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(54) Title: PROCESS FOR THE PREPARATION OF SELEXIPAG AND INTERMEDIATES THEREOF

(57) Abstract: The present invention provides processes for the preparation of Selexipag compound of formula (1). The present in - vention also provides processes for the preparation of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-l-ol (2), and 4-isopro - pylamino-butan-l-ol of formula (3), which are intermediates for the synthesis of Selexipag (1).

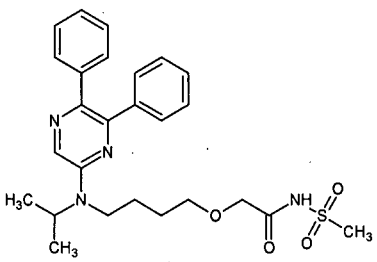
TITLE OF THE INVENTION:

PROCESS FOR THE PREPARATION OF SELEXIPAG AND INTERMEDIATES THEREOF

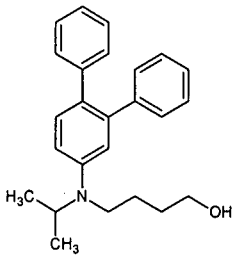
This application claims priority from provisional Indian patent applications 347/MUM/2015 and 4862/MUM/2015 which is incorporated herein by reference.

FIELD OF THE INVENTION:

The present invention relates to improved and novel processes for the preparation of Selexipag (1). The present invention also relates to novel processes for the preparation of 4-[(5,6-diphenyl-pyrazin-2-y!)-isopropyl -amino]-butan-1-ol (2), and 4-isopropylamino-butan-1-ol of formula (3), which are intermediates for the synthesis of Selexipag (1).



(1)



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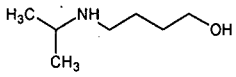


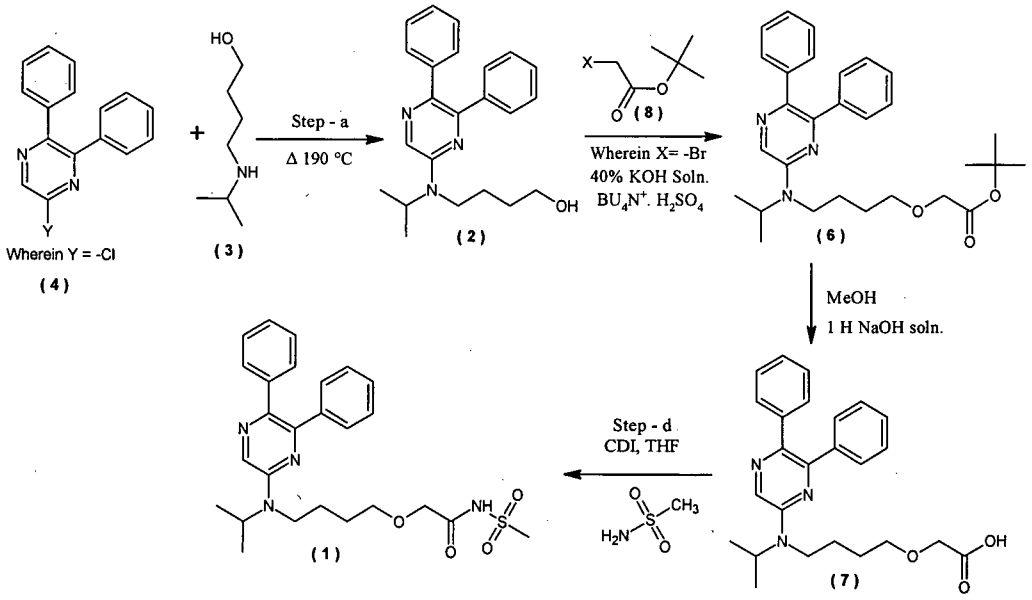
(3)

BACKGROUND OF THE INVENTION:

2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropyl-amino]butyloxy}-N-(methyl sulfonyl) acetamide (herein "Selexipag") also known as Uptravi®, has a CAS number of 475086-01-2, a molecular formula of $C_{26}H_{32}N_4O_4S$, the molecular weight of 496.6 and it is structurally represented by formula (1).

Selexipag, originally discovered and synthesized by Nippon Shinyaku, is a potent, orally available, selective IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension (PAH).

U.S. Patent No. 7,205,302 describes the synthesis of Selexipag as shown in Scheme-I. Further, the patent also describes processes to make Selexipag and pharmaceutically acceptable salts.

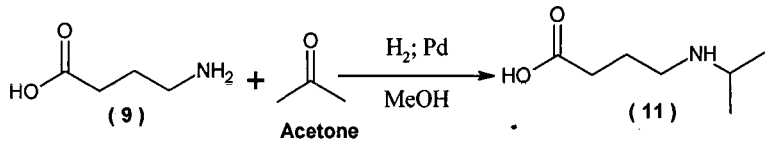


Scheme - 1

The process reported in the prior art involves use of multi-step synthesis wherein reactions are conducted in hazardous solvents and the intermediates are isolated by means of column chromatography purifications. The isolation and column purification(s) is very critical, expensive and tedious job in production; wherein the production executives are exposed to solvent vapors and may lead to many health hazards. The time required for production of a batch substantially increases as the number of isolations and column chromatography purifications are increased during the production scale and thus multi-step reactions involving multiple chromatography

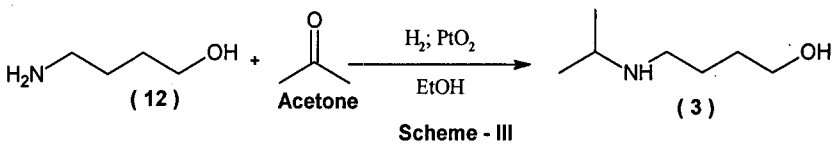
purifications are not suitable for the production. The reaction also requires longer time to complete and the yields obtained are not satisfactory. The reported process also involves use of hazardous and toxic solvents such as benzene and diethyl ether which not only poses the problem of handling but also provides Selexipag with less yield and more impurities.

CN102020574 discloses a process for preparation of compound of formula (11) as depicted in scheme - II below, wherein, 4-aminobutanoic acid of formula (9) is condensed with acetone with successive reduction of imine using H_2/Pd in Methanol to obtain 4-isopropyl-amino-butyric acid of formula (11). The process reported in CN'574 involves the use of hazardous and tedious hydrogenation reaction, which is not industrially feasible. Further, CN'574 does not disclose the process for preparation of 4-isopropylamino-butan-1-ol of formula (3).



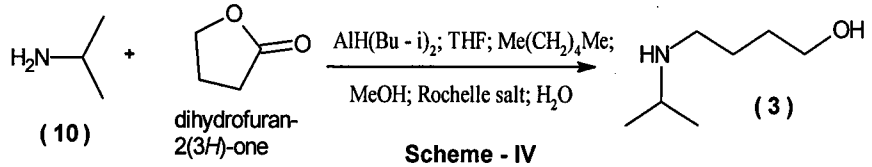
Scheme - II

Bioorganic & Medicinal Chemistry, 15(21), 6692-6704; 2007 discloses the process for preparation of 4-isopropylamino-butan-1-ol of formula (3) as depicted in scheme - III below, wherein, 4-aminobutan-1-ol (12) is condensed with acetone followed by reduction of carbonyl moiety using H_2;PtC>2 in presence of ethanol. The reported process involves use of expensive reducing agent like platinum oxide, and involves hydrogenation step, which makes the process tedious.



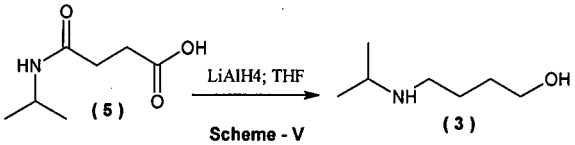
Scheme - III

Organic & Bio-molecular Chemistry, 10(32), 6504-651 1; 2012 discloses the process for preparation of 4-isopropylamino-butan-1-ol of formula (3) depicted in scheme -IV below. The reported process is complex, expensive time consuming and results in low yield.



Scheme - IV

Journal of Organic Chemistry, 26, 1744-7; 1961 discloses reduction of 4-(isopropylamino)-4-oxobutanoic acid of formula (5) to obtain 4-isopropylamino-butan-1-ol of formula (3) in THF as depicted in scheme - V below. The reported process is a complex, expensive, time consuming and results in lower yield.



Scheme - V

Hence, there remains a need for providing efficient, industrially feasible and economically viable process for the manufacture of Selexipag and its intermediates to substantially eliminate the problems associated with the prior art, and that will be suitable for large-scale preparation such that the process will be safe to handle, simple and easy to carry out with high yield and purity of the product.

OBJECTS OF THE PRESENT INVENTION

The object of the present invention is to provide efficient, economic and industrially viable processes for the preparation of Selexipag (1).

Yet another object of the present invention is to provide efficient, industrially viable and cost effective processes for the preparation of 4-[(5,6-diphenyl-

pyrazin-2-yl)-isopropyl -amino]-butan-1-ol (2), which is a useful intermediate for preparation of Selexipag (1).

Yet another object of the present invention is to provide novel processes for preparation of 4-isopropylamino-butan-1-ol of formula (3), a Selexipag (1) precursor.

DETAILED DESCRIPTION OF THE INVENTION:

Before the present invention is described, it is to be understood that this invention is not limited to particular methodologies and materials described, as these may vary as per the person skilled in the art. It is also to be understood that the terminology used in the description is for the purpose of describing the particular embodiments only, and is not intended to limit the scope of the present invention.

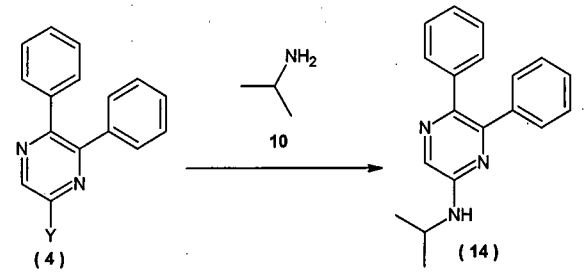
Before the present invention is described, it is to be understood that unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Further, it is to be understood that the present invention is not limited to the methodologies and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described, as these may vary within the specification indicated. Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having", means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various

combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims. Further the terms disclosed embodiments are merely exemplary methods of the invention, which may be embodied in various forms.

As used herein in the present application, the term "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

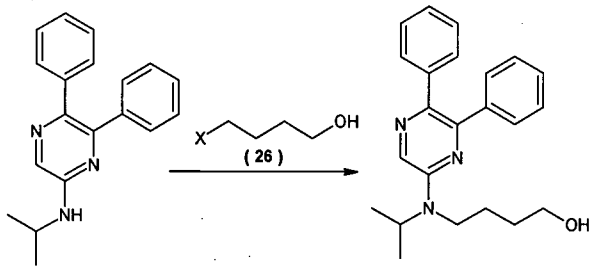
In one of the embodiments of the invention, there is provided a novel process for the preparation of a 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butan-1-ol (2), a key intermediate for the synthesis of Selexipag; the process comprising:

a) reacting a compound of formula (4) with a compound of formula (10) in a solvent and in presence of suitable base to provide a compound of formula (14), which may be optionally isolated; and



Wherein: Y is -OH, Halogen

b) condensing the compound of formula (14) with a compound of formula (26) in a solvent and in the presence of a suitable base, to provide the compound of formula (2).



(14) (2)

Wherein: X is Halogen

According to another embodiment of the present invention, the intermediate compound (14) of step (a) can be used in next stage without isolating the intermediate compound (14).

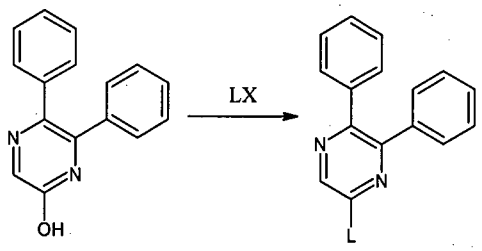
The solvent used in the embodiment is selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide, water or mixtures thereof.

The base used in the embodiment is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarboriates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) ; 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases like primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, and pyrrole methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine; and their mixtures thereof.

According to another embodiment of the invention, there is provided a novel process for the preparation of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol (2), an intermediate for the synthesis of Selexipag, the process comprising:

a) activating hydroxyl group of a compound of formula (4a) by reacting it with suitable reagent having formula (LX) in a solvent, in the presence

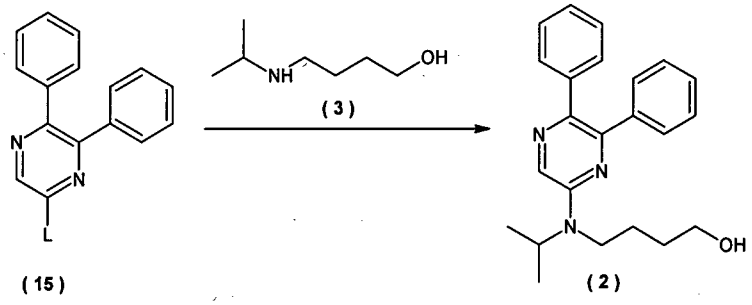
of a suitable base to provide a compound of formula (15) , which may or may not be isolated; and



(4a) (15)

L = Halogen, OSO_2CH_3, OSO_2CF_3, OTs, OBs, OCH_2OCH_3, $OC(CH_3)_3$, OCH_2Ph, O-p-methoxybenzyl, OTMS.OTES, OTBDMS, OTBDPS, OTIPS,$OCPh_3$,OCOR,$OCOC(CH_3)_3$,OR; R is selected from the group consisting of alkyl, acetyl, aryl, substituted aryl, etc. X is Halogen.

b) condensing the compound of formula (15) with a compound of formula (3) in a solvent and optionally in presence of a suitable base to providea compound of formula (2);



(15) (2)

L = Halogen, OSO_2CH_3, OSO_2CF_3, OTs, OBs, OCH_2OCH_3, $OC(CH_3)_3$, OCH_2Ph, O-p-methoxybenzyl, OTMS.OTES, OTBDMS, OTBDPS, OTIPS,$OCPh_3$,OCOR,$OCOC(CH_3)_3$,OR; R is selected from the group consisting of alkyl, acetyl, aryl, substituted aryl, etc.

According to another embodiment of the present invention, the intermediate compound (15) of step (a) can be used in next stage without isolating the intermediate compound (15).

The solvent used in the embodiment is selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate;

aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide, water or mixtures thereof.

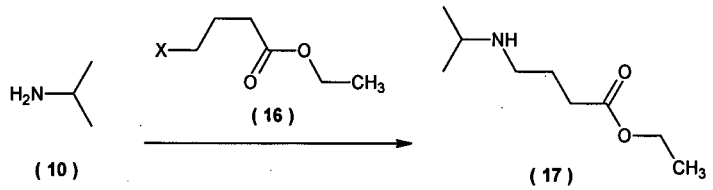
The base used in the embodiment is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarboriates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-

Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) ; 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases like primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, and pyrrole methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine; and their mixtures thereof.

The "suitable reagent" having formula LX, used for the activation of hydroxyl group used herein the present invention is selected from thionyl chloride, oxalyl chloride, phosphorous trichloride, phosphorous pentachloride, phosphorous tribromide, methanesulfonyl chloride, methanesulfonic anhydride, trifluoromethanesulfonyl chloride, trifluoromethanesulfonic anhydride, p- toluenesulfonyl chloride, p-halobenzene sulfonyl chloride, p-nitrobenzenesulfonyl chloride, benzenesulfonyl chloride, halomethyl methyl ether (MOM),t-butyl chloride, t-butyl bromide, benzyl bromide, benzyl acetate, benzyl ethers, benzyl benzoate, benzyl chloride, p-methoxybenzyl chloride, halotrimethylsilanes, halotrimethylsilanes, t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride, triisopropylsilyl chloride, triphenylmethyl chloride, acyl chloride, acetic anhydride, t-butylacetyl chloride, t-butylacetic anhydride, alkyl halides and the like.

Another embodiment of the present invention provides a novel process for preparation of compound of formula (2), an intermediate for the synthesis of Selexipag, the process comprising:

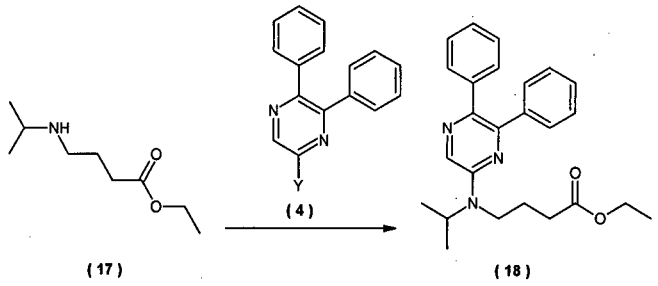
a) reacting compound of formula (10) with compound of formula (16) in a solvent and in presence of a suitable base to provide a compound of formula (17), which may be optionally isolated;



(10) (16) (17)

Wherein: X is Halogen

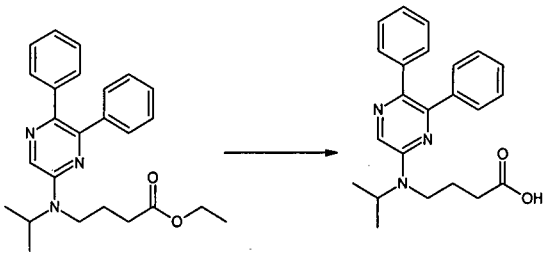
b) condensing the compound of formula (17) with a compound of formula (4) in a solvent and in the presence of a suitable base, to provide a compound of formula (18);



(17) (4) (18)

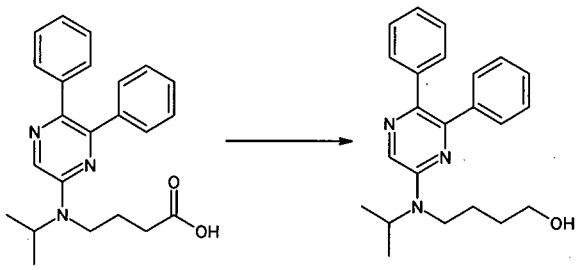
Wherein: Y is -OH, Halogen

c) hydrolyzing compound of formula (18) with a suitable base in a solvent to provide a compound of formula (19);



(18) (19)

d) reducing the compound of formula (19) with a suitable reducing agent in a solvent and optionally in the presence of suitable base, to provide the compound of formula (2);



(19) (2)

According to another embodiment of the present invention, the intermediate compounds (17), (18), and (19) of steps (a), (b) and (c) respectively can be used in next stages without isolating the said intermediates.

The solvent used in the embodiment is selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not

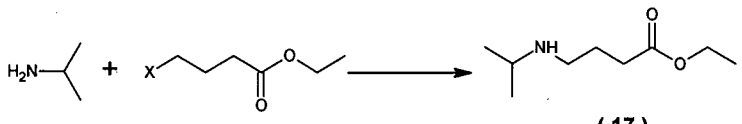
limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide, water or mixtures thereof.

The base used in the embodiment is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarboriates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases like primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, and pyrrole methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine; and their mixtures thereof.

The "suitable reducing agent" used in the present embodiment is selected from diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, $NaBH_4$, NaBH4/BF3-diethyl ether, $LiBH_4$ and $LiAlH_4$.

According to another embodiment, the present invention provides a process for preparation of 4-isopropylamino-butan-1-ol (3), a Selexipag precursor the process comprising:

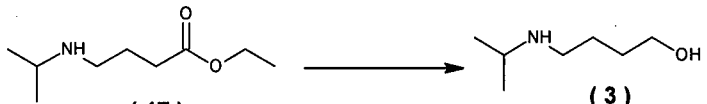
a) reacting compound of formula (10) with compound of formula (20) to obtain compound of formula (17); and



(10) (20) (17)

Wherein, X= Halogen or a leaving group selected from -OH, -OTs, -OCF $_3$, -OBOP, -OPyBrOP, OSO2CH3, OSO2CF3, OBs, OCH2OCH3, OC(CH $_3$)3, OCH $_2$Ph, O-p-methoxybenzyl, OTMS, OTES, OTBDMS, OTBDPS, OTIPS,OCPh3, OR; R is selected from the group consisting of alkyl, aryl, and substituted aryl

b) reducing the obtained compound of formula (17) in a solvent and in presence of a suitable reducing agent optionally in combination with a suitable catalyst to obtain compound of formula (3).



(17) (3)

The compound of formula (17) can be optionally isolated from the reaction mass and further purified by involving at least one of the following methods like solvent extraction, precipitation or distillation methods.

The step (a) of the present invention can be carried out optionally in a solvent and a base.

The solvent used in step (a) is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not

limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide; water or mixtures thereof.

Preferably, the solvent used in step (a) is ethers and hydrocarbons. More preferably, the solvent used is cyclic ethers such as tetrahydrofuran and halogenated hydrocarbons such as dichloromethane.

The solvent used in step (b), is selected from the group comprising of aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether, di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited

to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; or mixtures thereof.

Preferably, the solvent used in step (b) is ethers. More preferably, the solvent used is cyclic ethers such as tetrahydrofuran.

The base used in step (a) is selected from inorganic bases such as alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarbonates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert-butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) ; 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases such as primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole and methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine; and mixtures thereof.

Preferably, the base used in step (a) is tertiary amines. More preferably, the base used is triethyl amine.

The suitable Reducing agent used in step (b) is selected from the diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, Diisobutylaluminum hydride (DIBAL-H), Lithiumaluminiumhydride **(IJAIH4),** Sodium borohydride ($NaBH_4$), **$NaBH_4$/BF3-**etherate, Lithiumborohydride ($LiBH_4$), Sodiumcyanoborohydrie **(NaCNBH4),** Raney-Nickel, Sodium bis(2-methoxyethoxy)aluminumhydride (Vitride), and Sodium bis(2-methoxyethoxy) aluminumhydridepyrolidine (Red-ALP), Lithium triethylborohydride **(LiBHEt3),** magnesium tetrahydroborate [**Mg(BH_4)2],** Aluminum borohydride [**Al(BH_4)3],** Calcium borohydride [**Ca(BH_4)3],** Zinc borohydride [**Zn(BH_4)2],** Cerium borohydride **Ce(BH4)3,** Sodium triacetoxyborohydride [NaBH(OAc)3], Sodium cyanoborohydride [NaBI-bCN], Mg**(BH4)2** ($NaBH_4$+$AlCl_3$), **Al(BH_4)3(NaBH4+AlCl3),** Ca(BH_4)3**(NaBH4** +$CaCl_2$), $Zn(BH_4)_2$($NaBH_4$**+ZnCl2),** Ce(BH_4)3($NaBH_4$+$CeCl_3$), $NaBH_3CN$($NaBH_4$+HCN), or their mixtures thereof. Preferably, the reducing agent used in step (b) is Lithiumaluminiumhydride ($LiAlH_4$).

The reducing agent used in step (b) is in the molar ratio of 0.8 to **4.**

Step (a) of the embodiment is carried out at a temperature of 0°C to the reflux temperature of the solvent. More preferably temperature is 5°C to 20°C.

Step (b) of the embodiment is carried out at a temperature of -10°C to the reflux temperature of the solvent. More preferably temperature is - 10°C to 5°C.

Suitable catalyst used in step (b) may be selected from Lewis acid, acid as a catalyst, catalyst or their mixtures thereof.

Lewis Acid used in step (b) is selected from Aluminum Chloride **(AICI3-),** Zinc chloride (ZnCfc), Boron trifluoride **(BF3),** Boron trialkoxide (**B(OR)3),** Trimethylaluminium ($Al(CH_3)_3$), $Sn^{2+}B(CH_3)_3$, Iodine(I_2), **Bromine(Br2),** Carbenes, Hydrogen ion(H^+), Lithium ion(Li^+), Sodium ion(Na^+), Potassium ion(K^+), Aluminum ion (Al^{3+}), Magnesium ion (Mg^{2+}), Calcium ion(Ca^{2+}), Ferrous ion (Fe^{2+}), Cobalt ion (Co^{2+}), Copper ion (Cu^{2+}), Zinc ion (Zn^{2+}), Lead ion (Pb^{2+}), Copper ion (Cu^+), Silver ion (Ag^+), mercury ion(Hg^+), Palladium ion(Pd^{2+}), Acetic acid .

Acid used in step (b) may be an organic acid, or an inorganic acid, selected from sulfuric acid **(H2SO4),** Trifluoroacetic acid (TFA), Trichloroacetic acid **(CCI3COOH),** Dichloroacetic acid (CHCbCOOH), Trifluoroacetic acid **(CF3COOH),** Methanesulfonic acid **(CH3SO3H),** Trifluoromethanesulfonic acid (CF_3S03H), and p-toluene sulfonic acid (**P-CH3C6H4SO3H),** Nitric acid **(HNO3),** hydroiodic acid (HI), Hydrobromic acid (HBr), Perchloric acid **(HClO4),** Chloric acid **(HClO3),** Hydrochloric acid (HCl) .

Catalyst used in step (b) is selected from Iodine **(I2),** Trialkyl amine, Dimethyl selane **(SiH2Me2),** trimethylsilyl chloride (MesSiCl), Titanium chloride (TiCU), dialkyl silane **(R2Se2), MeSe20H.**

The step (a) further comprises isolation and purification of compound of formula (17); wherein the said process comprises the steps of:

i. treating the reaction mass of step (a) with water arid organic solvent;

ii. acidifying the reaction mass of step (i);
iii. separating the organic layer and aqueous layer of step (ii);
iv. adjusting the pH of aqueous layer of step (iii) to 9-12 with 10 % sodium hydroxide solution;
v. extracting the product from reaction mass of step (iv) with an organic solvent; and
vi. concentrating the organic layer of step (v) to obtain the compound of formula (17).

The organic solvent used in steps (i) and (v) of isolation process is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, isopropyl acetate; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; or mixtures thereof.

Preferably, the organic solvent used in steps (i) & (v) is halogenated aliphatic hydrocarbons. More preferably, the solvent used is dichloromethane.

The step (b) further comprises isolation and purification of compound of formula (3); wherein the said process comprises the steps of:

i. treating the reaction mass of step (b) with water or optionally with mixture of alcohol and water;
ii. extracting the reaction mass of step (i) with an organic solvent;
iii. separating the organic layer of step (ii) followed by washing it with water; and

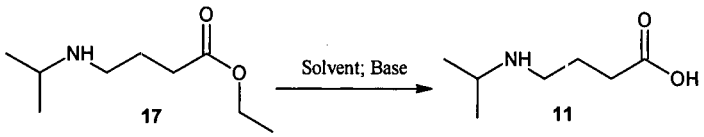
iv. concentrating the organic layer of step (iii) to obtain the compound of formula (3).

Alcohol used in step (i) is selected from but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol.

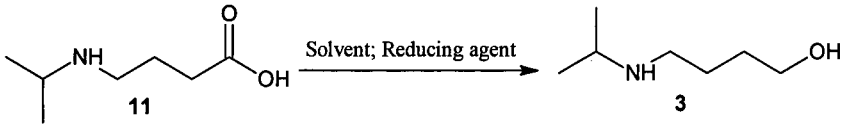
The organic solvent used in step (ii) isolation process is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone; or mixtures thereof.
Preferably, the organic solvent used in step (ii) is hydrocarbons. More preferably, the organic solvent is halogenated aliphatic hydrocarbons such as dichloromethane.

According to another embodiment, the present invention provides a process for preparation of 4-isopropylamino-butan-1-ol of formula (3), the process comprising:

a. reacting a compound of formula (17) with a suitable base in a solvent to obtain compound of formula (11); and



b. reducing the compound of formula (11) using a suitable reducing agent in a solvent to obtain compound of formula (3).



The compound of formula (11) can be optionally isolated from the reaction mass and further purified by solvent extraction, precipitation or distillation method.

The reducing agent used in step (b) is in the molar ratio of 0.8 to 4.

Step (a) of the embodiment is carried out at a temperature of 0°C to the reflux temperature of the solvent.

Step (b) of the embodiment is carried out at a temperature of -10°C to the reflux temperature of the solvent.

The solvent used in step (a) is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether, di-methyl ether, and methyl butyl ether; cyclic

ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide; water; or mixtures thereof.

The solvent used in step (b) is selected from the group comprising of aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di¬ ethyl ether, di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; or mixtures thereof.

The base used in step (a) is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarbonates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal

alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert-butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases like primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole and methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine; and mixtures thereof.

The suitable Reducing agent used in step (b) is selected from the diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, Diisobutylaluminum hydride (DIBAL-H), Lithiumaluminiumhydride **(L1AlH4),** Sodium borohydride (NaBhU), $NaBH_4/BF_3$-etherate, Lithiumborohydride **(UBH4),** Sodiumcyanoborohydrie (NaCNBH4), Raney-Nickel, Sodium bis(2-methoxyethoxy)aluminumhydride (Vitride), and Sodium bis(2-methoxyethoxy) aluminumhydridepyrolidine (Red-ALP), Lithium triethylborohydride (LiBHEt3), magnesium tetrahydroborate [**Mg(BH4)2],** Aluminum borohydride [$Al(BH_4)_3$], Calcium borohydride [**Ca(BH4)3_,** Zinc borohydride [**Zn(BH4)2],** Cerium borohydride **Ce(BH4)3,** Sodium triacetoxyborohydride [NaBH(OAc)3], Sodium cyanoborohydride [NaBhhCN], $Mg(BH4)_2(NaBH_4+AlCl_3)$, **$Al(BH_4)_3$(NaBH4+AlCl3),** $Ca(BH_4)_3$**(NaBH4** $+CaCl_2$),

$Zn(BH_4)_2$(NaBH4+ZnCl2), $Ce(BH_4)_3$(NaBH$_4$+CeCl3), $NaBH_3CN$(NaBH$_4$+HCN), or their mixtures thereof.

The step (b) of the said embodiment further comprises isolation and purification of compound of formula (3); wherein the said process for isolation and purification comprises the steps of:

I. treating the reaction mass of step (b) with an alcohol and water;
II. extracting the reaction mass of step (I) with an organic solvent;
III. separating the organic layer of step (II) followed by washing it with water; and
IV. concentrating the organic layer of step (III) to obtain the compound of formula (3).

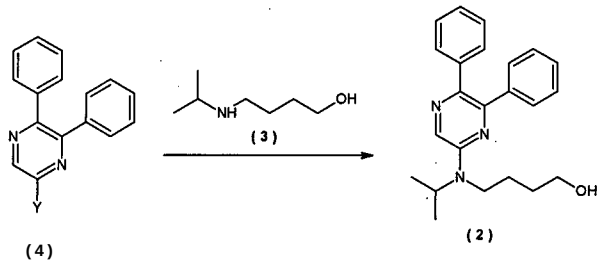
Alcohol used in step (I) is selected from but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol.

The organic solvent used in step (II) isolation process is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether, di¬ methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; esters; ketones such as but not limited to

acetone, methyl ethyl ketone, and methyl isobutyl ketone; or mixtures thereof.

According to yet another embodiment, there is provided an improved process for the preparation of Selexipag (1), the process comprising:

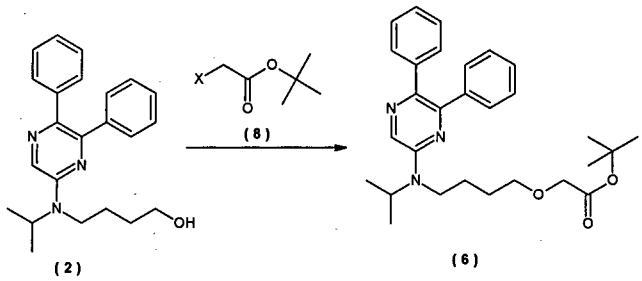
a) reacting the compound of formula (4) with the compound of formula (3) to provide a compound of formula (2);



(4) (3) (2)

Wherein: Y is -OH, Halogen

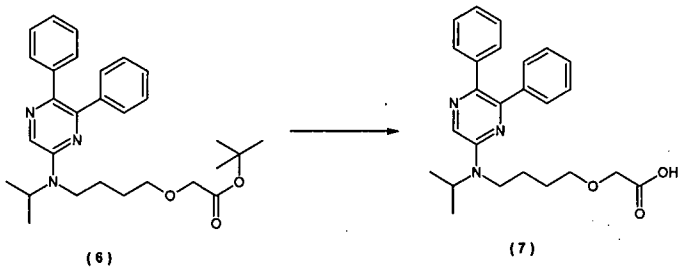
b) condensing the compound of formula (2) with a compound of formula (8) in a solvent, in presence of a suitable base and optionally in presence of a phase transfer catalyst to provide a compound of formula (6);



(2) (8) (6)

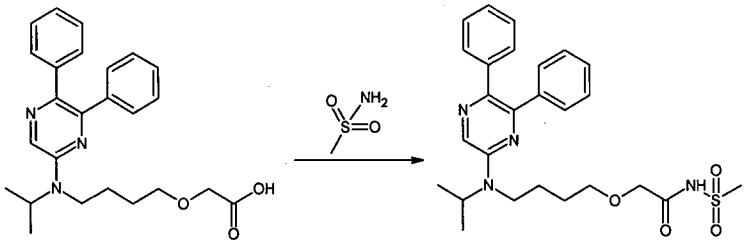
Wherein: X is Halogen

c) hydrolyzing the compound of formula (6) in a solvent and in presence of a suitable base to provide a compound of formula (7); and



(6) (7)

d) condensing compound of formula (7) with methane sulfonamide in a solvent, in presence of suitable base and coupling agent, to provide Selexipag (1).



(7) (1)

According to another embodiment of the present invention, the intermediate compounds (2), (6), and (7) of steps (a), (b) and (c) respectively can be used in next stages without isolating the said intermediates.

The step (a) can be carried out optionally in presence of a solvent and a base. The solvent used for step (a) is selected from the group consisting of aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene; dialkylformamides such as but not limited to dimethyl formamide; cyclic amide such as but not limited to N- methyl-2-pyrrolidone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide.

Preferably, the solvent used in step (a) is amides. More preferably, the solvent used is N- methyl-2-pyrrolidone and dimethyl formamide.

The solvent used for step (b) is selected from the group consisting of aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; water or mixtures thereof. Preferably, the solvent used in step (b) is mixture of water and aromatic hydrocarbons. More preferably, the aromatic solvent used is toluene.

The solvent used for step (c) is selected from the group consisting of aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; water or mixtures thereof. Preferably, the solvent used in step (c) is mixture of water and alcohols. More preferably, the alcohol used is methanol.

The solvent used for step (d) is selected from the group consisting of halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and dialkylacetamides such as but not limited to N,N-dimethyl acetamide. Preferably, the solvent used in step (d) is cyclic ether. More preferably, the solvent used is Tetrahydrofuran.

The base used in step (a) is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium .

carbonate, and cesium carbonate; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert butoxide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; and organic bases like secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole, and methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, and N,N-dimethylethyl amine; and their mixtures thereof.

Preferably, the base used in steps (a) is metal carbonate. More preferably, the base used is potassium carbonate.

The base used in step (b) and (c) is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide; and their mixtures thereof.

Preferably, the base used in steps (b) and (c) is alkali metal hydroxide. More preferably, the base used is sodium hydroxide.

Preferably, the base used in step (d) is amidines. More preferably, the base used is 1,8-diazabicyclo[5.4.0]undec-7ene (DBU).

The coupling agent used in step (d) is selected from but not limited to N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) or its salts, 1,1'-carbonyldiimidazole (CDI),

diphenylphosphoryl azide (DPPA), diethylphosphoryl cyanide (DEPC), 3-(diethoxyphosphoryloxy)-l ,2,3-benzotriazin-4(3H)-one (DEPBT), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), 1-[bis(dimethylamino)methylene]-1 H-1 ,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), (0-(7-azabenzotriazole-1 -yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) (TATU), 2-(1H-benzotriazole-1-yl)-1,1 ,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazole-1-yl)-1 ,1 ,3,3-tetra methyluronium tetrafluoroborate (TBTU), boric acid or its derivatives, phenyl boronic acid, trimethyl borate and the like. Preferably, the coupling agent used in step (d) is 1,1-cabonyldiimidazole (CDI).

The "phase transfer catalyst" refers to catalyst used in step (b) is selected from the group consisting of but not limited to tetra butyl ammonium bromide, tetra propyl ammonium bromide, tributyl benzyl ammonium bromide, tetra octyl ammonium bromide, tetra butyl ammonium iodide, tetra butyl ammonium hydrogen sulfate, benzyl trimethyl ammonium chloride, benzyl triethyl ammonium chloride, tetra butyl ammonium acetate, tetra butyl ammonium iodide, ethyl triphenyl phosphonium bromide, more preferably tetra butyl ammonium bromide or alkali iodides like sodium iodide, potassium iodide and lithium iodide.

Preferably, the phase transfer catalyst used in step (b) tetra butyl ammonium bromide (TBAB).

The step (a) is carried out at temperature in the range of 100°C -190 °C; More preferably temperature at 180-1 90 °C.

The step (b) is carried out at temperature in the range of 20°C to reflux temperature of the said solvent. More preferably temperature at 25-35 °C.

The step (c) is carried out at temperature in the range of 20°C to reflux temperature of the said solvent. More preferably temperature at 60-65 °C.

The step (d) is carried out at temperature in the range of 20°C to reflux temperature of the said solvent. More preferably temperature at 25-35 °C.

According to the present invention, the process for isolation followed by purification of compound of the formula (2) from reaction mass of step (a), comprises the steps of:

i. adding the water and suitable organic solvent to the reaction mass of step (a);
ii. separating the aqueous layer and organic layer of step (i);
iii. washing the organic layers of step (ii) with base
iv. concentrating the organic solvent of step (iii) under reduced pressure;
v. adding suitable organic solvent to the obtained syrup of step (iv);
vi. adding suitable anti-solvent to the solution of step (v); and
vii. filtering the solid obtained in step (vi) and drying to provide pure compound (2).

Preferably, the solvent used in steps (i) and (v) is alkyl acetate. More preferably, the solvent used is ethyl acetate.

Preferably, the anti-solvent used in steps (vi) is hydrocarbons. More preferably, the anti-solvent used is n-heptane.

According to the present invention, isolation followed by purification of compound of the formula (7) from reaction mass of step (c) comprises the steps of:

i. concentrating the reaction mass of step (c) ;
ii. adding water and suitable organic solvent to the mass of step (i);
iii. separating the organic and aqueous layers of step (ii);
iv. adjusting the pH of the aqueous layer of step (iii) to 2.0-2.5 of using 1N HCl;
v. filtering and washing the solid obtained in step (iv) with water to provide compound (7);
vi. suspending compound (7) of step (v) in a suitable organic solvent; and
vii. filtering and drying the solid of step (vi) to provide pure compound (7).

Preferably, the solvent used in steps (ii) is alkyl acetate. More preferably, the solvent used is ethyl acetate.

Preferably, the solvent used in steps (vi) is alcohol. More preferably, the solvent used is methanol.

According to the present invention, isolation followed by purification of compound of the formula (1) from reaction mass of step (d), comprises the steps of:

i. concentrating the reaction mass of step (d);
ii. adding water and suitable organic solvent to the mass of step (i);
iii. separating the organic and aqueous layers of step (ii)
iv. adjusting the pH of the aqueous layer of step (iii) between 5.0 to 6.0 using 1N HCl
v. extracting the solid obtained in step (iv) using suitable organic solvent;

vi. concentrating the said organic layer of step (v) to obtain residue;
vii. crystallising the obtained residue in suitable organic solvent; and
viii. filtering and drying the solid obtained in step (vii) to provide pure compound (1).

Preferably, the solvent used in steps (ii) is ether. More preferably, the solvent used is methyl tertiary butyl ether (MTBE).

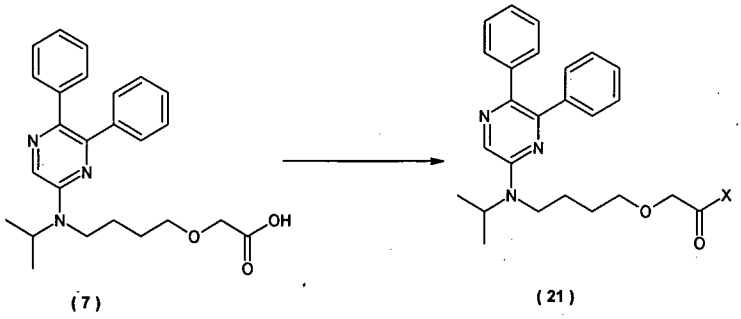
Preferably, the solvent used in steps (v) is alkyl acetate. More preferably, the solvent used is ethyl acetate.

Preferably, the solvent used in step (vii) is alcohol. More preferably, for step (vii) the solvent used is ethanol.

The obtained crystalline product of step (vii) can be optionally suspended in a suitable solvent to control the acid or amide impurity that may be generated in the process; wherein the suitable solvent is selected from alcohol. Preferably, the alcohol is isopropanol.

According to yet another embodiment, there is provided a novel process for the preparation of Selexipag (1), the process comprising:

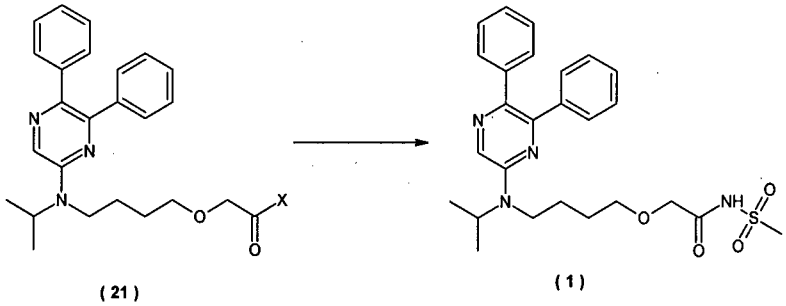
a) reacting compound of formula (7) with a suitable halogenating agent in a solvent to provide a compound of formula (21), which may be optionally isolated; and



(7) (21)

Wherein: X is Halogen

b) condensing compound of formula (21) with methane sulfonamide in a suitable solvent to provide Selexipag (1).



(21) (1)

Wherein: X is Halogen

The intermediate compounds (21) of step (a) of the present embodiment can be used in next stages without isolating the said intermediate.

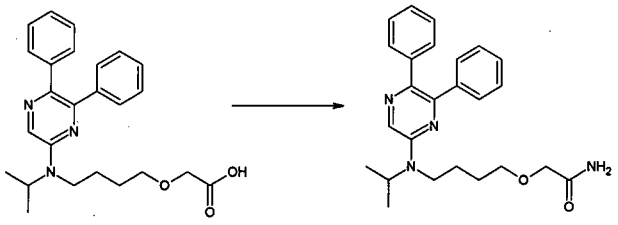
The solvent(s) used in the embodiment is selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane;

substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide, water or mixtures thereof.

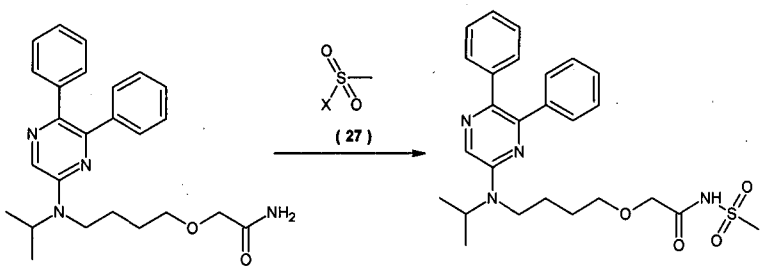
The "suitable halogenating agent" used for the present embodiment is selected from thionyl chloride, oxalyl chloride, phosphorous trichloride, phosphorus oxychloride, phosphorous pentachloride, phosphorous tribromide, phosphorous penta bromide, N-bromo succinamide, N-chloro succinamide, chlorine, bromine, sulfuryl chloride, copper (II) chloride, copper (II) bromide, ferric chloride, and ferric bromide.

According to yet another embodiment, there is provided a novel process for the preparation of Selexipag (1), the process comprising:

a) reacting compound of formula (7) with thionyl chloride followed by ammonia to provide a compound of formula (22), which may be optionally isolated; and



b) condensing compound of formula (22) with compound of formula (27) in presence of base in a solvent to provide a compound of formula (1).



(22) (1)

Wherein: X is Halogen

According to another embodiment of the present invention, the intermediate compounds (22) of step (a) can be used in next stages without isolating the said intermediate.

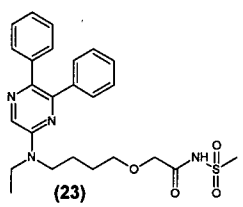
The solvent(s) used in the embodiment is selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl

acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide, water or mixtures thereof.

The base used in the embodiment is selected from inorganic bases like alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarboriates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases like primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, and pyrrole methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine; and their mixtures thereof.

Selexipag prepared according to any of the processes of the present invention has less than 0.15% of N-(2-{4-[(5,6-diphenyl-pyrazin-2-yl)-ethyl-amino]-butoxy}-acetyl)-methanesulfonamide (23); has less than 0.15% of 2-

{4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butoxy}-acetamide (22); or has less than 0.15% of N-[2-(5,6-diphenyl-pyrazin-2-yloxy)-acetyl]-methane sulfonamide (24).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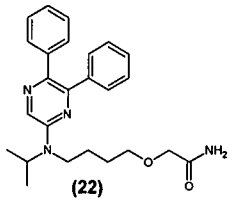
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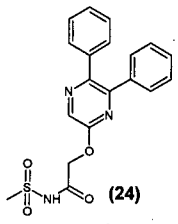

(24)

BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION

The present invention is described in the examples given below; further these are provided only to illustrate the invention and therefore should not be construed to limit the scope of the invention.

EXAMPLE-1 : (5,6-diphenyl-pyrazin-2-yl)-isopropyl-amine

A mixture of 5-Chloro-2,3-diphenyl-pyrazine (10.00 g, 37.5 mmol) and a 70% solution of isopropylamine in water (44.32 g, 74.9 mmol) in isopropanol (100 ml) was heated at 150 °C for 24 h in a autoclave with 200-400 psi pressure. The reaction progress was monitored by HPLC and after completion of reaction; resulting mass was cooled to 25-30° C and concentrated. The residue was diluted with water and extracted with dichloromethane, after which the extract was distilled completely to obtain solid (5,6-diphenyl-pyrazin-2-yl)-isopropyl-amine (7.0g, 76%) as pale yellowish solid. **[Yield= 7g]**

EXAMPLE-2: Preparation of 4-[(5,6-diphenyl-pyrazin-2-yl)-isoprdpyl-amino]-butan-1-ol

To a suspension of NaH (60% dispersion in oil, 1.2 g, 50 mmol) in DMF (100 ml) was added the (5,6-diphenyl-pyrazin-2-yl)-isopropyl-amine (10 g, 34 mmol) at room temperature, and the mixture was stirred at 80 °C for 35 min.

The mixture was ice cooled to 15-20 °C and a solution of **1-chloro-4-butanol** (11.25 g, 100 mmol) in DMF (21 ml) was added dropwise. The mixture was stirred at room temperature for 2-3 hrs, diluted with ice water, and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. After the solvent was evaporated, the crude product of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol (8 gm, 64%) as pale yellow solid. **[Yield= 8g]**

EXAMPLE-3: Preparation of Toluene-4-sulfonic acid 5,6-diphenyl-pyrazin-2-yl ester

The 5,6-diphenyl-pyrazin-2-ol (40 g, 161 mmol) was added dichloromethane (400 ml_), then added the diisopropylethylamine (DIPEA) at 25-30 °C. The reaction mass was cooled to 10-15 °C and p-toluenesulfonyl chloride was added. The resulting mixture was stirred for 1 hr at 10-15 °C. The reaction progress was monitored by HPLC and after completion of reaction; resulting mass was cooled to 25-30° C and water added. Separate the dichloromethane layer and washed with water. Then the dichloromethane layer was removed by distillation at below 40 °C. Charged methanol to cool reaction mass and stirred for 30 min, filtered the reaction mass to obtain titled compound **[Yield=40g; Purity(HPLC)=98.64%].**

EXAMPLE-4: Preparation of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol

To the stirred mixture of Toluene-4-sulfonic acid 5,6-diphenyl-pyrazin-2-yl ester (15) (100 g, 0.248 mol) & 4-isopropyl amino butane-1-ol (130.44 g, 0.99 mol) was added at room temperature. Reaction mixture was stirred at 185-190°C temperature for 2 hr. Reaction was monitored by HPLC analysis. After completion of reaction, charged purified Water and product extracted in Ethyl acetate, which was washed using 5% sodium bicarbonate to remove the

hydroxyl impuritiy produced during the reaction. Then the ethyl acetate layer was concentrated to obtain the 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol. **[Yield = 90 g; Purity (HPLC) = 89.71%]**

EXAMPLE-5: Preparation of 4-isopropylamino-butyric acid ethyl ester

Ethyl 4-bromobutyrate (20 g; 102.6 mmol) was combined with Isopropyl amine (30.32 g; 0.514 mol) and heated to 100X in a sealed tube for 24 h. The contents of the reaction were cooled to ambient temperature, the volatiles were removed in vacuo and the crude product was dissolved in 1 N hydrochloric acid. The aqueous layer was extracted twice with diethyl ether and the organic layer discarded. The aqueous layer was adjusted to pH 9 with 2.5 N sodium hydroxide. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts (from the pH 9 aqueous layer) were washed with brine and the solvent was removed in vacuo to afford the title **compound.[Yield = 14.2 g; Purity (HPLC) = 89.71%]**

EXAMPLE-6: Preparation of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butyric acid ethyl ester.

To the stirred mixture of 5-chloro 2-3 diphenyl pyrazine (100 g, 0.375 mol) & 4-Isopropylamino-butyric acid ethyl ester (257.97 g, 1.49 mol) was added at room temperature. Reaction mixture was stirred at 185-190°C temperature for 24 hr. Reaction was monitored by HPLC analysis. After completion of reaction, charged purified Water and product extracted in Ethyl acetate, which was washed using 5% sodium bicarbonate to remove the hydroxyl impuritiy produced during the reaction. Then the ethyl acetate layer was concentrated to obtain the 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butyric acid ethyl ester. **[Yield = 90 g; Purity (HPLC) = 88.71%]**

EXAMPLE-7: Preparation of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butyric acid

20 ml of ethanol and 2.61 ml of a 1N aqueous solution of sodium hydroxide were added to 389 mg of 4-[(5,6-Diphenyl-pyrazin-2-yl)-isopropyl-amino]-butyric acid ethyl ester. The obtained mixture was stirred at room temperature for 4 hours and at 50°C for 10 minutes and neutralized with 1N hydrochloric acid. The crystals precipitated were recovered by filtration to obtain the 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butyric acid.

[Yield = 305 mg; Purity (HPLC) = 96.01 %]

EXAMPLE-8: Preparation of 4-[(5,6-diphenyl-pyrazin-2 -yl)-isopropyl -amino]-butan-1 -ol.

To a mixture of **UAIH4** (760 mg) in anhydrous THF (45 ml) was added a solution of 4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butyric acid (1.75 g) in anhydrous THF (5 ml) at 0 °C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature. After stirring for 10 hr, the reaction was quenched with 6 mL of 20% aqueous NaOH solution at 0 °C and then filtered. The filter cake was washed with ethyl acetate (10 mL × 4). Combined organic layers were concentrated under reduced pressure and residue was isolated from 9:1 heptane and ethyl acetate to obtain 4-[(5,6-Diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol. **[Yield=1.54g;Purity (HPLC)=96%]**

EXAMPLE-9: Preparation of 4-[(5,6-Diphenyl-pyrazin-2-yl)-isopropyl-amino]-butan-1-ol

To the stirred mixture of 5-chloro 2-3 diphenyl pyrazine (100 g, 0.375 mol) & 4-isopropyl amino butane-1-ol (196.7 g, 1.49 mol) was added at room temperature. Reaction mixture was stirred at 185-190°C temperature for 24

hr. Reaction was monitored by HPLC analysis. After completion of reaction, charged purified Water and product extracted in Ethyl acetate, which was washed using 5% sodium bicarbonate to remove the hydroxyl impuritiy produced during the reaction. Then the ethyl acetate layer was concentrated to obtain the 4-[(5,6-Diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol.

[Yield = 90 g; Purity (HPLC) = 89.71 %]

EXAMPLE-10: Preparation of 4-[(5,6-Diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1 -ol

To the stirred mixture of 5-chloro 2-3 diphenyl pyrazine (100 g, 0.375 mol) & 4-isopropyl amino butane-1-ol (172.17 g, 1.31 mol) was added at room temperature. The resultant reaction mixture was heated at 180-185°C and maintain at same temperature for 24 hrs. After completion of reaction by HPLC analysis, cool the reaction mass and diluted it with ethyl acetate (1000 ml), purified water (1500 ml) and product was extracted: in ethyl acetate further aqueous layer was rewashed with ethyl acetate (500 ml). After combining the both ethyl acetate layers, wash it with 5% sodium bicarbonate (1000 ml) to remove the hydroxyl impurity formed during the reaction followed by washing of 10% sodium chloride solution (1000 ml). Ethyl acetate layer was concentrated under reduced pressure to obtain thick syrup of compound (4). Obtained thick syrup was diluted with ethyl acetate (20 ml) and n-heptane (500 ml) was added to the diluted mass and stirred for 60-90 min. the resultant isolated solid was filtered and washed with n-heptane (100 ml), suck dried and dried the solid under vacuum at 35-40 °C for 3-4 hrs.

[Yield = 95.0 g; Purity (HPLC) = 91.5%]

EXAMPLE-11: Preparation of 4-[(5,6-Diphenyl-pyrazin-2-yl)-isopropyl -amino]-butan-1-ol

To the stirred solution of 5-chloro 2-3 diphenyl pyrazine (10.0 g, 0.0375 mol) in NMP (100 ml) anhydrous potassium carbonate (5.77 g, 0.037 mol) was added followed by addition of 4-isopropyl amino butane-1-ol (14.72 g, 0.1 12 mol) was added at room temperature. The resultant reaction mixture was heated at 180-190°C and maintain at same temperature for 28 hrs. After completion of reaction by TLC, cool the reaction mass and diluted it with purified water (100 ml) and product was extracted in ethyl acetate (100 ml) further aqueous layer was rewashed with ethyl acetate (50 ml). After combining the both ethyl acetate layers, wash it with 10% sodium chloride solution (100 ml). Ethyl acetate layer was concentrated under reduced pressure to obtain thick syrup of compound. **[Yield = 14.0 g; Purity (HPLC) = 49.01%]**

EXAMPLE-12: Preparation of 2-{4-[IM-(5, 6-dipheny!pyrazin-2-yl)-N-isopropyl amino] butyloxy} acetic acid

The tetra butyl ammonium bromide (129.5 g, 0.664 mol) was added at 15-20°C to the mixture of 4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropyl amino]-1-butanol (80 g, 0.22 mol) in toluene (704 ml) and aqueous 35% sodium hydroxide solution (704 ml). The tert-butyl bromoacetate (129.52 g, 0.664 mol) was added drop wise at 5-1 0°C to reaction with constant stirring. Then the reaction is stirred at 25-30 °C for 5-6 hr. After the reaction, biphasic layers were separated and concentrated toluene layer completely to obtain the {4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropyl amino] butyloxyjacetic acid tert-butyl ester (104 g).

{4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropyl amino] butyloxyjacetic acid tert-butyl ester (104 g) was dissolved in methanol (1050 ml) and 1N sodium hydroxide solution (300 ml) was added at RT after mixture was heated at reflux for 2 hours, The progress of the reaction was monitored by the HPLC.

After reaction completes, add the water and wash the impurities using ethyl acetate. Then adjust the pH 2.0-2.5 of the aqueous layer using 1N HCl solution (300 ml) to obtain the product precipitation, which was filtered and washed with water (210 ml) to obtain crude product. The crude 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy} acetic acid was added Methanol (630 ml) and refluxed for 2 hr, which was cooled gradually to 25-30 °C, Then the precipitation of the product is filtered and dried to obtain pure 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy} acetic acid.

[Yield = 64 g; Purity (HPLC) = 99.1%]

EXAMPLE-13: Preparation of 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy} acetic acid

To the stirred mixture of 4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropyl amino]-1-butanol (100 g, 0.27 mol) in toluene (700 ml) and aqueous 35% sodium hydroxide solution (700 ml) the tetra butyl ammonium bromide (29.42 g, 0.088 mol) was charged at 15-20°C. The resultant reaction mass was cooled at 5-10 °C and tert-butyl bromoacetate (161.9 g, 0.82 mol) was added drop wise with constant stirring. Then the temperature of reaction mass was raised at 25-30 °C and maintain at same temperature for 5-6 h. After the reaction completion by HPLC analysis, both the biphasic layers were separated and concentrated toluene layer completely under reduced pressure to obtain the {4-[N-(5,6-diphenylpyrazine-2-yl)-N-isopropyl amino] butyloxyjacetic acid tert-butyl ester (131 g).

The compound (131 g) was dissolved in methanol (1000 ml) to the resultant solution 4 % sodium hydroxide solution (400 ml) was added at 25-30 °C and mixture was heated at 60-65 °C and maintain at same temperature for 2 hrs. After completion of reaction monitored by HPLC analysis, reaction solvent was removed by distillation under reduced pressure at below 55 °C to obtain

the residue. To the resultant residue purified water (1000 ml) was added and impurities are washed using two times ethyl acetate (2 × 500 ml) extraction. Adjust the pH of the aqueous layer 2.0-2.5 using 1N HCl solution (458 ml). The precipitated product was filtered and washed with water (350 ml) to provide crude product. The crude compound was suspended in Methanol (800 ml) and heated at 60-65 °C and maintain at same temperature for 30-45 min. The resultant suspension was gradually cooled at 25-30 °C and further chilled at 0-5 °C then the suspension of the product is filtered and dried under reduced pressure at 45-50 °C to obtained pure compound 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy} acetic acid.

[Yield = 84.0 g ; Purity (HPLC) = 99.0%]

EXAMPLE-14: Preparation of 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide

The reaction mixtures of 2-{4-[N-(5, 6-diphenynylpyrazin-2-yl)-N-isopropyl amino] butyloxy} acetic acid (25 g, 59 mmol) anhydrous tetrahydrofuran (375 ml) and 1,1carbonyl diimidazole (12.5 g, 77 mmol) were heated to 65-70 °C and stirred for 45 min. The addition of methanesulfonamide (7.36 g, 77 mmol) and 1,8-diazabicyclo{5,4,0}-7-undecane (12.5 ml) were done at 25-30 °C with vigorous stirring. The reaction is maintained for 3 hr and monitor using the HPLC analysis. Then after the completion of the reaction removed THF completely, followed by the addition of water, aqueous layer was washed with MTBE then adjust the pH of the solution to 5-6 using 1N Hydrochloric acid. The product obtained was extracted from ethyl acetate, distillation of ethyl acetate completely at below 50 °C to obtain crude 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide.

Purification of Selexipaq

Selexipag crude (100 g) wet solid was dissolved in Ethanol (1000.0 ml) at 25-30 °C. heat the solution to 80 -85 °C and stir for 2 hr. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained for 45-60 min. Obtained solid was filtered, washed with ethanol (100.0 ml), suck dried and dried under vacuum at 55-60°C to afford pure Selexipag **.[Yield = 20 g; Purity (HPLC) = 99.7%]**

EXAMPLE-15

Preparation of 2-{4-[N-(5, 6-diphynylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide (1)

The reaction mixtures of 2-{4-[N-(5, 6-diphynylpyrazin-2-yl)-N-isopropyl amino]butyloxy} acetic acid (7) (50.0 g, 0.119 mol) anhydrous tetrahydrofuran (250.0 ml) and 1,1carbonyl diimidazole (25.1 g, 0.154 mol) were heated at 65-70 °C and maintained at same temperature for 30-45 min. The resultant reaction mass was cooled at 25-30 °C then charge methane sulfonamide (14.7 g, 0.154 mol) and 1,8-diazabicyclo{5,4,0}-7-undecane (25.0 ml). The reaction mass was maintained at 25-30 °C for 3 hrs and progress of reaction was monitor by HPLC analysis. After the completion of the reaction, tetrahydrofuran was removed under reduced pressure to obtain thick syrup. The obtained syrup was diluted with purified water, and impurities are removed from aqueous layer by extracting it with MTBE (3 × 250 ml). The pH of aqueous layer was adjusted to 5-6 using 1N hydrochloric acid (450 ml). The obtained product was extracted in ethyl acetate (500 ml) followed by distillation of ethyl acetate completely at below 50 °C under reduced pressure to obtain semi solid of selexipag (1). The obtained semisolid of (1) was dissolved in ethanol (500 ml) and heated at 80-85 °C and maintained at same temperature for 30-60 min. then solution was cooled to 25-30 °C and further chilled at 0-5 °C and maintain for 30-60 min. obtained solid was

filtered and washed with pre-chilled ethanol (50 ml) and suck dried the crude Selexipag (1) [Yield = 60.0 g, Purity (HPLC) = 98.3%].

Purification of Selexipag

The wet solid of crude Selexipag (60.0 g) was suspended in isopropanol (500 ml) at 25-30 °C. Heat the suspension at 80-85 °C and maintain at same temperature for 30-60 min. The resulting solution was gradually cooled at room temperature then further chilled at 0-5°C and maintained for 45-60 min. the obtained solid was filtered, washed with pre-chilled isopropanol (50.0 ml) and suck dried to give wet solid of Selexipag (1). [Yield = 55.0 g, Purity (HPLC) = 99.40%]

The obtained wet solid of selexipag **(1)** was dissolved in ethanol (500 ml) and heated at 80-85 °C and maintained at same temperature for 30-60 min. then solution was cooled at 25-30 °C and maintain for 30-60 min. The obtained solid was filtered and washed with pre-chilled ethanol (50 ml), suck dried and dried under vacuum at 55-60°C to afford pure Selexipag (1).

[Yield = 44.0 g; Purity (HPLC) = 99.75%]

EXAMPLE-16: Preparation of 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide

The thionyl chloride (21.36 g, 0.178 mol) is added to {4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butoxy}-acetic acid (50 g, 0.1 191 mol) in dichloromethane (500 ml) drop wise at 25-30 °C. Stir the reaction mass for 2 hr at 25-30 °C, followed by heat the reaction mass 35-40 °C and stir for 2 hr. cool the reaction mass and charge methane sulfonamide (19.25 g, 0.202 mol) at 25-30 °C. Temperature was increased to 40 °C and stirs for 2 hr. after reaction completion, cool the reaction mass and charge water layer separation. Then the product dichloromethane layer was back washed with water, followed by washing the product solution with 2 % sodium bicarbonate

solution. Distilled out the dichloromethane layer completely to obtain the crude 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide, which was isolated and purified using the ethanol solvent. **[Yield = 40 g; Purity (HPLC) = 99.62%]**

EXAMPLE-17: Preparation of 2-{4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butoxy}-acetamide

The thionylchloride (124.8 g, 1.048 mol) is added to {4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butoxy}-acetic acid (50 g, 0.1 191 mol) drop wise at 25-30 °C. Stir the reaction mass for 5 hr at 25-30 °C and pour the reaction mass to ammonia solution at 10-25 °C, then extracted with toluene. Distilled out toluene completely and isolation of the product from 10-20 % ethyl acetate in heptane to obtain 2-{4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butoxy}-acetamide. **[Yield = 30 g; Purity (HPLC) = 96%]**

EXAMPLE-18: Preparation of 2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide

To the suspension of 60% Sodium hydride (1.92 mg, 0.080 mole) in Tetrahydrofuran (100 ml), the solution of 2-{4-[(5,6-diphenyl-pyrazin-2-yl)-isopropyl-amino]-butoxy}-acetamide (25 g, 0.06 mole) in Tetrahydrofuran (250 ml) was added at room temperature and stirred for 20 minutes. A solution of methane sulfonyl chloride (6.2 ml, 0.080 moles) in Tetrahydrofuran (150 ml) was added at 0-5° C and stirred at 15-25° C for 3 hours. Tetrahydrofuran was distilled under vacuum, dilute hydrochloric acid was added to the reaction mixture to and extracted with Ethyl Acetate (250 ml). Ethyl acetate layer was dried over Sodium sulphate and distilled under vacuum to provide2-{4-[N-(5, 6-diphenylpyrazin-2-yl)-N-isopropyl amino] butyloxy}-N-(methylsulfonyl) acetamide. **[Yield=15g;Purity(HPLC)= 99.22%]**

EXAMPLE-19: Preparation of 4-isopropylamino-butyric acid ethyl ester

Ethyl 4-bromobutyrate (50 g; 0.26mol) was added to isopropyl amine (45.45 g; 0.76mol) at below 10 °C, stirred to 6-8 hr. at below 10 °C. Upon completion of the reaction (monitored by TLC), the contents of the reaction mass were distilled out at a temperature below 50 °C under vacuum, the volatiles were removed in vacuum and the crude product was dissolved in tetrahydrofuran, cooled and filtered to afford the title compound.

meld = 37.0 q (83.31%): Purity (HPLC) = 89.71 %]

EXAMPLE-20: Preparation of 4-isopropylamino-butyric acid ethyl ester

Ethyl 4-bromobutyrate (100.0 g; 0.512 mol) was added to isopropyl amine (90.91 g; 1.53 mol) at 10-15 °C and maintain the reaction mixture at 10-15 °C for 20-22 hrs. Upon completion of the reaction monitored by HPLC, the contents of the reaction mass was distilled out at temperature below 55 °C under reduced pressure to obtain the residue. Obtained residue was diluted in purified water (200 ml) and pH of aqueous layer was adjusted to less than 2.0 using 1N hydrochloric acid solution (100 ml), followed by extracting impurities in MDC (2 × 200 ml). Further the pH of aqueous layer was adjusted to 9-12 using 10% sodium hydroxide solution (120.0 ml) followed by extracting the product in MDC (3 * 200 ml). The resultant organic layer was concentrated under reduced pressure to obtain the pure oil compound.

meld = 56.0 q (63.03%): Purity (HPLC) = 98.20%1

EXAMPLE-21 : Preparation of 4-isopropylamino-butyric acid ethyl ester

To the stirred solution of isopropyl amine (90.91 g; 1.53 mol) in tetrahydrofuran (200 ml), ethyl 4-bromobutyrate (100.0 g; 0.512 mol) was added at 10-15 °C and maintain the reaction mixture at 10-15 °C for 20 hrs. Upon completion of the reaction monitored by HPLC, the contents of the

reaction mass was distilled out at temperature below 55 °C under reduced pressure to obtain the residue. Obtained residue was diluted in purified water (200 ml) and pH of aqueous layer was adjusted to less than 2.0 using 1N hydrochloric acid solution (100 ml), followed by extracting impurities in MDG (2 × 200 ml). Further the pH of aqueous layer was adjusted to 9-12 using 10% sodium hydroxide solution (120.0 ml) followed by extracting the product in MDC (3 * 200 ml). The resultant organic layer was concentrated under reduced pressure to obtain the pure oil of titled compound **!Yield = 51.0 g (57.43%): Purity (HPLC) = 98.50%1**

EXAMPLE-22: Preparation of 4-isopropyl-amino-butyric acid

Ethanol (20 ml) and aqueous solution of sodium hydroxide (2.61 ml; 1N) were added to 389 mg of 4-isopropyl-amino]-butyric acid ethyl ester, and was stirred at room temperature for 4 hours at room temperature. The mixture was further stirred at 50°C for 10 minutes and neutralized with 1N hydrochloric acid. The crystals precipitated were recovered by filtration to obtain the 4-isopropyl-amino]-butyric acid. **!Yield = 305 mg; Purity (HPLC) = 86.01 %1**

EXAMPLE-23: Preparation of 4-isopropyl -aminobutan-1-ol

To a mixture of LJAIH4 (6.0 gm) in anhydrous THF (105 ml), a solution of 4-isopropylamino-butyric acid ethyl ester (15 gm) was added in anhydrous MDC (75 ml) at -0 to -10 °C under nitrogen atmosphere. The reaction mass was stirred for 1-2 hr, and then allowed to reach the temperature to 20-25 °C and stirred overnight. The reaction mass was chilled to -0 to -10 °C and MeOH (75 ml) was added. The reaction mass was extracted with MDC and purified water, MDC layer containing the product was separated and the product was extracted from aqueous layer using MDC. The combined

organic MDC layers were concentrated under reduced pressure to afford required 4-isopropyl -amino]-butan-1-ol. **!Yield = 7g : Purity (HPLC) = 96%1**

EXAMPLE-24: Preparation of 4-isopropyl -aminobutan-1-ol

To a mixture of **UAIH4** (15.33 g; 0.40 mol.) in anhydrous THF (525 ml), a solution of 4-isopropylamino-butyric acid ethyl ester (35.0 g; 0.20 mol.) was added in anhydrous THF (70 ml) at -10 to 0 °C under nitrogen atmosphere. The reaction mass was maintained at same temperature for 2-3 hrs. After completion of reaction by GC reaction mass quenched with purified water (350.0 ml) and maintain the reaction mass at 25-30 °C for 2 hrs. Filter the reaction mass and wash the filter bed with MDC (70 ml). Concentrate the filtrate under reduced pressure to obtain residue. The obtained residue was diluted in purified water (175 ml) and pH of aqueous layer was adjusted to 12-14 using 10% sodium hydroxide solution (120 ml), followed by extracting product in MDC (3 × 175 ml). The MDC layer was washed with purified water (175 ml) and resultant organic layer was concentrated under reduced pressure to obtain the pure oil compound **[Yield=22g;Purity(HPLC)= 97.0%]**

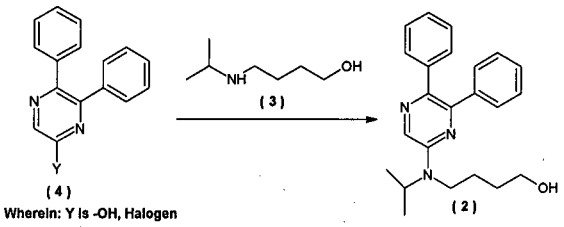
EXAMPLE-25: Preparation of 4-isopropyl -aminobutan-1-ol

To a mixture of LiAIH4 (760 mg) in anhydrous THF (45 ml) was added a solution of 4-isopropyl-amino]-butyric acid (1.75 g) in anhydrous THF (5 ml) at 0 °C under nitrogen atmosphere. The mixture was allowed to warm to room temperature. After stirring for 10 hr., the reaction was quenched with 6 mL of 20% aqueous NaOH solution at 0 °C and then filtered. The filtered cake was washed with ethyl acetate (10 mL × 4). The combined organic layers were concentrated under reduced pressure. The residue was isolated using 9:1 heptane and ethyl acetate to obtain 4-isopropyl amino-butan-1-ol.
meld = 1.54 g; Purity (HPLC) = 96%1

We claim:

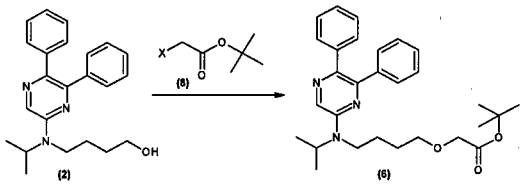
1. A process for preparing Selexipag of formula (1), the process comprising:

a) reacting a compound of formula (4) with a compound of formula (3) optionally in a solvent and a base, to provide a compound of formula (2);



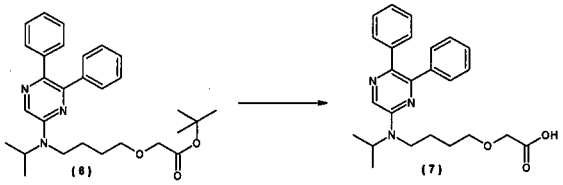
Wherein: Y is -OH, Halogen

b) condensing the compound of formula (2) with a compound of formula (8) in a solvent, in presence of a suitable base and optionally in presence of a phase transfer catalyst to provide a compound of formula (6);

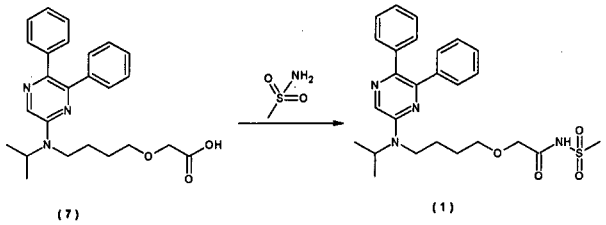


Wherein: X is Halogen

c) hydrolyzing the compound of formula (6) in a solvent and in presence of a suitable base to provide compound of formula (7); and



d) condensing compound of formula (7) with methane sulfonamide in a solvent, in presence of suitable base and coupling agent, to provide Selexipag (1).



2. The process of claim 1, wherein intermediate compounds (2), (6), and (7) of steps (a), (b) and (c) respectively can be used in next stages without isolating the said intermediates.

3. The process of claim 1, wherein the solvent used in step (a), (b), (c), (d) may be either same or different and is selected from the group consisting of alkyl acetate; aliphatic hydrocarbons; aromatic hydrocarbons; halogenated aliphatic hydrocarbons; dialkylformamides; ethers; cyclic ethers; substituted cyclic ethers; alcohols; esters; ketones; dialkylsulfoxides; dialkylacetamides; nitriles; ionic liquids; hexamethylphosphorous triamide; hexamethylphosphoramide; water; or mixtures thereof.

4. The process of claim 1, wherein the base used in step (a), (b), (c) and (d) may be same or different and are selected from inorganic bases such as but not limited to alkali metal carbonates; alkali metal bicarboriates; alkali metal hydroxides; metal hydrides, metal alkoxides; alkali metal amide; alkali metal hydrides; amidines; and organic bases such as but not limited primary amines; secondary amines; tertiary amines or mixtures thereof.

5. The process of claim 1, wherein the coupling agent used in step (d) selected from N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) or its salts, 1,1'-carbonyldiimidazole *\CD\),* diphenylphosphoryl azide (DPPA), diethylphosphoryl cyanide (DEPC), 3-(diethoxyphosphoryloxy)-1 ,2,3-benzotriazin-4(3H)-one (DEPBT), 4-(4,6-dimethoxy-1 ,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), 1-[bis(dimethylamino)methylene]-1 H-1 ,2,3-triazolo[4,5-b]pyridinium 3-oxid

hexafluorophosphate (HATU), (O-^-azabenzotriazole-l-yh-N.N.N'.N'-tetramethyluronium tetrafluoroborate) (TATU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazole-1-yl)-1 ,1,3,3-tetra methyluronium tetrafluoroborate (TBTU), boric acid or its derivatives, phenyl boronic acid, and trimethyl borate.

6. The process of claim 1, wherein the phase transfer catalyst used in step (b) selected from tetra butyl ammonium bromide, tetra propyl ammonium bromide, tributyl benzyl ammonium bromide, tetra octyl ammonium bromide, tetra butyl ammonium iodide, tetra butyl ammonium hydrogen sulfate, benzyl trimethyl ammonium chloride, benzyl triethyl ammonium chloride, tetra butyl ammonium acetate, tetra butyl ammonium iodide, ethyl triphenyl phosphonium bromide, more preferably tetra butyl ammonium bromide or alkali iodides like sodium iodide, potassium iodide and lithium iodide.

7. The process of claim 1, wherein the process for isolation and purification of compound of the formula (2) from reaction mass of step (a) is carried out by:

i. adding the water and suitable organic solvent to the reaction mass of step (a);
ii. separating the aqueous layer and organic layer of step (i);
iii. washing the organic layers of step (ii) with base
iv. concentrating the organic solvent of step (iii) under reduced pressure;
v. adding suitable organic solvent to the obtained syrup of step (iv);
vi. adding suitable anti-solvent to the solution of step (v); and
vii. filtering the solid obtained in step (vi) and drying to provide pure compound (2).

8. The process of claim 7, wherein the solvent used in (i) and & (v) is alkyl acetate; and the anti-solvent used in step (vi) is hydrocarbon.

9. The process of claim 1, wherein, the isolation and purification of compound of the formula (7) from reaction mass of step (c) is carried out by:

i. concentrating the reaction mass of step (c) ;
ii. adding water and suitable organic solvent to the mass of step (i);
iii. separating the organic and aqueous layers of step (ii);
iv. adjusting the pH of the aqueous layer of step (iii) to 2.0-2.5 of using 1N HCl;
v. filtering and washing the solid obtained in step (iv) with water to provide compound (7);
vi. suspending compound (7) of step (v) in a suitable organic solvent; and
vii. filtering and drying the solid of step (vi) to provide pure compound (7).

10. The process of claim 9, wherein the solvent used in step (ii) is alkyl acetate; and the solvent used in step (vi) is alcohol.

11. The process of claim ,1, wherein, the compound of the formula (1) is isolated and purified from reaction mass of step (d), the process comprising:

i. concentrating the reaction mass of step (d);
ii. adding water and suitable organic solvent to the mass of step (i);
iii. separating the organic and aqueous layers of step (ii)

iv. adjusting the pH of the aqueous layer of step (iii) between 5.0 to 6.0 using 1N HCl

v. extracting the solid obtained in step (iv) using suitable organic solvent;

vi. concentrating the said organic layer of step (v) to obtain residue;

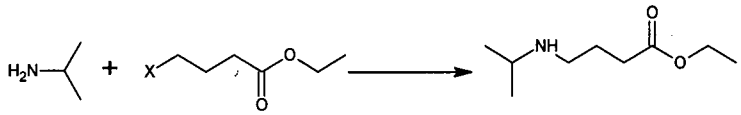
vii. crystallising the obtained residue in suitable organic solvent; and

viii. filtering and drying the solid obtained in step (vii) to provide pure compound (1).

12. The process of claim 11, wherein the solvent used in step (ii) is ether; the solvent used in step (v) is alkyl acetate; and the solvent used in step (vii) is alcohol.

13. A process for preparing compound of formula (3), a selexipag precursor, the said process comprising:

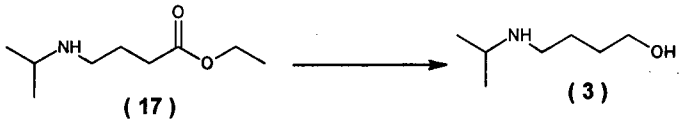
a) reacting a compound of formula (10) with a compound of formula (16) to obtain a compound of formula (17); and



(10) (20) (17)

Wherein, X= Halogen or a leaving group selected from -OH, -OTs, -OCF$_3$, -OBOP, -OPyBrOP, OSO2CH3, OSO2CF3, OBs, OCH2OCH3, OC(CH$_3$)3, OCH$_2$Ph, O-p-methoxybenzyl, OTMS, OTES, OTBDMS, OTBDPS, OTIPS,OCPh3, OR; R is selected from the group consisting of alkyl, aryl, and substituted aryl

b) reducing the obtained compound of formula (17) in a solvent and in presence of a suitable reducing agent optionally in combination with a suitable catalyst to obtain compound of formula (3).



(17) (3)

14. The process of claim 13, wherein step (a) is optionally carried out in a solvent and in presence of a base.

15. The process of claim 14, wherein the solvent used in step (a) is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di¬ ethyl ether and di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide, water or mixtures thereof.

16. The process of claim 13, wherein the solvent used in step (b) is selected from the group comprising of aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic

hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether di-methyl ether, and methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; or mixtures thereof.

17. The process of claim 13, wherein the base used in step (a) may be either same or different and is selected from inorganic bases such as alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarbonates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, and potassium tert-butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride; amidines such as but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); 1,4-diazabicyclo[2.2.2]octane (DABCO); and organic bases such as primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but

not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, and pyrrole methylethanolamine; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and mixtures thereof.

18. The process of claim 13, wherein the reducing agents used in step (b) is selected from the diborane, borane-dimethyl sulfide, borane-THF complex, sodium triacetoxyborohydride, sodium cyanoborohydride, Diisobutylaluminum hydride (DIBAL-H), Lithiumaluminiumhydride **(UAIH4),** Sodium borohydride (NaBhU), NaBI**-WBF3**-etherate, Lithiumborohydride **(L1BH4),** Sodiumcyanoborohydrie **(NaCNBH4),** Raney-Nickel, Sodium bis(2-methoxyethoxy)aluminumhydride (Vitride), and Sodium bis(2-methoxyethoxy) aluminumhydridepyrolidine (Red-ALP), Lithium triethylborohydride **(LiBHEt3),** magnesium tetrahydroborate [**Mg(BH4)2],** Aluminum borohydride [**AI(BH4)3],** Calcium borohydride [**Ca(BH4)3],** Zinc borohydride **[Zn(BH4)2],** Cerium borohydride **Ce(BH4)3,** Sodium triacetoxyborohydride [$NaBH(OAc)_3$], Sodium cyanoborohydride [$NaBH_3CN$], Mg**(BH4)2** ($NaBH_4$+$AlCl_3$), Al(BH_4)**3(NaBH4** +$AlCl_3$), Ca(BH_4)**3(NaBH4** +$CaCl_2$), **Zn**(BH_4)**2**(**NaBH**$_4$**+ZnCl2),** **Ce**(BH_4)**3(NaBH4+CeCl3),** $NaBH_3CN$($NaBH_4$+HCN), or their mixtures thereof.

19. The process of claim 13, wherein the catalyst used in step (b) is selected from Lewis acid, acid as a catalyst, catalyst or their mixture thereof.

20. The process of claim 19, wherein the catalyst used in step (b) is selected from Lewis acid such as Aluminum Chloride **(AICl3-),** Zinc chloride (ZnCb),

Boron trifluoride (BF3), Boron trialkoxide (B(OR)3), Trimethylaluminium ($Al(CH_3)3$), $Sn^{2+}B(CH_3)3$, Iodine(I_2), Bromine(Br_2), Carbenes, Hydrogen ion(H^+), Lithium ion(Li^+), Sodium ion(Na^+), Potassium ion(K^+), Aluminum ion (Al^{3+}), Magnesium ion (Mg^{2+}), Calcium ion(Ca^{2+}), Ferrous ion (Fe^{2+}), Cobalt ion (Co^{2+}), Copper ion (Cu^{2+}), Zinc ion (Zn^{2+}), Lead ion (Pb^{2+}), Copper ion (Cu^+), Silver ion (Ag^+), mercury ion(Hg^+), Palladium ion(Pd^{2+}), and acetic acid.

21. The process of claim 19, wherein the catalyst used in step (b) is selected from acid such as an organic acid, or an inorganic acid, selected from sulfuric acid (H2SO4), Trifluoroacetic acid (TFA), Trichloroacetic acid (CCI3COOH), Dichloroacetic acid ($CHCl_2COOH$), Trifluoroacetic acid (CF3COOH), Methanesulfonic acid ($CH3S0_3H$), Trifluoromethanesulfonic acid (CF3SO3H), and p-toluene sulfonic acid (P-CH3C6H4SO3H), Nitric acid (HNO3), hydroiodic acid (HI), Hydrobromic acid (HBr), Perchloric acid (HCIO4), Chloric acid (HCIO3), and Hydrochloric acid (HCI).

22. The process of claim 19, wherein the catalyst used in step (b) is selected from Iodine (I2), Trialkyl amine, Dimethyl selane (SiH2Me2), trimethylsilyl chloride (MesSiCI), Titanium chloride (T1CI4), dialkyl silane (R2Se2), and MeSe20H.

23. The process of claim 13, wherein the compound of the formula (17) is isolated and purified from reaction mass of step (a) comprises the step of:

i. treating the reaction mass of step (a) with water and organic solvent;
ii. acidifying the reaction mass of step (i);
iii. extracting the impurities from reaction mass of step (ii) with an organic solvent;

iv. separating the organic layer and aqueous layer of step (iii);
v. adjusting the pH of aqueous layer .of step (iv) to 9-12 with 10 % sodium hydroxide solution;
vi. extracting the product from reaction mass of step (v) with an organic solvent; and
vii. concentrating the organic layer of step (vi) to obtain the compound of formula (17).

24. The process of claim 23, wherein the solvent used in step (i), (iii) and (vi) of isolation process is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, and isopropyl acetate; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di¬ ethyl ether and di-methyl ether, methyl butyl ether; or mixtures thereof.

25. The process of claim 13, wherein, the compound of the formula (3) is isolated and purified from reaction mass of step (b), the process comprising:
i. treating the reaction mass of step (b) with water or optionally with mixture of alcohol and water;
ii. extracting the reaction mass of step (i) with an organic solvent;
iii. separating the organic layer of step (ii) followed by washing it with water; and
iv. concentrating the organic layer of step (iii) to obtain the compound of formula (3).

26. The process of claim 25, wherein the solvent used in step (ii) is selected from the group comprising of esters such as alkyl acetate including but not limited to ethyl acetate, isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone; or mixtures thereof.