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(71) Applicant: **CIPLA LIMITED** [IN/IN]; Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Mumbai, Maharashtra 400013 (IN).

(72) Inventors: **PHULL, Manjinder Singh**; Gobind Niwas, Bhattipada Road, Bhandup, Mumbai,Maharashtra 400 078 (IN). **SHAH, Bhavik**; A-wing, Flat no. 11&12, Arihant Apartment, Dada Save road, Near Swaminarayan temple, Kandivali-East, Mumbai, Maharashtra 400101 (IN). **KADLAG, Manoj**; C6/624, Madhav Srishti Shiv-Parvati CHS, Ltd., Khadakpada, Kalyan (west), Thane, Maharashtra 421301 (IN). **RAO, Dharmaraj Ramachandra**; 4/403, Garden Enclave, Pokhran Road 2, Thane (West), Thane, Maharashtra 400 601 (IN). **MALHOTRA, Geena**; 3403 Springs, Island City, Centre, Next to Wadala, Telephone Exchange, G. D Ambekar Marg, Dadar (East), Mumbai, Maharashtra 400014 (IN).

(74) Agent: **P., Aruna Sree**; Gopakumar Nair Associates'Shivmangal', 3rd Floor, Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai, Maharashtra 400 101 (IN).

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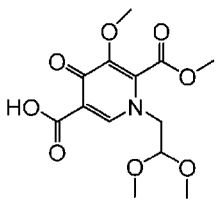
(54) Title: CONTINUES FLOW PROCESS FOR THE PREPARATION OF ACTIVE PHARMACEUTICAL INGREDIENTS - POLYCYCLIC CARBAMOYL PYRIDONE DERIVATIVES AND INTERMEDIATES THEREOF

(57) Abstract: The present invention discloses continues flow process for the preparation of polycyclic carbamoyl pyridone derivatives and intermediates thereof. In particular, the present invention discloses a process for the preparation of intermediate. Formule (V).



V

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Continues Flow Process For The Preparation Of Active Pharmaceutical Ingredients - Polycyclic Carbamoyl Pyridone Derivatives And Intermediates Thereof.

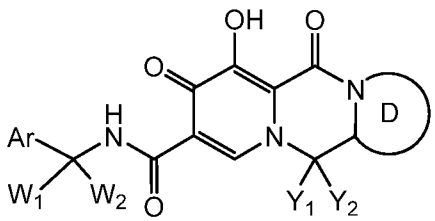
Technical filed:

The present invention relates to continues flow process for the preparation of polycyclic carbamoyl pyridone derivatives and intermediates thereof

Background and Prior art:

Polycyclic carbamoyl pyridone derivatives are known to act as human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitors (INSTI) in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

US8129385 B2 and WO2014100323, US9216996 B2 incorporated herein in their entirety by reference, describe various polycyclic carbamoyl pyridone derivatives and processes for their preparation. Among these polycyclic compounds, are disclosed the following tricyclic carbamoyl pyridone derivatives, of formula (A):



Formula A

or a stereoisomer or pharmaceutically acceptable salt thereof; wherein,

Ar is aryl substituted with one to three halogens;

W1 and W2 are each independently, hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; or

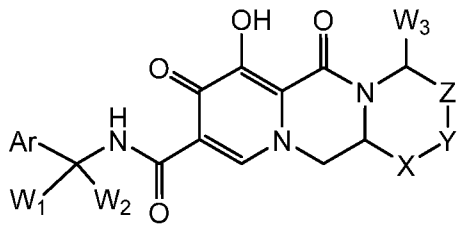
W1 and W2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^x, wherein each R^x is, independently, hydrogen, halo,

hydroxyl or C 1-6 alkyl, or wherein two R^x groups together with the carbon atom to which they are attached, form =0;

Y_1 and Y_2 are independently hydrogen, hydroxy, optionally substituted C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkenyl or C_{1-8} alkoxy, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted aryloxy or optionally substituted heterocyclic group; and

D ring is optionally substituted and optionally condensed monocyclic or bicyclic, 5 to 7 membered heterocycle containing 1 to 2 hetero atom(s); wherein heteroatom is selected from N, O or S.

Preferred tricyclic carbamoyl pyridone derivatives of formula (A) include those compounds of formula (B):



Formula B

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

Ar is aryl substituted with one to three halogens;

W_1 and W_2 are each independently, hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl; or

W_1 and W_2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^x group;

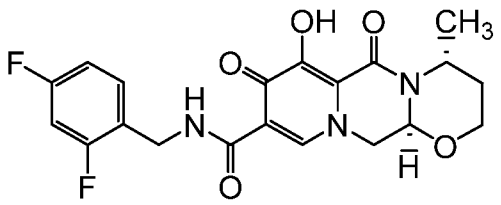
X is -0- or $–NW_4$ -or $–CHW_4$;

Y is $–CHW_5$;

W_3, W_4 and W_5 are each independently, hydrogen or C_{1-8} alkyl, C_{6-14} aryl, C_{1-8} alkyl, C_{6-14} aryl or alkoxy; or wherein W_3 and W_4 or W_3 and W_5 taken together form -L- wherein L is a carbocyclic ring containing having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms wherein the carbocyclic or

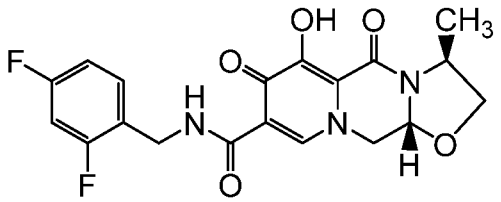
heterocyclic ring is optionally substituted with one or more R^x group, wherein each R^x is, independently, hydrogen, halo, hydroxyl or C_{1-8} alkyl, or wherein two R^x groups together with the carbon atom to which they are attached, form =0;
Z is a bond, $[-CH_2-]n$ or Y and Z taken together form $[-CH_2-]_n$; wherein n is an integer of 0 to 3.

Preferred tricyclic carbamoyl pyridone derivatives of formula (B) include those compounds of Formula (I),



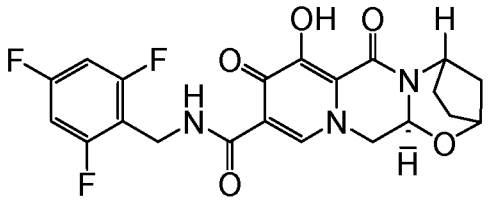
Formula I

wherein, n is an integer of 2;
Formula II



Formula II

wherein, n is an integer of 1;
and Formula III

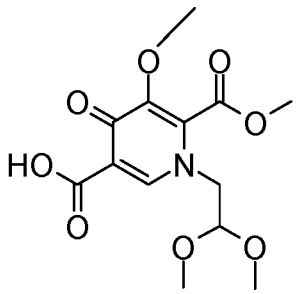


Formula III

Structure–activity studies have demonstrated that these tricyclic series of carbamoyl pyridines have superior potency against resistant viral strains.

The fact that tricyclic series of carbamoyl pyridines are effective against viral strains is of utmost importance. At the same time it is necessary that these effective compounds are available at an economic rate and are easily manufactured. It is also necessary that these compounds are easily manufactured with no or minimal production hazards and that there exist simple and efficient methods to manufacture the same on the production floor.

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V)



Formula V

is one of the key intermediate compounds used in the synthesis of tricyclic carbamoyl pyridone derivatives.

Several approaches are described in the literature to make compound V and its conversion to tricyclic carbamoyl pyridone derivatives.

H. Wang et al., *Organic Letters*, 2015, 17(3), 564-567 discloses the synthesis of GSK1265744, a tricyclic carbamoyl pyridone derivative having antiretroviral activity.

EP2527007A, WO 2014100323, discloses certain polycyclic carbamoyl pyridine derivatives and a process for preparing such compounds.

Although a number of processes for preparing tricyclic carbamoyl pyridone derivatives have been previously disclosed and claimed, the processes disclosed in the prior art are multistep and hence cumbersome. Importantly, the methods disclosed in the art are performed in the batch process mode.

The batch process is a single- or multi-stage process in which a certain quantity of inputs
(starting materials, solvents, catalysts, energy, etc.) are fed into the chemical reaction unit
under conditions suitable for obtaining the desired reaction (temperature, pressure, required time, etc.).

In the batch process, so long as the batch has not undergone the entire series of actions, there is no possibility of preparing a further batch. The batch process can be undertaken in one reactor in which all the actions are carried out one after the other, or in a series of reactors in each of which a different stage of the process is carried out.

With the batch process, concentration of reactants and products varies so long as the reaction progresses. After completion of the process, the reaction mixture is removed from the reactor and it then subjected to a suitable separation or purification steps to obtain desired degree of purity. The quality of the end product may be controlled by the addition of appropriate separation stages between the various other stages as required. Unreacted reactants are then separated from the reaction mixture, may be returned for a further reaction (usually after they have undergone a purification step), thus maximizing yield.

The batch process have several advantages. Batch reactors can be used for multiple products and processes, they are easy to scale up from bench chemistry. Unfortunately, they require human intervention at nearly every step of the process. The reactors need to be cleaned between every run and requires work force for several days depending upon the batch size.

An improved process for the preparation of compounds of Formula (I) is published in the article "7-Step Flow Synthesis of the HIV Integrase Inhibitor Dolutegravir" (Ziegler_et_al- May, 2018-Angewandte_Chemie_International_Edition).

Therefore, there exists a need to develop a simple, more economical, cost effective and efficient method of manufacturing the tricyclic carbamoyl pyridone derivatives that is suitable for industrial scale-up.

The process of the present invention enables a large scale synthesis of tricyclic carbamoyl pyridone derivatives having a high degree of chromatographic and optical purity controlled particle size, and low residual solvent content.

Objects of the invention:

The object of the present invention is to provide a continuous flow process for preparing intermediate, 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine -3-carboxylic acid (V).

Yet another object of the present invention is to provide a continuous flow process for preparing tricyclic carbamoyl pyridone derivatives of formula (B); more preferably compound of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof by using the intermediate, 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V).

Yet another object of the present invention is to provide a continuous flow process for preparing tricyclic carbamoyl pyridone derivatives of formula (B) and of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof from methyl-4-methoxy acetoacetate (IX).

Yet another object of the present invention is to provide, large scale synthesis of tricyclic carbamoyl pyridone derivatives of formula (B) and of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof having high degree of chromatographic and optical purity, controlled particle size and low residual solvent content.

Yet another object of the present invention is to provide a continuous flow process for the synthesis of tricyclic carbamoyl pyridone derivatives of formula (B) and of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof which is simple, economical and suitable for industrial scale-up.

Summary of the Invention:

The present invention relates to a new method for the preparation of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), useful in the synthesis of tricyclic carbamoyl pyridone derivatives of formula (B), more preferably compound of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, said method comprises an integrated continuous flow process for reactions wherein a succession of integrated flow reactors are used to perform a series of reaction steps to yield the final product.

In one aspect the process is a multistep synthesis of intermediate, 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), in a flow without isolation of intermediates produced during the flow.

In the context of the present invention, the term "without isolation" means that the product referred is not isolated as a solid, for example it is not isolated from the reaction mass and dried to form a solid. Thus, "without isolation" may mean that the product remains in solution and is then used directly in the next synthetic step,

In another aspect the process is a multistep synthesis of tricyclic carbamoyl pyridone derivatives of formula (B) and of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, in a flow from the intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), prepared by the process of the present invention.

In yet another aspect the process is a multistep synthesis of tricyclic carbamoyl pyridone derivatives of formula (B) and of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, in a flow from the intermediate, methyl-4-methoxy acetoacetate (IX).

In yet another aspect the work-up is done in classical batch equipment. It is a mixed process with continuous reactions and batch workup.

The continuous flow process of the present invention has many advantage over the batch process as follows:-

1. Minimizes handling of intermediates, toxic and corrosive reagents and solvents.
2. Reduces solvent load, minimizes effluents and waste generation and hence more greener chemistry approach.
3. Dramatically reduced reaction times, less down streaming processing and increases process efficiency.
4. High through put, high yield and controlled particle size of active pharmaceutical ingredients.

In another aspect, the present invention provides tricyclic carbamoyl pyridone derivatives of formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, obtainable by the processes substantially as herein described with reference to the examples.

In another aspect, the present invention provides a use of tricyclic carbamoyl pyridone derivatives of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, obtainable by the process of the present invention for the manufacture of therapeutic agent, preferably an antiretroviral for the treatment of HIV-AIDS.

In another aspect the present invention provides a use of tricyclic carbamoyl pyridone derivatives of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, obtainable by the process of the present invention, for treating HIV-AIDS.

In another aspect the present invention provides a method of treating HIV-AIDS, comprising administering the tricyclic carbamoyl pyridone derivatives of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof, obtainable by a process of the present invention.

In another aspect, the present invention provides a process substantially as herein described with reference to the examples.

Further features of the present invention are defined in the dependent claims.

DESCRIPTION OF THE DRAWINGS:

Figure 1 illustrates in schematic view, continuous chemical flow synthesis of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), in accordance with a preferred embodiment of the present invention.

Figure 2 illustrates in schematic view, continuous chemical flow synthesis of sodium salt of Formula (I), from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), in accordance with a preferred embodiment of the present invention.

Figure 3 illustrates in schematic view, continuous chemical flow synthesis of sodium salt of Formula (I), from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), in accordance with a preferred embodiment of the present invention.

Figure 4 illustrates in schematic view, semi multi-step continuous chemical flow synthesis of intermediate (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) for the total synthesis of sodium salt of Formula (I), in accordance with a preferred embodiment of the present invention.

Figure 5 illustrates in schematic view, continuous chemical flow synthesis of sodium salt of Formula (II), starting from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), in accordance with a preferred embodiment of the present invention.

Figure 6 illustrates in schematic view, continue chemical flow synthesis of sodium salt of Formula (III), starting from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), in accordance with a preferred embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention describes an integrated, continuous flow method for the preparation of tricyclic carbamoyl pyridone derivatives of formula (B). More preferably the invention relates to an integrated, continuous flow method for the

preparation of compounds of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof.

Translating reactions into continuous-flow systems is aiding more efficient, safer, and automated reactions. The ability of continuous-flow systems to rapidly heat and cool reactions, micromix solutions, and improve reaction homogeneity affords opportunities to explore novel transformations while being environmentally conscious and creative.

At the core of continuous-flow systems are pumps that drive fluids through channels, tubes, or packed beds in a continuous fashion. Multi-step continuous-flow platforms are essentially several reactors connected into a single flow sequence.

The injected fluid flows into reactor coils where the specific transformation is subjected to a range of conditions. For example, the fluid entering the reactor coil can be rapidly heated or cooled to mediate an effective transformation.

The residence time of the fluid within the system is determined by the internal diameter and length of the reactor coil.

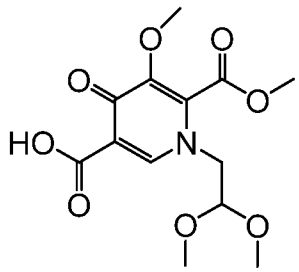
Mixers and unions connect reactor coils together, and allow the addition of new reagents to the continuous-flow stream. The solution can be flowed through packed bed reactors to ensure efficient mixing, or to provide exposure to immobilized reagents for synthetic transformations.

Furthermore, in-line separation of immiscible fluids (e.g. MDC and water) is possible through the use of membrane-based liquid–liquid separators.

Subjecting the continuous-flow stream to a backpressure allows solvents to be used above their atmospheric boiling points while ensuring reaction homogeneity as the solution passes between reactor coils at different temperatures.

A continuous-flow systems allow the possibility of in-line purification and reagent introduction at set points in the continuous-flow sequence.

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V),



V

is one of the important intermediates useful in the synthesis of compounds of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salts thereof.

In a first aspect the present invention provides an integrated, continuous flow method for the preparation of intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V). Said method comprises four major chemical synthetic steps, performed in a succession of flow reactors that are connected in such a way to give an integrated flow manufacturing system without batch work-up.

Optionally, all flow reactors may be connected with batch equipment to get the right purity before introducing the flow in the next following continuous reaction step.

The four consecutive reactions are achieved in one single flow in four different types of continuous reactors as depicted in Figure 1.

Step 1: Methyl (Z)-2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (VIII)

In the Step 1, methyl-4-methoxy acetoacetate (IX) is reacted with N,N-dimethylformamide dimethylacetal in a micro channel reactor to yield methyl (Z)-2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (VIII). In an embodiment, Step 1 would typically be run, essentially without the use of any solvent. The residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 30 seconds to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 10°C and 100°C, preferably between 20°C and 80°C and even more preferably between 20°C and 60°C.

Step 2: Methyl (Z)-2-(((2,2-dimethoxyethyl)amino)methylene)-4-methoxy-3-oxobutanoate (VII)

In the Step 2, methyl (Z)-2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (VIII) is further introduced into micro channel reactor and reacted with amino acetaldehyde dimethylacetal to yield methyl (Z)-2-(((2,2-dimethoxyethyl)amino)methylene)-4-methoxy-3-oxobutanoate (VII). In an embodiment, Step 2 would typically be run, essentially without the use of any solvent. The residence time of said mixture in the reactor is typically anywhere between 15 seconds and 20 minutes, preferably about 15 seconds to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 10°C and 150°C , preferably between 20°C and 120°C and even more preferably between 20°C and 100°C.

Step 3: Dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (VI)

In the Step 3, methyl (Z)-2-(((2,2-dimethoxyethyl)amino)methylene)-4-methoxy-3-oxobutanoate (VII) is further introduced into a tube reactor and reacted with a solution of dimethyl oxalate in methanol in the presence of sodium methoxide to yield dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-

dicarboxylate (VI). The residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 30 seconds to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 60°C and 100°C.

Step 4: 1-(2,2-Dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V)

In the Step 4, dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (VI) on further hydrolysis in a tube flow reactor, with solution of sodium bicarbonate and sodium hydroxide in water, yields 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V). The residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 60°C and 100°C.

Preferably, 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) obtained by the continuous flow reactions, may be optionally purified within said flow reactor or in a batch, after step 4 is completed, e.g. by using alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, t-butanol and the like by the processes known in the art.

All the reactions in steps 1 to 4 described in Figure 1, are performed in flow reactors connected to each other in such a way to provide an integrated system. There are many configurations of such connected reactor system, that a person skilled in the art is aware of.

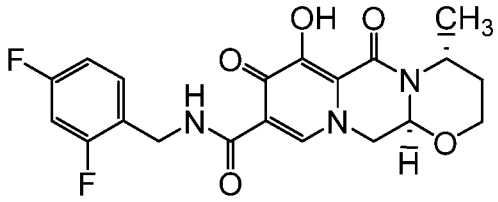
In Ziegler et al, the overall reaction time from Step 1 to Step 3 is 73.3 minutes with overall yield of isolated intermediate (VI) is 56%. The process of the present invention is advantages as it reduces the overall reaction time from Step 1 to Step 4, from about 74 minutes to 6 minutes, with overall yield of isolated intermediate (V) is 90%.

The other advantages of this continuous reactor system are:

- The temperature used in each module of reactor can be adapted at the kinetic rate of reaction
- Overall reaction time is reduced from about 19 hours to about 20 minutes
- Use of less toxic dimethyl carbonate as green solvent,
- Reduced volume of dimethyl carbonate (4.55 volume) as compared to ACN (13 volumes) as reported in the prior art.
- Avoids use and handling of toxic reagents such as lithium hydride.
- The overall yield after the 4 consecutive reactions in a continuous process that takes less than 20 minutes ,is up to 90% and produced intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V).
- The overall purity of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) is to > 99.5%
- Avoids isolation of intermediates at each stage and tedious work up procedure.
- This process afforded greater yields than what is previously reported in batch systems, adding yet another example of improved yields in continuous flow.

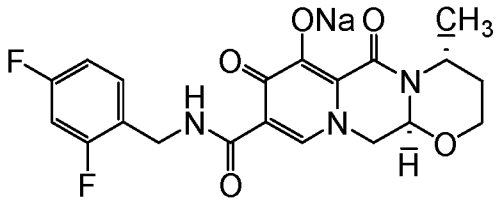
The key intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) obtained by the flow process, is further used in the synthesis of compounds of Formula (I), Formula (II) and Formula (III) or a stereoisomer or pharmaceutically acceptable salt thereof.

In a second aspect the present invention provides an integrated, continuous flow method for the preparation of Compound of formula (I).



Compound I

Preferably, Compound of formula (I) is isolated in the form of its sodium salt ,



Sodium salt of Compound(I)

and the said method comprises five major chemical synthetic steps, performed in a succession of flow reactors that are connected in such a way to give an integrated flow manufacturing system without batch work-up.

The five consecutive reactions are achieved in one single flow in five different types of continuous reactors as depicted in Figure 2.

Step 5a: 5-Methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa)

In the Step 5a, 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) obtained in step 4 is introduced in a micro channel reactor and deprotected with methane sulfonic acid in the solvent mixture of acetic acid and dimethyl carbonate to yield 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa). In an embodiment the residence time of said mixture in the reactor is

typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

The advantage is reaction time is reduced drastically to 20 minutes from storing at (-10°C) over 3 days as reported in the prior art.

Step 6a: (4S,12aR)-7-Methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa)

In the Step 6a, 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) is introduced in Tube Flow Reactor and cyclized with solution of R-3 amino-1-butanol in dimethyl carbonate followed by quenching with Aq. HCl solution and separating organic layer to yield (4S,12aR)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa). In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

Step 7a : (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa)

In the Step 7a, organic layer containing (4S,12aR)-7-Methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa) is first mixed with N-methyl morpholine in chlorinated

solvent preferably MDC and then further reacted with solution of 2,4-diflurobenzylamine in MDC in presence of ethyl chloroformate.

In an embodiment the residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between -20°C and 30°C, preferably between -10°C and 20°C and even more preferably between -5°C and 15°C.

Optionally, (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) is isolated in a suitable solvent, preferably in IPA, after acid base workup. The compound (IIa) obtained by flow process has purity of >99% and yield of 120% w/w.

Preferably, (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) is not isolated and may be used in the next flow process.

Step 8a : Compound (I)

In step 8a, a solution of (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) is further introduced in next flow reactor and demethylated with lithium bromide in the presence of a suitable solvent typically THF. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 10 minutes to about 30 minutes, preferably about 15 minutes to 20 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 100°C, preferably between 50°C and 80°C and even more preferably between 60°C and 70°C.

Step 9a1 : Sodium salt of compound (I)

In step 9a1, a solution of compound (I) is introduced in Tube Flow Reactor and mixed with a solution of sodium hydroxide in methanol. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 1 minute to about 30 minutes, preferably about 5 minutes to 15 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 0°C and 50°C, preferably between 10°C and 40° C and even more preferably between 20°C and 30°C.

In alternative embodiment, the method comprises conversion of (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido [1',2':4,5] pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) to sodium salt of compound (I) using flow process.

Alternatively, the consecutive reactions are achieved in one single flow in different types of continuous reactors as depicted in Figure 3.

Step 9a2 : Sodium salt of compound (I) from compound (IIa)

(4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) obtained from step 7a is mixed with polar solvent such as n-butanol or methanol, in a Tube Flow Reactor and reacted with a solution of sodium hydroxide in methanol. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 5 minutes to about 30 minutes, preferably about 10 minutes to 20 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 70°C and 100°C.

Sodium salt of compound I is isolated by simple filtration.

All the reactions in steps 5a to 9a1 described in Figure 2 or in steps 5a to 9a2 as described in Figure 3, are performed in flow reactors connected to each other in such a way to provide an integrated system.

There are many configurations of such connected reactor system, that a person skilled in the art is aware of.

In yet an alternative embodiment, there is provided continuous chemical flow synthesis of compound (I) or sodium salt of compound (I), from methyl-4-methoxy acetoacetate (IX), wherein key intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) is not isolated but put into further continuous flow.

The Sodium salt of compound (I) obtained by the process of the present invention has chiral purity of at least 98% ee. This forms one aspect of the present invention.

The Sodium salt of compound (I) obtained by the process of the present invention has particle size of d90 NMT 30µm, preferably NMT 20 µm, more preferably NMT 15 µm. This forms another aspect of the present invention.

In yet an alternative embodiment the compound (I) is isolated by classical batch technology. Preferably, in step 8, after a residence time of about 15 minutes, the reaction mass is cooled to room temperature and treated with 10% Aq. HCl soln. Extraction with dichloromethane followed work up yields compound (I) having purity > 99.0% & yield > 75%w/w.

In yet an alternative embodiment, the consecutive reactions steps 5a, 6a, and 7a are achieved in one single flow in three different types of continuous reactors, whereas step 8a is achieved in a separate flow to yield compound (I).

In yet an alternative embodiment, compound (IIa) obtained by flow synthesis is first isolated and then converted to either compound (I) or sodium salt of compound (I) by flow synthesis.

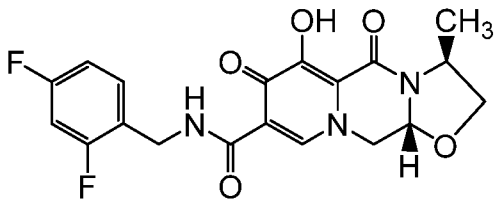
The semi multi-step continuous chemical flow synthesis of intermediate (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido [1',2':4,5] pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) for the total synthesis of sodium salt of Formula (I), in accordance with a preferred embodiment of the present invention is as depicted in Figure 4.

The advantages of this continuous reactor system are:

- The temperature used in each module of reactor can be adapted at the kinetic rate of reaction
- Overall reaction time is reduced from about 75 hours as reported in US8889877 B2 to less than 50 minutes.
- Avoids handling of toxic reagents and multiple solvent systems at each stage.
- Avoids isolation of intermediates at each stage and tedious work up procedure
- The overall yield for the 5 consecutive reactions is up to 90% in a continuous process that takes less than 50 minutes.
- Sodium salt of compound (I) obtained by the batch process as reported in the prior art, has unmicronized particle size of d90 about 60-70 μm. Hence requires minimum three micronizations to achieve the desired particle size. Further, due to low minimum ignition temperature of sodium salt of compound (I), it is unsafe to micronize the API on large scale. The sodium salt of compound (I)obtained by the flow process of the present invention, has particle size of d90< 10 μm, d50< 5 μm and d10< 2 μm. Thus, avoids repeated micronization making it safe on large scale.

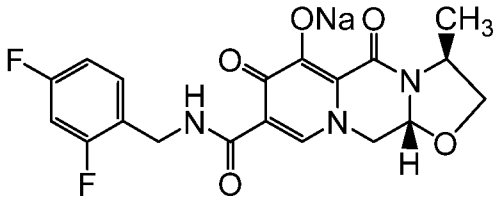
- This process afforded greater yields than what is previously reported in batch systems, adding yet another example of improved yields in continuous flow.
- The above synthetic conditions allow stereo selectivity in favour of Compound (I) and sodium salt thereof from 98% (ee) which is a marked improvement over the methods used so far. The desired product was obtained in 98% conversion and 98% ee
- Minimising waste
- Reducing purification steps and production time w r t batch synthetic route.
- high yielding system requiring only minimal downstream processing was achieved.
- The key intermediate (V) for the synthesis of tricyclic carbamoyl pyridone derivatives of formula (B), was synthesized in 90% conversion and 75% yield.
- In this comparative study between batch and continuous flow, translating the reaction into a continuous-flow system increased yield, purity and conversion while decreasing by-products formation
- Without departing from the scope of the invention , many parameters such as solvents and reagents, heat and mass transfer, mixing and residence times, direct in-line purification and analysis techniques can readily altered to obtain desired products with high yield and purity.
- Advantageously, the flow reactor configuration can also be readily customised to meet the specific demands of the reaction and continuous processing requirements.

In a fifth aspect by following similar protocol, the scope of the present invention may be further extended to an integrated, continuous flow method for the preparation of Compound of formula (II).



Compound II

Preferably, Compound of formula (II) is isolated in the form of its sodium salt ,



Sodium salt of Compound II

and the said method comprises five major chemical synthetic steps, performed in a succession of flow reactors that are connected in such a way to give an integrated flow manufacturing system without batch work-up.

The five consecutive reactions are achieved in one single flow in five different types of continuous reactors as depicted in Figure 5.

Step 6b : (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIIb)

In the Step 6b, 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) is introduced in Tube Flow Reactor and cyclized with solution of (S)-2-amino-propan-1-ol in in dimethyl carbonate followed by quenching with Aq. HCl solution and separating organic layer to yield Compound (IIIb). In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature. The operation temperature

in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

Step 7b: (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb)

In an embodiment, organic layer containing (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIIb) from step 6b, is first mixed with N-methyl morpholine in a chlorinated solvent preferably MDC and then further reacted with solution of 2,4-diflurobenzylamine in MDC in presence of ethyl chloroformate.

The residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between -20°C and 30°C, preferably between -10°C and 20°C and even more preferably between -5°C and 15°C.

Optionally, (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) is isolated in a suitable solvent, preferably in IPA, after acid base workup. The compound (IIb) obtained by flow process has purity of >95% and yield of 100% w/w.

Preferably, (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) is not isolated and may be used in the next flow process.

Step 8b : Compound (II)

A solution of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) in MDC is further introduced in next flow reactor and demethylated with lithium bromide in the presence of a suitable solvent typically THF. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 10 minutes to about 30 minutes, preferably about 15 minutes to 20 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 100°C, preferably between 50°C and 80°C and even more preferably between 60°C and 70°C.

Step 9b1 : Sodium salt of compound (II)

In step 9b1, a solution of compound (II) is introduced in Tube Flow Reactor and mixed with a solution of sodium hydroxide in methanol. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 1 minute to about 30 minutes, preferably about 5 minutes to 15 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 0°C and 50°C, preferably between 10°C and 40° C and even more preferably between 20°C and 30°C.

In alternative embodiment, the method comprises conversion of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) to sodium salt of compound (II) using flow process.

Step 9b2 : Sodium salt of compound (II) from (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb)

(3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro oxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) obtained

from step 7b is mixed with polar solvent such as n-butanol or methanol in a Tube Flow Reactor and reacted with a solution of sodium hydroxide in methanol. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 5 minutes to about 30 minutes, preferably about 10 minutes to 20 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 70°C and 100°C.

All the reactions in steps 5a to 9b1 described in Figure 5 or in steps 5a to 9b2 as described in Figure 5, are performed in flow reactors connected to each other in such a way to provide an integrated system.

There are many configurations of such connected reactor system, that a person skilled in the art is aware of.

In yet an alternative embodiment, there is provided continuous chemical flow synthesis of compound (II) or sodium salt of compound (II), from methyl-4-methoxy acetoacetate (IX), wherein key intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) is not isolated but put into further continuous flow.

The Sodium salt of compound (II) obtained by the process of the present invention has chiral purity of 95%ee. This forms one aspect of the present invention.

The Sodium salt of compound (II) obtained by the process of the present invention has particle size of d90 NMT 15µm. This forms another aspect of the present invention.

In yet an alternative embodiment the compound (II) is isolated by classical batch technology. Preferably, in step 8b, after a residence time of about 15 minutes, the

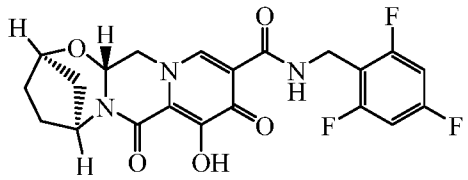
reaction mass is cooled to room temperature and treated with 5% acetic acid solution to yield compound (II), having purity > 95.0% & yield > 80%w/w.
In yet an alternative embodiment, the consecutive reactions steps 5a, 6b, and 7b are achieved in one single flow in three different types of continuous reactors, whereas step 8b is achieved in a separate flow to yield compound (II).

In yet an alternative embodiment, there is provided semi multi-step continuous chemical flow synthesis of intermediate (IIb) for the total synthesis of either compound (II) or sodium salt of compound (II).

The advantages of this continuous reactor system are:

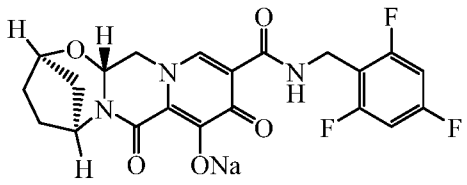
- Overall reaction time is reduced
- Avoids handling of toxic reagents and multiple solvent systems at each stage.
- Avoids isolation of intermediates at each stage and tedious work up procedure
- Desired particle size is achieved without further micronization.
- Retains enantiomeric purity
- Improves yield and purity

In a fifth aspect by following similar protocol, the scope of the present invention may be further extended to an integrated, continuous flow method for the preparation of Compound (III).



Compound III

Preferably, Compound (III) is isolated in the form of its sodium salt,



Sodium salt of Compound III

and the said method comprises five major chemical synthetic steps, performed in a succession of flow reactors that are connected in such a way to give an integrated flow manufacturing system without batch work-up.

The five consecutive reactions are achieved in one single flow in five different types of continuous reactors as depicted in Figure 6.

Step 6c : (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1 ',2':4,5]pyrazino[2,1-b][1 ,3]oxazepine-10-carboxilic acid (IIIc)

In the Step 6c, 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) is introduced in Tube Flow Reactor and cyclized with solution of (1R,3S)-3-aminocyclopentanol in dimethyl carbonate followed by quenching with Aq. HCl solution and separating organic layer to yield (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1 ',2':4,5]pyrazino[2,1-b][1 ,3]oxazepine-10-carboxilic acid (IIIc). In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

The advantage is reaction time is reduced drastically to about 20 minutes from storing at overnight stirring at RT as reported in the prior art.

Step 7c: (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc)

In an embodiment, organic layer containing (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3] oxazepine-10-carboxilic acid (IIIc) from step 6c, is first mixed with N-methyl morpholine in a chlorinated solvent preferably MDC and then further reacted with solution of (2,4,6-trifluorophenyl) methanamine in MDC in presence of ethyl chloroformate.

The residence time of said mixture in the reactor is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between -20°C and 30°C, preferably between -10°C and 20°C and even more preferably between -5°C and 15°C.

Optionally, (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide(IIc) is isolated in a suitable solvent, preferably in IPA, after acid base workup. The compound (IIc) obtained by flow process has purity of >95% and yield of 90% w/w.

Preferably, (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) is not isolated and may be used in the next flow process.

The advantage is reaction time is reduced drastically to about 10 minutes from 90 minutes and avoids use of condensing agent like HATU as reported in the prior art.

Step 8c : Compound (III)

In step 8c, a solution of (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) is further introduced in next flow reactor and demethylated with lithium bromide in the presence of a suitable solvent typically THF. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 30 seconds to about 10 minutes, preferably about 1 minute to 5 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 100°C, preferably between 50°C and 80°C and even more preferably between 60°C and 70°C.

Step 9c1 : Sodium salt of compound (III)

In step 9c, a solution of compound (III) is introduced in Tube Flow Reactor and mixed with a solution of sodium hydroxide in alcohol. In an embodiment, the residence time of said mixture in the reactor is typically anywhere between 1 minute to about 30 minutes, preferably about 5 minutes to 15 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 0°C and 50°C, preferably between 10°C and 40° C and even more preferably between 20°C and 30°C.

In alternative embodiment, the method comprises conversion of (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) to sodium salt of compound (III) using flow process.

Step 9c2 : Sodium salt of compound (III) from compound (IIc)

(2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) obtained from step 7c is mixed with polar solvent in a Tube Flow Reactor and reacted with a solution of sodium hydroxide in methanol. In an

embodiment, the residence time of said mixture in the reactor is typically anywhere between 5 minutes to about 30 minutes, preferably about 10 minutes to 20 minutes depending on the temperature. The operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 70°C and 100°C.

All the reactions in steps 5a to 9c1 described in Figure 6 or in steps 5a to 9c2 as described in Figure 6, are performed in flow reactors connected to each other in such a way to provide an integrated system.

There are many configurations of such connected reactor system, that a person skilled in the art is aware of.

In yet an alternative embodiment, there is provided continuous chemical flow synthesis of compound (III) or sodium salt of compound (III), from methyl-4-methoxy acetoacetate (IX), wherein key intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) is not isolated but put into further continuous flow.

The Sodium salt of compound (III) obtained by the process of the present invention has chiral purity of not less than 95%. This forms one aspect of the present invention.

The Sodium salt of compound (III) obtained by the process of the present invention has particle size of d90 NMT 20µm. This forms another aspect of the present invention.

In yet an alternative embodiment, the compound (III) is isolated by classical batch technology. Preferably, in step 8c, after a residence time of about 15 minutes, the reaction mass is cooled to room temperature and treated with 10% Aq. HCl soln.

Extraction with dichloromethane followed work up yields compound (III), having purity > 95.0% & yield > 90%w/w.

In yet an alternative embodiment, the consecutive reactions steps 5a, 6c, and 7c are achieved in one single flow in three different types of continuous reactors, whereas step 8c is achieved in a separate flow to yield compound (III).

In yet an alternative embodiment, (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) obtained by flow process is first isolated and then converted to either compound (III) or sodium salt of compound (III) by flow synthesis.

In yet an alternative embodiment, there is provided semi multi-step continuous chemical flow synthesis of intermediate (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) for the total synthesis of either compound (III) or sodium salt of compound (III).

The advantages of this continuous reactor system are:

- Overall reaction time is reduced
- Avoids handling of toxic reagents and multiple solvent systems at each stage.
- Avoids isolation of intermediates at each stage and tedious work up procedure
- Desired particle size is achieved without further micronization.
- Retains enantiomeric purity
- Improves yield and purity

The compounds of the present invention may be prepared according to the following examples, or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. All the reactions are performed in flow reactors connected to each other in such a way to provide an integrated system. There are many configurations of such connected reactor system, that a person skilled in the art is aware of.

EXAMPLES:

Example 1 : Preparation of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V)

Methyl-4-methoxy acetoacetate (IX) (5.0 kg, 34 moles on reaction with N, N-dimethyl formamide dimethyl acetal (61.1kg, 51 moles) in micro channel reactor at 30°C and residence time of 40 s, gives methyl (Z)-2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (VIII). The mixture coming out from this first reactor is introduced continuously in second micro channel reactor in which amino acetaldehyde dimethyl acetal (5.35 kg, 51 moles) is continuously added at 70°C and residence time of 40 s to yield methyl (Z)-2-(((2,2-dimethoxyethyl)amino)methylene)-4-methoxy-3-oxobutanoate (VII). Then the mixture is introduced continuously in a tube flow reactor, in which 2M solution of Dimethyl oxalate in methanol (8.35 kg, 70moles) is added in presence of Sodium methoxide (3.82 kg, 70 moles) at 70°C. After a residence time of 3min yields dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (VI). The mixture is then introduced continuously in a Tube Flow reactor in which a solution of Sodium bicarbonate (6.08 kg, 72 moles) and Sodium hydroxide (3.64 Kg, 91 moles) in water is added at 45°C. After a residence time of 5 min gives crude1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V), which was further purified in isopropyl alcohol.

HPLC purity: 99.6%

Yield: 80%.

Example 2: Preparation of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (5.0Kg, 15.8 moles) and methane sulfonic acid (533.0 g, 5.6 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C gives 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa). The reaction mixture was further introduced in a Tube Flow reactor and cyclised with solution of R-3 amino butanol (1.97 kg, 22.2 moles) in Dimethyl carbonate at 100°C at a residence time of 5.15 mins followed by quenching with Aq HCl solution. The organic layer containing (4S,12aR)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (III) was separated and introduced in a Tube Flow Reactor with a solution of N-Methyl Morpholine (2.25 Kg, 22.22 moles) and a solution of 2,4-diflurobenzylamine(3.18 kg, 22.2 moles) in MDC solvent and reacted in presence of Ethyl chloroformate (1.73 Kg, 20.63 moles) at 0°C. After a residence time of 1.15mins yields (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) which was isolated in IPA after acid base workup.

HPLC purity: 99.0%

Yield: 80.0%.

Example 3: Preparation of (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7 -dioxo-2,3,5,7,11 ,11a-hexahydro[1,3]oxazolo[3,3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (Compound I)

A solution of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) (3.9 kg, 9.0 moles) in THF was then introduced in a Tube Flow Reactor and demethylated with Lithium bromide (1.56 kg, 18.0 moles) in THF at

temperature of 60°C. After a residence time of 15 mins, the reaction mass was cooled to RT, treated with 10% Aq. HCl solution and extracted in dichloromethane. The organic layer was concentrated & solid was isolated in isopropyl alcohol to yield Compound (I).

HPLC purity : 99.0%

Yield : 86%.

Chiral Purity:98.0%

Example 4: Preparation of Sodium salt of (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7 -dioxo-2,3,5,7,11 ,11a-hexahydro[1,3]oxazolo[3,3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (Compound I)

A solution of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) (3.9 Kg, 9.0 moles) in n-butanol was mixed with a solution of sodium hydroxide (3.6 kg, 90.0 moles) in methanol in Tube Flow Reactor at 100°C with residence time of 20 mins to yield Sodium salt of Compound (I).

HPLC purity : 99.0%

Yield : 90.0%.

Particle size :d90 NMT 15µm.

Example 5: Preparation of Sodium salt of (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7 -dioxo-2,3,5,7,11 ,11a-hexahydro[1,3]oxazolo[3,3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide Compound (I)

A solution of Compound (I) (3.0 kg, 7.16 moles)in MDC was mixed with a solution of sodium hydroxide (0.48 kg, 12.17 moles)in methanol in Tube Flow Reactor at 25°C with residence time of 10 mins to give Sodium salt of Compound (I).

HPLC purity : 99.0%

Yield : 90.0%.

Particle size :d90 NMT 10µm.

Example 6: Preparation of Sodium salt of (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7 -dioxo-2,3,5,7,11 ,11a-hexahydro[1,3]oxazolo[3,3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide Compound (I)

A solution of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (100.0 g, 0.23 moles) in n-butanol was mixed with a solution of sodium hydroxide (92.37g, 2.3 moles) in methanol in Tube Flow Reactor at 100°C with residence time of 20 mins to yield Na salt of Compound (I).

HPLC purity : 98.0%

Yield : 85.0%.

Particle size : d90 NMT 10 µm

Example 7: Sodium salt of (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7 -dioxo-2,3,5,7,11 ,11a-hexahydro[1,3]oxazolo[3,3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide (Compound I)

(4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (3.9 Kg, 9.0 moles) was demethylated with Lithium bromide (1.56 kg, 18.0 moles) in Methanol / IPA/ THF at temperature of 60°C. After 6 hrs, the reaction mass was cooled to RT, treated with 10% Aq. HCl solution and extracted in dichloromethane. The organic layer was concentrated & solid was isolated in isopropyl alcohol to yield Compound (I).

HPLC purity : 99.0%

Yield : 92.0%.

Chiral Purity:99.0%

A solution of Compound (I) (2.5 kg, 5.96 moles) in MDC was mixed with a solution of sodium hydroxide(2.38 kg, 59.66 moles) in methanol in Tube Flow Reactor at 25°C with residence time of 10 mins to give Sodium salt of Compound (I).

HPLC purity : 99.0%

Yield : 85.0%.

Particle size :d90 NMT 10µm.

Example 8: Sodium salt of Compound (I) from Compound (V)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (25.0g, 0.079 moles) and methane sulfonic acid (3.81g, 0.039 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C gives 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IV). The reaction mixture was further introduced in a Tube Flow reactor and cyclised with solution of R-3 amino butanol (8.45g, 0.094 moles) in Dimethyl carbonate at 100°C at a residence time of 5.15 mins followed by quenching with Aq HCl solution. The organic layer containing (4S,12aR)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (III) was separated and introduced in a Tube Flow Reactor with a solution of N-Methyl Morpholine (12.04g, 0.119 moles) and a solution of 2,4-diflurobenzylamine (17.03g, 0.119 moles) in MDC solvent and reacted in presence of Ethyl chloroformate (12.05g, 0.111 moles) at 0°C . After a residence time of 1.15mins yields (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) which was isolated in IPA after acid base workup.

HPLC purity : 99.0%

Yield : 80.0%.

A solution of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) (20.0g, 0.05 moles) in n-butanol was mixed with a solution of sodium hydroxide (18.47g, 0.46 moles) in methanol in Tube Flow Reactor at 100°C with residence time of 20 mins to yield Sodium salt of Compound (I).

HPLC purity : 99.0%

Yield : 90.0%.

Particle size :d90 NMT 15µm.

Example 9: Sodium salt of Compound (I) from Compound (V)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (200 g, 0.63moles) and methane sulfonic acid (6.10g, 0.06 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C gives 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IV). The reaction mixture was further introduced in a Tube Flow reactor and cyclised with solution of R-3 amino butanol (73.0g, 0.819moles) in Dimethyl carbonate at 100°C at a residence time of 5.15 mins followed by quenching with Aq HCl solution. The organic layer containing (4S,12aR)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (III) was separated and introduced in a Tube Flow Reactor with a solution of N-Methyl Morpholine (95.58g, 0.94 moles) and a solution of 2,4-diflurobenzylamine (118.1g, 0.825 moles) in MDC solvent and reacted in presence of Ethyl chloroformate (82.04g, 0.756 moles) at 0°C . After a residence time of 1.15mins yields (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) which was isolated in IPA after acid base workup.

HPLC purity: 99.0%

Yield : 85%.

A solution of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) (170.0g, 0.392 moles) in THF was then introduced in a Tube Flow Reactor and demethylated with Lithium bromide (68.19g, 0.785 moles) in THF at temperature of 60°C. After a residence time of 15 mins, the reaction mass was cooled to RT, treated with 10% Aq. HCl solution and extracted in

dichloromethane. The organic layer was concentrated & solid was isolated in isopropyl alcohol to yield Compound (I).
HPLC purity : 99.0%
Yield : 83%.
Chiral Purity:99.0%

A solution of Compound (I) (135.0g, 0.322 moles) in MDC was mixed with a solution of sodium hydroxide (21.9g, 0.54 moles) in methanol in Tube Flow Reactor at 25°C with residence time of 10 mins to give Sodium salt of Compound (I).
HPLC purity : 99.0%
Yield : 85.0%.
Particle size :d90 NMT 10µ.

Example 10 : Preparation of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (25.0g,0.079 moles) and methane sulfonic acid (3.79 g,0.039 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C, the reaction mixture containing 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) was further introduced into a second Tube Flow reactor and cyclised with solution of (S)-2-amino-propan-1-ol in (8.35g,0.11 moles) in Dimethyl carbonate at 100°C at a residence time of 6 mins followed by quenching with Aq HCl solution. The organic layer containing (3S,11aR)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a] pyrido[1,2-*d*]pyrazine -8-carboxylic acid (III b) was separated and introduced into a third Tube Flow Reactor with a solution of N-Methyl Morpholine (12.0g,0.119 moles) and a solution of 2,4-diflurobenzylamine (15.8g,0.12moles) in MDC solvent and reacted in presence of Ethyl chloroformate (12.06g,0.11 moles)

at 0°C . After a residence time of 2 mins yields (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d]*pyrazine -8-carboxylic acid (IIb) which was isolated in IPA after acid base workup.

HPLC purity : 98.0%

Yield : 85.0%.

Example 11 : Preparation of Compound (II) from Compound (IIb)

A solution of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d]*pyrazine -8-carboxylic acid (IIb) (20.0g,0.48 moles) in THF was then introduced in a Tube Flow Reactor and demethylated with Lithium bromide (8.2 g,0.095 moles) in THF at temperature of 60°C. After a residence time of 15 mins, the reaction mass was cooled to RT, treated with 10% Aq. HCl solution and extracted in dichloromethane. The organic layer was concentrated & solid was isolated in isopropyl alcohol to yield Compound (II).

HPLC purity > 95.0%

Yield > 80%w/w

Example 12 : Preparation of Sodium salt of Compound (II)

A solution of Compound (II) (20.0g,0.049 moles) in MDC was mixed with a solution of sodium hydroxide (2.56g,0.06 moles) in methanol in Tube Flow Reactor at 25°C with residence time of 10 mins to give Sodium salt of Compound (II).

HPLC purity : >98%

Yield : > 90%.

Particle size : d90 NMT 20 μm.

Example 13 : Preparation of Sodium salt of Compound (II) from Compound (IIb)

A solution of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) (20.0g,0.047 moles) in n-butanol was mixed with a solution of sodium hydroxide (19.0g,0.48 moles) in methanol in Tube Flow Reactor at 100°C with residence time of 20 mins to yield Sodium salt of Compound (II).

Particle size : d90 NMT 20 µm.

Example 14 : Preparation of Compound (II) from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxy carbonyl) -4-oxo-1,4-dihydropyridine-3-carboxylic acid (V)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (50g,0.158 moles) and methane sulfonic acid (0.72g,0.079 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C, the reaction mixture containing 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) was further introduced into a second Tube Flow reactor and cyclised with solution of (S)-2-amino-propan-1-ol in (16.7g,0.22 moles) in Dimethyl carbonate at 100°C at a residence time of 6 mins followed by quenching with Aq HCl solution. The organic layer containing (3S,11aR)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a] pyrido[1,2-*d*]pyrazine -8-carboxylic acid (III b) was separated and introduced into a third Tube Flow Reactor with a solution of N-Methyl Morpholine (22.5g,0.22 moles) and a solution of 2,4-diflurobenzylamine (31.5g,0.22 moles) in MDC solvent and reacted in presence of Ethyl chloroformate (22.39,0.21moles) at 0°C . After a residence time of 2 mins, the solution was of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) in was then introduced into a fourth Tube Flow Reactor and demethylated with Lithium bromide (34.5g,0.39 moles) in THF at temperature of 60°C. After a residence time

of 15 mins, the reaction mass was cooled to RT, treated with 10% Aq. HCl solution and extracted in dichloromethane. The organic layer was concentrated & solid was isolated in isopropyl alcohol to yield Compound (II).

HPLC purity > 95.0%

Yield > 80%w/w

Example 15 : Preparation of Sodium salt of Compound (II) from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (20.0g,0.06 moles) and methane sulfonic acid (3.05g,0.03 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C, the reaction mixture containing 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) was further introduced into a second Tube Flow reactor and cyclised with solution of (S)-2-amino-propan-1-ol in (5.72g,0.076 moles) in Dimethyl carbonate at 100°C at a residence time of 6 mins followed by quenching with Aq HCl solution. The organic layer containing (3S,11aR)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (III b) was separated and introduced into a third Tube Flow Reactor with a solution of N-Methyl Morpholine (9.63g,0.095moles) and a solution of 2,4-diflurobenzylamine (13.6g,0.095 moles) in MDC solvent and reacted in presence of Ethyl chloroformate (9.34 moles) at 0°C . After a residence time of 2 mins the solution of (3S,11aR)-N-(2,4-Difluorobenzyl)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo-[3,2-a]pyrido[1,2-*d*]pyrazine -8-carboxylic acid (IIb) was mixed with a solution of sodium hydroxide (25.39g, 0.63 moles) in methanol in Tube Flow Reactor at 100°C with residence time of 20 mins to yield Sodium salt of Compound (II).

Particle size : d90 NMT 20 µm.

Example 16: Preparation of (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc)

A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (10g,0.032 moles) and methane sulfonic acid (0.30g,0.003 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C, the reaction mixture containing 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) was further introduced into a second Tube Flow reactor and cyclised with solution of (1R,3S)-3-aminocyclopentanol (3.85g,0.038 moles) in Dimethyl carbonate at 100°C at a residence time of 6 mins followed by quenching with Aq HCl solution. The organic layer containing (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1 ',2':4,5]pyrazino[2,1-b][1 ,3]oxazepine-10-carboxilic acid (III c) was separated and introduced into a third Tube Flow Reactor with a solution of N-Methyl Morpholine (4.81g,0.048 moles) and a solution of (2,4,6-trifluorophenyl) methanamine (6.12g,0.038 moles) in MDC solvent and reacted in presence of Ethyl chloroformate (4.82g,0.044 moles) at 0°C . After a residence time of 2 mins yields (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)- 2,3,4,5, 7,9, 13, 13a-octahydro-2,5-ethanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide(IIc) which was isolated in IPA after acid base workup.

HPLC purity : 95.0%

Yield : 80%.

Example 17: Preparation of Compound (III) from Compound (IIc)

A solution of (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (IIc) (75g,0.237moles) in THF was then introduced in a Tube Flow Reactor and demethylated with Lithium bromide (30.98g,0.356 moles) in THF at temperature of 60°C. After a residence time of 15 mins, the reaction mass was cooled to RT, treated with 10% Aq. HCl solution and

extracted in dichloromethane. The organic layer was concentrated & solid was isolated in isopropyl alcohol to yield Compound (III).

HPLC purity > 98.0%

Yield > 85%w/w

Example 18: Preparation of Sodium salt of Compound (III)

A solution of Compound (III) (10g,0.022 moles) in MDC was mixed with a solution of sodium hydroxide (7.12g,0.178 moles) in methanol in Tube Flow Reactor at 25°C with residence time of 10 mins to give Sodium salt of Compound (III).

Particle size : d90 NMT 15 µm.

Example 19: Preparation of Sodium salt of Compound (III) from 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V)

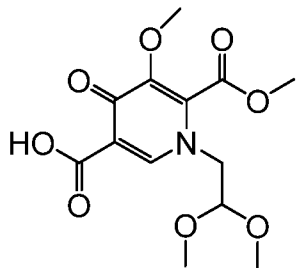
A solution of 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) in acetic acid / Dimethyl carbonate (25g,0.079 moles) and methane sulfonic acid (2.66g,0.028 moles) were introduced in micro channel reactor. After residence time of 9 mins at 130°C, the reaction mixture containing 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) was further introduced into a second Tube Flow reactor and cyclised with solution of (1R,3S)-3-aminocyclopentanol (9.62g,0.095 moles) in Dimethyl carbonate at 100°C at a residence time of 6 mins followed by quenching with Aq HCl solution. The organic layer containing (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1 ',2':4,5]pyrazino [2,1-b][1 ,3] oxazepine-10-carboxilic acid (III c) was separated and introduced into a third Tube Flow Reactor with a solution of N-Methyl Morpholine (12g,0.118moles) and a solution of (2,4,6-trifluorophenyl)methanamine (17.8g,0.111moles) in MDC solvent and reacted in presence of Ethyl chloroformate (12.9g,0.118 moles) at 0°C . After a residence time of 2 mins (2R,5 S, 13aR)-8-methoxy -7 ,9-dioxo-N -(2,4,6-trifluorobenzyl)-2,3,4,5, 7,9, 13, 13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-

b][1,3]oxazepine-10-carboxamide(IIc) was mixed with a solution of sodium hydroxide (25.37g,0.63 moles) in methanol in Tube Flow Reactor at 100°C with residence time of 20 mins to yield Sodium salt of Compound (III).

Particle size : d90 NMT 15 µm.

Claims:

1. A process of preparing 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid, a compound of Formula (V):



V

comprising:

Step 1: reacting, methyl-4-methoxy acetoacetate (IX) with N,N-dimethylformamide dimethylacetal to yield methyl (Z)-2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (VIII);

Step 2: reacting, methyl (Z)-2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (VIII) with amino acetaldehyde dimethylacetal to yield methyl (Z)-2-(((2,2-dimethoxyethyl) amino)methylene)-4-methoxy-3-oxobutanoate (VII);

Step 3: reacting, methyl (Z)-2-(((2,2-dimethoxyethyl)amino)methylene)-4-methoxy-3-oxobutanoate (VII) with a solution of dimethyl oxalate in methanol in the presence of sodium methoxide to yield dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (VI); and

Step 4: hydrolysing, dimethyl 1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (VI), with solution of sodium bicarbonate

and sodium hydroxide in water, to yield 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V);

wherein said process is performed using continuous flow reaction conditions.

2. The process as claimed in claim 1, wherein the residence time of said mixture in the reactor in Step 1, is typically anywhere between 30 seconds and 20 minutes, preferably about 30 seconds to 10 minutes depending on the temperature.

3. The process as claimed in claim 1 or 2 , wherein the operation temperature in the reactor is typically anywhere between 10°C and 100°C, preferably between 20°C and 80°C and even more preferably between 20°C and 60°C.

4. The process as claimed in claim 1, 2 or 3 , wherein Step 1 is run, without the use of any solvent.

5. The process as claimed in claim 1, wherein the residence time of said mixture in the reactor in Step 2,is typically anywhere between 15 seconds and 20 minutes, preferably about 15 seconds to 10 minutes.

6. The process as claimed in claim 1 or 5 , wherein the operation temperature in the reactor is typically anywhere between 10°C and 150°C , preferably between 20°C and 120°C and even more preferably between 20°C and 100°C.

7. The process as claimed in claim 1, 5 or 6 , wherein the Step 2 is run, without the use of any solvent.

8. The process as claimed in claim 1, wherein the residence time of said mixture in the reactor in Step 3, is typically anywhere between 30 seconds and 20

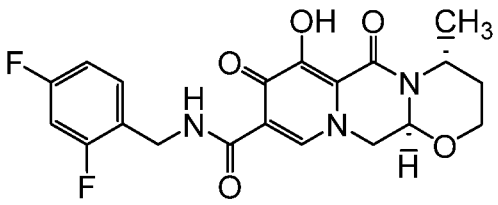
minutes, preferably about 30 seconds to 10 minutes depending on the temperature.

9. The process as claimed in claim 1 or 8 , wherein the operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 60°C and 100°C.

10. The process as claimed in claim 1, wherein the residence time of said mixture in the reactor in Step 4, is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature.

11. The process as claimed in claim 1 or 10 , wherein the operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 60°C and 100°C.

12. The process as claimed in claim 1, wherein the intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) is further used in the synthesis of compounds of Formula (I)

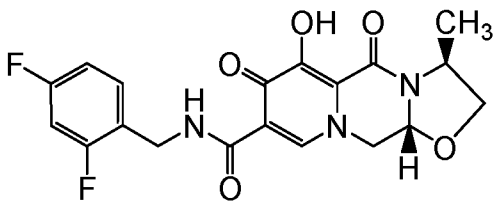


Compound I

;

,

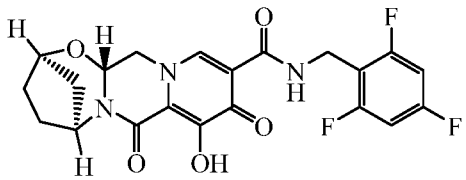
Formula (II)



Compound II ;

and

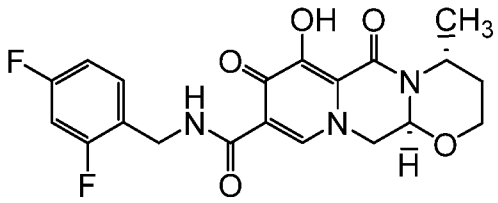
Formula (III)



Compound III

or a stereoisomer or pharmaceutically acceptable salt thereof.

13. A process of preparing Compound of formula (I).



Compound I

comprising:

Step 5a: deprotecting ,1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (V) obtained in step 4, with methane sulfonic acid in the solvent mixture of acetic acid and dimethyl carbonate to yield 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa);

Step 6a: cyclising 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) is with a solution of R-3 amino-1-butanol in dimethyl carbonate followed by quenching with Aq. HCl solution and separating organic layer to yield (4S,12aR)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa);

Step 7a : mixing, the organic layer containing (4S,12aR)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa) with N-methyl morpholine in chlorinated solvent preferably MDC and then further reacting with solution of 2,4-diflurobenzylamine in MDC in presence of ethyl chloroformate to yield (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) ;

Step 8a : demethylating, a solution of the (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) with lithium bromide in the presence of a suitable solvent typically THF to yield Compound (I) and;

Step 9a1 : mixing with a solution of sodium hydroxide in methanol to obtain sodium salt of Compound (I);

wherein said process is performed using continuous flow reaction conditions.

14. The process as claimed in claim 13, wherein the residence time of said mixture in the reactor in Step 5a, is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature.

15. The process as claimed in claim 13 or 14 , wherein the operation temperature in the reactor is typically anywhere between 30°C and 150°, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

16. The process as claimed in claim 13, wherein the residence time of said mixture in the reactor in Step 6a, is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature.

17. The process as claimed in claim 13 or 16 , wherein the operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

18. The process as claimed in claim 13, wherein the residence time of said mixture in the reactor in Step 7a, is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature.

19. The process as claimed in claim 13 or 18 , wherein the operation temperature in the reactor is typically anywhere between -20°C and 30°C, preferably between -10°C and 20°C and even more preferably between -5°C and 15°C.

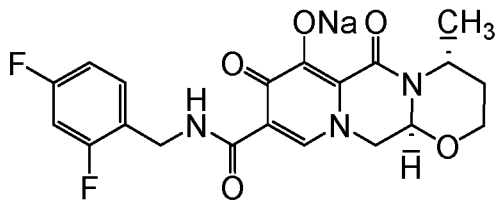
20. The process as claimed in claim 13, wherein the residence time of said mixture in the reactor in Step 8a, is typically anywhere between 10 minutes to about 30 minutes, preferably about 15 minute to 20 minutes depending on the temperature.

21. The process as claimed in claim 13 or 20 , wherein the operation temperature in the reactor is typically anywhere between 30°C and 100°C, preferably between 50°C and 80°C and even more preferably between 60°C and 70°C.

22. The process as claimed in claim 13, wherein the residence time of said mixture in the reactor in Step 9a1, is typically anywhere between 1 minute to about 30 minutes, preferably about 5 minutes to 15 minutes depending on the temperature.

23. The process as claimed in claim 13 or 22, wherein the operation temperature in the reactor is typically anywhere between 0°C and 50°C, preferably between 10°C and 40° C and even more preferably between 20°C and 30°C.

24. A process of preparing sodium salt Compound of formula (I)



Sodium salt of Compound(I)

comprising,

obtaining a solution of (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) from step 7a of claim 13; and

Step 9a2: mixing with polar solvent such as n-butanol or methanol, in a Tube Flow Reactor and reacting with a solution of sodium hydroxide in methanol.

wherein said process steps 5a, 6a, 7a and 9a2 are performed using continuous flow reaction conditions.

25. The process as claimed in claim 24, wherein the residence time of said mixture in the reactor in Step 9a2, is typically anywhere between 5 minutes to

about 30 minutes, preferably about 10 minutes to 20 minutes depending on the temperature.

26. The process as claimed in claim 24 or 25, wherein the operation temperature in the reactor is typically anywhere between 30°C and 150°C, preferably between 50°C and 120°C and even more preferably between 70°C and 100°C.

27. The process as claimed in claims 13 or 24, wherein the Sodium salt of compound (I) has chiral purity of at least 98% ee.

28. The process as claimed in claims 13 or 24, wherein the Sodium salt of compound (I) has particle size of d90 NMT 30µm, preferably NMT 20 µm, more preferably NMT 15 µm.

29. A process for preparation of (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide, compound of formula (IIa) which comprises;

Step 5a: Deprotecting 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid, the compound of formula (V) with methane sulfonic acid in the solvent mixture of acetic acid and dimethyl carbonate to obtain 5-Methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa);

Step 6a: Cyclizing the 5-methoxy-6-(methoxycarbonyl)-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine-3-carboxylic acid (IVa) with solution of R-3 amino-1-butanol in dimethyl carbonate to obtain (4S,12aR)-7-Methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa); and

Step 7a: Reacting the (4S,12aR)-7-Methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxylic acid (IIIa) with N-Methyl Morpholine and 2,4-diflurobenzylamine in presence of Ethyl chloroformate to yield (4S,12aR)-N-(2,4-Difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa).

30. The process as claimed in claim 29, wherein, the residence time of said mixture in the reactor in Step 5a, is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature.

31. The process as claimed in claim 29, wherein, the operation temperature in the reactor in step 5a and step 6a is typically anywhere between 30°C and 150°, preferably between 50°C and 130°C and even more preferably between 80°C and 130°C.

32. The process as claimed in claim 29, wherein, the residence time of said mixture in the reactor in step 6a is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 15 minutes depending on the temperature.

33. The process as claimed in claim 29, wherein, the residence time of said mixture in the reactor in step 7a is typically anywhere between 30 seconds and 20 minutes, preferably about 1 minute to 10 minutes depending on the temperature.

34. The process as claimed in claim 29, wherein, the operation temperature in the reactor in step 7a is typically anywhere between -20°C and 30°C, preferably between -10°C and 20°C and even more preferably between -5°C and 15°C.

35. The process as claimed in claim 29, wherein, the (4S,12aR)-N-(2,4-difluorobenzyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-

pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (IIa) is optionally isolated in a suitable solvent after acid base workup.

I/VI

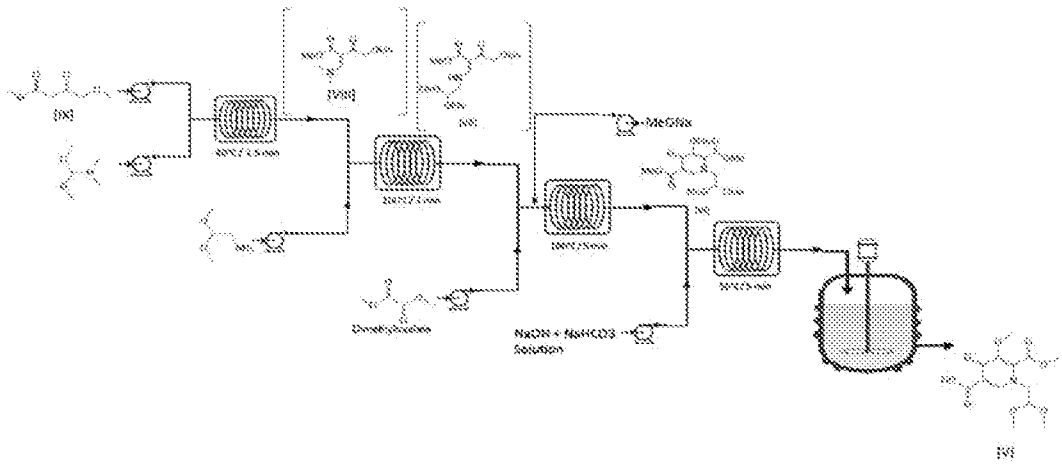


Figure 1: Continuous Flow Synthesis of Compound (V)

II/VI

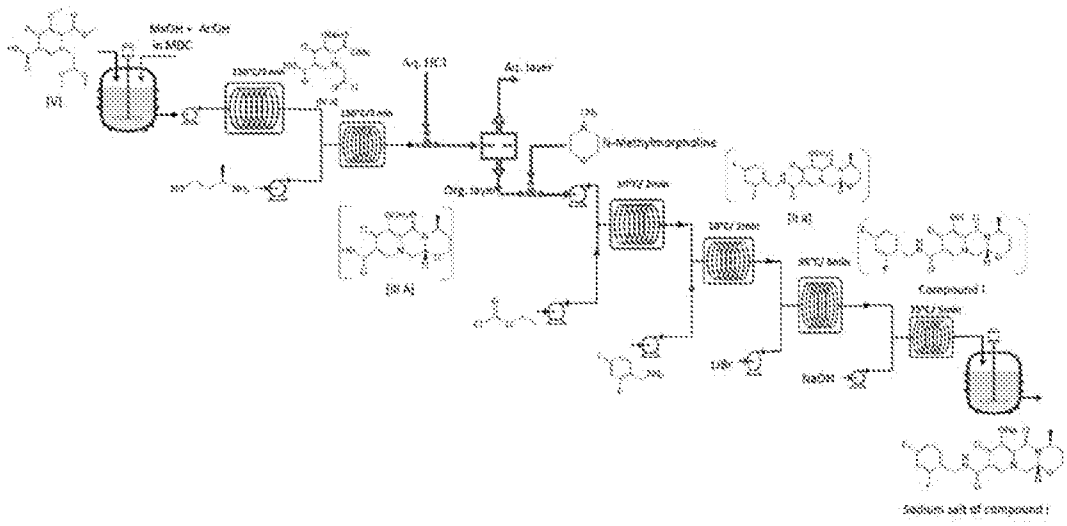


Figure 2: Continuous Flow Synthesis of Na salt of Compound (I)

III/VI

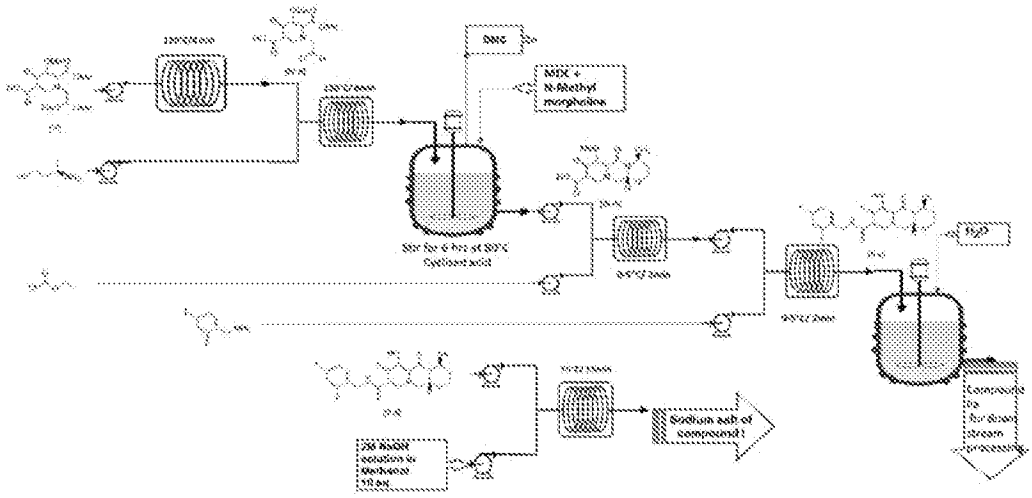


Figure 3: Continuous Flow Synthesis of Na salt of Compound(I)

IV/VI

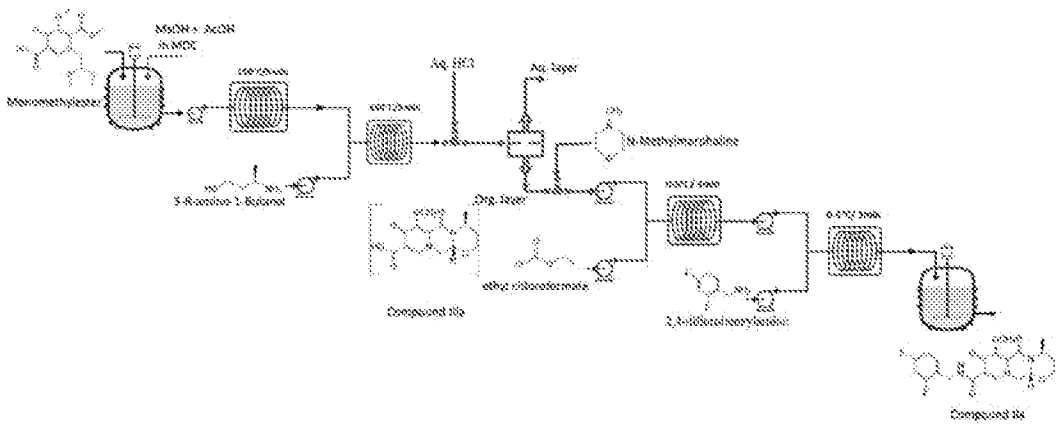


Figure 4: Continuous Flow Synthesis of Compound (IIa)

V/VI

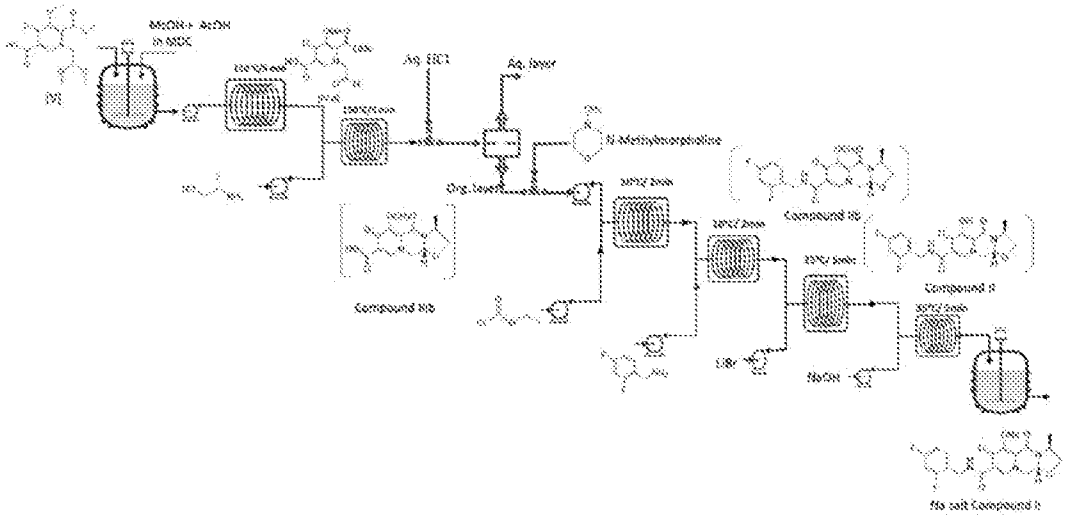


Figure 5: Continuous Flow Synthesis of Na salt of Compound (II)

VI/VI

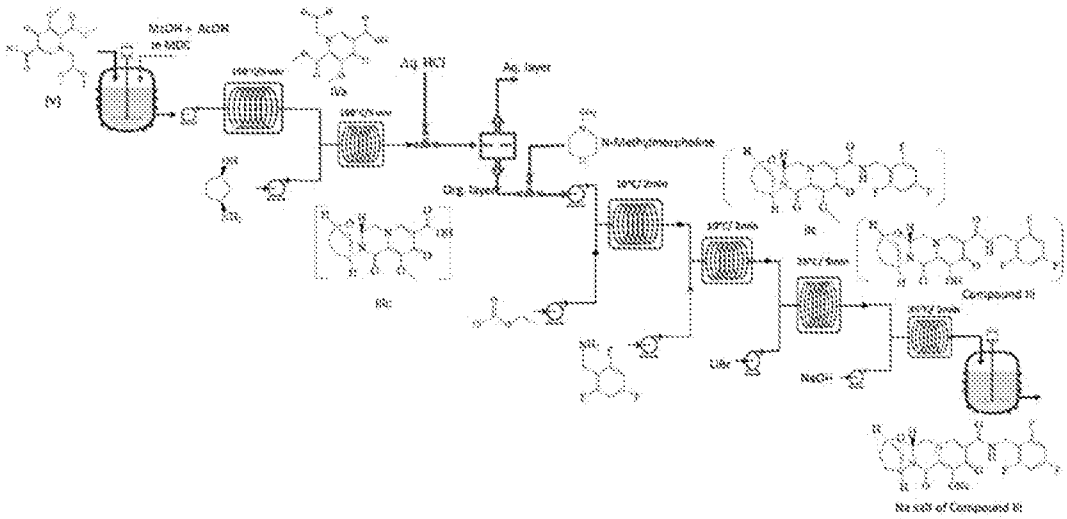


Figure 6: Continuous Flow Synthesis of Na salt of Compound (III)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2019/050122

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/79 C07D213/803 C07D498/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/119566 A1 (GLAXOSMITHKLINE LLC [US]; WANG HUAN [US] ET AL.) 29 September 2011 (2011-09-29) scheme on p. 5; examples; pages 5-8	1-35
A	WO 2015/019310 A1 (MYLAN LAB LTD [IN]) 12 February 2015 (2015-02-12) example 2	1-12
A	WO 2015/177537 A1 (CIPLA LTD [IN]; KING LAWRENCE [GB]) 26 November 2015 (2015-11-26) the whole document	1-35
A	WO 2016/125192 A2 (MYLAN LAB LTD [IN]) 11 August 2016 (2016-08-11) claims 1-34; examples 10-16	1-35

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2019	03/05/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schuemacher, Anne

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HUAN WANG ET AL: "An Efficient and Highly Diastereoselective Synthesis of GSK1265744, a Potent HIV Integrase Inhibitor", ORGANIC LETTERS, vol. 17, no. 3, 6 February 2015 (2015-02-06), pages 564-567, XP055203185, ISSN: 1523-7060, DOI: 10.1021/ol503580t cited in the application preparation of (4b), (6d), (7d) and (9) in the supporting information https://pubs.acs.org/doi/suppl/10.1021/ol503580t/suppl_file/ol503580t_si_001.pdf -----	1-35
X,P	ROBERT E. ZIEGLER ET AL: "7-Step Flow Synthesis of the HIV Integrase Inhibitor Dolutegravir", ANGEWANDTE CHEMIE, INTERNATIONAL EDITION, vol. 57, no. 24, 14 May 2018 (2018-05-14), pages 7181-7185, XP055582488, DE ISSN: 1433-7851, DOI: 10.1002/anie.201802256 cited in the application the whole document -----	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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