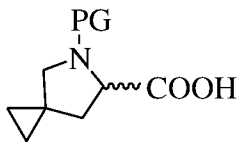
which comprises :

(i) reacting the compound of Formula VIa



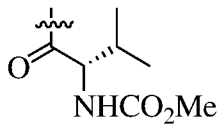
Formula VIa

with the compound of Formula VIh

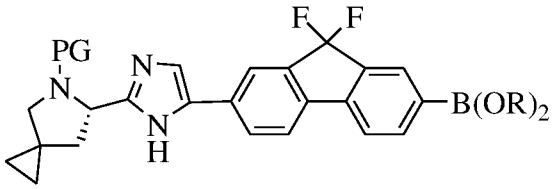


Formula VIh

or its salts wherein PG represents a Protecting group or the group of Formula

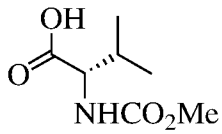


to give a compound of Formula VIi,



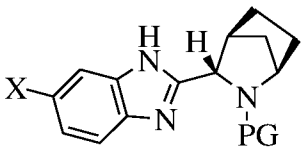
Formula VIi

(ii) optional deprotecting the compound of Formula VIi when PG represents a protecting group followed by reaction with compound of Formula



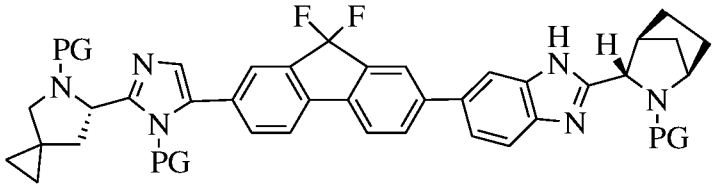
or its reactive derivative,

(iii) coupling the compound of Formula VIi with compound of Formula V



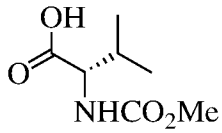
Formula V

wherein X is halo or leaving group, to give compound of Formula IXi, and



Formula IXi

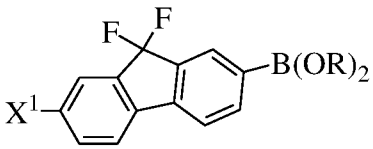
(iv) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

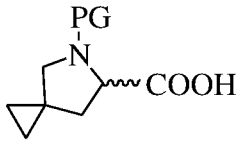
In yet another aspect, the present invention provides an improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VIb



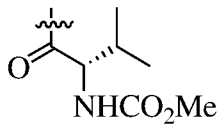
Formula VIb

wherein X^1 is halo or leaving group, with the compound of Formula VIh or its salts

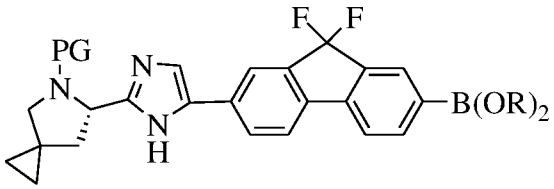


Formula VIh

wherein PG represents a protecting group or the group of Formula

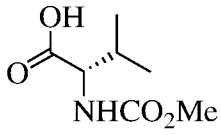


to give a compound of Formula VIi,



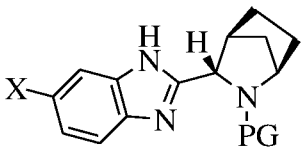
Formula VIi

(ii) optional deprotecting the compound of Formula VIi when PG represents a protecting group followed by reaction with compound of Formula



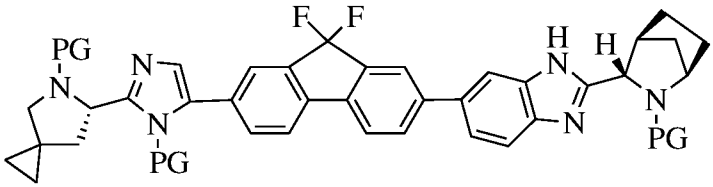
or its reactive derivative,

(iii) coupling the compound of Formula VIi with compound of Formula V



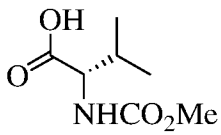
Formula V

wherein X is halo or leaving group, to give compound of Formula IXi, and



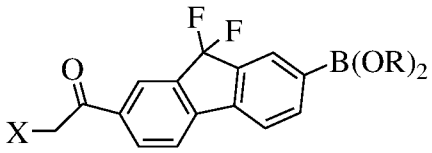
Formula IXi

(iv) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



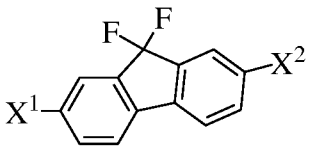
or its reactive derivative to give Ledipasvir of Formula I.

In another aspect, the present invention also provides a process for the preparation of compound of Formula VIa

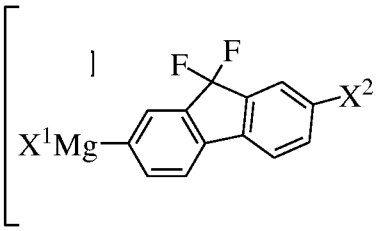

Formula VIa

wherein X represents halogen or a leaving group; R represent hydrogen, an alkyl group, cycloalkyl group or other conventional boronate groups which comprises :

i) converting the compound of Formula VI

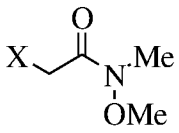

Formula VI

wherein X^1 and X^2 are halogens to give the compound of Formula VIc

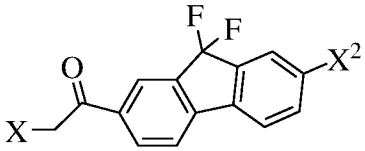

Formula VIc

wherein X^1 and X^2 are as defined above

ii) coupling the compound of Formula VIc with compound of Formula VId

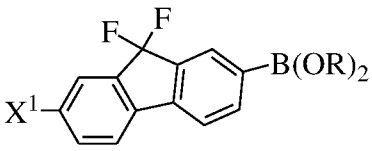

Formula VId

wherein X is halo or leaving group, to give compound of Formula VIe, and


Formula VIe

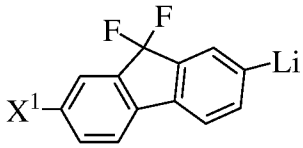
iii) converting the obtained compound of Formula VIe to compound of Formula VIa by reacting with boric acid or its derivatives such as trialkyl borates.

In yet another aspect, the present invention provides a process for the preparation of the compound of Formula VIb


Formula VIb

which comprises :

i) reacting the compound of Formula VI when X^2 represents halogen with organolithium reagents to give compound of Formula VIg having the following structure



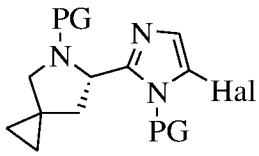
Formula VIg

wherein X1 is as defined above, and

(ii) finally converting the compound of Formula VIg to compound of Formula VIb by reacting with boric acid or its derivatives such as trialkyl borates.

In yet another aspect, the compound of Formula VIb can also obtained by reacting the compound of Formula VI when X^2 represents halogen with boric acid or its derivatives such as trialkyl borates using a metal catalyst.

In yet another aspect, the present invention provides a process for the preparation of compound of Formula VIII



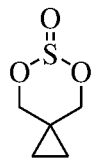
Formula VIII

which comprises :

i) converting the compound of Formula C1 having the following structure

Formula C1

to compound of Formula C2 employing thionyl chloride in the presence of base to give compound of Formula C2



Formula C2

ii) halogenating the compound of Formula C2 to give compound of Formula C3

Formula C3

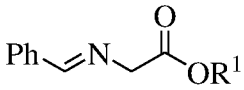
wherein X^4 represents halogen

iii) converting the compound of Formula C3 to give compound of Formula C4

Formula C4

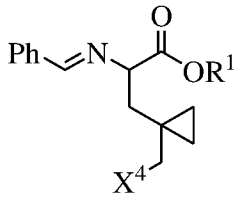
wherein L is a leaving group and X^4 is as defined above,

iv) coupling the compound of Formula C4 with compound of Formula C5



Formula C5

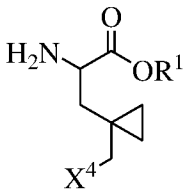
wherein R^1 represents hydrogen, alkyl or a chiral auxiliary, in the presence of a base to give compound of Formula C6



Formula C6

wherein R^1 and X^4 are as defined above

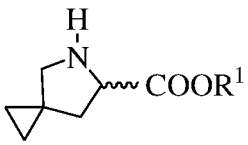
v) converting the compound of Formula C6 to compound of Formula C7 under mild acidic conditions



Formula C7

wherein R^1 and X^4 are as defined above

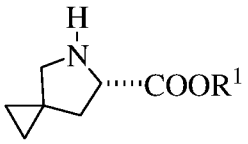
vi) the obtained compound of Formula C7 is cyclized to compound of Formula C8



Formula C8

wherein R^1 is as defined above,

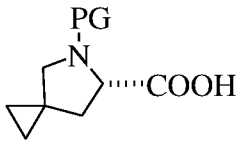
vii) optionally resolving the compound of Formula C8 when it is racemic and isolating the compound of Formula C8 as an acid addition salt of Formula C9



Formula C9

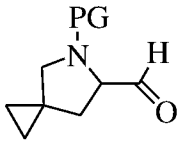
wherein R^1 represents hydrogen or alkyl group,

viii) protecting the compound of Formula C9 with a suitable protecting group to give compound of Formula C15 or its salts



Formula C15

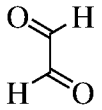
ix) converting the obtained protected compound of Formula C15 to compound of Formula C10



Formula C10

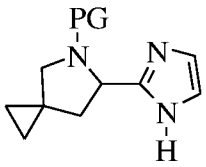
wherein PG represents protecting group

x) coupling the compound of Formula C10 with compound of Formula C11



Formula C11

to give compound of Formula C12

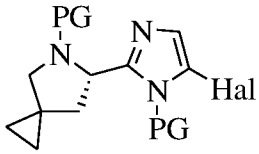


Formula C12

wherein PG represents protecting group, and

xi) converting the compound of Formula C12 to compound of Formula VIII.

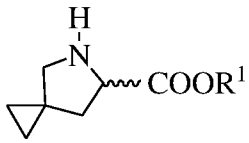
In yet another aspect, the present inventions relates to an improved process for the preparation of compound of Formula VIII.



Formula VIII

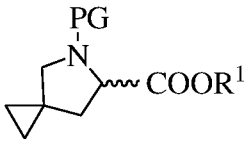
which comprises :

i) protecting the compound of Formula C8



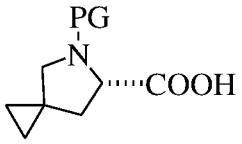
Formula C8

wherein R^1 is as defined above, to give compound of Formula C14



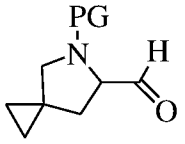
Formula C14

ii) optionally resolving the compound of Formula C14 when it is racemic and isolating the compound of Formula C15 or its salts



Formula C15

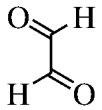
iii) converting the obtained protected compound of Formula C14 or Formula C15 to compound of Formula C10



Formula C10

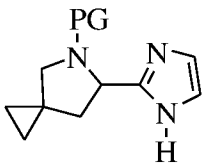
wherein PG represents protecting group

iv) coupling the compound of Formula C10 with compound of Formula C11



Formula C11

to give compound of Formula C12



Formula C12

wherein PG represents protecting group, and

v) transforming the compound of Formula C12 to compound of Formula VIII.

In an another aspect, the present inventions provides a process for the resolution of compound of Formula C8 and Formula C14 which involves kinetic resolution or enzymatic hydrolysis of ester and hydrolysis of ester followed by resolution with chiral amine reagents.

DETAILED DESCRIPTION OF THE INVENTION

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

Examples of suitable leaving groups X, X^1, X^2, X^3 and L that can be applied in the process according to the invention are halogens, in particular Cl, Br, F or I; alkyl boronate esters, cycloalkyl boronate esters, mesyloxy, acyloxy, tosyloxy, benzyloxy, trifluoromethylsulfonyloxy, nonafluorobutylsulfonyloxy, (4-bromo-phenyl)sulfonyloxy, (4-nitro-phenyl)sulfonyloxy, (2-nitro-phenyl)sulfonyloxy, (4-isopropyl-phenyl)sulfonyloxy, (2,4,6-tri-isopropyl-phenyl)sulfonyloxy, (2,4,6-trimethyl-phenyl)sulfonyloxy, (4-rertbutyl-

phenyl)sulfonyloxy, and (4-methoxy-phenyl)sulfonyloxyp. For practical reasons Cl is preferably chosen as leaving group.

The protecting group is selected from Carbobenzyloxy (Cbz), tert-Butyloxycarbonyl (BOC), p-Methoxybenzyl carbonyl (Moz or MeOZ), 9-Fluorenylmethyloxycarbonyl (FMOC), Acetyl (Ac), Benzoyl (Bz), Benzyl (Bn), benzyl Carbamate, p-Methoxybenzyl (PMB), 3,4-Dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), Tosyl (Ts), sulfonamides.

The compound of Formula VIa is coupled with compound of V employing metal catalyst in a solvent in the presence of a base yielding compound of Formula VII. This compound of Formula VII is condensed with compound of Formula VIh or its salts in the presence of solvent to give compound of Formula IX. The compound of formula IX is cyclized in the presence of suitable reagent in a solvent to give compound of formula IXi. The protecting groups on compound of Formula IXi are removed followed by peptide coupling with 2-methoxycarbonylamino-3-methyl-butyric acid in the presence of condensing agent to yield Ledipasvir in good yield.

Alternatively, the protecting groups of compound of Formula IXi are removed after the coupling with 2-methoxycarbonylamino-3-methyl butyric acid.

The compound of Formula V is coupled with compound of VI employing metal catalyst in a solvent yielding compound of Formula VIIi. This compound of Formula VIIi is condensed with compound of Formula VIII to give compound of Formula IXi. The protecting groups on compound of Formula IXi are removed followed by peptide coupling with 2-methoxycarbonylamino-3-methyl-butyric acid to yield Ledipasvir in good yield.

Alternatively, the protecting groups of compound of Formula IXi are removed after the coupling with 2-methoxycarbonylamino-3-methyl butyric acid.

Accordingly the present invention provides a novel process for the preparation of Ledipasvir or its pharmaceutically acceptable salts. The compounds of formulae (C1-C15), (IV), (V), (VI), (VIa), (VIc), (VId), (VIe), (VIh), (VIi), (VIg), (VII), (VIIi), (VIII), (IX) and (IXi) or their salts used in the present invention may be isolated or not. Any of the above reactions may be carried out in-situ reactions to obtain Ledipasvir or its salts. The above compounds may isolated as salts or free bases, if the above compounds are isolated as salts they are converted to their free bases first and used for further reactions. Further, the above compound may isolated as crystalline Forms or isolated as an amorphous form or optionally recrystallized and used for further reactions.

“Solvent” as defined in the presence invention is selected from water or "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the

like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, dimethylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 2-methoxyethanol and dimethoxyethane, or "Amide solvents" such as formamide, DMF, DMAC, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, 1-ethenyl-2-pyrrolidone and/or mixtures thereof.

"Base" as defined in the presence invention is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof.

"Condensing agent" as defined in the presence invention is selected from HOBt, HBTU, TBTU, HOAt, DCC, EDC-HCl, CDI, BOP, T_3P and PyBOP or and/or mixtures thereof.

"Metal catalyst" as defined in the presence invention is selected from Palladium (0) or (II) complexes, selected from tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, palladium dppf chloride, Bis(triphenylphosphine)palladium(II) acetate, Bis(triethylphosphine)palladium(II) chloride.

"Cyclization" as defined in the presence invention is carried out in the presence of ammonium acetate in a solvent.

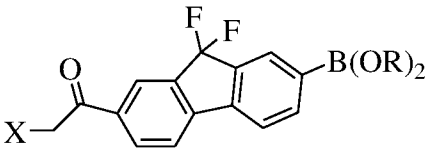
"Deprotection" as defined in the presence invention is carried out in the presence of metal catalyst, hydrogen source, wherein the metal catalyst is selected from Pd, Ni, Pt, Rh or the deprotection may carried out in the presence of an acid which is selected from strong acids such as HCl or CF_3COOH or the deprotection may carried out in the presence of a base, which is selected from primary or secondary amines.

"Boronate ester or its derivative" as defined in the presence invention is prepared using Boronate reagent which is selected from pinacolboronates, alkyl boronates and aryl boronates.

"Acid or acidic condition" as defined in the presence invention is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid.

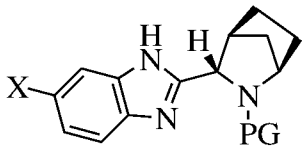
In a preferred embodiment, the present invention provides a process for the preparation of Ledipasvir of Formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting the compound of Formula VIa or its salts



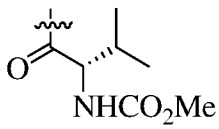
Formula VIa

wherein X is halo or leaving group, R is C_{1-6} alkyl, aryl or R groups combined together to form cycloalkyl group, with the compound of Formula V or its salts

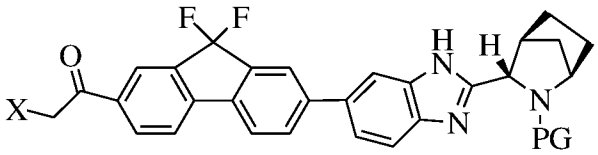


Formula V

wherein X is halo or leaving group, wherein PG represents a protecting group or the group of Formula

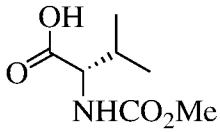


using a metal catalyst and a base in the presence of a solvent, to give a compound of Formula VII,



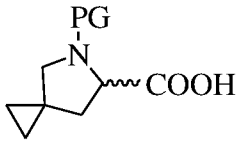
Formula VII

(ii) optional deprotecting the compound of Formula VII when PG represents a protecting group in an acid reagent in a solvent followed by reaction with compound of Formula



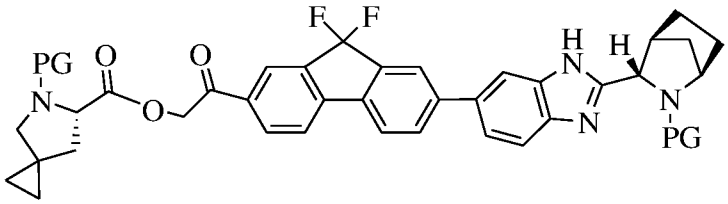
or its reactive derivative,

(iii) coupling the compound of Formula VII with compound of Formula VIh or its salts



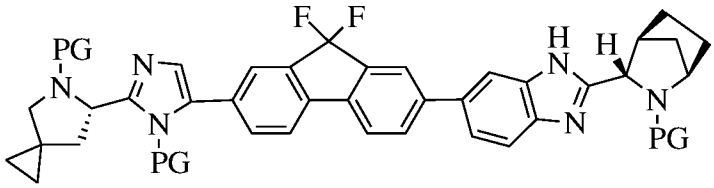
Formula VIh

in the presence of a solvent and optionally using a catalyst to give compound of Formula IX,



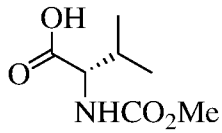
Formula IX

(iv) cyclizing compound of formula IX using a cyclizing agent in a solvent to give compound of formula IXi, and



Formula IXi

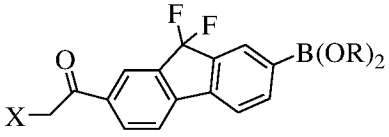
(v) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative in the presence of a condensing agent and a solvent to give Ledipasvir of Formula I.

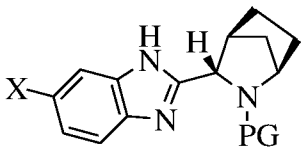
In a more preferred embodiment, the present invention provides a process for the preparation of a Ledipasvir of Formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting the compound of Formula VIa or its salts



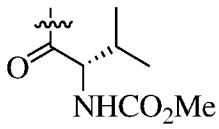
Formula VIa

wherein X is Cl, R is a cycloalkyl group, with the compound of Formula V or its salts

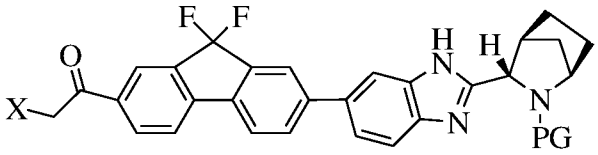


Formula V

wherein PG represents a protecting group or the group of Formula

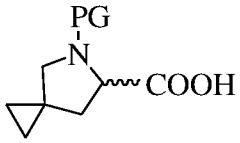


using palladium dppf chloride, palladium tetrakis triphenylphosphine and potassium carbonate in dimethyl ether and water to give a compound of Formula VII,



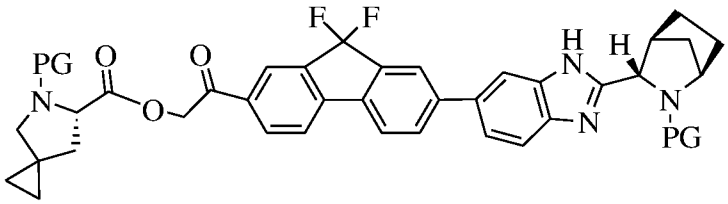
Formula VII

(ii) coupling the compound of Formula VII with compound of Formula VIh or its salts



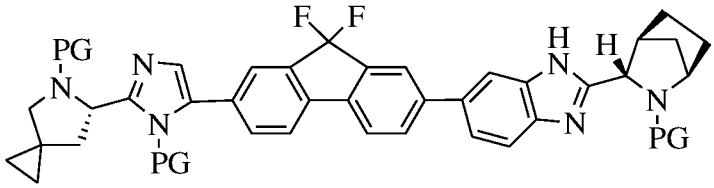
Formula VIh

in acetone to give compound of Formula IX,



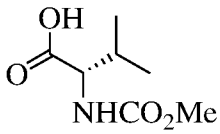
Formula IX

(iii) cyclizing compound of formula IX using ammonium acetate, in the presence of toluene and catalytic amount of 2-methoxy ethanol to give compound of formula IXi, and



Formula IXi

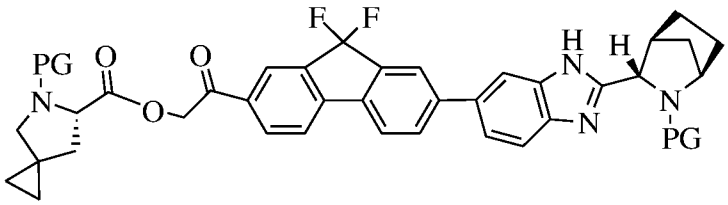
(iv) deprotecting the compound of Formula IXi when PG represents a protecting group using HCl in acetonitrile followed by reaction with compound of Formula



or its reactive derivative in the presence of dimethyl formamide, EDC.HCl, HOBt.H_2O and N-methyl morpholine to give Ledipasvir of Formula I.

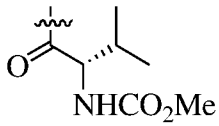
In a preferred embodiment, the present invention provides an improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) cyclizing compound of Formula IX

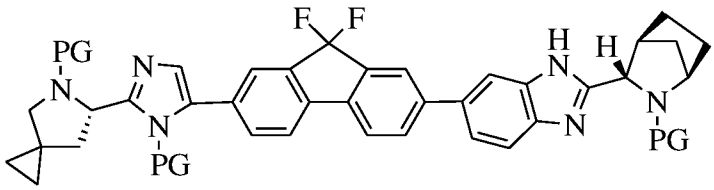


Formula IX

wherein PG represents protecting group or the group of Formula

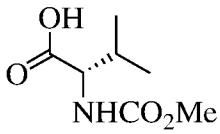


using ammonium acetate, in the presence of toluene and catalytic amount of 2-methoxy ethanol to give compound of formula IXi, and



Formula IXi

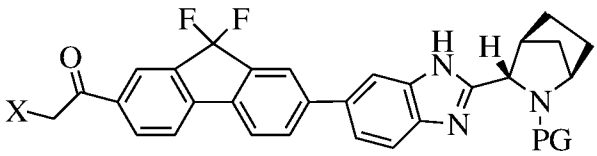
(ii) deprotecting the compound of Formula IXi when PG represents a protecting group using HCl in acetonitrile followed by reaction with compound of Formula



or its reactive derivative in the presence of dimethyl formamide, EDC.HCl, HOBt.H_2O and N-methyl morpholine to give Ledipasvir of Formula I.

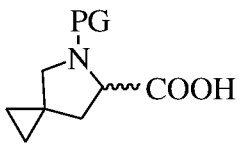
In a preferred embodiment, the present invention provides an improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VII



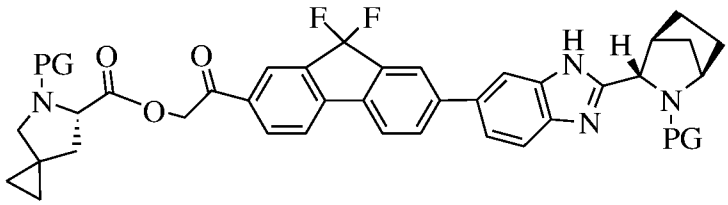
Formula VII

with compound of Formula VIh or its salts



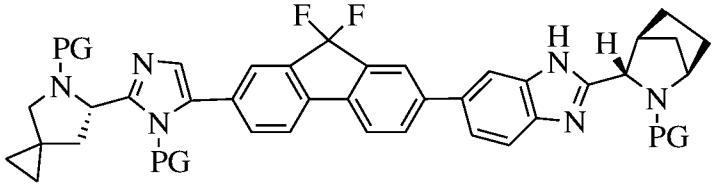
Formula VIh

in acetone to give compound of Formula IX,



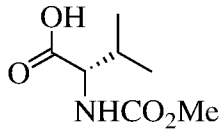
Formula IX

(ii) cyclizing compound of formula IX using ammonium acetate, in the presence of toluene and catalytic amount of 2-methoxy ethanol to give compound of formula IXi, and



Formula IXi

(iii) deprotecting the compound of Formula IXi when PG represents a protecting group using HCl in acetonitrile followed by reaction with compound of Formula



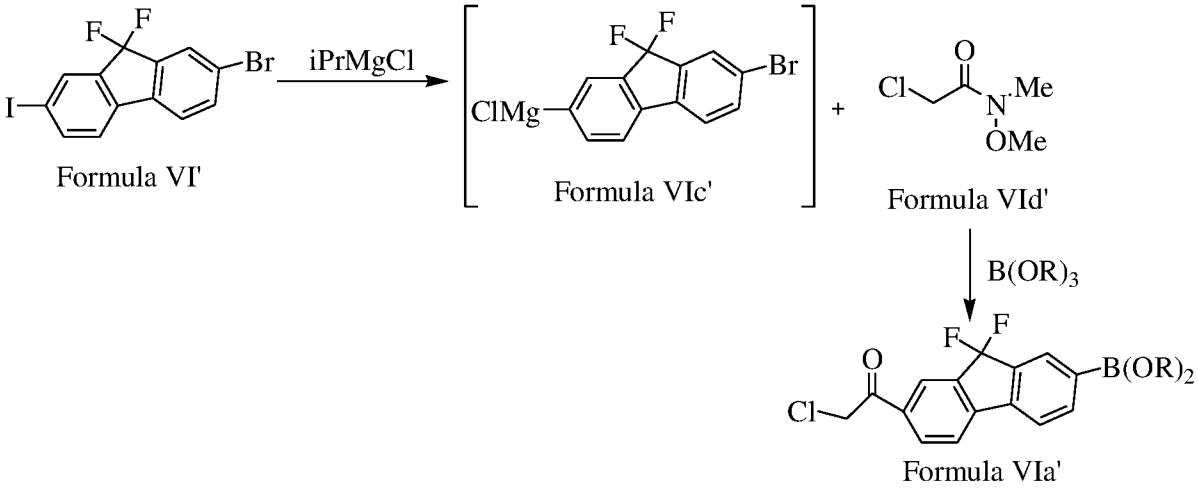
or its reactive derivative in the presence of dimethyl formamide, EDC.HCl, HOBt.H_2O and N-methyl morpholine to give Ledipasvir of Formula I.

The present invention also describes and improved process for the preparation of the Intermediate compounds of Formula VIII.

The compounds of Formula I and intermediates of Formula VIII are purified with solvents.

The compound of Formula VIa is an important coupling precursor for the preparation of Ledipasvir. The compound of Formula VIa' is prepared by first converting the compound VI' to VIc' wherein the end product may be or may not be isolated. The compound of Formula VIc' is then coupled with compound of Formula VId' to yield compound of Formula VIa'.

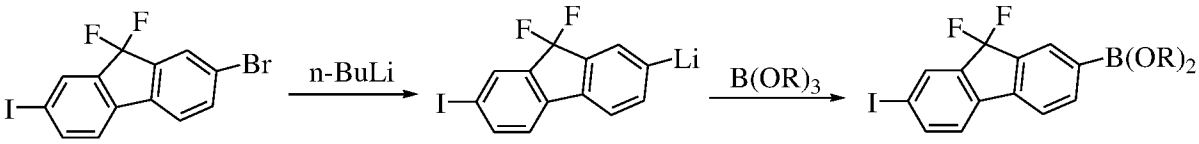
The preparation of compound of Formula VIa' is depicted as below:



Formula VI' Formula VIc' Formula VId'

Formula VIa'

Alternatively, the compound of Formula VI' is converted to the lithium derivative by treatment with organolithium reagents and the resulting compound of Formula VIg' is converted to the boronate derivative of compound of Formula VIb'. The process is shown in the scheme given below:



Formula VI' Formula VIg' Formula VIb'

The compound of Formula VIII is an important intermediate during the synthesis of compound of Formula I. An improved methodology has been designed so as to enable the compound of Formula VIII in good yields and good purity. In this synthesis the compound of Formula C1 is first treated with thionyl chloride in the presence of base to give compound of Formula C2. The compound of Formula C2 is then converted to Compound of Formula C3 which is then converted in the presence of base like triethylamine to give the compound of Formula C4. This C4 compound is coupled with compound of Formula C5 in the presence of base to afford the compound of Formula C6 which is not isolated and taken up further under mild acidic conditions to give compound of Formula C7. This compound of Formula C7 is cyclized to compound of Formula C8 which is then hydrolysed under basic condition to give the hydroxyl compound which is then resolved under dynamic resolution method to afford compound of Formula C9. The compound of Formula C9 is optionally isolated as its acid addition salt. The compound of Formula C9 is converted to compound of Formula C10 followed by condensation to compound of Formula C11 to yield compound of Formula C12. The compound of Formula C12 is then transformed to compound of Formula VIII.

Example1: Preparation of 2-chloro-1-(9,9-difluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-fluoren-2-yl)ethanone

To (8 volumes) of tetrahydrofuran (THF), (0.2457 mol) of 2-bromo-9,9-difluoro-7-iodo-9H-fluorene was charged and the resultant reaction mixture was cooled to about -15°C. To this reaction mixture isopropyl magnesium chloride (1M in tetrahydrofuran (THF)) was added at about -15°C and stirred for about 30 min. Then a solution of 2-chloro N,N-methylmethoxyacetamide in toluene was added at about -15°C and stirred for about 90 min. Then the temperature of the resultant reaction mixture was raised to about 0°C and stirred for about 30 min. Then 1N HCl was added to the reaction mixture and extracted with ethyl acetate for thrice. The organic layer was separated and dried with anhydrous sodium sulphate, the organic layer was separated and distilled under vacuum below 45°C followed by isolation in isopropyl alcohol. To (20 volumes) of 1,4-dioxane the isolated solid was charged and stirred for about 15 min. Then added bis pinacolato diboron, potassium acetate and palladium dppf chloride and the temperature of the resultant reaction mixture was raised to about 90°C and maintained at about 90-95°C for about 16 hrs. Then cooled to about room temperature and diluted with water followed by extraction with ethyl acetate (3 times). The organic layer was separated and washed with brine solution, the organic layer was separated and dried with anhydrous sodium sulphate and then distilled the solvent completely at below 45°C under vacuum to yield the title compound. Yield: 58%.

Example 2: Preparation of (1R,3S,4S)-tert-butyl 3-(6-(7-(2-chloroacetyl)-9,9-difluoro-9H-fluoren-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To a mixture solution of dimethyl ether (DME) (7 volumes) and water (3 volumes) was charged 2-chloro-1-(9,9-difluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-fluoren-2-yl)ethanone and potassium carbonate. The resultant reaction mixture was stirred at room temperature for about 10 min., and was added palladium dppf chloride, palladium tetrakis triphenylphosphine,(1R,3S,4S)-tert-butyl-3-(6-bromo-1H-benzo[d]imidazol-2-yl)-2-azabicyclo-[2.2.1]heptane-2-carboxylate. The temperature of the resultant reaction mixture was raised to about 90°C and stirred at 90-95°C for about 16-18 hrs. Then cooled to room temperature and diluted with water followed by extraction with ethyl acetate (3 times). The organic layer was separated and washed with brine solution, then dried with anhydrous sodium sulphate and distilled the solvent completely at below 45°C under vacuum to yield the title compound. Yield: 96%.

Example 3: Preparation of 1,1-bis(iodomethyl)cyclopropane

To (5 volumes) of dichloro methane was charged a solution of imidazole and triphenylphosphine. The resultant reaction mixture was cooled to about 0°C. Then added a solution of iodine in dichloro methane (5 volumes) at about 0°C for about 60 min.. Then added a solution of cyclopropane-1,1-diyldimethanol in dichloro methane (5 volumes) at about 0°C for about 30 min. and stirred at 10-15°C for about 3 hrs. Then the reaction mass was diluted with brine solution at 10-15°C. The organic and aqueous layers were separated and to the organic layer n-heptane (10 volumes) was charged. The total organic layer was washed with saturated sodium sulphite solution (2 times). 70 % of the organic layer was distilled at below 45°C under vacuum. Then (10 volumes) of n-heptane was added and 12 volumes of the solvent was distilled at below 45°C under vacuum. The slurry was filtered on silica bed and washed with n-heptane, the filterate mls were distilled below 45°C under vacuum to yield the title compound. Yield: 46%

Example 4: Preparation of 5-tert-butyl 6-ethyl 5-azaspiro[2.4]heptane-5,6-dicarboxylate

To dimethyl acetamide (4 volumes) was charged sodium hydride 60 % dispersion in mineral oil and cooled to about 0°C. Then added 1,1-bis(iodomethyl)cyclopropane and solution of ethyl 2-(tert-butoxycarbonylamino)acetate in dimethyl acetamide (4 volumes) at 0-10°C in 3 hrs. The resultant reaction mixture was stirred at 0-10°C for about 2 hrs and then added acetic acid at the same temperature over about 3 hrs. The resultant reaction mixture was stirred at 0-10°C for about 12 hrs. The reaction mass was diluted with (15 volumes) of methyl tertiary butyl ether (MTBE), and water (7 volumes). The organic and aqueous layers were separated, the organic layer was washed with saturated sodium bicarbonate solution and then with brine solution. The organic layer was distilled completely at below 45°C under vacuum and then charged acetonitrile (3 volumes), n-hexane (2 volumes) to the oily mass. The obtained layers were separated and distilled at below 45°C under vacuum to yield the title compound. Yield: 86%.

Example 5: Preparation of potassium 5-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylate

To water (1.5 volumes) was charged lithium hydroxide monohydrate, 2-methyl tetrahydrofuran (3.5 volumes). Then charged a solution of 5-tert-butyl 6-ethyl 5-azaspiro[2.4]heptane-5,6-dicarboxylate in 2-methyltetrahydrofuran (1.5 volumes) at room temperature. The temperature of the resultant reaction mixture was raised to 50-55°C and

maintained for about 24 hrs. The organic, aqueous layers were separated and the aqueous layer was diluted with 2-methyl-tetrahydrofuran (5 volumes) and added HCl (0.75 volumes). Then the organic, aqueous layers were separated and the organic layer was distilled at below 45°C under vacuum. The obtained crude was diluted with 2-methyl tetrahydrofuran (5.5 volumes) and heated to about 40°C and added potassium tert-butoxide solution (1 M in tetrahydrofuran (THF)) at same temperature and stirred for at 40°C for about 1 hr. and then cooled to 10-15°C, stirred for 2 hrs. Further cooled to 5-10°C and stirred for about 30 min. The precipitated solid was filtered and the solid obtained was washed with 2-methyltetrahydrofuran to yield the title compound. Yield: 60%.

Example 6: Preparation of (S)-6-(2-(7-(2-((1R,3S,4S)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazol-6-yl)-9,9-difluoro-9H-fluoren-2-yl)-2-oxoethyl) 5-tert-butyl 5-azaspiro[2.4]heptane-5,6-dicarboxylate

To acetone (10 volumes) was charged (1R,3S,4S)-tert-butyl 3-(6-(7-(2-chloroacetyl)-9,9-difluoro-9H-fluoren-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate and potassium 5-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylate. The resultant reaction mixture was heated to about 55°C and stirred at 50-55°C for 5-6 hrs. Then added water (3 volumes) to the reaction mass, stirred for about 30 min. and again added water (1 volume), stirred at 40-45°C for about 1 hr. Then cooled to room temperature and stirred for about 2 hrs. The precipitated solid was filtered and the solid obtained was washed with mixture of acetone and water to yield the title compound. Yield: 80%.

Example 7: Preparation of (1R,3S,4S)-tert-butyl 3-(6-(7-(2-((S)-5-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-5-yl)-9,9-difluoro-9H-fluoren-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

To toluene (10 volumes) was added (S)-6-(2-(7-(2-((1R,3S,4S)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazol-6-yl)-9,9-difluoro-9H-fluoren-2-yl)-2-oxoethyl) 5-tert-butyl 5-azaspiro[2.4]heptane-5,6-dicarboxylate, ammonium acetate and catalytic amount of 2-methoxyethanol. The resultant reaction mixture was heated to 90-95°C and maintained for 5-6 hrs. n-heptane (10 volumes) was added to the reaction mass at 50-55°C and stirred for about 1 hr. at the same temperature. Then cooled to room temperature and diluted with n-heptane (8 volumes) and stirred for about 2 hrs. The precipitated solid was filtered and washed with n-heptane to yield the title compound. Yield: 81%.

Example 8: Preparation of 6-(7-(2-((S)-5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-5-yl)-9,9-difluoro-9H-fluoren-2-yl)-2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazole hydrochloride

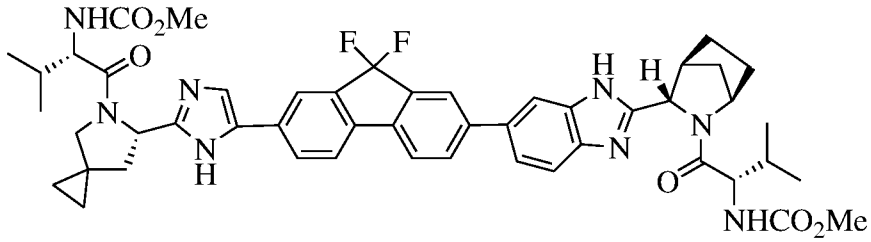
To acetonitrile (5 volumes) was added (1R,3S,4S)-tert-butyl 3-(6-(7-(2-((S)-5-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-5-yl)-9,9-difluoro-9H-fluoren-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate and heated to 60-65°C. 5N HCl was added to the reaction mass slowly at 60-65°C and stirred for about 12 hrs. The reaction mass was diluted with acetonitrile (7 volumes) and allowed to room temperature. Then added acetonitrile (16 volumes) and stirred for about 2 hrs. at room temperature. The solid obtained was filtered and washed with acetonitrile to yield the title compound. Yield: 79%.

Example 9: Preparation of methyl [(2S)-1-{(6S)-6-[5-(9,9-difluoro-7-{2-[(1R,3S,4S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1H-benzimidazol-6-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate (Ledipasvir)

To dimethyl formamide (DMF) (8 volumes) was charged 6-(7-(2-((S)-5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-5-yl)-9,9-difluoro-9H-fluoren-2-yl)-2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazole hydrochloride, ethylene dichloride. HCl, HOBt.H_2O and MOC-L-valine at room temperature. N-methyl morpholine was added at 0-5°C. Temperature of the resultant reaction mixture was raised to room temperature and maintained for about 16 hrs. The reaction mass was diluted with water (15 volumes) and extracted with ethyl acetate (3 times). The organic layer was washed with water (4 times), brine (2 times) and the organic layer was dried with anhydrous sodium sulphate and distilled at below 45°C under vacuum and isolated the solid in acetone to afford the pure title compound. Yield: 49%.

We Claims:

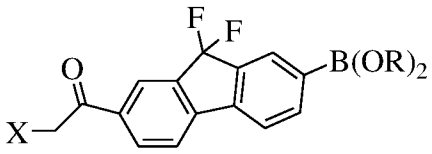
1. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof



Formula I

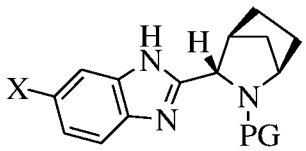
which comprises :

(i) reacting the compound of Formula VIa or its salts



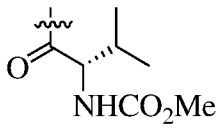
Formula VIa

wherein X is halo or leaving group, R is C_{1-6} alkyl, aryl or R groups combined together to form cycloalkyl group, with the compound of Formula V or its salts

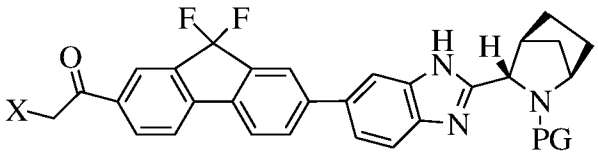


Formula V

wherein X is as defined above, wherein PG represents protecting group or the group of Formula

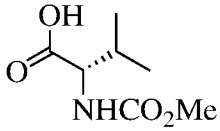


to give a compound of Formula VII,



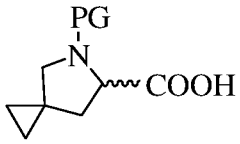
Formula VII

(ii) optional deprotecting the compound of Formula VII when PG represents a protecting group followed by reaction with compound of Formula



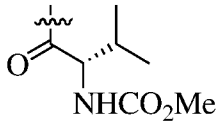
or its reactive derivative,

(iii) coupling the compound of Formula VII with compound of Formula VIh or its salts

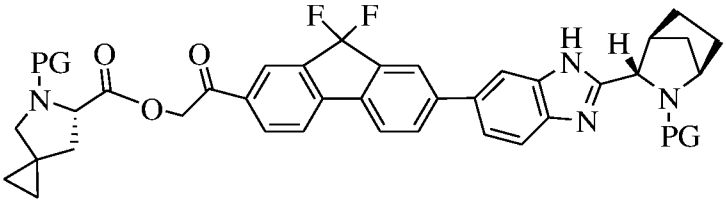


Formula VIh

wherein PG represents protecting group or the group of Formula

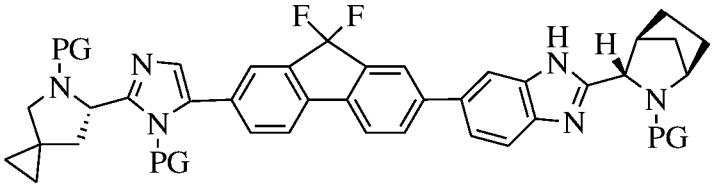


to give compound of Formula IX,



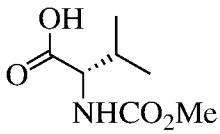
Formula IX

(iv) converting compound of formula IX to compound of formula IXi, and



Formula IXi

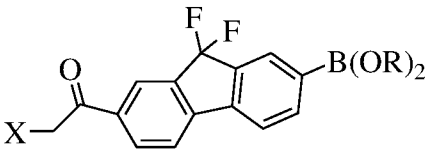
(v) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

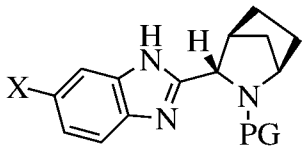
2. A process for the preparation of Ledipasvir of Formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting the compound of Formula VIa or its salts



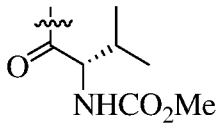
Formula VIa

wherein X is halo or leaving group, R is C_{1-6} alkyl, aryl or R groups combined together to form cycloalkyl group, with the compound of Formula V or its salts

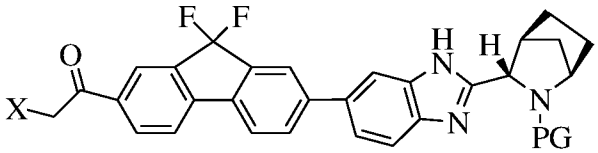


Formula V

wherein X is as defined above, PG represents a protecting group or the group of Formula

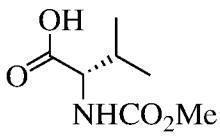


using a metal catalyst and a base in the presence of a solvent, to give a compound of Formula VII,



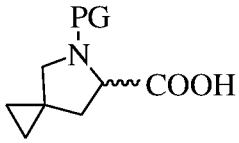
Formula VII

(ii) optional deprotecting the compound of Formula VII when PG represents a protecting group in an acid reagent in a solvent followed by reaction with compound of Formula



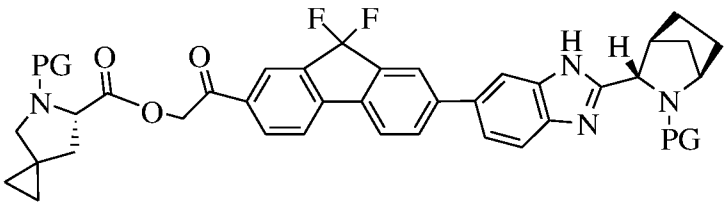
or its reactive derivative,

(iii) coupling the compound of Formula VII with compound of Formula VIh or its salts



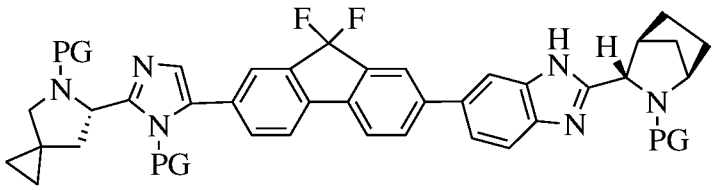
Formula VIh

in the presence of a solvent and optionally using a catalyst to give compound of Formula IX,



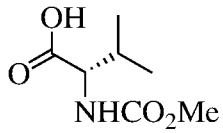
Formula IX

(iv) cyclizing compound of formula IX using a cyclizing agent in a solvent to give compound of formula IXi, and



Formula IXi

(v) optional deprotecting the compound of Formula IXi when PG represents a protecting group in an acid reagent in a solvent followed by reaction with compound of Formula



or its reactive derivative in the presence of a condensing agent and a solvent to give Ledipasvir of Formula I.

3. The process as claimed in claim 2, wherein the metal catalyst used in step (i) is selected from Palladium (0) or (II) complexes, selected from tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, palladium dppf chloride, Bis(triphenylphosphine)palladium(II) acetate, Bis(triethylphosphine)palladium(II) chloride and/or mixtures thereof.

4. The process as claimed in claim 2, wherein the base used in step (i) is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof.

5. The process as claimed in claim 2, wherein the acid reagent used in steps (ii) and (v) is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof.

6. The process as claimed in claim 2, wherein the catalyst used in step (iii) is selected from acid or base, wherein the acid is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof and base is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof.

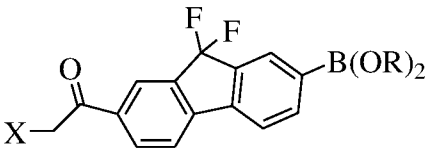
7. The process as claimed in claim 2, wherein the reagent used for cyclization in step (iv) is ammonium acetate.

8. The process as claimed in claim 2, wherein the condensing agent used in step (v) is selected from HOBt, HBTU, TBTU, HOAt, DCC, CDI, EDC-HCl, BOP, T_3P and PyBOP or and/or mixtures thereof.

9. The process as claimed in claim 2, wherein the solvent used is water or "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, dimethylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 2-methoxyethanol and dimethoxyethane, or “Amide solvents” such as formamide, DMF, DMAC, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, 1-ethenyl-2-pyrrolidone and/or mixtures thereof.

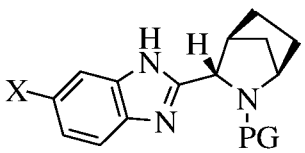
10. A process for the preparation of a Ledipasvir of Formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting the compound of Formula VIa or its salts



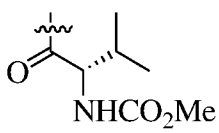
Formula VIa

wherein X is Cl, R is a cycloalkyl group, with the compound of Formula V or its salts

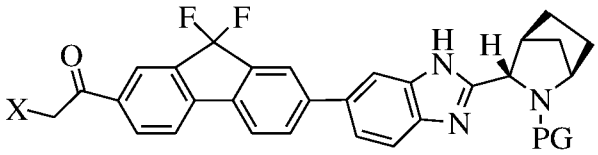


Formula V

wherein PG represents a protecting group or the group of Formula

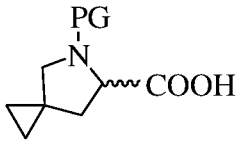


using palladium dppf chloride, palladium tetrakis triphenylphosphine and potassium carbonate in dimethyl ether and water to give a compound of Formula VII,



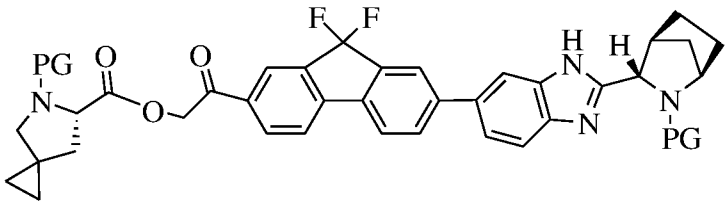
Formula VII

(ii) coupling the compound of Formula VII with compound of Formula VIh or its salts



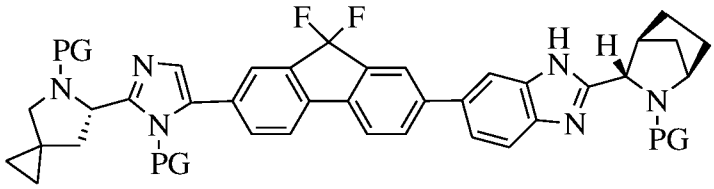
Formula VIh

in acetone to give compound of Formula IX,



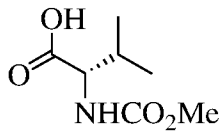
Formula IX

(iii) cyclizing compound of formula IX using ammonium acetate, in the presence of toluene and catalytic amount of 2-methoxy ethanol to give compound of formula IXi, and



Formula IXi

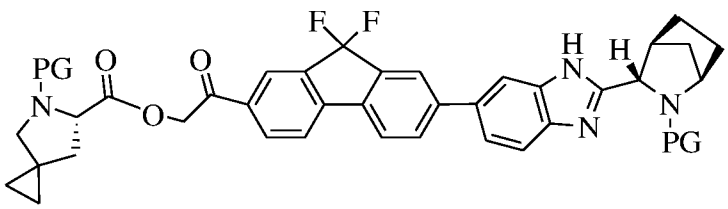
(iv) deprotecting the compound of Formula IXi when PG represents a protecting group using HCl in acetonitrile followed by reaction with compound of Formula



or its reactive derivative in the presence of dimethyl formamide, EDC.HCl, HOBt.H_2O and N-methyl morpholine to give Ledipasvir of Formula I.

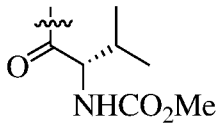
11. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) cyclizing compound of Formula IX

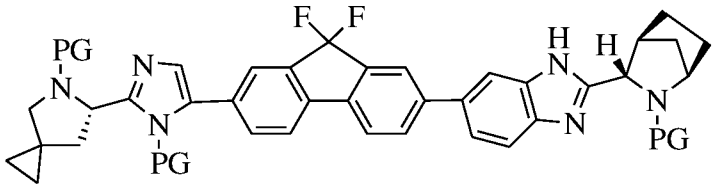


Formula IX

wherein PG represents protecting group or the group of Formula

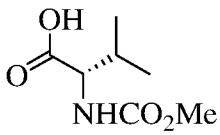


in the presence of a cyclizing agent and a solvent to give compound of formula IXi, and



Formula IXi

(ii) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula

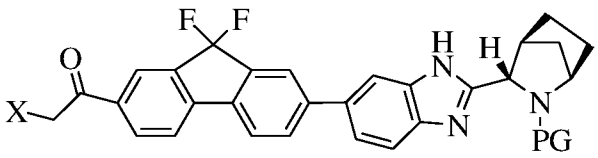


or its reactive derivative to give Ledipasvir of Formula I.

12. The process as claimed in claim 11, where the cyclization in step i) is carried out by reacting compound of formula IX with ammonium acetate in the presence of toluene and a catalytic amount of 2-methoxy ethanol.

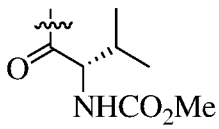
13. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VII

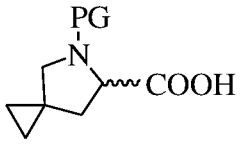


Formula VII

wherein X is halo or leaving group, PG represents protecting group or the group of Formula

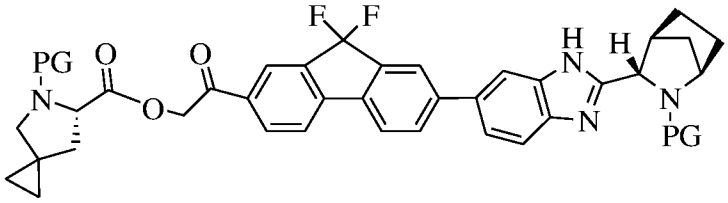


with compound of Formula VIh or its salts



Formula VIh

to give compound of Formula IX,



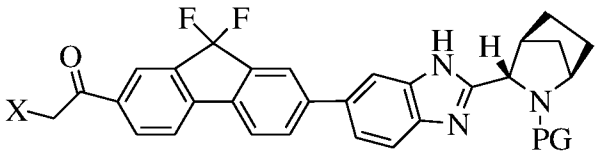
Formula IX

(ii) converting compound of formula IX to Ledipasvir of Formula I.

14. The process as claimed in claim 13, where the compound of formula VII is reacted with the potassium salt of compound of formula VIh in acetone to give compound of formula IX.

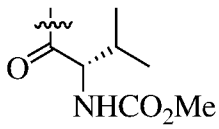
15. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VII

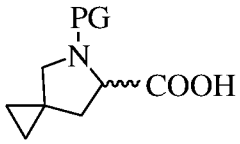


Formula VII

wherein X is halo or leaving group, PG represents protecting group or the group of Formula

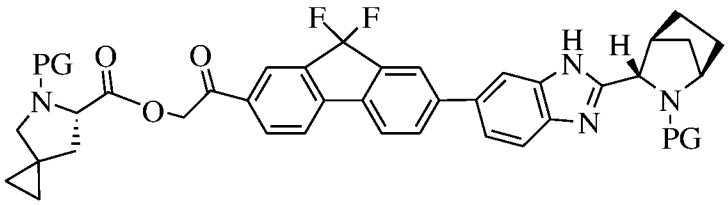


with compound of Formula VIh or its salts



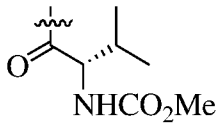
Formula VIh

to give compound of Formula IX,

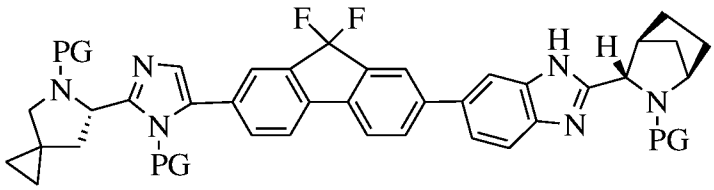


Formula IX

wherein PG represents N-protecting group or the group of Formula



(ii) cyclizing compound of Formula IX in the presence of a cyclizing agent and a solvent to give compound of formula IXi, and



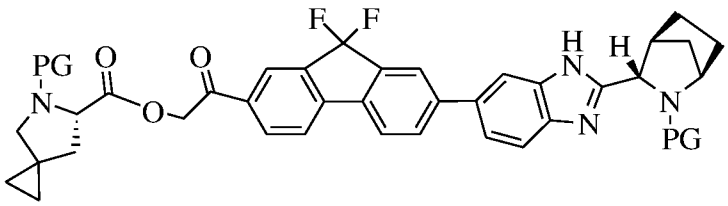
Formula IXi

(iii) converting compound of formula IXi to Ledipasvir of Formula I.

16. The process as claimed in claim 15, where step i) is carried out by reacting formula VII is reacted with the potassium salt of compound of formula VIh in acetone to give compound of formula IX.

17. The process as claimed in claim 15, wherein the cyclization in step ii) is carried out by reacting compound of formula IX with ammonium acetate in the presence of toluene and a catalytic amount of 2-methoxy ethanol.

18. Compound of formula IX or its salts, an intermediate of Ledipasvir.

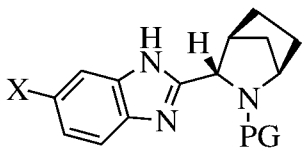


Formula IX

wherein PG represents protecting group.

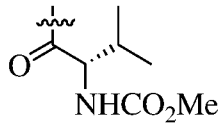
19. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula V

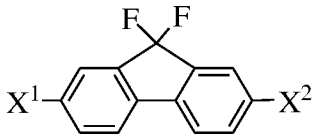


Formula V

wherein X is halo or leaving group, PG is hydrogen or a conventional protecting group, or a group of Formula

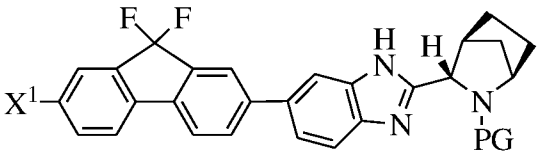


with compound of Formula VI



Formula VI

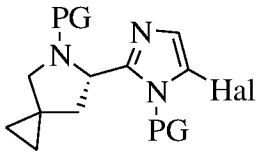
wherein X^1 represents halogen or a leaving group, and X^2 represents boronate esters, to give compound of Formula VIIi



Formula VIIi

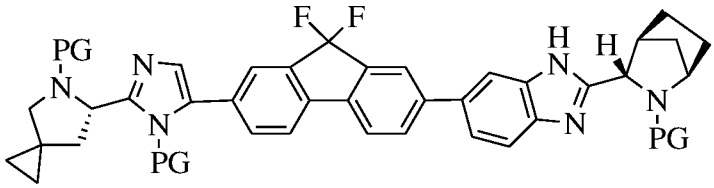
wherein PG, X^1 are as defined above,

(ii) condensation of compound of Formula VIIi with compound of Formula VIII



Formula VIII

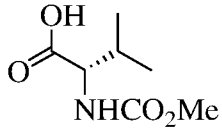
wherein PG is as defined above and Hal means halogen, in a solvent to give compound of Formula IXi



Formula IXi

wherein PG is as defined above, and

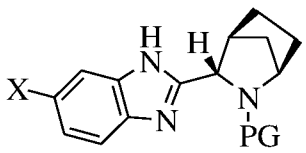
(iii) optional deprotection of the compound of Formula IXi when PG represents a conventional protecting group, followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

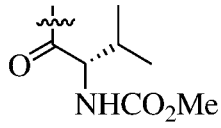
20. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula V

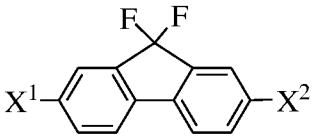


Formula V

wherein X is a halo or leaving group PG is a conventional protecting group, or a group of Formula

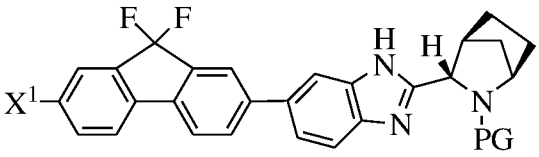


with compound of Formula VI



Formula VI

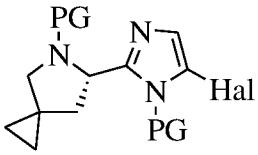
wherein X^1 represents halogen or a leaving group, and X^2 represents boronate esters, optionally using a metal catalyst, which is selected from is selected from Palladium (0) or (II) complexes, selected from tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, palladium dppf chloride, Bis(triphenylphosphine)palladium(II) acetate, Bis(triethylphosphine)palladium(II) chloride and/or mixtures thereof, in the presence of solvent to give compound of Formula VIIi



Formula VIIi

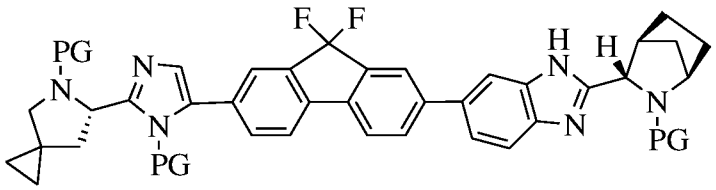
wherein PG, X^1 are as defined above,

(ii) condensation of compound of Formula VIIi with compound of Formula VIII



Formula VIII

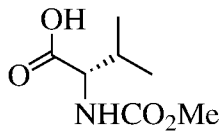
wherein PG is as defined above and Hal means halogen, optionally using a catalyst, which is selected from Palladium (0) or (II) complexes, selected from tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, palladium dppf chloride, Bis(triphenylphosphine)palladium(II) acetate, Bis(triethylphosphine)palladium(II) chloride and/or mixtures thereof, in a solvent to give compound of Formula IXi



Formula IXi

wherein PG is as defined above, and

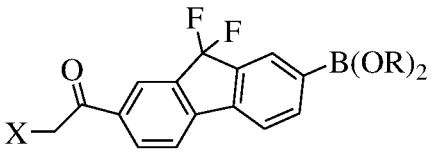
(iii) deprotecting the compound of Formula IXi when PG represents a protecting group in an acid reagent, which is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof, in a solvent followed by reaction with compound of Formula



or its reactive derivative in the presence of a condensing agent, which is selected from HOBt, HBTU, TBTU, HOAt, DCC, CDI, EDC-HCl, BOP, T_3P and PyBOP or and/or mixtures thereof, and a solvent to give Ledipasvir of Formula I.

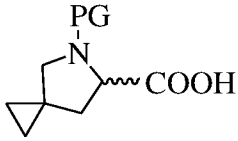
21. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VIa



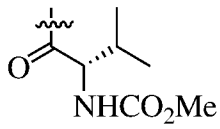
Formula VIa

wherein X is halo or leaving group, with the compound of Formula VIh

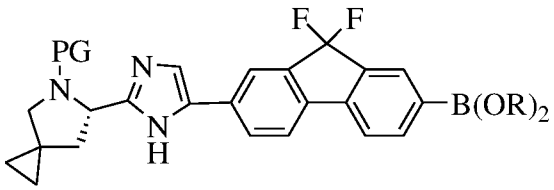


Formula VIh

or its salts wherein PG represents a Protecting group or the group of Formula

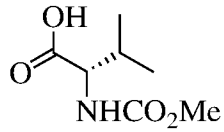


to give a compound of Formula VIi,



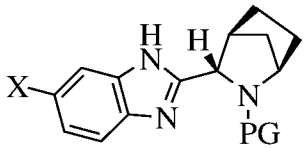
Formula VIi

(ii) optional deprotecting the compound of Formula VIi when PG represents a protecting group followed by reaction with compound of Formula



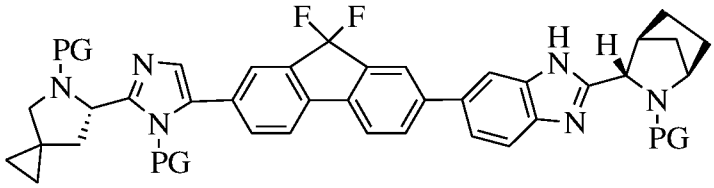
or its reactive derivative,

(iii) coupling the compound of Formula VIi with compound of Formula V



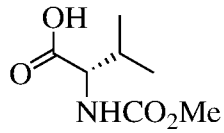
Formula V

wherein X is halo or leaving group, to give compound of Formula IXi, and



Formula IXi

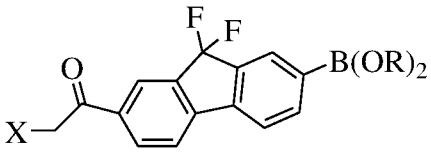
(iv) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

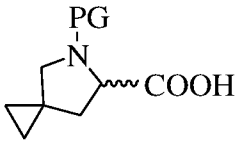
22. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VIa



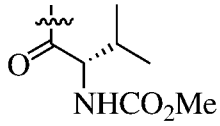
Formula VIa

wherein X is halo or leaving group, with the compound of Formula VIh

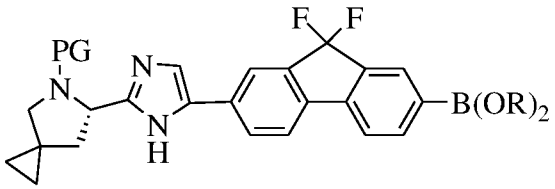


Formula VIh

or its salts wherein PG represents a Protecting group or the group of Formula

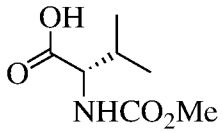


in the presence of a solvent and optionally using a catalyst, which is selected from acid or base, wherein the acid is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof and base is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof, to give a compound of Formula VIi,



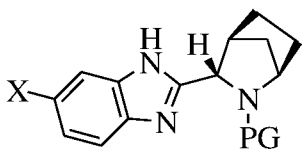
Formula VIi

(ii) optional deprotecting the compound of Formula VIi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative,

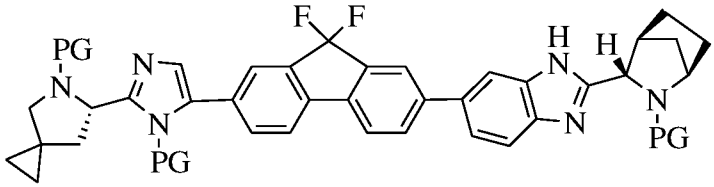
(iii) coupling the compound of Formula VIi with compound of Formula V



Formula V

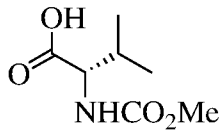
wherein X is halo or leaving group, using a metal catalyst, which is selected from Palladium (0) or (II) complexes, selected from tetrakis(triphenylphosphine)palladium,

tris(dibenzylideneacetone)dipalladium, palladium dppf chloride, Bis(triphenylphosphine)palladium(II) acetate, Bis(triethylphosphine)palladium(II) chloride and/or mixtures thereof, in the presence of solvent to give compound of Formula IXi, and



Formula IXi

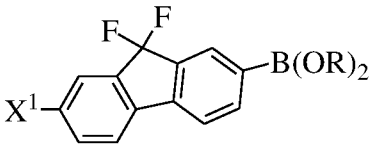
(iv) deprotecting the compound of Formula IXi when PG represents a protecting group in an acid reagent, which is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof, in a solvent followed by reaction with compound of Formula



or its reactive derivative in the presence of a condensing agent, which is selected from HOBt, HBTU, TBTU, HOAt, DCC, CDI, EDC-HCl, BOP, T_3P and PyBOP or and/or mixtures thereof, and a solvent to give Ledipasvir of Formula I.

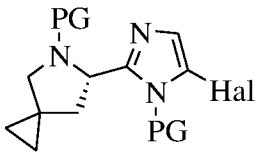
23. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VIb



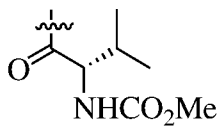
Formula VIb

wherein X^1 is halo or leaving group, with the compound of Formula VIII or its salts

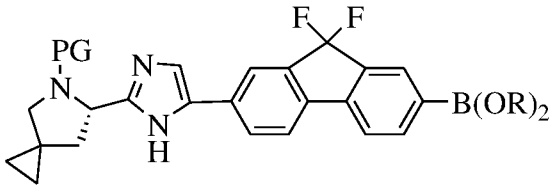


Formula VIII

wherein PG represents a protecting group or the group of Formula

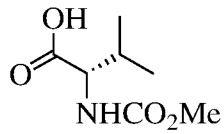


to give a compound of Formula VIi,



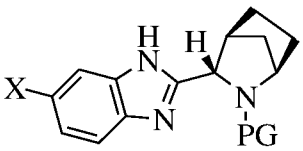
Formula VIi

(ii) optional deprotecting the compound of Formula VIi when PG represents a protecting group followed by reaction with compound of Formula



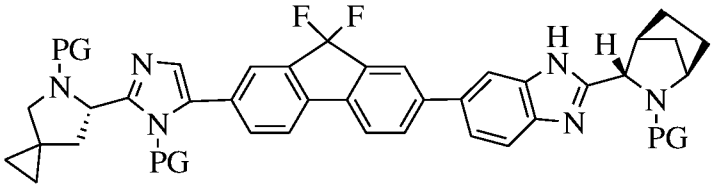
or its reactive derivative,

(iii) coupling the compound of Formula VIi with compound of Formula V



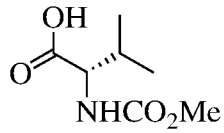
Formula V

wherein X is halo or leaving group, to give compound of Formula IXi, and



Formula IXi

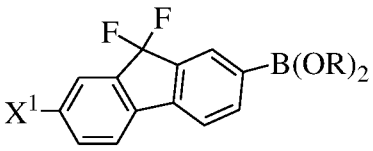
(iv) optional deprotecting the compound of Formula IXi when PG represents a protecting group followed by reaction with compound of Formula



or its reactive derivative to give Ledipasvir of Formula I.

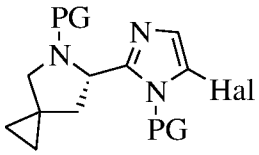
24. An improved process for the preparation of Ledipasvir compound of formula I or a pharmaceutically acceptable salt or solvate thereof, which comprises :

(i) reacting compound of Formula VIb



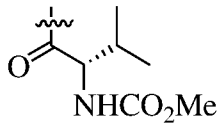
Formula VIb

wherein X^1 is halo or leaving group, with the compound of Formula VIII or its salts

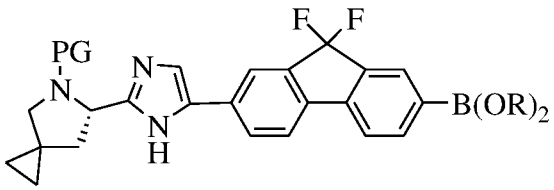


Formula VIII

wherein PG represents a protecting group or the group of Formula

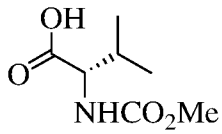


in the presence of a solvent and optionally using a catalyst, which is selected from acid or base, wherein the acid is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof and base is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof, to give a compound of Formula VIi,



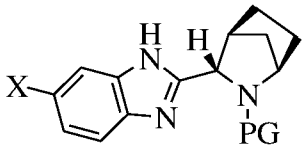
Formula VIi

(ii) optional deprotecting the compound of Formula VIi when PG represents a protecting group followed by reaction with compound of Formula



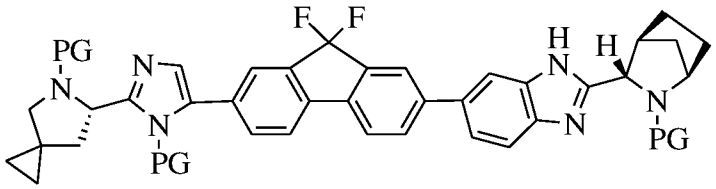
or its reactive derivative,

(iii) coupling the compound of Formula VIi with compound of Formula V



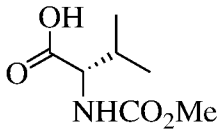
Formula V

wherein X is halo or leaving group, using a metal catalyst which is selected from Palladium (0) or (II) complexes, selected from tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, palladium dppf chloride, Bis(triphenylphosphine)palladium(II) acetate, Bis(triethylphosphine)palladium(II) chloride and/or mixtures thereof, in the presence of solvent to give compound of Formula IXi, and



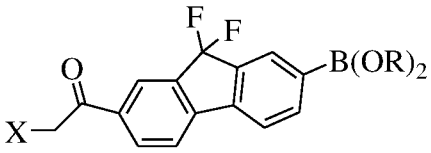
Formula IXi

(iv) deprotecting the compound of Formula IXi when PG represents a protecting group in an acid reagent, which is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof,in a solvent followed by reaction with compound of Formula



or its reactive derivative in the presence of a condensing agent which is selected from HOBt, HBTU, TBTU, HOAt, DCC, CDI, EDC-HCl, BOP, T_3P and PyBOP or and/or mixtures thereof, and a solvent to give Ledipasvir of Formula I.

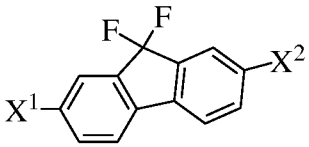
25. An improved process for the preparation of compound of formula VIa, an intermediate of Ledipasvir,



Formula VIa

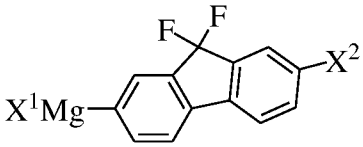
wherein X represents halo or a leaving group, which comprises :

i) converting the compound of Formula VI



Formula VI

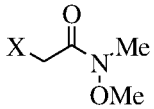
wherein X^1 and X^2 are halogens or leaving groups, to give the compound of Formula VIc



Formula VIc

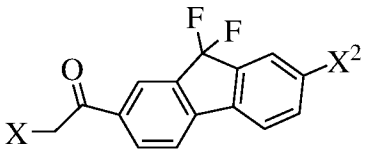
wherein X^1 and X^2 are as defined above,

ii) coupling compound of Formula VIc with compound of Formula VId



Formula VId

wherein X is halo or leaving group, to give compound of Formula Vie, and

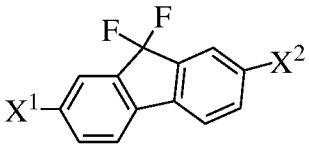


Formula VIe

iii) converting the obtained compound of Formula VIe to compound of Formula VIa by reacting with boric acid or its derivatives.

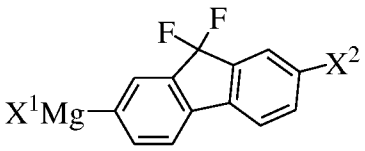
26. An improved process for the preparation of compound of formula VIa, an intermediate of Ledipasvir, which comprises :

i) reacting compound of Formula VI



Formula VI

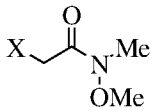
wherein X^1 and X^2 are halogens or leaving groups, with Grignard reagent, which is selected from RMGX, wherein R is C_{1-6} alkyl, in the presence of a solvent to give the compound of Formula VIc, which is optionally isolated



Formula VIc

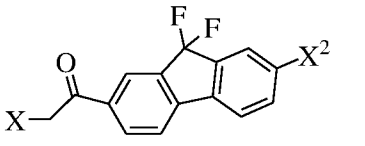
wherein X^1 and X^2 are as defined above,

ii) coupling compound of Formula VIc with compound of Formula VId



Formula VId

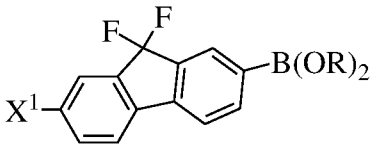
wherein X is halo or leaving group, using base in the presence of a solvent and optionally using catalyst which is selected from acid or base, wherein the acid is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof and base is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof, to give compound of Formula VIe, and



Formula VIe

iii) reacting compound of Formula VIe with pinacolboronates to give compound of Formula Via.

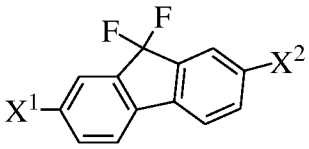
27. An improved process for the preparation of compound of formula VIb, an intermediate of Ledipasvir,



Formula VIb

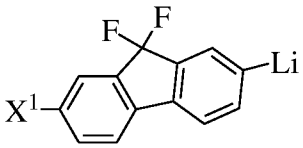
wherein X^1 is a halogen or a leaving group, R is C_{1-6} alkyl, aryl or R groups combined together to form cycloalkyl group, which comprises :

i) reacting the compound of Formula VI



Formula VI

wherein X^1, X^2 represents halogens or leaving groups, with organolithium reagent to give compound of Formula VIg



Formula VIg

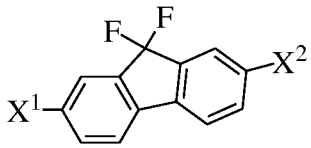
wherein X^1 is as defined above, and

(ii) converting the compound of Formula VIg to compound of Formula VIb by reacting with boric acid or its derivatives.

28. The process as claimed in claim 27, wherein the organolithium reagent used in step i) is selected from methyllithium, ethyllithium, n-butyllithium, sec-butyllithium, isopropyllithium, tert-butyllithium, phenyllithium.

29. The process as claimed in claim 27, wherein compound of formula VIg is reacted with boric acid or its derivatives, preferably selected from pinacolboronates, alkyl boronates or aryl boronates to give compound of formula VIb.

30. An improved process for the preparation of compound of formula VIb, an intermediate of Ledipasvir which comprises reacting the compound of Formula VI

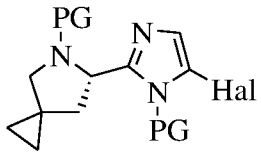


Formula VI

wherein X^1, X^2 represents halogens or leaving groups, with boric acid or its derivatives.

31. The process as claimed in claim 30, wherein compound of formula VI is reacted with pinacolboronates, alkyl boronates or aryl boronates to give compound of formula VIb.

32. An improved process for the preparation of compound of formula VIII, an intermediate of Ledipasvir,



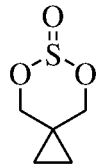
Formula VIII

which comprises :

i) converting the compound of Formula C1

Formula C1

to compound of Formula C2 using thionyl chloride in the presence of base to give compound of Formula C2



Formula C2

ii) halogenating the compound of Formula C2 to give compound of Formula C3

Formula C3

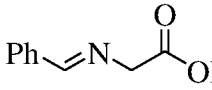
wherein X^4 represents halogen

iii) converting the compound of Formula C3 to give compound of Formula C4

Formula C4

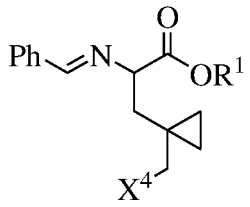
wherein L is a leaving group and X^4 is as defined above,

iv) coupling the compound of Formula C4 with compound of Formula C5



Formula C5

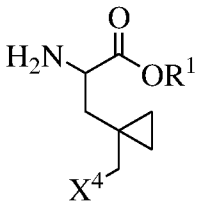
wherein R^1 represents hydrogen, alkyl or a chiral auxiliary, in the presence of a base to give compound of Formula C6



Formula C6

wherein R^1 and X^4 are as defined above

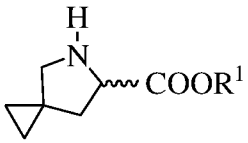
v) converting the compound of Formula C6 to compound of Formula C7 under mild acidic conditions



Formula C7

wherein R^1 and X^4 are as defined above

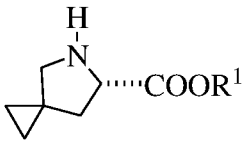
vi) cyclizing compound of Formula C7 to compound of Formula C8



Formula C8

wherein R^1 is as defined above,

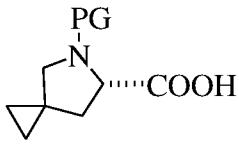
vii) optionally resolving the compound of Formula C8 when it is racemic and isolating the compound of Formula C8 as an acid addition salt of Formula C9



Formula C9

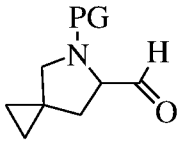
wherein R^1 represents hydrogen or alkyl group,

viii) protecting the compound of Formula C9 with a suitable protecting group to give compound of Formula C15 or its salts



Formula C15

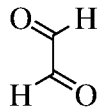
ix) converting the obtained protected compound of Formula C15 to compound of Formula C10



Formula C10

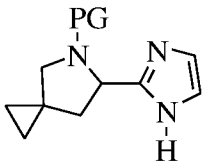
wherein PG represents protecting group

x) coupling the compound of Formula C10 with compound of Formula C11



Formula C11

to give compound of Formula C12



Formula C12

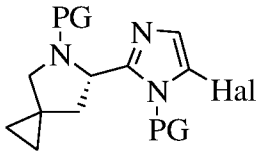
wherein PG represents protecting group, and

xi) converting the compound of Formula C12 to compound of Formula VIII,

wherein the base used is selected from C_{1-6} alkyl amines, NH_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NH_4OH, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, KOH, NaOH, NaH, KH, KOtBu, CH_3COONa, CH_3COOK, $(CH_3)_3CONa$, LiOH, N-Methylmorpholine and/or mixtures thereof,

wherein the acid used is selected from hydrochloric, hydrobromic, sulfuric, phosphoric, oxalic, maleic, succinic, citric, acetic and p-toluenesulfonic acid and/or mixtures thereof.

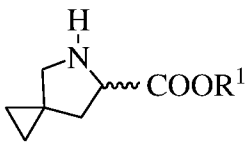
33. An improved process for the preparation of compound of formula VIII, an intermediate of Ledipasvir, which comprises :



Formula VIII

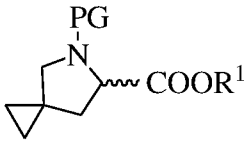
wherein PG represents a protecting group and Hal represents a halogen group, which comprises :

i) protecting the compound of Formula C8



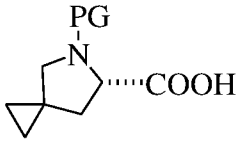
Formula C8

wherein R^1 represents hydrogen, alkyl or a chiral auxiliary, to give Formula C14



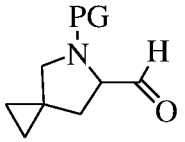
Formula C14

ii) optionally resolving the compound of Formula C14 when it is racemic and isolating the compound of Formula C15 or its salts



Formula C15

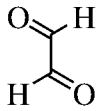
iii) converting compound of Formula C14 or Formula C15 to compound of Formula C10



Formula C10

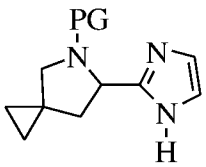
wherein PG represents protecting group

iv) coupling the compound of Formula C10 with compound of Formula C11



Formula C11

to give compound of Formula C12



Formula C12

wherein PG represents protecting group, and

v) transforming the compound of Formula C12 to compound of Formula VIII.

34. A process for the resolution of compound of Formula C8 and Formula C14 which involves kinetic resolution or enzymatic hydrolysis of ester and hydrolysis of ester followed by resolution with chiral amine reagents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/059982

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4164,C07D403/14,C07D403/04,A61K31/4184 Version=2016.01

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)

A61K, C07D

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)

PATSEER, IPO-INTERNAL DATABASE, STN: process, preparation, ledipasvir, suzuki coupling, intermediate.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/184702 A1, (GILEAD SCIENCES, INC. [US]) 12 December 2013 (12.12.2013) See Description Pages 26-57, Examples, Claims	1-34
Y	WO 2010/132601 A1 (GILEAD SCIENCES INC. US]; GUO HONGYAN [US]; KATO DARRYL [US]; KI RSCHBE) 18 November 2010 (18.11.2010) See Example IB, IS, JL, JP & JR	1-34

☐ 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)
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