March 2022

Processes For The Preparation of ({(12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin--11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate

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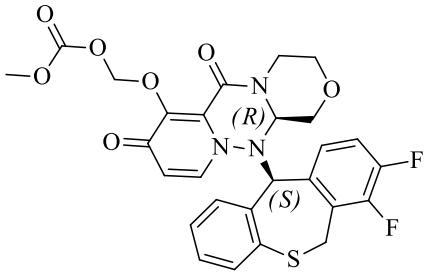
Processes for the preparation of ({(12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo [b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido [2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate

Field of the Invention:

The present invention provides various processes for the preparation of ({(12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate represented by the following structural formula-1.



Formula-1

Background of the Invention:

({(12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate is commonly known as Baloxavir marboxil.

Baloxavir marboxil is designed and developed by Genentech Inc. It is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Baloxavir marboxil is approved by USFDA on Oct 24, 2018 and is being marketed under the brand name XOFLUZA™.

US10392406B2 specifically describes Baloxavir marboxil, its intermediates and processes for preparation thereof.

Still, there is a significant need in the art for the development of novel processes for the preparation of Baloxavir marboxil.

Brief description of the invention:

The first embodiment of the present invention is to provide a process for the preparation of compound of formula-1.

The second embodiment of the present invention is to provide a process for the preparation of compound of formula-1 involving the use of compound of formula-38 as illustrated in scheme-I.

The third embodiment of the present invention is to provide another process for the preparation of compound of formula-1.

The fourth embodiment of the present invention is to provide a process for the preparation of compound of formula-1 involving the use of compound of formula-27 as illustrated in scheme-III.

The fifth embodiment of the present invention is to provide a process for the preparation of compound of formula-29.

The sixth embodiment of the present invention is to provide a process for the preparation of compound of formula-1 involving the use of compound of formula-33 as illustrated in scheme-IV.

The seventh embodiment of the present invention is to provide a process for the preparation of compound of formula-1 involving the use of compound of formula-35 as illustrated in scheme-IV.

Detailed description of the Invention:

The "solvent" used in the present invention can be selected from but not limited to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and the like; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as

acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and the like; "polar solvents" such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

Various conversions/steps in the processes of the present invention can be carried out in the presence or absence of a solvent or mixture of solvents. The said solvent(s) can be selected from those as described above.

The "base" used in the present invention can be selected from but not limited to "inorganic bases" selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal amides" such as sodium amide, potassium amide, lithium amide and the like; ammonia; "organic bases" like "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, lithium methoxide, lithium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; alkali metal and alkali earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; dimethylamine, diethylamine, diisopropyl mine, diisopropylethylamine (DIPEA), diisobutylamine, trimethylamine, triethylamine, triisopropylamine, tributylamine, tert.butyl amine, pyridine, piperidine, 4-dimethylamino pyridine (DMAP), quinoline, imidazole, N-methylimidazole, l,8-diazabicyclo[5.4.0]undec-7-ene (DBU), l,5-diazabicyclo[4.3.0]non-5-ene (DBN), dimethylaniline, N-methylmorpholine (NMM), l,4-diazabicyclo[2.2.2]octane (DABCO), 2,6-lutidine and the like; "organolithium bases" such as methyl lithium, n-butyl lithium, lithium diisopropylamide (LDA) and the like; "organosilicon bases" such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) and the like or mixtures thereof.

The ‘acid’ used in the present invention can be selected from but not limited to "inorganic acids" such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, boric acid, perchloric acid, carbonic acid and the like; and "organic acids" such as formic acid, acetic acid, trifluoroacetic acid, propionic acid, butyric acid, valeric acid, substituted/unsubstituted alkyl/aryl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid and the like.

The ‘‘base” used in the present invention for hydrolysis step can be selected from but not limited to alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide and the like; alkaline earth metal hydroxides such as barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; alkaline earth metal carbonates such as magnesium carbonate, calcium carbonate and the like; alkali metal bicarbonates such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate and the like.

The hydrolysis step in the present invention can also be carried out in the presence of “Lewis acids”.

The “Lewis acid” used in the present invention can be selected from but not limited to LiCl, LiBr, LiI, NaBr, NaI, KBr, KI, CsCl, CsBr, CsI, $BeCl_2$, $BeBr_2$, $MgCl_2$, $MgBr_2$, MgI_2, $CaCl_2$, $CaBr_2$, CaI_2, $ZnCl_2$, $ZnBr_2$, $BaCl_2$, $BaBr_2$, BaI_2, $AlCl_3$, BBr_3, BF_3, $FeCl_3$ and the like.

The “deprotecting agent” used in the present invention can be selected based on the protecting group employed. The “deprotecting agent” can be selected from but not limited to Lewis acids, substituted/unsubstituted C_1-C_6 straight chain or branched chain alkyl/aryl magnesium halides (Grignard reagent) such as methyl magnesium halide, isopropyl magnesium halide and the like; acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, trifluoroacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like; acetyl chloride in combination with alcohols; bases such as alkali metal hydroxides, alkali metal carbonates, cesium carbonate/imidazole, alkali metal bicarbonates, ammonia, aqueous ammonia,

ammonium cerium(IV) nitrate (CAN); and organic bases such as methylamine, ethylamine, diethylamine, triethylamine, piperidine; hydrogenating agents such as Pd/C, $Pd(OH)_2/C$ (Pearlman's catalyst), palladium acetate, platinum oxide, platinum black, Rh/C, Ru, sodium borohydride, Na-liquid ammonia, Raney-Ni, Zn-acetic acid, tri(C_1-C_6)alkylsilanes, tri(C_1-C_6) alkylsilyl halides and the like.

The "dehydrating agent" can be selected from but not limited to propylphosphonic anhydride (T_3P), acetic anhydride, trifluoroacetic anhydride (TFAA), trifluoromethanesulfonic anhydride, phthalic anhydride, trifluoroacetic acid (TFA), oxalyl chloride, thionyl chloride, P_2O_5, phosphoric acid, polyphosphoric acid, $POCl_3$ optionally in presence of imidazole, cyunaric chloride, sulfuric acid, dicyclohexylcarbodiimide (DCC), carbonyldiimidazole (CDI), sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid, methanesulfonyl chloride, p-toluenesulfonyl chloride, formic acid, acetyl chloride, trichloroacetyl chloride, phosgene, diphosgene, triphosgene and the like.

The ''coupling agent'' can be selected from N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), l-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HC1), N,N'-carbonyl diimidazole(CDI), l-[bis(dimethylamino) methylene] -lH-l,2,3-triazolo[4,5-b]pyridinium 3- oxide hexafluorophosphate (HATU), 2-(lH-benzotriazol-l-yl)-l,l,3,3-tetramethyluronium hexafluorophosphate (HBTU), lH-benzotriazolium l-[bis(dimethylamino)methylene]-5- chloro-hexafluorophosphate (1-) 3-oxide (HCTU), alkyl/aryl/aralkyl chloroformates such as methyl chloroformate, ethyl chloroformate, isopropyl chloroformate, phenyl chloroformate, benzyl chloroformate and the like; diphenylphosphoroazidate (DPPA), thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, 4-methyl-2- oxopentanoyl chloride (i-BuCOCOCl), (benzotriazol-l-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP), benzotriazol-l-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), alkyl/aryl sulfonyl chlorides such as methanesulfonyl chloride, ethanesulfonyl chloride, benzenesulfonyl chloride, p-toluenesulfonyl chloride and the like optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxy benzotriazole (HOBt), l-hydroxy-lH-l,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-l-yl)-N,N,N',N'-tetramethyluronium

tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS) and the like.

The decarboxylation process in the present invention can be carried out by heating the compound in presence of alkali/alkaline earth metal hydroxides.

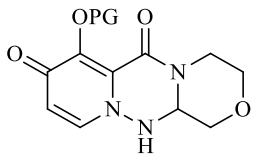
'Chiral acid'' used in the present invention can be selected from (+)-tartaric acid, (+)-malic acid, (+)-mandelic acid, and (+)-camphor-10-sulfonic acid, (+)-tetrahydrofuran-2-carboxylic acid, alpha-bromocamphoric acid, methoxyacetic acid, diacetyltartaric acid, di p-toluoyl tartaric acid, dibenzoyl tartaric acid, lactic acid, ibuprofen, pyrrolidone-5-carboxylic acid, naproxen, 3-(2-amino-2-oxoethyl)-5-methylhexanoic acid and the like.

In the present invention 'PG' and 'PG_1' represents ''hydroxyl protecting groups'' which can be selected from but not limited to methyl, ethyl, tert-butyl, acetyl, pivaloyl, benzyl, benzoyl, silyl protecting groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and the like; tetrahydropyranyl, tetrahydrofuranyl, triphenyl methyl (trityl), methoxymethyl acetal (MOM), methoxypropyl acetal (MOP), ethoxyethyl acetal, benzyloxymethyl acetal (BOM), methoxymethyl, benzyloxymethyl, tert-butoxymethyl, methoxyphenyl, methoxytrityl (MMT), dimethoxytrityl (DMT) and the like.

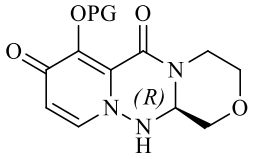
In the present invention 'PG_2' represents "amine protecting group" selected from but not limited to alkoxycarbonyl such methoxycarbonyl (Moc), ethoxycarbonyl, tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), p-methoxybenzyl carbonyl (Moz or MeOZ), 9-fluorenylmethyloxy carbonyl (Fmoc), acetyl (Ac), benzoyl (Bz), benzyl (Bn), carbamate group, p-methoxyphenyl (PMP), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), tosyl (Ts), trifluoroacetyl (TFA), trichloroethoxycarbonyl (Troc), pivaloyl (Piv), triphenylmethyl (trityl or Trt) and the like.

The first embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) resolution of compound of formula-3 by treating it with a chiral acid to provide compound of formula-4,



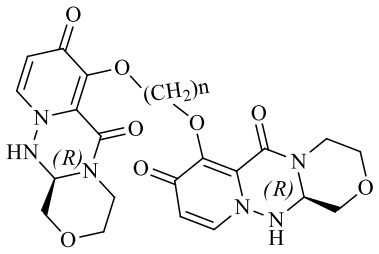
Formula-3



Formula-4

wherein, 'PG' represents hydroxyl protecting group;

b) deprotection of compound of formula-4 with a deprotecting agent followed by reacting the obtained compound with compound of formula-5 to provide compound of formula-6,



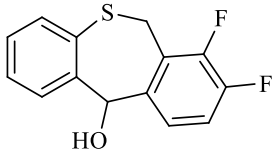
R_1-$(CH_2)_n$-R_2

Formula-5

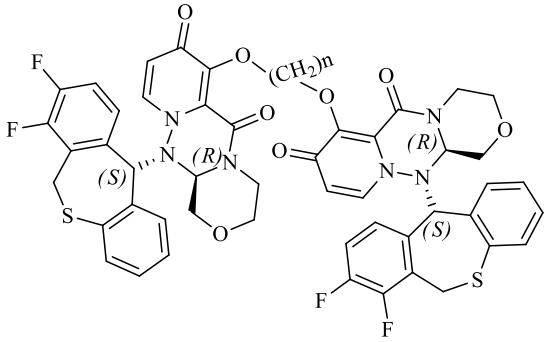
Formula-6

wherein, 'R_1' and 'R_2' are same or different and can be independently selected from OH, halogens such as F, Cl, Br, I and substituted or unsubstituted alkyl/aryl sulfonyloxy such as methanesulfonyloxy (OMs), benzenesulfonyloxy, p-toluenesulfonyloxy (OTs) and the like; and 'n' is an integer selected from 1 to 10;

c) reacting compound of formula-6 with compound of formula-7 optionally in presence of a dehydrating agent to provide compound of formula-8,

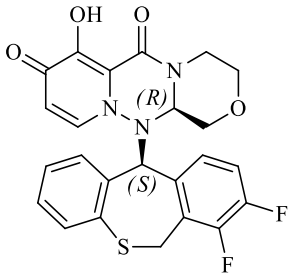


Formula-7



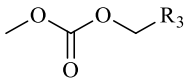
Formula-8

d) hydrolyzing the compound of formula-8 in presence of an acid, a base or a Lewis acid to provide compound of formula-2,



Formula-2

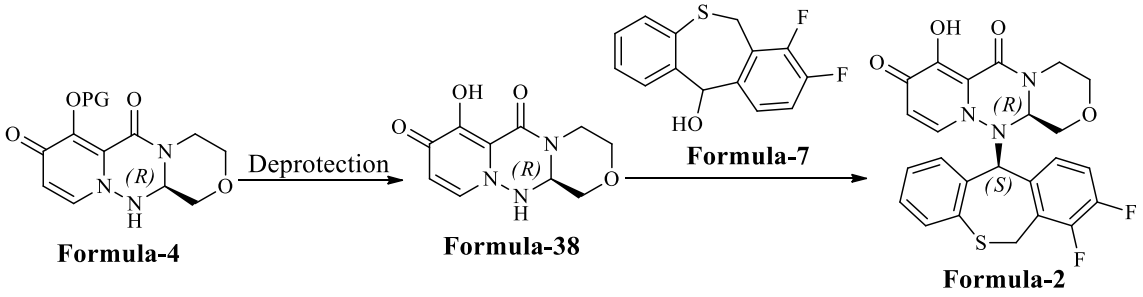
e) reacting compound of formula-2 with compound of formula-9 optionally in presence of a base to provide compound of formula-1.



Formula-9

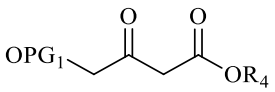
wherein, 'R_3' is selected from OH, halogens such as F, Cl, Br, I and substituted or unsubstituted alkyl/aryl sulfonyloxy such as methanesulfonyloxy (OMs), benzenesulfonyloxy, p-toluenesulfonyloxy (OTs) and the like.

The second embodiment of the present invention provides a process for the preparation of compound of formula-1 involving the use of compound of formula-38 as illustrated in scheme-I, comprising treating compound of formula-4 with a deprotecting agent to provide compound of formula-38 which on further reaction with compound of formula-7 optionally in presence of a dehydrating agent provides compound of formula-2. This can be further converted to compound of formula-1 as per the process described above.

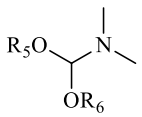


The third embodiment of the present invention provides another process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-10 with compound of formula-11



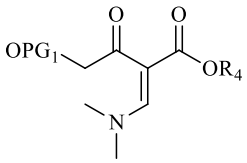
Formula-10



Formula-11

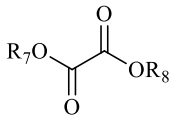
wherein, 'R_4', 'R_5' and 'R_6' are selected from straight or branched chain C_1-C_6 alkyl; and 'PG_1' represents hydroxyl protecting group;

optionally in presence of a base to provide compound of formula-12,

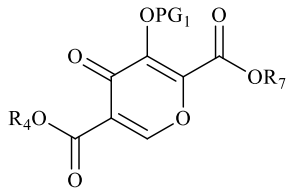


Formula-12

b) reacting compound of formula-12 with compound of formula-13 optionally in presence of a base to provide compound of formula-14,



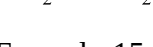
Formula-13



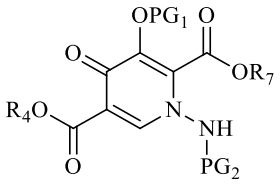
Formula-14

wherein, 'R_7', 'R_8' are same or different and can be selected from straight/branched chain C_1-C_6 alkyl groups;

c) reacting compound of formula-14 with compound of formula-15 optionally in presence of a base to provide compound of formula-16,



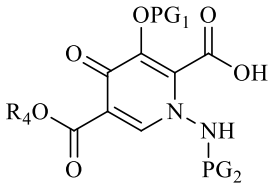
Formula-15



Formula-16

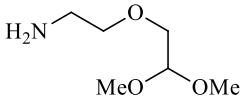
wherein, 'PG_2' represents amine protecting group;

d) treating compound of formula-16 with a deprotecting agent to provide compound of formula-17,

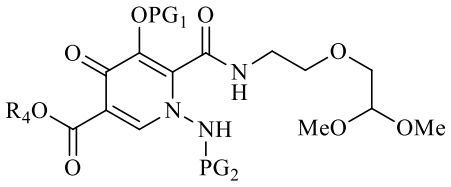


Formula-17

e) reacting compound of formula-17 with compound of formula-18 optionally in presence of a coupling agent and/or a base to provide compound of formula-19;

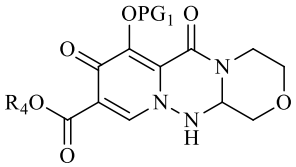


Formula-18



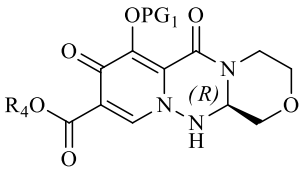
Formula-19

f) treating compound of formula-19 with a deprotecting agent followed by cyclization of the obtained compound to provide compound of formula-20,



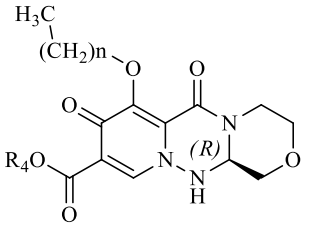
Formula-20

g) resolution of compound of formula-20 by treating it with a chiral acid to provide compound of formula-21,



Formula-21

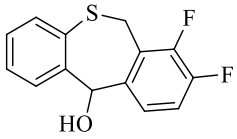
h) treating the compound of formula-21 with a deprotecting agent followed by reacting the obtained compound with CH_3-$(CH2)_n$-OH optionally in presence of a base to provide compound of formula-22,



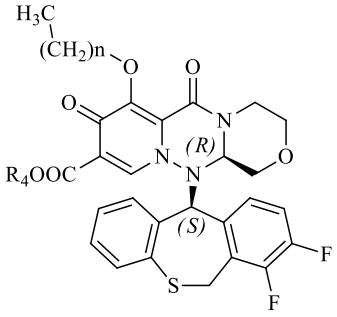
Formula-22

wherein, 'n' is an integer selected from 1 to 10;

i) reacting compound of formula-22 with compound of formula-7 optionally in presence of a dehydrating agent to provide compound of formula-23,

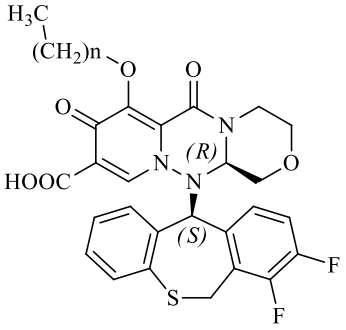


Formula-7



Formula-23

j) hydrolyzing the compound of formula-23 in presence of an acid or a base to provide compound of formula-24,



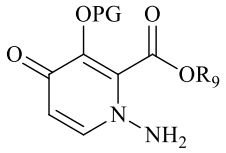
Formula-24

k) hydrolyzing compound of formula-24 in presence of an acid, a base or a Lewis acid followed by decarboxylation of the obtained compound to provide compound of formula-2,

l) converting the compound of formula-2 to compound of formula-1 as per the process described above.

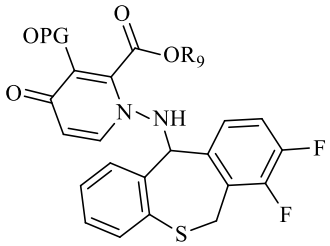
The fourth embodiment of the present invention provides a process for the preparation of compound of formula-1 involving the use of compound of formula-27 as illustrated in scheme-III, comprising;

a) reacting compound of formula-7 with compound of formula-25 to provide compound of formula-26,



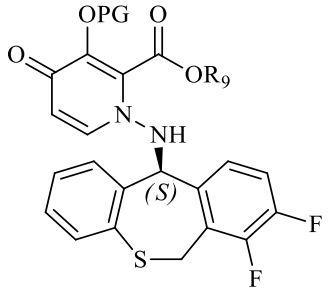
Formula-25

wherein, 'R_9' is selected from straight or branched chain C_1-C_6 alkyl; and 'PG' represents hydroxyl protecting group;



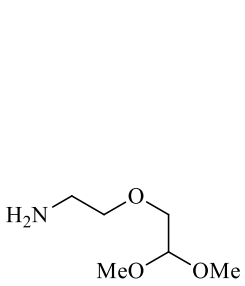
Formula-26

b) resolution of compound of formula-26 by treating it with a chiral acid to provide compound of formula-27,

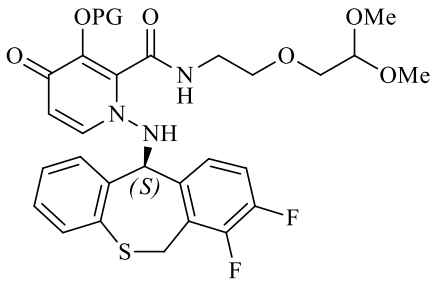


Formula-27

c) reacting compound of formula-27 with compound of formula-18 optionally in presence of a coupling agent and/or a base to provide compound of formula-29,



Formula-18

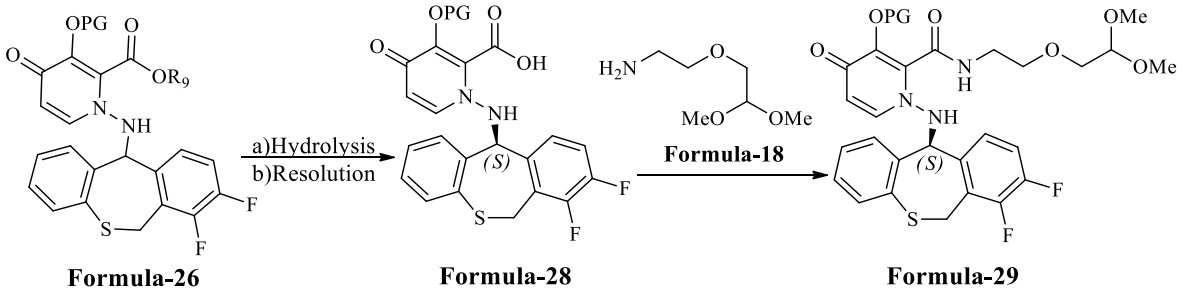


Formula-29

d) treating compound of formula-29 with a deprotecting agent followed by cyclization of the obtained compound to provide compound of formula-2,

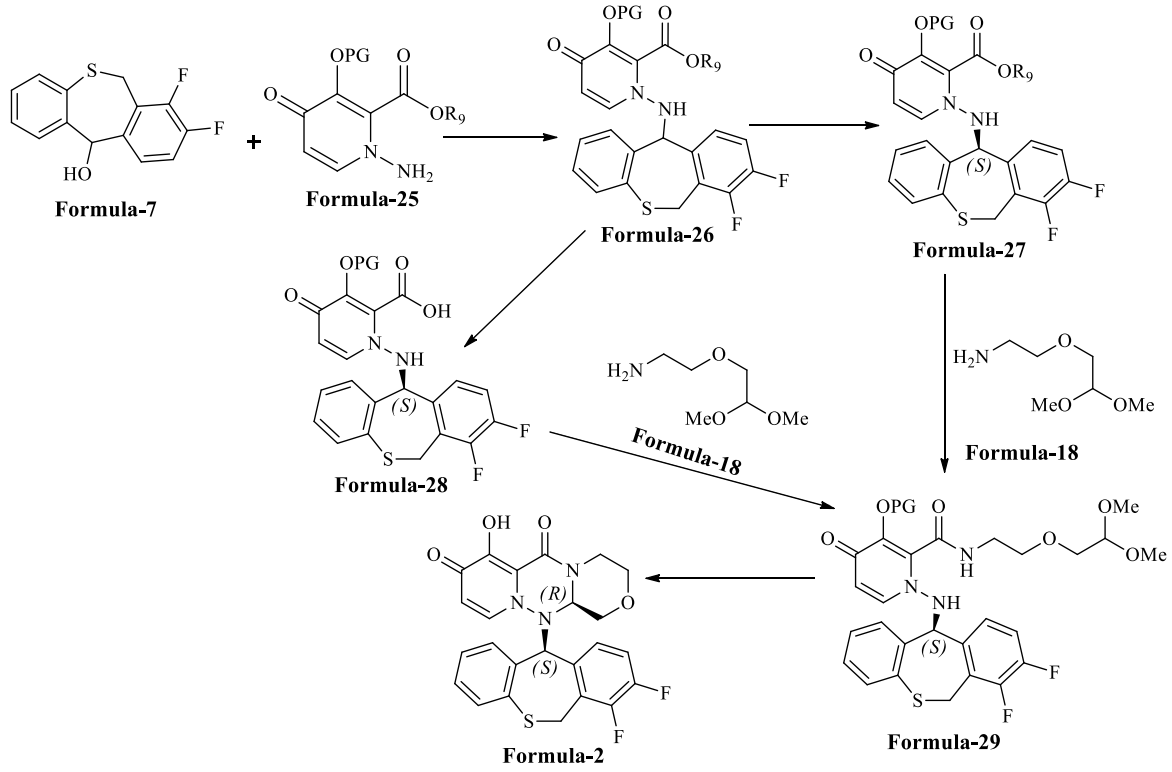
e) converting compound of formula-2 to compound of formula-1 as per the process described above.

The fifth embodiment of the present invention provides a process for the preparation of compound of formula-29, comprising hydrolysis of compound of formula-26 followed by resolution by treating with a chiral acid to provide compound of formula-28 which on reaction with compound of formula-18 optionally in presence of a coupling agent and/or a base to provide compound of formula-29.



Formula-26 **Formula-28** **Formula-29**

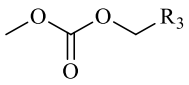
An embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising at least one of the following conversions



wherein, R_9 is selected from straight/branched chain C_1-C_6 alkyl;

'PG' represents ''hydroxyl protecting groups'' which can be selected from methyl, ethyl, tert-butyl, acetyl, pivaloyl, benzyl, benzoyl, silyl protecting groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl; tetrahydropyranyl, tetrahydrofuranyl, triphenyl methyl (trityl), methoxymethyl acetal (MOM), methoxypropyl acetal (MOP), ethoxyethyl acetal, benzyloxymethyl acetal (BOM), methoxymethyl, benzyloxymethyl, tert-butoxymethyl, methoxyphenyl, methoxytrityl (MMT), dimethoxytrityl (DMT).

The compound of formula-2 obtained by the above described process can be further converted to compound of formula-1 by reacting compound of formula-2 with compound of formula-9 optionally in presence of a base



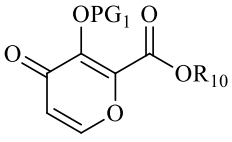
Formula-9

wherein, 'R_3' is selected from OH, halogens such as F, Cl, Br, I and substituted or unsubstituted alkyl/aryl sulfonyloxy such as methanesulfonyloxy (OMs), benzenesulfonyloxy, p-toluenesulfonyloxy (OTs).

Various conversions in the above described process are carried out by using appropriate reagents/solvents/catalysts etc as described in the present invention and by the procedures as described herein in the present invention.

The sixth embodiment of the present invention provides a process for the preparation of compound of formula-1 involving the use of compound of formula-33 as illustrated in scheme-IV, comprising;

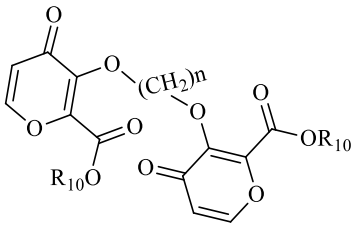
a) treating compound of formula-30 with a deprotecting agent followed by reacting the obtained compound with compound of formula-5 optionally in presence of a base to provide compound of formula-31,



Formula-30

R_1-$(CH2)_n$-R_2

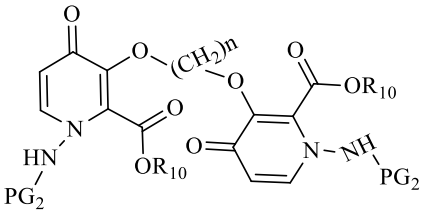
Formula-5



Formula-31

wherein, 'R_1', 'R_2' are as defined above; 'PG_1' represents hydroxyl protecting group; R_{10}' is selected from straight or branched chain C_1-C_6 alkyl; 'n' is as defined above;

b) reacting compound of formula-31 with compound of formula-15 to provide compound of formula-32,



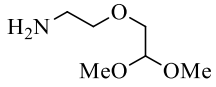
NH_2-NH-PG_2

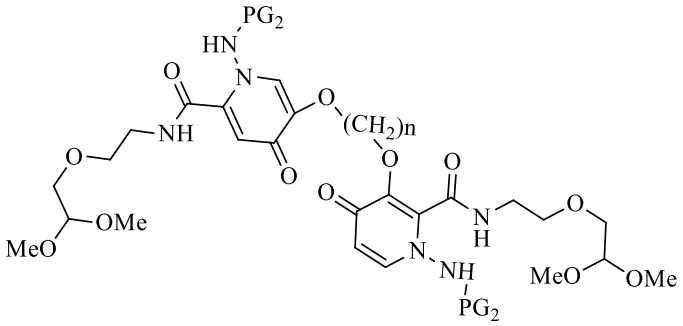
Formula-15

Formula-32

wherein, 'PG_2' represents amine protecting group;

c) reacting compound of formula-32 with compound of formula-18 optionally in presence of a coupling agent and/or a base to provide compound of formula-33,

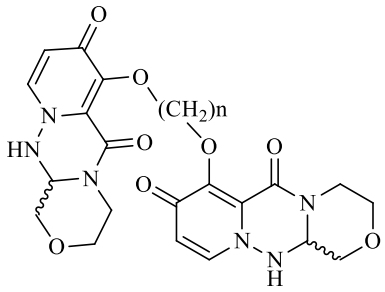




Formula-18

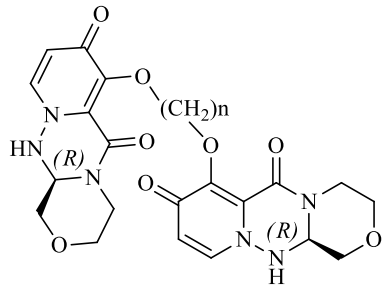
Formula-33

d) treating compound of formula-33 with a deprotecting agent followed by cyclization of the obtained compound to provide compound of formula-34,



Formula-34

e) resolution of compound of formula-34 by treating it with a chiral acid to provide compound of formula-6,

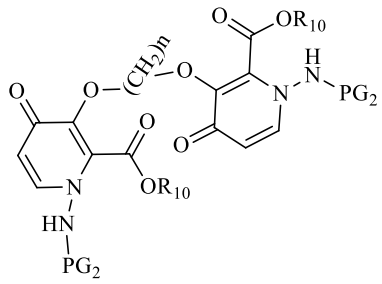


Formula-6

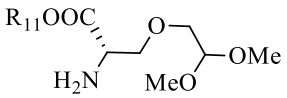
f) converting compound of formula-6 to compound of formula-1 as per the process described above.

The seventh embodiment of the present invention provides a process for the preparation of compound of formula-1 involving the use of compound of formula-35 as illustrated in scheme-IV, comprising;

a) reacting compound of formula-32 with compound of formula-37 optionally in presence of a coupling reagent and/or a base to provide compound of formula-35,

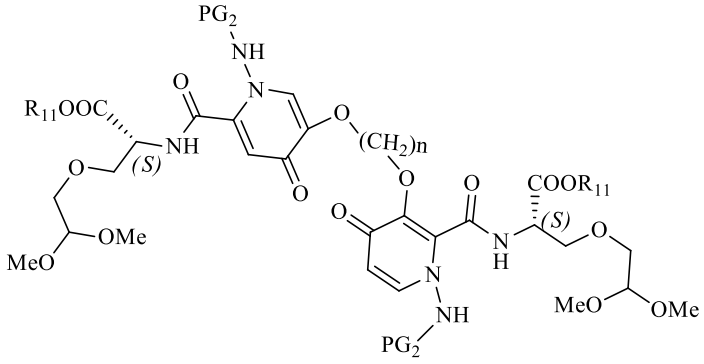


Formula-32



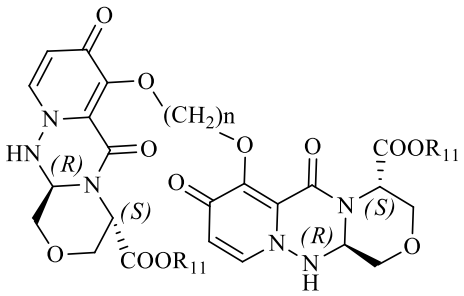
Formula-37

wherein, 'R_{10}' is as defined above; 'R_{11} is selected from hydrogen, C_1-C_6 straight chain or branched chain alkyl, aryl or aralkyl groups;



Formula-35

b) treating compound of formula-35 with a deprotecting agent followed by cyclization of the obtained compound to provide compound of formula-36,



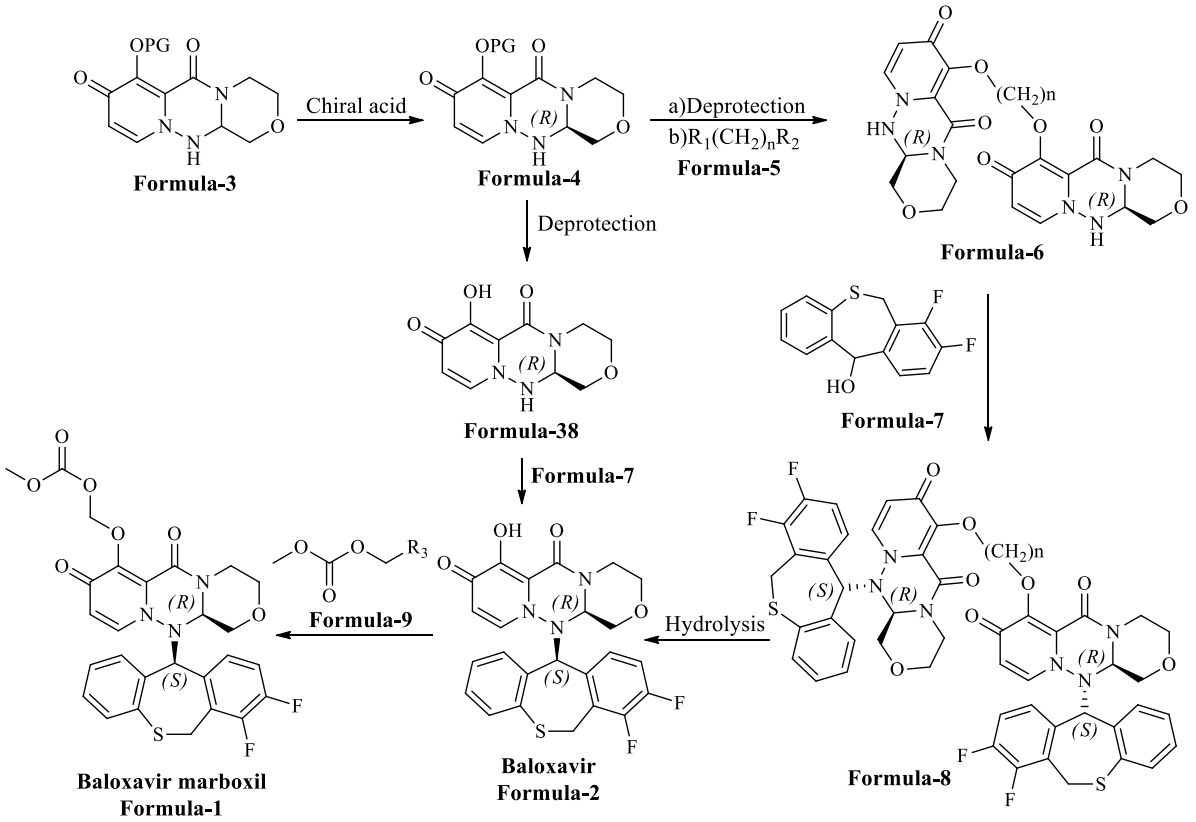
Formula-36

c) decarboxylation of compound of formula-36 (if R_{11}= H) or hydrolysis of compound of formula-36 followed by decarboxylation of the obtained compound (if $R_{11}\neq$ H) to provide compound of formula-6,

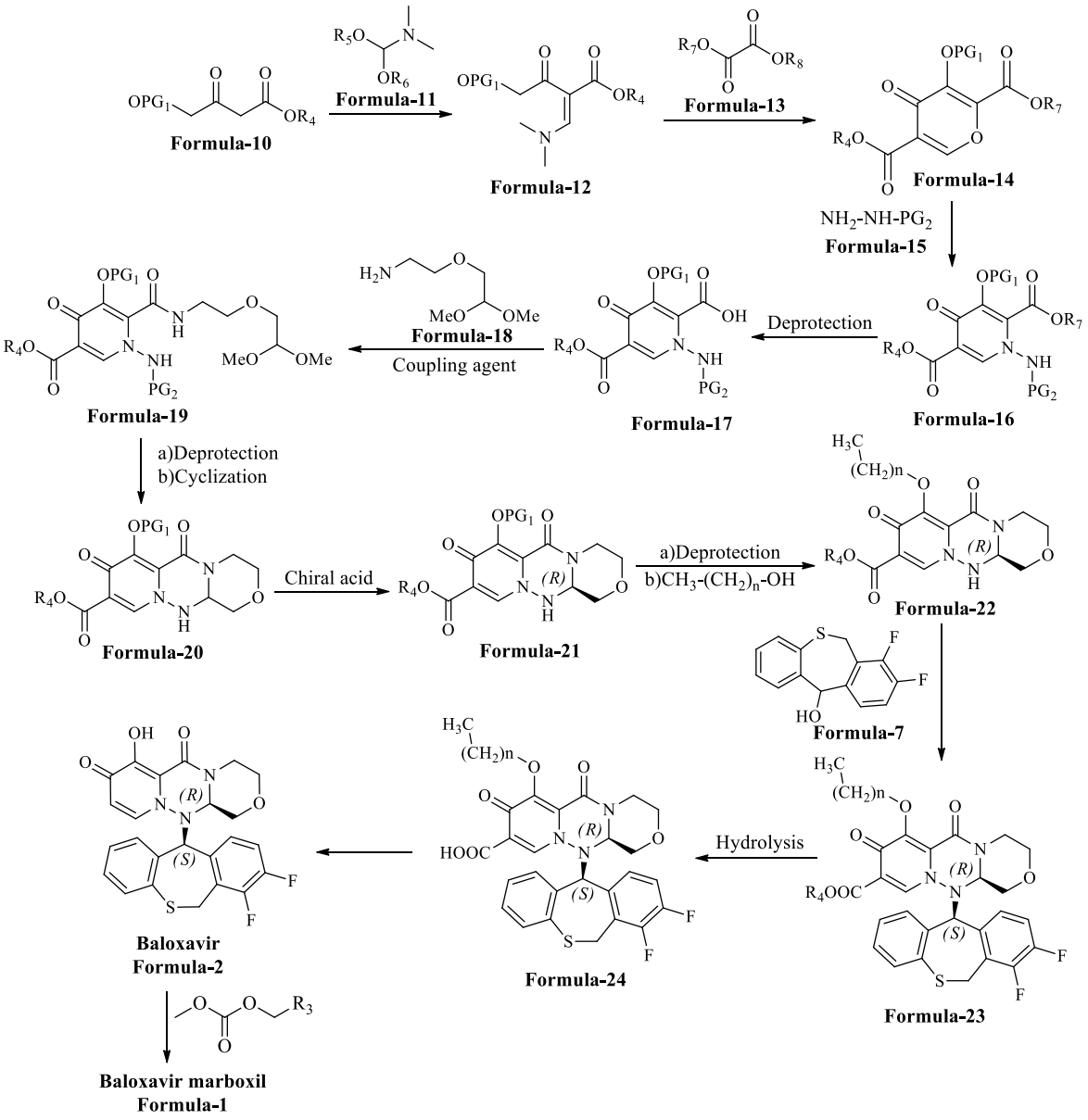
d) converting compound of formula-6 to compound of formula-1 as per the process described above.

The present invention is schematically represented as follows:

Scheme-I:



Scheme-II:



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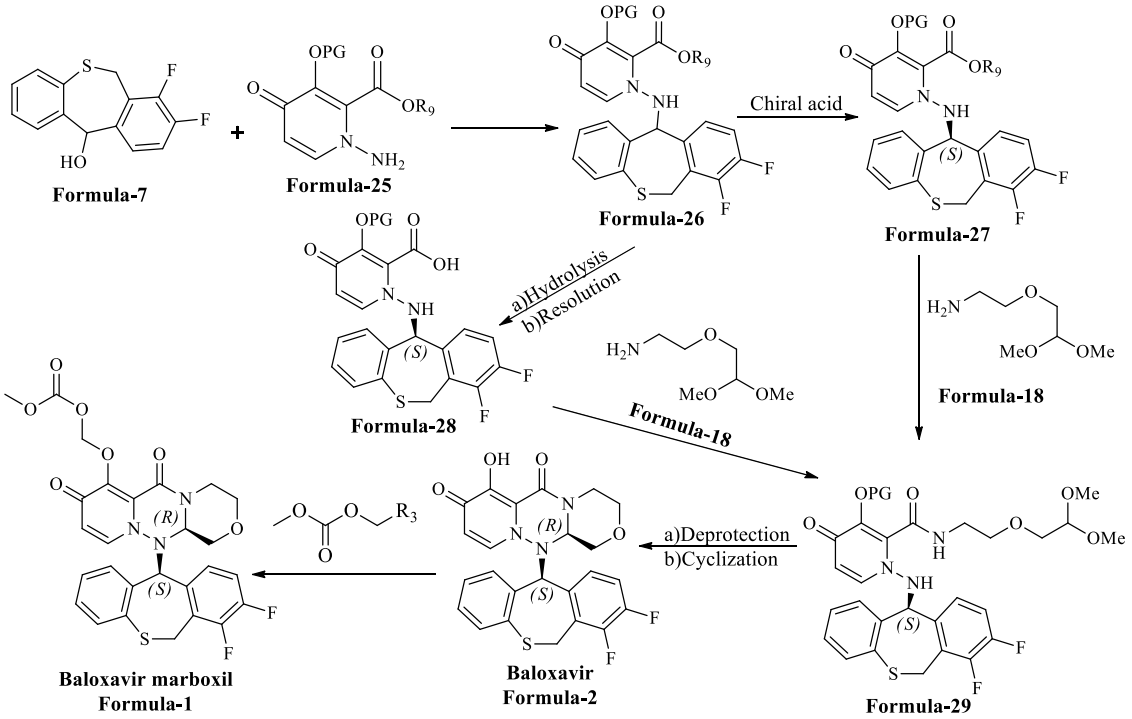
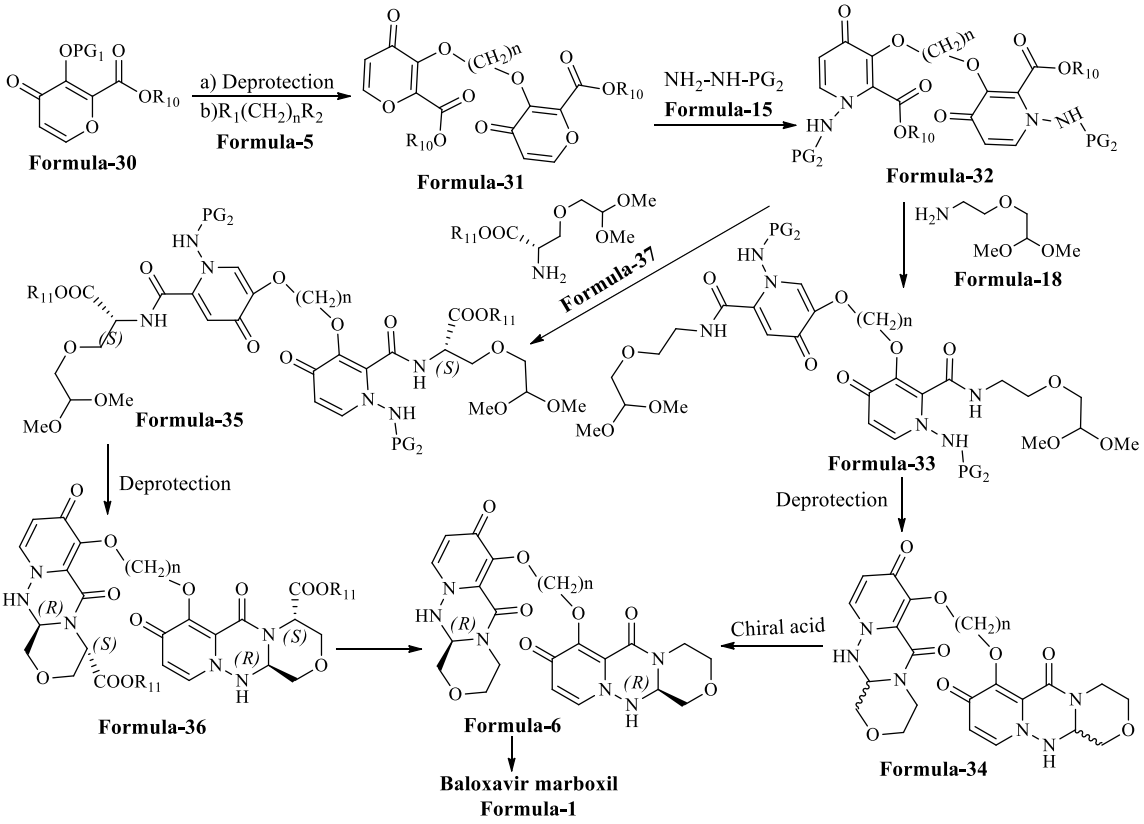
Scheme-III:



Scheme-IV:



In the above schemes-I, II, III and IV, 'n' is an integer selected from 1 to 10;

'R_1' and 'R_2' are same or different and can be independently selected from OH, halogens such as F, Cl, Br, I and substituted or unsubstituted alkyl/aryl sulfonyloxy such as methanesulfonyloxy (OMs), benzenesulfonyloxy, p-toluenesulfonyloxy (OTs) and the like;

'R_3' is selected from OH, halogens such as F, Cl, Br, I and substituted or unsubstituted alkyl/aryl sulfonyloxy such as methanesulfonyloxy (OMs), benzenesulfonyloxy, p-toluenesulfonyloxy (OTs) and the like;

R_4, R_5, R_6, R_7, R_8, R_9, R_{10} are independently selected from straight/branched chain C_1-C_6 alkyl; R_{11} is selected from H, C_1-C_6 straight/branched chain alkyl, aryl or aralkyl groups;

'PG' and 'PG_1' represents ''hydroxyl protecting groups'' which can be selected from but not limited to methyl, ethyl, tert-butyl, acetyl, pivaloyl, benzyl, benzoyl, silyl protecting groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and the like; tetrahydropyranyl, tetrahydrofuranyl, triphenyl methyl (trityl), methoxymethyl acetal (MOM), methoxypropyl acetal (MOP), ethoxyethyl acetal, benzyloxymethyl acetal (BOM), methoxymethyl, benzyloxymethyl, tert-butoxymethyl, methoxyphenyl, methoxytrityl (MMT), dimethoxytrityl (DMT) and the like;

'PG_2' represents "amine protecting group" selected from but not limited to alkoxycarbonyl such methoxycarbonyl (Moc), ethoxycarbonyl, tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), p-methoxybenzyl carbonyl (Moz or MeOZ), 9-fluorenylmethyloxy carbonyl (Fmoc), acetyl (Ac), benzoyl (Bz), benzyl (Bn), carbamate group, p-methoxyphenyl (PMP), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), tosyl (Ts), trifluoroacetyl (TFA), trichloroethoxycarbonyl (Troc), pivaloyl (Piv), triphenylmethyl (trityl or Trt) and the like.

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