Title: A PROCESS FOR PREPARATION OF TICAGRELOR AND INTERMEDIATES THEREOF

Abstract: An improved process for the preparation of ticagrelor and its intermediates thereof, wherein the said process substantially eliminates the potential impurities.
TITLE OF THE INVENTION:
A PROCESS FOR PREPARATION OF TICAGRELOR AND INTERMEDIATES THEREOF

This application claims priority from Indian patent application no. 3723/MUM/2012 filed on 31st December, 2012.

FIELD OF THE INVENTION:
The present invention relates to a method for the preparation of [1S-(1a, 2a,3P(1'S',2R'),5p)]-3-[7-[2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidine-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol, ticagrelor of formula (I), and its intermediates thereof.

![Formula (I)](image)

The present invention also relates to a method for the preparation of ticagrelor wherein, the said invention substantially eliminates the impurities formed during the preparation of ticagrelor.

BACKGROUND OF THE INVENTION:
[1S-(1α, 2α,3β(1'S',2R'),5p)]-3-[7-[2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidine-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol (alternatively named as (18,28^,58)-3-[7-[(^,28)-2-(3,4-difluorophenyl) cyclopropyl] amino]-5(propylthio)-3H-[1,2,3]-triazolo [4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol), (herein...
"ticagrelor") also known as Brilinta®, has a CAS number of 274693-27-5, a molecular formula of $\text{C}_{23}\text{H}_{28}\text{F}_2\text{N}_6\text{O}_4\text{S}$ and the following structure:

![Diagram of ticagrelor structure]

Ticagrelor acts as an adenosine uptake inhibitor, platelet aggregation inhibitor, P2Y12 purinoceptor antagonist and a coagulation inhibitor drug, used for the prevention and treatment of thrombosis, angina, ischemic heart diseases, and coronary artery diseases.

US6251910 patent discloses a method for preparing derivative of ticagrelor as shown in scheme-1 and the intermediates used for preparation of ticagrelor and its derivatives.
US6525060 patent discloses a method for preparing ticagrelor by condensing compound of formula (MA) with, compound of formula (III) in the presence of N, N-diisopropylethylamine in tetrahydrofuran (THF) as solvent to produce compound of formula (IV), followed by reduction in the presence of iron in acetic acid to produce compound of formula (V). The compound of formula (V) is reacted with isoamyl nitrile in acetonitrile to produce compound of formula (VI), followed by reaction with ammonia in THF to produce compound of formula (VII), followed by reaction with trifluoromethanesulfonyloxyacetic acid methyl ester in butyl lithium and THF.
to produce compound of formula (VIII). The obtained compound is further brominated using isoamylnitrile and bromoform to produce compound of formula (IX), followed by condensation with compound of formula (X) in N,N-diisopropylethylamine in methylene dichloride (MDC) as a solvent to produce compound of formula (XI), followed by reaction with DIBAL-H in THF and sodium potassium tartrate to produce compound of formula (XII). The obtained compound of formula (XII) is deprotected using trifluoroacetic acid in water and ethyl acetate to produce ticagrelor compound of formula (I) as shown in scheme-2.

The process for the preparation of ticagrelor of formula (I) and its intermediates disclosed in the above mentioned prior art have the following limitations:

i. condensation of compound of formula (IIA) with (III) is carried out under pressure for longer time hence, there is a need for special apparatus like pressure reactor, which is not production friendly;

ii. requires longer reaction time, results in low yields and low purities of the intermediates and product thereof.
PCT publication number WO01/92263 discloses a method for preparing ticagrelor by condensation of compound of formula (II) with compound of formula (XV) in ethanol and triethylamine to produce compound of formula (XVI), followed by diazotization and ring formation using sodium nitrite in acetic acid to produce compound of formula (XVII). The obtained compound of formula (XVII) is further condensed with compound of formula (X) in acetonitrile in presence of triethylamine to produce compound of formula (XII). The compound of formula (XII) is deprotected with aqueous hydrochloric acid in methanol to furnish ticagrelor compound of formula (I) as shown in scheme-3.
The process for the preparation of ticagrelor of formula (I) and its intermediates disclosed in the above mentioned prior art have the following limitations:

i. requires longer reaction time (about 30 hrs.) for condensation reaction between compound of formula (II) and compound of formula (XV), hence, results in low throughput;

ii. condensation reaction between compound of formula (II) and compound of formula (XV) does not undergo completion hence, results in low yield i.e. about 35%;

iii. the condensation reaction has to be conducted in autoclave under pressure hence, not production friendly;

iv. IMP-1 is formed during the synthesis of compound of formula (I).

Hence, there is a need for a solution that overcomes the above stated limitations.

The present invention proposes an improved process for preparation of ticagrelor and its intermediates thereof; which is economic, efficient, eco-friendly, and eliminates extensive laborious work-up.

**OBJECTS OF THE PRESENT INVENTION**

The primary object of the present invention is to provide an improved process for preparation of ticagrelor of formula (I):

Another object of the present invention is to provide improved process for preparation of intermediates of ticagrelor.
Yet another object of the present invention is to provide a process for preparation of ticagrelor of formula (I); wherein the said process eliminates laborious workup and extensive purifications. Hence, makes the process simple, easy and user friendly.

Yet another object of the present invention is to provide a process for preparation of ticagrelor of formula (I), which is substantially free from impurities, and thereby eliminating the required purification steps and further making the process cost effective and efficient.

Yet another object of the present invention is to provide crystalline solid compound of formula (IV), (XVI), (XX), (XXI) and (XXII).

**BRIEF DESCRIPTION OF DRAWINGS**

Figure 1 illustrates X-ray powder diffraction (XRD) pattern of compound of formula (XVI), prepared according to example 1.

Figure 2 illustrates Infrared spectrum (IR) of compound of formula (XVI), prepared according to example 1.

Figure 3 illustrates X-ray powder diffraction (XRD) pattern of ticagrelor compound of formula (I), prepared according to example 4.

Figure 4 illustrates Infrared spectrum (IR) of compound of formula (I), prepared according to example 4.
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" and the like, 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.
A term herein "reflux temperature" means the temperature at which the solvent or the solvent system refluxes or boils at atmospheric pressure. The term "substantially free of in reference to a composition, as used herein, means that an absent substance cannot be detected in the composition by methods known to those skilled in the art at the time of the filing of this application.

In one of the embodiments, the present invention provides a process for the preparation of ticagrelor of formula (I) comprising:

a) reacting, 2-{{[3aR,4S,6R,6aS]-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[0][1,3]-dioxol-4-yl}oxy}-1-ethanol or salt of formula (II) with 4,6-dichloro-2-(propylthio)-5-pyrimidinamine of formula (XV) or salt thereof in a solvent and a base in presence of a catalyst to obtain 2-{{[3aR,4S,6R,6aS]-4-[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl}oxy]-1-ethanol of formula (XVI), and optionally isolating compound of formula (XVI);

b) reacting compound of formula (XVI) of step (a) using a diazotizing agent in an acid and a solvent to prepare 2-{{[3a/?,4S,6/?,6aS]-7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyl tetrahydro-3aH-cyclopenta[1,3]dioxal-4-yl oxy}-1-ethanol compound of formula (XVII);
c) condensing compound of formula (XVII) with trans-(1R,2S)-2-(3,4-difluorophenyl) cyclopropanamine or salt of formula (X) in a solvent, a base, and optionally in presence of a catalyst to produce 2-((3aR4S,6f?,6aS)-6-[7-{{(1f?,2S)-2-(3,4-difluorophenyl)-cyclopropyl}amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxal-4-yl]oxy)-1-ethanol of formula (XII);

d) deprotecting compound of formula (XII) using an aqueous acid in solvent to obtain ticagrelor of formula (I), and isolating compound of formula (I);

e) purifying ticagrelor of formula (I).
According to another embodiment of the present invention, deprotection step (c) of the said process can be carried out insitu or without isolation of intermediate of formula (XII).

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be further purified either by acid-base treatment, or solvent crystallization, or converting into its acid addition salts.

The acid addition salts of ticagrelor of formula (I) can be prepared by treating the same with suitable acids; wherein the said acid includes organic acids such as tartaric acid, fumaric acid, acetic acid, succinic acid, maleic acid, formic acid, oxalic acid and the like and inorganic acids such as but not limited to hydrochloric acid, sulfuric acid, hydrobromic acid and the like.

The solvent(s) used in step (a), (b), (c) and (d) of the present invention is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofurane, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofurane and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol,
ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkyl sulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N,N',-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrite; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramid and water or mixtures thereof.

The solvents used in steps (a), (b), (c) and (d) of the present invention may be either same or different.

The base used in step (a) and (c) of the present invention may be organic or inorganic base; preferably organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, η,η-dimethly aniline, n,n-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethyleneethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarboriates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not
limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The base used in steps (a) and (c) of the present invention may be either same or different.

The catalyst used in step (a) and (c) of the present invention is selected from organic, inorganic catalyst or phase transfer catalyst.

The organic catalyst is selected from 1, 8-Diazabicycloundec-7-ene (DBU) or 1, 5-Diazabicyclo(4.3.0)non-5-ene (DBN) or dimethylaminopyridine and like.

The inorganic catalyst is selected from groups comprising alkali metal iodide, iodine, potassium iodide, p-toluene sulfonic acid, tertiary alkyl ammonium halide, sodium iodide, lithium iodide and the like.

The catalyst used in steps (a) and (c) of the present invention may be either same or different.

The step (a) is carried out at temperature in the range of 25°C to 150X. Preferably, the reaction is carried out at temperature in the range of 60°C to 135°C.

According to another embodiment of the present invention, compound of formula (XVI) may be isolated as crystalline solid.

According to the present invention, isolation of compound of the formula (XVI) from reaction mass of step (a) comprises the steps of:
i. extracting the compound of formula (XVI) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XVI),

v. optionally, purifying the compound of formula (XVI) obtained in step (iv) by:
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XVI) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from 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 or mixtures thereof.

According to another embodiment of the present invention, isolation of compound of formula (XVI) from reaction mass of step (a) can also be alternatively performed by:

i. isolating compound of formula (XVI) from the reaction mass;

ii. drying the said compound of formula (XVI) obtained from step (i);

iii. crystallizing the said dried compound of formula (XVI) using solvent to obtain purified Compound of formula (XVI) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XVI) includes, but does not limit to esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to disopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, isopropanol, isobutanol and the like, ketone such as but not limited to acetone, ethylmethyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylene dichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

The diazotizing agent used in step (b) for the preparation of compound of formula (XVII) includes but does not limit to resin nitrite, metal nitrite such as
but not limited to sodium nitrite, potassium nitrite, silver nitrite, aluminum nitrite, lithium nitrate, rubidium nitrate, cesium nitrate, and the like organic nitriles such as but not limited to isoamyl nitrite, isopentyl nitrite, methyl nitrite and the like.

The acid used in step (b) may be organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, paratoluene sulphonic acid and the like.

The aqueous acid used in step (d) may be either organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, oxalic acid, fumaric acid, maleic acid, paratoluene sulphonic acid and the like or inorganic acid inorganic acid such as but not limited to hydrochloric acid, hydrobromic acid, sulphuric acid, hydrobromic acid in acetic acid, boron trifluoride in ether and the like.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be isolated from the reaction mass to obtain crystalline solid of compound of formula (I).

According to the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (d) comprises the steps of:

i. extracting the ticagrelor compound of formula (I) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),

v. optionally, purifying the compound of formula (I) obtained in step (iv) by:
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to di-isopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, Isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylenedichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

According to another embodiment of the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (d) can also be alternatively performed by:

i. isolating ticagrelor of formula (I) from the reaction mass;
ii. drying the said ticagrelor of formula (I) obtained from step (i);

iii. crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

In a preferred embodiment, the solvent used for purification of ticagrelor compound of formula (I) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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 , hexamethylphosphoramid e and water or mixtures thereof.

According to another embodiment, the present invention provides a process for the preparation of ticagrelor of formula (I) comprising:
a) reacting, \(2-\{(3a?,4S,6R6aS)-6\text{-amino}-2,2\text{-dimethyltetrahydro-3aH-cyclopenta[d]}[1,3]\text{-dioxol-4-yl} \text{oxy}\} -1\text{-ethanol or salt of formula (II)} \) with 4,6-dichloro-2-(propylthio)pyrimidin-5-nitro of formula (III) in a solvent and base to obtain \(2-\{(3aR,4S,6R,6aS)-6\{5\text{-nitro} \text{-6-chloro-2-(propylthio)-4-pyrimidinyl}\text{amino}\}-2,2\text{-dimethyltetrahydro-3aH-cyclopenta[d]}[1,3]\text{-dioxol-4-yl} \text{oxy}\} -1\text{-ethanol of formula (IV)};\)

b) reducing compound of formula (IV) with metal optionally with metal halide and in presence of acid in a solvent to obtain \(2-\{(3a?,4S,6R,6aS)-6\{5\text{-amino} -6\text{-chloro-2-(propylthio)-4-pyrimidinyl}\text{amino}\}-2,2\text{-dimethyltetrahydro-3aH-cyclopenta[cf]}[1,3]\text{-dioxol-4-yl} \text{oxy}\} -1\text{-ethanol of formula (XVI)};\) optionally isolating compound of formula (XVI);

c) reacting compound of formula (XVI) of step (b) with diazotizing agent in an acid and a solvent to prepare compound of formula (XVII);

d) condensing \(2-\{(3aR,4S,6R,6aS)-6\{7\text{-chloro-5-(propylthio)-3H-[1,2,3]}\text{-triazolo[4,5-cf]pyrimidin-3-yl}\}-2,2\text{-dimethyltetrahydro-3aH-cyclopenta[d]}\)
[1,3] dioxal-4-yl] oxy)-1-ethanol of formula (XVII) with trans-(1R,2S)-2-(3,4-Difluorophenyl) cyclopropanamine or salt of formula (X) in a solvent, a base, and optionally in presence of a catalyst to produce 2-(((3a/?,4S,6R6aS)-6-[7-(((1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl] amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c][pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta [cf][1,3]dioxal-4-yl]oxy)-1-ethanol of formula (XII);

e) deprotecting compound of formula (XII) using aqueous acid in solvent to obtain ticagrelor of formula (I), and isolating compound of formula (I);

f) optionally, purifying ticagrelor of formula (I).

According to another embodiment of the present invention, deprotection step (e) of the said process can be carried out insitu or without isolation of intermediate of formula (XII).

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be further purified either by acid-base treatment, or solvent crystallization, or converting into its acid addition salts. The acid addition salts of ticagrelor of formula (I) can be prepared by treating the same with suitable acids; wherein the said acid includes organic and
inorganic acids such as but not limited to hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic carboxylic acid like tartaric acid, fumaric acid, acetic acid, succinic acid, maleic acid, formic acid, oxalic acid and the like.

The solvent(s) used in step (a), (b), (c), (d) and (e) of the present invention is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform; ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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 and water or mixtures thereof.
The solvents used in steps (a), (b), (c), (d) and (e) of the present invention may be either same or different.

The base used in step (a) and (d) of the present invention may be organic or inorganic base; preferably organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to \( N,N \)-diisopropyl amine, dimethylamine, diethyl amine, \( N \)-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, \( \eta,\eta \)-dimethly aniline, \( \eta,\eta \)-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, \( N,N \)-dimethyleneethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The base used in step (a) and (d) of the present invention may be either same or different.

The step (a) is carried out at temperature in the range of \( 0^\circ C \) to \( 50^\circ C \).
The metal used in step (b) for the preparation of compound of formula (XVI) is a transition metal like iron, palladium, tin, nickel, copper, zinc, silver, platinum and the like.

The metal halide used in step (b) for the preparation of compound of formula (XVI) is a transition metal halide like ferric chloride, tin chloride, cupric chloride, and the like.

According to another embodiment of the present invention, compound of formula (XVI) may be isolated as crystalline solid.

According to the present invention, isolation of compound of the formula (XVI) from reaction mass of step (b) comprises the steps of:

i. extracting the compound of formula (XVI) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XVI),

v. optionally, purifying the compound of formula (XVI) obtained in step (iv) by:

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.
Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XVI) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N,N-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramidate or mixtures thereof.

According to another embodiment of the present invention, isolation of compound of formula (XVI) from reaction mass of step (b) can also be alternatively performed by:

i. isolating compound of formula (XVI) from the reaction mass;
ii. drying the said compound of formula (XVI) obtained from step (i);
iii. crystallizing the said dried compound of formula (XVI) using solvent to obtain purified compound of formula (XVI) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XVI) is an organic solvent selected from the group consisting of
alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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, hexamethylphosphoramidate and water or mixtures thereof.

The diazotizing agent used in step (c) for the preparation of compound of formula (XVII) includes but does not limit to resin nitrite, metal nitrite such as but not limited to sodium nitrite, potassium nitrite, silver nitrite, aluminum nitrite, lithium nitrate, rubidium nitrate, cesium nitrate, and the like organic nitrites such as but not limited to isoamyl nitrite, isopentyl nitrite, methyl nitrite and the like.
The acid used in step (c) may be organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, paratoluene sulphonic acid and the like.

The catalyst used in step (d) for preparation of compound of formula (XII) is selected from organic, inorganic catalyst or phase transfer catalyst.

The organic catalyst is selected from 1,8-Diazabicycloundec-7-ene (DBU) or 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) or dimethylaminopyridine and like.

The inorganic catalyst is selected from groups comprising alkali metal iodide, iodine, potassium iodide, p-toluene sulfonic acid, tertiary alkyl ammonium halide, sodium iodide, lithium iodide and the like.

The aqueous acid used in step (e) may be either organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, oxalic acid, fumaric acid, maleic acid, paratoluene sulphonylic acid and the like or inorganic acid inorganic acid such as but not limited to hydrochloric acid, hydrobromic acid, sulphuric acid, hydrobromic acid in acetic acid, boron trifluoride in ether and the like.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be as a crystalline solid.

According to the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (e) comprises the steps of:

i. extracting ticagrelor compound of formula (I) from the reaction mass with solvent,
ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),

v. optionally, purifying the ticagrelor compound of formula (I) obtained in step (iv) by
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylenedichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.
According to another embodiment of the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (e) can also be alternatively performed by:

i. isolating ticagrelor of formula (I) from the reaction mass;

ii. drying the said ticagrelor of formula (I) obtained from step (i);

iii. crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

In a preferred embodiment, the solvent used for purification of ticagrelor compound of formula (I) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; dialkylformamides such as but not limited to dimethylformamide; 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 and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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, hexamethylphosphoramidate and water or mixtures thereof.

According to another embodiment, the present invention provides a process for the preparation of ticagrelor of formula (I) comprising:

a) reacting, compound of formula (XVIII) or salt thereof with 7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c]pyrimidine of formula (XIX); in a solvent and base to obtain 2-(((3aR,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3]dioxal-4-yl] oxy)-1-ethanol of formula (XVII);

wherein R is a good leaving group consisting of halogen (F, Cl, Br, I), mesyloxy, tosylxy, p-nitro phenol, imidazole, diazole, tetrazole, trihalomethoxy;

b) condensing, compound of formula (XVII) with trans-(1R,2S)-2-(3,4-difluorophenyl) cyclopropanamine or salt of formula (X) in solvent, base, and optionally in presence of a catalyst to produce 2-(((3aR,4S,6R,6aS)-6-[7-([(1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl] amino)-5-(propylthio))-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-yl]-2,2-dimethyl tetrahydro-3aH-cyclopenta[c][1,3]dioxal-4-yl]oxy)-1-ethanol of formula (XII);
c) deprotecting 2-{((3aR,4S,6f?,6aS)-6-[7-{{(1R,2S)-2-(3,4-difluorophenyl)-
cyclopropynaminoi-S-ipropylthioJ-SH-tl ... o f formula (XII) using aqueous acid in solvent to obtain ticagrelor of
formula (I), and isolating compound of formula (I);

\[ \text{Formula (XII)} \]

\[ \text{Aqueous acid in solvent} \]

\[ \text{Formula (I)} \]

d) optionally, purifying ticagrelor of formula (I).

According to another embodiment of the present invention, deprotection step (b) of the said process can be carried out \textit{insitu} or without isolation of intermediate of formula (XII).

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be further purified either by acid-base treatment, or solvent crystallization, or converting into its acid addition salts. The acid addition salts of ticagrelor of formula (I) can be prepared by treating the same with suitable acids; wherein the said acid includes organic and inorganic acids such as but not limited to hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic carboxylic acid like tartaric acid, fumaric acid, acetic acid, succinic acid, maleic acid, formic acid, oxalic acid and the like.

The solvent used in step (a), (b) and (c) of the present invention is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons.
such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride and the like; 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; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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, hexamethylphosphoramidate and water or mixtures thereof.

The solvent used in step (a), (b) and (c) of the present invention may be either same or different.

The base used in step (a) and (b) of the present invention may be organic or inorganic base; preferably organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methyl ethanolamine, and the like; tertiary amines like triethylamine, η,η-dimethyl aniline, n,n-diisopropyl
ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The base used in step (a) and (b) of the present invention may be either same or different.
The step (a) is carried out at temperature in the range of 0°C to 100°C.
The catalyst used in step (b) for preparation of compound of formula (XII) is selected from organic, inorganic catalyst or phase transfer catalyst.

The organic catalyst is selected from 1,8-Diazabicycloundec-7-ene (DBU) or 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) or dimethylaminopyridine and like.
The inorganic catalyst is selected from groups comprising alkali metal iodide, iodine, potassium iodide, p-toluene sulfonic acid, tertiary alkyl ammonium halide, sodium iodide, lithium iodide and the like.

The aqueous acid used in step (c) may be either organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, oxalic acid, fumaric acid, maleic acid, paratoluene sulphonic acid and the like or inorganic acid inorganic acid such as but not limited to
hydrochloric acid, hydrobromic acid, sulphuric acid, hydrobromic acid in acetic acid, boron trifluoride in ether and the like.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be isolated as crystalline solid.

According to the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (c) comprises the steps of:

i. extracting the ticagrelor compound of formula (I) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),

v. optionally, purifying the ticagrelor compound of formula (I) obtained in step (iv) by

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and
the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, Isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylenedichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

According to another embodiment of the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (c) can also be alternatively performed by:

i. isolating ticagrelor of formula (I) from the reaction mass;
ii. drying the said ticagrelor of formula (I) obtained from step (i);
iii. crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

In a preferred embodiment, the solvent used for purification of ticagrelor compound of formula (I) includes, but does not limit to nitriles, ketones, alkylacetates, dimethylformamide, dimethylsulfoxide, ethers, esters, alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated aliphatic hydrocarbons, cyclic ethers, substituted cyclic ethers, dialkylacetamides, ionic liquids, and water or mixtures thereof.

In one of the embodiments, the present invention provides a process for the preparation of ticagrelor of formula (I) comprising:

a) reacting, 2-\{[(3a/?,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy\}-1 -ethanol or salt of formula (II) with 4,6-
dichloro-2-(propylthio)-5-pyrimidinamine of formula (XV) or salt thereof in a solvent and base in presence of a catalyst to obtain 2-[(3a/?4S,6f?,6aS)-6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3a/+-cyclopenta[c][1,3]dioxol-4-yl]oxy]-1-ethanol of formula (XVI), optionally isolating compound of formula (XVI);

b) deprotecting obtained compound of formula (XVI) using acid in solvent to prepare compound of formula (XX);

c) reacting compound of formula (XX) of step (b) with diazotizing agent in acid and solvent to obtain compound of formula (XXI);

d) condensing compound of formula (XXI) with trans-(1R2S)-2-(3,4-difluorophenyl) cyclopropanamine or salt of formula (X) in solvent, base, and optionally in presence of a catalyst to produce ticagrelor of formula (I); and
According to another embodiment of the present invention, the said process can be carried out *insitu*.

According to another embodiment of the present invention, compound of formula (XVI), compound of formula (XX) and compound of formula (XXI) may be isolated as crystalline solid.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be further purified either by acid-base treatment, or solvent crystallization, or converting into its acid addition salts.

The acid addition salts of ticagrelor of formula (I) can be prepared by treating the same with suitable acids; wherein the said acid includes organic and inorganic acids such as but not limited to hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic carboxylic acid like tartaric acid, fumaric acid, acetic acid, succinic acid, maleic acid, formic acid, oxalic acid and the like.

The solvent used in step (a), (b), (c) and (d) of the present invention is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane,
pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, η,η-dimethyl aniline, n,n-diisopropyl

The solvent used in step (a), (b), (c) and (d) of the present invention may be either same or different.

The base used in step (a) and (d) for of the present invention may be organic or inorganic base; preferably organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, η,η-dimethyl aniline, n,n-diisopropyl
ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The base used in step (a) and (d) of the present invention may be either same or different.

The catalyst used in step (a) and (d) of the present invention is selected from organic, inorganic catalyst or phase transfer catalyst.

The organic catalyst is selected from 1, 8-Diazabicycloundec-7-ene (DBU) or 1, 5-Diazabicyclo(4.3.0)non-5-ene (DBN) or dimethylaminopyridine and like.

The inorganic catalyst is selected from groups comprising alkali metal iodide, iodine, potassium iodide, p-toluene sulfonic acid, tertiary alkyl ammonium halide, sodium iodide, lithium iodide and the like.

The catalyst used in step (a) and (d) of the present invention may be either same or different.
The step (a) is carried out at temperature in the range of 25°C to 150°C. Preferably, the reaction is carried out at temperature in the range of 60°C to 135°C.

According to another embodiment of the present invention, compound of formula (XVI) may be as a crystalline solid.

According to the present invention, isolation of compound of the formula (XVI) from reaction mass of step (a) comprises the steps of:

i. extracting the compound of formula (XVI) from the reaction mass with solvent,
ii. washing the organic layer of step (i) with water,
iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XVI),
v. optionally, purifying the compound of formula (XVI) obtained in step (iv) by:
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XVI) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic
hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitrites such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramidate or mixtures thereof.

According to another embodiment of the present invention, isolation of compound of formula (XVI) from reaction mass of step (a) can also be alternatively performed by:

i. isolating compound of formula (XVI) from the reaction mass;
ii. drying the said compound of formula (XVI) obtained from step (i);
iii. crystallizing the said dried compound of formula (XVI) using solvent to obtain purified compound of formula (XVI) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XVI) includes, but does not limit to esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as
but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylene dichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

Deprotection of compound of formula (XVI) is carried out using acid in solvent; wherein the acid may be organic or inorganic acid and the solvent used for deprotection is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkyl sulfoxides 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 and water or mixtures thereof.

The step (b) is carried out at temperature in the range of 25°C to 50°C.

According to another embodiment of the present invention, compound of formula (XX) may be isolated as a crystalline solid.

According to the present invention, isolation of compound of the formula (XX) from reaction mass of step (b) comprises the steps of:

i. extracting the compound of formula (XX) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XX),

v. optionally, purifying the compound of formula (XX) obtained in step (iv) by:

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XX) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons...
selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from 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 or mixtures thereof.

According to another embodiment of the present invention, isolation of compound of formula (XX) from reaction mass of step (b) can also be alternatively performed by:

i. isolating compound of formula (XX) from the reaction mass;

ii. drying the said compound of formula (XX) obtained from step (i);

iii. crystallizing the said dried compound of formula (XX) using solvent to obtain purified compound of formula (XX) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XX) includes, but does not limit to esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as
but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, isopropanol, isobutanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylene dichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

The diazotizing agent used in step (c) for the preparation of compound of formula (XXI) includes but does not limit to resin nitrite, metal nitrite such as but not limited to sodium nitrite, potassium nitrite, silver nitrite, aluminum nitrite, lithium nitrate, rubidium nitrate, cesium nitrate, and the like organic nitriles such as but not limited to isoamyl nitrite, isopentyl nitrite, methyl nitrite and the like.

The acid used in step (c) may be organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, paratoluene sulphonylic acid and the like.

According to another embodiment of the present invention, compound of formula (XXI) may be isolated as crystalline solid.

According to the present invention, isolation of compound of the formula (XXI) from reaction mass of step (c) comprises the steps of:
  i. extracting the compound of formula (XXI) from the reaction mass with solvent,
  ii. washing the organic layer of step (i) with water,
  iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XXI),

v. optionally, purifying the compound of formula (XXI) obtained in step (iv) by:
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XXI) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from 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, hexamethylphosphoramidate or mixtures thereof.
According to another embodiment of the present invention, isolation of compound of formula (XXI) from reaction mass of step (c) can also be alternatively performed by:

i. isolating compound of formula (XXI) from the reaction mass;
ii. drying the said compound of formula (XXI) obtained from step (i);
iii. crystallizing the said dried compound of formula (XXI) using solvent to obtain purified compound of formula (XXI) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XXI) includes, but does not limit to esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, Isopropanol, isobutanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylene dichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be as a crystalline solid.

According to the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (d) comprises the steps of:
i. extracting the ticagrelor compound of formula (I) from the reaction mass with solvent,
ii. washing the organic layer of step (i) with water,
iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),
v. optionally, purifying the ticagrelor compound of formula (I) obtained in step (iv) by
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to di-isopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylenedichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.
According to another embodiment of the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (d) can also be alternatively performed by:

i. isolating ticagrelor of formula (I) from the reaction mass;
ii. drying the said ticagrelor of formula (I) obtained from step (i);
iii. Crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

In a preferred embodiment, the solvent used for purification of ticagrelor compound of formula (I) includes, but does not limit to nitriles, ketones, alkylacetates, dimethylformamide, dimethylsulfoxide, ethers, esters, alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, cyclic ethers, substituted cyclic ethers, dialkylacetamides, ionic liquids, halogenated aliphatic hydrocarbons and water or mixtures thereof.

According to another embodiment, the present invention provides a process for the preparation of ticagrelor of formula (I) comprising:

a) reacting, \(2-\{(3aR4S,6R,6aS)-6-\text{amino}-2,2\text{-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl} \}\text{oxy} \}-1\text{-ethanol}\) or salt of formula (II) with \(4,6\text{-dichloro-2-(propylthio)}\text{pyrimidin-5-nitro}\) of formula (III) in a solvent and base to obtain \(2-\{((3aR,4S,6R,6aS)-6-\{(5\text{-nitro-6-chloro-2-(propylthio)}\text{-4-pyrimidinyl})\text{amino} \}-2,2\text{-dimethyltetrahydro-3aH-cyclopenta[d]}\text{[1,3]}\text{dioxol-4-yl} \}\text{oxy} \}-1\text{-ethanol}\) of formula (IV); optionally isolating compound of formula (IV);
b) deprotecting compound of formula (IV) of step (a) using acid in solvent to obtain compound of formula (XXII);

c) reducing compound of formula (XXII) with metal with or without metal halide and in presence of acid in a solvent to obtain compound of formula (XX);

d) reacting compound of formula (XX) of step (c) using diazotizing agent in acid and solvent to obtain compound of formula (XXI);

e) condensing compound of formula (XXI) with trans-(1R2S)-2-(3,4-Difluorophenyl) cyclopropanamine or salt of formula (X) in solvent, base, and optionally in presence of a catalyst to produce ticagrelor of formula (I); and
optionally, purifying ticagrelor of formula (I).

According to another embodiment of the present invention, the said process can be carried out *insitu*.

According to another embodiment of the present invention; compound of formula (IV), compound of formula (XX), compound of formula (XXI) and compound of formula (XXII) may be isolated as crystalline solid.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be further purified either by acid-base treatment, or solvent crystallization, or converting into its acid addition salts. The acid addition salts of ticagrelor of formula (I) can be prepared by treating the same with suitable acids; wherein the said acid includes organic and inorganic acids such as but not limited to hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic carboxylic acid like tartaric acid, fumaric acid, acetic acid, succinic acid, maleic acid, formic acid, oxalic acid and the like.

The solvent used in step (a), (b), (c), (d) and (e) of the present invention is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to
toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; dialkylformannides 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to 2-methyl tetrahydrofuran and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to \(\text{N},\text{N}\)-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide and water or mixtures thereof.

The solvent used in step (a), (b), (c), (d) and (e) of the present invention may be either same or different.

The base used in step (a) and (e) of the present invention may be organic or inorganic base; preferably organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to \(\text{N},\text{N}\)-diisopropyl amine, dimethylamine, diethyl amine, \(\text{N}\)-methyl propyl amine, pyrrole methyl ethanolamine, and the like; tertiary amines like triethylamine, \(\text{N},\text{N}\)-dimethylaniline, \(\text{n},\text{n}\)-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, \(\text{N},\text{N}\)-dimethylene amine
and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The base used in step (a) and (e) of the present invention may be either same or different.

The step (a) is carried out at temperature in the range of 0°C to 50°C.

According to the present invention, isolation of compound of the formula (IV) from reaction mass of step (a) comprises the steps of:

i. extracting the compound of formula (IV) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (IV),

v. optionally, purifying the compound of formula (IV) obtained in step (iv) by:

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.
Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (IV) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N-dimethyl acetamide; nitrites such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide or mixtures thereof.

In a preferred embodiment, the solid obtained may be crystalline solid of compound of formula (IV).

According to another embodiment of the present invention, isolation of compound of formula (IV) from reaction mass of step (a) can also be alternatively performed by:

i. isolating compound of formula (IV) from the reaction mass;
ii. drying the said compound of formula (IV) obtained from step (i);
iii. crystallizing the said dried compound of formula (IV) using solvent to obtain purified compound of formula (IV) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (IV) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, \( n \)-hexane, \( n \)-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, \( 1,4 \)-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, \( n \)-propanol, iso-propanol, \( n \)-butanol, iso-butanol, \( n \)-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkyl sulfoxides 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, hexamethyolphosphorous triamide, hexamethylphosphoramide and water or mixtures thereof.

Compound of formula (IV) obtained in step (a) is deprotected using acid in solvent to obtain compound of formula (XXII); wherein the acid may be organic or inorganic acid and the solvent used for deprotection is an organic
solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride and the like; dialkyformamides 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; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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, hexamethylphosphoramidate and water or mixtures thereof.

The step (b) may be carried out at temperature 25°C to 50°C.

According to the present invention, isolation of compound of the formula (XXII) from reaction mass of step (b) comprises the steps of:

i. extracting the compound of formula (XXII) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XXII),

v. optionally, purifying the compound of formula (XXII) obtained in step (iv) by:
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XXII) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from 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 or mixtures thereof.

In a preferred embodiment, the solid obtained is crystalline compound of formula (XXII).
According to another embodiment of the present invention, isolation of compound of formula (XXII) from reaction mass of step (b) can also be alternatively performed by:

i. isolating compound of formula (XXII) from the reaction mass;

ii. drying the said compound of formula (XXII) obtained from step (i);

iii. crystallizing the said dried compound of formula (XXII) using solvent to obtain purified compound of formula (XXII) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XXII) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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 and water or mixtures thereof.

The metal used in step (c) for the preparation of compound of formula (XX) is a transition metal like Iron, palladium, Tin, nickel, copper, zinc, silver, platinum and the like.

The metal halide used in step (c) for the preparation of compound of formula (XX) is a transition metal halide like ferric chloride, tin chloride, cupric chloride, and the like.

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

i. extracting the compound of formula (XX) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XX),

v. optionally, purifying the compound of formula (XX) obtained in step (iv) by:

   a. crystallization using solvent to obtain solid, or

   b. acid-base treatment to obtain solid, or

   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XX) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from
cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from 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 or mixtures thereof.

In a preferred embodiment, the solid obtained is crystalline compound of formula (XX).

According to another embodiment of the present invention, isolation of compound of formula (XX) from reaction mass of step (c) can also be alternatively performed by:

i. isolating compound of formula (XX) from the reaction mass;

ii. drying the said compound of formula (XX) obtained from step (i);

iii. crystallizing the said dried compound of formula (XX) using solvent to obtain purified compound of formula (XX) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XX) is an organic solvent selected from the group consisting of
alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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, hexamethylphosphoramidic and water or mixtures thereof.

The diazotizing agent used in step (d) for the preparation of compound of formula (XXI) includes but does not limit to resin nitrite, metal nitrite such as but not limited to sodium nitrite, potassium nitrite, silver nitrite, aluminum nitrite, lithium nitrate, rubidium nitrate, cesium nitrate, and the like organic nitrites such as but not limited to isoamyl nitrite, isopentyl nitrite, methyl nitrite and the like.
The acid used in step (d) may be organic acid such as but not limited to formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, oxalic acid, fumaric acid, maleic acid, paratoluene suiphonic acid and the like. According to the present invention, isolation of compound of the formula (XXI) from reaction mass of step (d) comprises the steps of:

i. extracting the compound of formula (XXI) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XXI),

v. optionally, purifying the compound of formula (XXI) obtained in step (iv) by:
   a. crystallization using solvent to obtain solid, or
   b. acid-base treatment to obtain solid, or
   c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XXI) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected
from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides selected from 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, hexamethylphosphoramid or mixtures thereof.

In a preferred embodiment, the solid obtained is crystalline compound of formula (XXI).

According to another embodiment of the present invention, isolation of compound of formula (XXI) from reaction mass of step (d) can also be alternatively performed by:

1. isolating compound of formula (XXI) from the reaction mass;
2. drying the said compound of formula (XXI) obtained from step (i);
3. crystallizing the said dried compound of formula (XXI) using solvent to obtain purified compound of formula (XXI) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XXI) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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, hexamethylphosphoramidate and water or mixtures thereof.

The catalyst used in step (e) for preparation of compound of formula (I) is selected from organic, inorganic catalyst or phase transfer catalyst.

The organic catalyst is selected from 1,8-Diazabicycloundec-7-ene (DBU) or 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) or dimethylaminopyridine and like.

The inorganic catalyst is selected from groups comprising alkali metal iodide, iodine, potassium iodide, p-toluene sulfonic acid, tertiary alkyl ammonium halide, sodium iodide, lithium iodide and the like.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be isolated from the reaction mass to obtain crystalline solid of compound of formula (I).
According to the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (e) comprises the steps of:

i. extracting the ticagrelor compound of formula (I) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),

v. optionally, purifying the ticagrelor compound of formula (I) obtained in step (iv) by

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, Isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylenedichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.
According to another embodiment of the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (e) can also be alternatively performed by:

- i. isolating ticagrelor of formula (I) from the reaction mass;
- ii. drying the said ticagrelor of formula (I) obtained from step (i);
- iii. crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

In a preferred embodiment, the solvent used for purification of ticagrelor compound of formula (I) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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;
According to another embodiment, the present invention provides a process for the preparation of ticagrelor of formula (I) comprising:

a) reacting, compound of formula (XVIII) or salt thereof with 7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c']pyrimidine of formula (XIX); in a solvent and base to obtain 2-(((3af?,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c']pyrimidin-3-yl]-2,2-dimethyl tetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl} oxy)-1-ethanol of formula (XVII);

b) deprotecting compound of formula (XVII) using acid in solvent to obtain , compound of formula (XXI); optionally isolating compound of formula (XXI)

c) condensing compound of formula (XXI) with trans-\(^{\wedge}R,2S\)-2-(3,4-difluorophenyl)cyclopropanamine or salt of formula (X) in solvent, base,
... and optionally in presence of a catalyst to produce ticagrelor of formula (I);

d) optionally, purifying ticagrelor of formula (I).

According to another embodiment of the present invention, the said process can be carried out insitu.

According to another embodiment of the present invention, ticagrelor compound of formula (I) may be further purified either by acid-base treatment, or solvent crystallization, or converting into its acid addition salts. The acid addition salts of ticagrelor of formula (I) can be prepared by treating the same with suitable acids; wherein the said acid includes organic and inorganic acids such as but not limited to hydrochloric acid, sulfuric acid, hydrobromic acid and the like; organic carboxylic acid like tartaric acid, fumaric acid, acetic acid, succinic acid, maleic acid, formic acid, oxalic acid and the like.

The solvent used in step (a), (b) and (c) of the present invention is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the
like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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 and water or mixtures thereof.

The solvent used in step (a), (b) and (c) of the present invention may be either same or different.

The base used in step (a) and (c) of the present invention may be organic or inorganic base; preferably organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, η,η-dimethly aniline, n,n-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to
potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The base used in step (a) and (c) of the present invention may be either same or different.

The step (a) is carried out at temperature in the range of 0°C to 100°C.

Compound of formula (XVII) obtained in step (a) is deprotected using acid in solvent to prepare compound of formula (XXI); wherein the acid may be organic or inorganic acid and the solvent used for deprotection is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-
butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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 and water or mixtures thereof.

According to the present invention, isolation of compound of the formula (XXI) from reaction mass of step (b) comprises the steps of:

i. extracting the compound of formula (XXI) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XXI),

v. optionally, purifying the compound of formula (XXI) obtained in step (iv) by:

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (XXI) comprises of esters selected from ethyl acetate, isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane, aromatic hydrocarbons
selected from benzene, toluene, xylene, naphthalene, halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride, ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers selected from tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers selected from 2-methyl tetrahydrofuran and the like; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; ketones selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkyl sulfoxides selected from 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 or mixtures thereof.

In a preferred embodiment, the solid obtained is crystalline compound of formula (XXI).

According to another embodiment of the present invention, isolation of compound of formula (XXI) from reaction mass of step (b) can also be alternatively performed by:

i. isolating compound of formula (XXI) from the reaction mass;
ii. drying the compound of formula (XXI) obtained from step (i); and
iii. crystallizing the said dried compound of formula (XXI) using solvent to obtain purified compound of formula (XXI) as solid.

In a preferred embodiment, the solvent used for purification of compound of the formula (XXI) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-
hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, ethylene dichloride and the like; 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, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; 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 and water or mixtures thereof.

The catalyst used in step (c) for preparation of compound of formula (I) is selected from organic, inorganic catalyst or phase transfer catalyst.

The organic catalyst is selected from 1,8-Diazabicycloundec-7-ene (DBU) or 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) or dimethylaminopyridine and like.

The inorganic catalyst is selected from groups comprising alkali metal iodide, iodine, potassium iodide, p-toluene sulfonic acid, tertiary alkyl ammonium halide, sodium iodide, lithium iodide and the like.
According to another embodiment of the present invention, ticagrelor compound of formula (I) may be isolated as a crystalline solid.

According to the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (c) comprises the steps of:

i. extracting the ticagrelor compound of formula (I) from the reaction mass with solvent,

ii. washing the organic layer of step (i) with water,

iii. decolorizing the said organic layer of step (ii) with activated charcoal,

iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),

v. optionally, purifying the ticagrelor compound of formula (I) obtained in step (iv) by

a. crystallization using solvent to obtain solid, or

b. acid-base treatment to obtain solid, or

c. crystallization in combination with acid-base treatment to obtain solid.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol,
ethanol, Isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylenedichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

According to another embodiment of the present invention, isolation of ticagrelor compound of formula (I) from reaction mass of step (c) can also be alternatively performed by:

i. isolating ticagrelor of formula (I) from the reaction mass;
ii. drying ticagrelor of formula (I) obtained from step (i); and
iii. crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

In a preferred embodiment, the solvent used for purification of ticagrelor compound of formula (I) includes, but does not limit to nitriles, ketones, alkylacetates, dimethylformamide, dimethylsulfoxide, ethers, esters, alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated aliphatic hydrocarbons, cyclic ethers, substituted cyclic ethers, dialkylacetamides, ionic liquids, and water or mixtures thereof.

According to another embodiment of the present invention, ticagrelor of formula (I) obtained is subjected for reduction in particle size by any of the processes known in the art such as milling, micronization and the like to obtain stable microcrystalline of ticagrelor with d(90) less than about 40 µ, preferably less than 20 µ and more preferably less than 10 µ.

Figure 1 illustrates X-ray powder diffraction (XRD) pattern of compound of formula (XVI), prepared according to example 1. It demonstrates the
crystalline nature of compound of formula (XVI). The X-ray diffractogram was measured on Brüker Axe, DS advance Power X-ray Diffractometer with Cu Kαα-1 Radiation source having the wavelength 1.541 A°.

The IR spectrum of crystalline form of compound of formula (XVI) having characteristic peaks at IR (KBr): 517.03, 669.30, 763.48, 853.51, 871.55, 951.55, 965.25, 986.23, 1049.62, 1076.68, 1095.24, 1121.20, 1162.27, 1189.11, 1208.05, 1246.12, 1265.61, 1309.33, 1341.81, 1373.85, 1403.83, 1455.27, 1481.37, 1567.32, 1644.23, 2869.38, 2939.22, 3246.07, 3383.87, 3437.38 cm⁻¹; having the following characteristic peaks 517.03, 763.48, 871.55, 951.55, 1049.62, 1121.20, 1162.27, 1246.12, 1309.33, 1455.27, 1567.32, 1644.23, 2869.38, 2939.22, 3246.07, 3383.87, 3437.38 cm⁻¹ (Figure 2). The IR spectra of compound of formula (XVI), of the invention has been recorded on a Fourier Transform Infrared Spectroscopy, PerkinElmer model 100 instrument using potassium bromide pellet method.

Figure 3 illustrates X-ray powder diffraction (XRD) pattern of ticagrelor compound of formula (I), prepared according to example 4. It demonstrates the crystalline nature of compound of formula (I). The X-ray diffractogram was measured on Brüker Axe, DS advance Power X-ray Diffractometer with Cu Kαα-1 Radiation source having the wavelength 1.541 A°.

Figure 4 illustrates Infrared spectrum (IR) of compound of formula (I), prepared according to example 4. The IR spectrum of crystalline form of ticagrelor of formula (I) having characteristic peaks at IR (KBr): 457.75, 536.32, 579.54, 618.83, 642.34, 671.61, 714.13, 753.65, 771.86, 790.62, 808.82, 826.94, 890.70, 934.77, 993.68, 1050.52, 1071.86, 1093.04, 1114.20, 1170.46, 1196.11, 1209.08, 1275.67, 1329.10, 1384.24, 1426.75,
1453.39, 1521.02, 1588.92, 1625.30, 2931.85, 2963.75, 3293.51, 3390.76 cm⁻¹, and having characteristic peaks at IR (KBr) 579.54, 618.83, 671.61, 771.86, 826.94, 993.68, 1050.52, 1093.04, 1114.20, 1196.11, 1275.67, 1329.10, 1426.75, 1453.39, 1521.02, 1588.92, 1625.30, 2931.85, 2963.75, 3293.51, 3390.76 cm⁻¹. The IR spectra of compound of formula (I), of the invention has been recorded on a Fourier Transform Infrared Spectroscopy, Perkin Elmer model 100 instrument using potassium bromide pellet method.

Further, the process of the present invention has less than about 0.20% (1S,2S,3R,5S)-3-{7-{[(1R, 2S)-2-(3,4-difluorophenyl)-cyclopropyl] amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl]- 5-(oxyethylacetate)-1,2-cyclopentanediol compound of formula (IMP-1),

![Chemical Structure](image)

**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.

**Preparation of Resin nitrite**

Amerlyst hydroxide A-26 (50 gm) was suspended in solution of sodium nitrite (29.57 gm 0.428 mol) in water (428.0 ml) and reaction mass was stirred for 10-15 min. The resultant mass was filtered and pH was adjusted to neutral using purified water to afford 44 gm Resin nitrite. (Ion exchange capacity of Resin nitrite = 2.6-3.6 mmol of nitrite/gm)
Example- 1
Preparation of 2-[(3a/?,4S,6R,6aS)-6-{[5-amino-6-chloro-2-(propylthio)-
4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[c][1,3]
dioxol-4-yl]oxy]-1-ethanol

To a mixture of 4,6-dichloro-2-(propylthio)-5-pyrimidinamine (50 gm, 0.21
mol) in ethylene glycol (500 ml), 2-[(3aR4S,6R6aS)-6-amino-2,2-
dimethyltetrahydro-3a/-/-cyclopenta[d][1 ,3]-dioxol-4-yl]oxy]-1 -ethanol, L-
tartaric acid (1:1) (84.82 gm; 0.23 mol) was added 1, 8-bicyclo [5.4.0] undec-
7-ene (5.0 gm), followed by addition of diisopropyl ethylamine (122.12 gm;
0.944 mol) at 20-25°C. Reaction mixture was heated at 120-125°C stirred
and maintained at same temperature for 2-3 hours, until completion of
reaction (monitored by TLC). After completion of reaction, resulting mass
was cooled to 20-30 °C, diluted with water (1000 ml) and pH of solution was
adjusted to 4.5 using concentrated hydrochloric acid. 2-[(3aR,4S,6R,6aS)-6-
{[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}-2,2-
dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl]oxy]-1 -ethanol
compound was extracted as oil from reaction mass twice with ethyl acetate
(1000 ml + 500 ml), followed by washing of ethyl acetate layer with water
(1000 ml) and 15% W/V sodium chloride solution (1000 ml). Ethyl acetate
was evaporated at 50-55°C under reduced pressure to produce 80.0 gm of 2-
[(3aR4S,6f?,6aS)-6-{[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}-
2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl]oxy]-1 -ethanol as
oil. Obtained oil was dissolved in ethyl acetate (120.0 ml), stirred and the
solution was heated at 50°C, followed by addition of n-heptane (600 ml) at
50°C and maintained for 30 min. The resulting isolated suspensions was
gradually cooled to room temperature then cooled to 0-5°C and maintained
at 0-5°C for 30-40 min. Obtained solid was filtered, washed with n-heptane
(80 ml), suck dried and dried at 50-55°C to afford white solid of 2-
Purification:
Obtained solid (55.0 gm) was dissolved in ethyl acetate (80 ml) stirred and heated to 50°C, n-heptane (400 ml) was added to the solution, stirred at 50°C for 30 min. The resulting solutions were gradually cooled to room temperature, further cooled to 0-5°C and maintained at 0-5°C for 30-40 min. The obtained solid was filtered, washed with chilled n-heptane (55 ml), sucked dried and dried at 50-55°C to give pure white crystalline solid of 2-
[((3aR,4S,6R,6aS)-6-[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]arnino)-
2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl)oxy]-1-ethanol.

Crystalline form of 2-
[((3a? ,4S,6/? ,6aS)-6-[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]arnino)-
2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl)oxy]-1-ethanol of formula (XVI) is characterized by its PXRD as illustrated in figure 1.

The IR spectrum of crystalline form of compound of formula (XVI) having peaks at IR (KBr): 517.03, 669.30, 763.48, 853.51, 871.55, 951.55, 965.25, 986.23, 1049.62, 1076.68, 1095.24, 1121.20, 1162.27, 1189.11, 1208.05, 1246.12, 1265.61, 1309.33, 1341.81, 1373.85, 1403.83, 1455.27, 1481.37, 1567.32, 1644.23, 2869.38, 2939.22, 3246.07, 3383.87, 3437.38 cm⁻¹ having the following characteristic peaks 517.03, 763.48, 871.55, 951.55, 1049.62, 1121.20, 1162.27, 1246.12, 1309.33, 1455.27, 1567.32, 1644.23, 2869.38, 2939.22, 3246.07, 3383.87, 3437.38 cm⁻¹ (Figure 2)

¹H NMR (CDCl₃) : δ= ppm 6.59-6.57 (d, NH), 5.04-5.02 (bs, 1H), 4.75-4.73 (s, NH₂), 4.53-4.52 (d, 1H), 4.48-4.46 (d, 1H), 4.31 (q 1H), 3.88 (q, 1H), 3.56-3.47 (t, 4H), 2.98-2.95 (t, 2H), 2.23-2.19 (q, 1H), 1.89-1.85 (dd, 1H), 1.66-1.61 (m, 2H), 1.37 (s, 3H), 1.21 (s, 3H), 0.97-0.93 (t, 3H) ppm.
Example- 2
Preparation of 2-(((3aR,4S,6R,6aS)-6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[cd][1,3]dioxol-4-yl)oxy]-1-ethanol

To a mixture of 4,6-dichloro-2-(propylthio)-5-pyrimidinamine (25.0 gms, 0.105 mol) in ethylene glycol (125 ml), 2-(((3aR,4S,6R,6aS)-6-amino-2,2-dimethyltetrahydro-SaH-cyclopentalcdll .Sl-dioxol^ylJoxy)-1 -ethanol, L-tartaric acid (1:1) (42.41 gms; 0.115 mol) was added 1, 8-bicyclo [5.4.0]undec-7-ene (1.25 gms), followed by addition of diisopropyl ethylamine (61.06 gms; 0.472 mol) at 20-25°C. Reaction mixture was heated at 120-125°C stirred and maintained at same temperature for 4-5 hours, until completion of reaction (monitored by TLC). After completion of reaction, resulting mass was cooled to 20-30 °C, diluted with water (500 ml). 2-(((3aR,4S,6R,6aS)-6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl)oxy]-1 -ethanol compound was extracted as oil from reaction mass twice with MDC (250 ml), followed by washing of MDC layer with water (500 ml). MDC was evaporated at 35-40°C under reduced pressure to produce 42.5 gms of 2-(((SaR^S.eR.eaSJ-e-iS-amino-e-chloro^-ipropylthioJ^-pyrimidinylJarnino)-2,2-dimethyltetrahydro-3aH-cyclopenta[cd] [1,3] dioxol-4-yl)oxy]-1-ethanol as oil. Obtained oil was dissolved in ethyl acetate (75.0 ml), stirred and the solution was heated at 50°C, followed by addition of n-heptane (500.0 ml) at 50°C and maintained for 30 min. The resulting isolated suspensions was gradually cooled to room temperature then cooled to 20-25°C and maintained at 20-25°C for 30-40 min. Obtained solid was filtered, washed
with n-heptane (50.0 ml), suck dried and dried at 50-55°C to afford white solid of 2-(((3aR,4S,6R,6aS)-6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidiny]amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl)oxy]-1-ethanol. [Yield = 34.0 gm (77.30%); purity (HPLC): 99.1 %]

Example- 3:
Preparation of 2-(((3a/?,4S,6A?,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-c]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxol-4-yl)oxy)-1-ethanol
To a solution of para-toluene sulphonic acid (9.11 gm, 0.048 mol) and water (50.0 ml) was added resin nitrite (20.0 gm) and the solution stirred for 10-15 min, followed by addition of 2-(((3aR,4S,6/?,6aS)-6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidiny]amino]-2,2-dimethyltetrahydro-3a/-/-cyclopenta[d] [1,3] dioxol-4-yl)oxy]-1-ethanol (10.0 gm, 0.024 mol) in acetonitrile (50 ml). The reaction mass was stirred for 60-90 min at room temperature. The progress of reaction was monitored by HPLC. After completion of reaction, resin was filtered and washed with acetonitrile (10 ml). The mother liquor was combined, followed by addition of purified water (100.0 ml) and ethyl acetate (100.0 ml), stirred followed by separation of aqueous and ethyl acetate layer. Ethyl acetate layer was washed with purified water (100 ml), then 15 % W/V sodium chloride solution. The ethyl acetate was evaporated at 50-55°C Under reduced pressure to produce 9.0 gm of 2-(((3aR,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3] triazolo^S-cdpymidin-S-yll^^-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl]oxy)-1-ethanol as an oil.

$^1$H NMR (CDCl$_3$) : $\delta$ = ppm 4.79-4.76(s,OH), 4.32-4.30 (t,1H), 4.04-4.01 (t,1H), 3.76-3.73(t,2H), 3.70-3.67(t,2H), 3.20-3.17(t,2H), 3.00-2.97 (q,1H), 2.43 (q,1H), 2.00 (m,4H), 1.85-1.80(s, 6H), 1.09-1.06 (t, 3H) ppm.

MS m/z (%): 430.0 [M+1]+(100).[Yield=9.0gm(87.72%);Purity(HPLC)= 92%]
Example- 4:
Preparation of 2-(((3a/?,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-c/]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl]oxy)-1-ethanol

To a solution of para-toluene sulphonic acid (6.8 gm, 0.035 mol) and water (50.0 ml) was added resin nitrite (20.0 gm) and the solution stirred for 10-15 min, followed by addition of 2-(((3a/?,4S,6f?,6aS)-6-{[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl]oxy)-1-ethanol (10.0 gm, 0.024 mol) in acetonitrile (50 ml). The reaction mass was stirred for 20-30 min at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, resin was filtered and washed with MDC (100 ml). The mother liquor was combined, followed by addition of purified water (100.0 ml), stirred followed by separation of aqueous and MDC layer. MDC layer was washed with 5% sodium bicarbonate solution (100 ml), and then wash using purified water (100 ml). The MDC was evaporated at 35-40°C under reduced pressure to produce 10.0 gm of 2-(((3aR,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl] oxy)-1-ethanol as an oil. [Yield=10gm(97.37%);Purity(HPLC)= 92%]

Example- 5:
Preparation of 2-(((3aR,4S,6R,6aS)-6-[7-{{(1 R,2S)-2-(3,4-difluorophenyl)-cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yI]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxal-4-yl]oxy)-1-ethanol
To the solution of 2-({(3aR,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3]dioxal-4-yl) oxy)-1-ethanol (10.0 gm, 0.023 mol) in acetonitrile (200.0 ml) was added fra/?s-(1R,2S)-2-(3,4-Difluorophenyl) cyclopropanamine (2R)-2-hydroxy-2-phenylethanoate (7.50 gm, 0.023 mol), followed by addition of anhydrous potassium carbonate (6.46.0 gm, 0.046 mol) under stirring at 25-30°C and maintained for 2-3 hrs (progress of reaction was monitored by HPLC). After completion of reaction, resulting mass was diluted with water (200 ml), extracted 2-({(3aR,4S,6R,6aS)-6-[7-[(1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxal-4-yl]oxy)-1-ethanol compound twice with ethyl acetate (100 ml + 50 ml), separate the aqueous and ethyl acetate layer, washing the ethyl acetate layer with water (100 ml) and 15% W/V sodium chloride solution (100 ml). The ethyl acetate was evaporated at 50-55°C under reduced pressure to produce 11.0 gm of 2-({(3aR,4S,6R6aS)-6-[7-{{(1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl}amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxal-4-yl]oxy)-1-ethanol as an oil.

\[ {\text{H NMR (CDCl}}_3 : {\delta} = \text{ppm } 7.47-74 \text{ (d, 1H), 7.37-7.31 } \text{ (dd, 2H), 5.25 } \text{ (s, OH), 5.14 } \text{ (s, NH), 4.85-4.85 } \text{ (t, 1H), 4.01-3.99 } \text{ (t, 1H), 3.61-3.56 } \text{ (m, 3H), 3.49-3.45 } \text{ (m, 1H), 3.14-2.97 } \text{ (m, 4H), 2.66-2.60 } \text{ (t, 2H), 2.50-2.48 } \text{ (t, 2H), 2.13-2.09 } \text{ (t, 2H), 1.72-1.65 } \text{ (m, 2H), 1.52 } \text{ (s, 3H), 1.34 } \text{ (s, 3H), 0.88-0.84 (t, 3H) ppm. MS } m/z (\%) : 563.1 [M+1]^+ (100). \]

[Yield = 11.0 gm (83.3%); Purity (HPLC) = 94.0%]

Example- 6:
Preparation of 2-({(3aR,4S,6/?,6aS)-6-[7-{{(1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl}amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-}
2,2-dimethyltetrahydro-3aH-cyclopenta[c][1,3]dioxal-4-yl]oxy)-1-ethanol

To the solution of 2-(((3aR,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H]-[1,2,3]triazolo[4,5- (^pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3]dioxal-4-yl] oxy)-1-ethanol (10.0 gm, 0.023 mol) in acetonitrile (70.0 ml) was added trans-\(^{\Delta}R\)-2-(3,4-Difluorophenyl) cyclopropanamine (7.50 gm, 0.023 mol), followed by addition of anhydrous potassium carbonate (6.46.0 gm, 0.046 mol) under stirring at 25-30°C and maintained for 2-3 hrs (progress of reaction was monitored by HPLC). After completion of reaction, resulting mass was diluted with water (200 ml), extracted 2-(((3aR,4S,6R,6aS)-6-[7-([(1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl]amino)-5-(propylthio)-3H]-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxal-4-yl]oxy)-1 -ethanol compound twice with MDC (100 ml + 50 ml), separate the aqueous and MDC layer, washing the MDC layer with water (100 ml). The MDG was evaporated at 35-40°C under reduced pressure to produce 13.0 gm of 2-(((3aR,4S,6R6aS)-6-[7-([(1R2S)-2-(3,4-difluorophenyl)-cyclopropyl]amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta [d][1,3]dioxal-4-yl]oxy)-1 -ethanol as an oil.

[Yield = 13.0 gm (98.85%); Purity (HPLC) = 94.0%]

Example- 7:
Preparation of (1S,2S,3A?,5S)-3-[7-([(1K,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino)-5(propylthio)-3H-[1,2,3]-triazolo[4,5-i]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1 ,2-diol.

2-(((3a?,4S,6R,6aS)-6-[7-([(1R2S)-2-(3,4-difluorophenyl)-cyclopropyl]amino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-cy]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta [d][1,3]dioxal-4-yl]oxy)-1 -ethanol (10.0 gm) was dissolved
in methylene dichloride (100.0 ml) and the solution was stirred for 10-15 minutes to the same solution was added concentrated hydrochloric acid (3.33 gm) and reaction mass was stirred for stirred for 60-90 min. The progress of reaction was monitored by HPLC. After completion of reaction, purified water (150 ml) was charged to the reaction mass, solution was basified to pH 8-9 using sodium hydroxide solution, stirred, and layers were separated. Methylene dichloride layer was washed using purified water (100.0 ml) and then 10 % W/V sodium chloride solution. The methylene dichloride was evaporated at 30-35°C under reduced pressure to produce 8.0 gm of (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]aminoJ-Sipropylthioi-SH-ll,2,3]-triazolo[4,5-d]pyrimidin-3-yl]S-(2-hydroxyethoxy) cyclopentane-1,2-diol (ticagrelor) as oil. To the same oil ethyl acetate (40.0 ml) was added, the solution was stirred and heated to 50-55 °C followed by addition of n-heptane (50.0 ml) and the solution was maintained at same temperature for 30 min. The resulting solution was gradually cooled to room temperature and further cooled and maintained at 0-5°C, for 30-40 min. Obtained solid was filtered, washed with pre-chilled n-heptane (8 ml), suck dried and dried at 50-55°C to give pure white crystalline solid of ticagrelor, 8.0 gm. (HPLC purity: 98.2 % by area).

**Purification:**

Above obtained solid (8.0 gm) was dissolved in ethyl acetate (40 ml), stirred and heated to 50°C followed by addition of n-heptane (50 ml) with stirring at 50°C and maintained for 30 min. The resulting solution was gradually cooled to room temperature and further cooled and maintained at 0-5°C for 30-40 min. Obtained solid was filtered, washed with pre-chilled n-heptane (8.0 ml), suck dried and dried at 50-55X to give pure white crystalline powder of ticagrelor. Crystalline form of ticagrelor of formula (I) is characterized by its PXRD as illustrated in Figure 3.
The IR spectrum of crystalline form of ticagrelor of formula (I) having characteristic peaks at IR (KBr): 457.75, 536.32, 579.54, 618.83, 642.34, 671.61, 714.13, 753.65, 771.86, 790.62, 808.82, 826.94, 890.70, 934.77, 993.68, 1050.52, 1071.86, 1093.04, 1114.20, 1170.46, 1196.11, 1209.08, 1275.67, 1329.10, 1384.24, 1426.75, 1453.39, 1521.02, 1588.92, 1625.30, 2931.85, 2963.75, 3293.51, and having characteristic peaks at IR (KBr) 579.54, 618.83, 671.61, 771.86, 826.94, 993.68, 1050.52, 1093.04, 1114.20, 1196.11, 1275.67, 1329.10, 1426.75, 1453.39, 1521.02, 1588.92, 1625.30, 2931.85, 2963.75, 3293.51, as illustrated in Figure 4. ^1H NMR (CDCl₃) : δ = ppm 9.38-9.37 (d, NH), 7.37-7.25 (dd, 2H), 7.07 (s, 1H), 5.13-5.12 (s, 1H), 5.07-5.06 (d, 1H), 4.98-4.92 (q, 1H), 4.63-4.60 (t, 1H), 5.57-5.52 (q, 1H), 3.75-3.73 (t, 1H), 3.51-3.49 (t, 4H), 3.16-3.13 (q, 1H), 2.95-2.90 (q, 1H), 2.88-2.81 (q, 1H), 2.64-2.61 (q, 1H), 2.13-2.10 (q, 1H), 2.05-2.00 (q, 1H) 1.56-1.51 (q, 1H), 1.50-1.46 (m, 2H), 1.39-1.36 (q, 1H), 0.82-0.78 (t, 3H) ppm. ^13C NMR (100 MHz, CDCl₃): δ = 169.17, 153.95, 149.43, 139.40, 123.17, 122.82, 117.13, 116.96, 114.85, 114.72, 81.78 (CH₂), 74.38 (CH₂), 73.68 (CH₂), 70.86 (CH₂), 60.30 (CH₂), 60.15 (CH), 35.70 (CH), 32.11 (CH), 24.06 (CH₂), 22.30 (CH₂), 13.21 (CH₂), 12.98 (CH₃), 62.48, 71.7 (CH₂), 35.10, 62.48, 112.41, 121.32, 125.35, 129.33, 135.99, 145.47, 149.5, 151.7, 155.15, 157.2, 157.69, 161.30 (CH) ppm. MS m/z (%): 523.0 [M+1]+ (100). Anal. Calcd. for CHNOS: (250.01): C, 52.81; H, 5.35; N, 16.07. Found: C, 52.69; H, 5.34; N, 15.93 % [Yield = 7.0 gm (75.27%); Purity (HPLC) = 99.5%]

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Example- 8:
Preparation of (1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5(propylthio)-3/H-[1,2,3]-triazolo[4,5-d]pyrim(din-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol.

2-({((3aR4S,6R,6aS)-6-[7-{[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-yl]-2,2-dimethyltetrahyd ro-3aH-cyclopenta [d] [1,3]dioxal-4-yl]oxy)-1-ethanol (50.0 gm) was dissolved in methylene dichloride (350.0 ml) and the solution was stirred for 10-15 minutes to the same solution was added concentrated hydrochloric acid (225.0 ml) and reaction mass was stirred for stirred for 60-90 min. The progress of reaction was monitored by HPLC. After completion of reaction, diluted with purified water (750 ml) and MDC (750.0 ml), stirred and layers were separated. Methylene dichloride layer was washed using purified water (750.0 ml) and then 5.0 % W/V sodium chloride solution (500.0 ml). The methylene dichloride was evaporated at 35-40°C under reduced pressure to produce 40.0 gm of (1S,2S,3R,5SJ-3-[7-{[(1R,2SJ-2-(3,4-difluorophenyl)cyclopropyl]amino}-5(propylthio)-3H-[1,2,3]-triazolo[4,5-c]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol (ticagrelor) as oil. To the same oil ethyl acetate (200.0 ml) was added, the solution was stirred and heated to 55-60 °C followed by addition of n-heptane (200.0 ml) and the solution was maintained at same temperature for 30 min. The resulting solution was gradually cooled to room temperature and further cooled and maintained at 0-5°C, for 30-40 min. Obtained solid was filtered, washed with pre-chilled n-heptane (40.0 ml), suck dried and dried at 50-55°C to give pure white crystalline solid of ticagrelor, 36.0 gm. (HPLC purity: 99.0 % by area).

Purification:
Above obtained solid (36.0 gm) was dissolved in ethyl acetate (180.0 ml), stirred and heated to 55-60°C followed by addition of n-heptane (180.0 ml)
with stirring at 55-60°C and maintained for 30 min. The resulting solution was gradually cooled to room temperature and further cooled and maintained at 0-5°C for 30-40 min. Obtained solid was filtered, washed with pre-chilled n-heptane (36.0 ml), sucked dried and dried at 50-55°C to give pure white crystalline powder of ticagrelor.

[Yield = 31.0gm (66.75%); Purity (HPLC) = 99.56%]

**Example- 9:**
**Preparation of 2-[[((3a/?,4S,6/?,6aS)-6-[[5-nitro-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl]oxy]-1-ethanol**

To a solution of 4,6-dichloro-2-(propylthio)pyrimidin-5-nitro (10 gm, 0.037 mol) in tetrahydrofuran (200 ml) was added 2-[[((3a/?,4S,6f/?,6aS)-6-amino-2,2-dimethyltetrahydro-3a/-/cyclopenta[cd[1 ,3]-dioxol-4-yl]oxy]-1 -ethanol, L-tartaric acid (1:1) (15.1 gm; 0.04 mol) followed by addition of diisopropyl ethylamine. The reaction mass was maintained at 0 - 5 °C for 2-3 hrs. The progress of reaction was monitored by TLC. After completion of reaction, the resulting reaction mass was washed with water (100 ml) and product was extracted twice with ethyl acetate (100 ml + 50 ml), followed by washing ethyl acetate layer with water (100 ml) and 15% W/V sodium chloride solution (100 ml). The ethyl acetate was evaporated at 50°C under reduced pressure to produce an oil of 2-[[((3af?,4S,6R,6aS)-6-[[5-nitro-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3aH-cyclopenta[ai ] [1,3] dioxol-4- yl]oxy]-1 -ethanol. [Yield = 13.0 gm (87.88%)]

**Example- 10:**
**Preparation of (1/?,2/?,3S,5/?)-3-[[5-amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino>-5-(2-hydroxyethoxy)cyclopentane-1,2-diol**
To a solution of 2-[(3aR,4S,6R,6aS)-6-{[5-nitro-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}^-dimethyltetrahydro-SaH-cyclopentalc] [1,3] dioxol-4-yl)oxy]-1-ethanol (10 gm, 0.02 mol) in methanol (120 ml) was added iron powder (9.95 gm; 0.17 mol) followed by addition of ferric chloride (0.83 gm; 0.005 mol) in water (5ml). The reaction mass was heated and maintained at 50-55 °C for 3-4 hrs. The progress of reaction was monitored by TLC. After completion of reaction, resulting mass was filtered and mother liquor was distilled under reduced pressure. The obtained residue was diluted with water (100 ml) and (1R,2R,3S,5R)-3-{[5-amino-6-chloro-2-(propylthio) pyrimidin-4-yl]amino}-5-(2-hydroxyethoxy)cyclopentane-1,2-diol was extracted twice with methylene dichloride (100 ml + 50 ml), followed by washing methylene dichloride layer with water (100 ml). The methylene dichloride layer was acidified using concentrated hydrochloric acid (20ml), the solution was stirred for 2-3 hrs. After deprotection of (1R,2R,3S,5R)-3-{[5-amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino}-5-(2-hydroxyethoxy) cyclopentane-1,2-diol, the above solution was diluted with water (100 ml) & basified using aqueous ammonia (25 ml). The layers were separated and methylene dichloride layer was washed with purified water (100 ml), methylene dichloride was evaporated under reduced pressure to give (1R,2R,3S,5R)-3-{[5-amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino}-5-(2-hydroxyethoxy) cyclopentane-1,2-diol as solid. [Yield = 6.0 gm (71.17%)].

Example- 11:
Preparation of (1R,2R,3S,5R)-3-[7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-c]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol
To a solution of (1R,2R,3S,5R)-3-{[5-amino-6-chloro-2-(propylthio) pyrimidin-4-yl]amino}-5-(2-hydroxyethoxy) cyclopentane-1,2-diol
(5.0 gm, 0.013 mol) in acetonitrile (100 ml) was added para-toluene sulphonic acid (7.52 gm, 0.04 mol) followed by addition of sodium nitrite (1.37 gm, 0.02 mol) in water (5.0 ml). The reaction mass was stirred for 30-40 min. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mass was diluted with purified water, basified using liquor ammonia and (1R,2R,3S,5R)-3-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol compound was extracted in ethyl acetate (100.0 ml). Ethyl acetate layer was washed with purified water (100 ml) then 15% WW sodium chloride solution. The ethyl acetate was evaporated at 50-55°C under reduced pressure to give an oil of (1R,2R,3S,5R)-3-[7-chloro-S-(propylthio)J3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. [Yield = 4.0 gm (68.5%)]

Example- 12:
Preparation of (1S,2S,3R,5S)-3-[7-{{(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5(propylthio)-3H-[1,2,3]-triazolo[4,5-c]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol
To a solution of (1R,2S,3S,5S)-3-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (3.0 gm 0.008 mol) in acetonitrile (60.0 ml) was added trans-(1R,2S)-2-(3,4-Difluorophenyl) cyclopropanamine (2fl)-2-hydroxy-2-phenylethanoate (2.47 gm, 0.008 mol) followed by addition of Anhydrous potassium carbonate (2.13 gm, 0.015 mol) under stirring at 25-30°C. The resultant mass was maintained at 25-30°C under stirring for 2-3 hrs, and the progress of reaction was monitored by TLC. After completion of reaction, resulting mass was diluted with water (60 ml). From same solution (1S,2S,3R,5S)-3-[7-{{(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5(propylthio)-3H-[1,2,3]-
triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol was extracted twice with ethyl acetate (60 ml + 30 ml), followed by washing the organic layer with water (100 ml), 15% WAF sodium chloride solution (100 ml). Ethyl acetate was evaporated at 50-55°C under reduced pressure to produce an oil of (1S,2S,3R,5S)-3-[(1R2S)-2-(3,4-difluorophenyl)cyclopropyl]amino)-5(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol (3.5 gm)(ticagrelor). To the same oil was added ethyl acetate (17.5 ml), the solution was stirred and heated to 50-55 °C, followed by addition of n-heptane (17.5 ml) and solution was maintained at 50-55°C for 30 min. The resulting solution was gradually cooled to room temperature, further cooled and maintained at 0-5°C for 30-40 min. obtained solid was filtered and washed with pre-chilled n-heptane (3.5 ml), suck dried and dried at 50-55°C to give pure white crystalline solid of ticagrelor, 3.0 gm. (HPLC purity: 96.0 % by area).

**Purification:**
Above obtained solid (3.0 grh) was dissolved in ethyl acetate (15 ml) stirred and heated to 50°C, followed by addition of n-heptane (15 ml). The solution was stirred at 50°C for 30 min. The resulting solution was gradually cooled to room temperature, further cooled and maintained at 0-5°C for 30-40 min. Obatined solid was filtered and washed with pre-chilled n-heptane (3.0 ml), suck dried and dried at 50-55°C to give pure white crystalline powder of ticagrelor, 2.5 gm. [Yield = 2.5 gm (62.19%); Purity (HPLC) = 98.5%]

**Example- 13:**
Preparation of 2-(((3a/?,4S,6R,6aS)-6-[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxal-4-yl]oxy)-1-ethanol
To the solution of 2-\{((3a/?,4S,6R,6aS)-6-\{[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino\}-2,2-dimethyltetrahydro-3a/-/-cyclopenta[c fl [1,3] dioxol-4-yl]oxy\}-1-ethanol (18.0 gm, 0.04 mol) in acetonitrile (360 ml) was added para-toluene sulphonic acid (24.61 gm, 0.13 mol), followed by addition of sodium nitrite (4.45 gm, 0.06 mol) in water (18.0 ml). The solution was stirred for 30-40 min. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mass was diluted with purified water, basified with liquor ammonia and 2-\{((3aR,4S,6R,6aS)-6-\{7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl]oxy\}-1-ethanol compound was extracted in ethyl acetate (180.0 ml). Ethyl acetate layer was washed with purified water (180 ml) then 15 % W/V sodium chloride solution. The ethyl acetate was evaporated at 50-55°C under reduced pressure to give an oil of 2-\{((3aR4S,6fi,6aS)-6-\{7-chloro-5-(propylthio)-3H-[1 ,2,3] triazolo[4,5-cflpyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d] [1,3] dioxal-4-yl} oxy\)-1-ethanol.

[Yield = 15.5 gm (83.91%)]

Example- 14
Preparation of (1R,2/?,3S,5/?)-3-[7-chloro-5-(propylthio)-3H-[1 ,2,3] triazolo[4,5-c]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

To a solution of para-toluene sulphonic acid (113.98 gm, 0.899 mol) and water (250.0 ml) was added resin nitrite (100.0 gm) and the solution stirred for 10-15 min, followed by addition of 2-\{((3a/?,4S,6R,6aS)-6-\{5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino\}-2,2-dimethyltetrahydro-3aH-cyclopentafd] [1,3] dioxol-4-yl]oxy\}-1-ethanol (50.0 gm, 0.119 mol) in acetonitrile (250.0 ml). The reaction mass was stirred for 90-120 min at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, resin was filtered and washed with Ethyl acetate
The mother liquor was combined, followed by addition of purified water (500.0 ml), stirred followed by separation of aqueous and Ethyl acetate layer. Ethyl acetate layer was washed with purified water (500.0 ml), and 5% sodium bicarbonate solution then 15% W/V sodium chloride solution (500.0 ml). The Ethyl acetate layer was evaporated at 50-55°C under reduced pressure to produce 38.0 gm of \((1R,2R,3S,5R)-3-[7\text{-chboro-5-(propylthio)-3H-[1,2,3]}\text{triazolo}[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol\) as crystalline Solid.

\[\text{Yield} = 38.0 \text{ gm (81.68%); Purity (HPLC) = 97.8\%}\]
We claim:

1. A process for preparation of ticagrelor of formula (I) wherein, the said process comprises:

   a) reacting, 2-\{([3aR,4S,6\text{aS},6\text{bS})-6\text{-[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy\}-1-ethanol or salt of formula (II) with 4,6-dichloro-2-(propylthio)-5-pyrimidinamine of formula (XV) or salt thereof in a solvent and a base in presence of a catalyst to obtain 2-\{([3aR4S,6\text{aS},6\text{bS})-6\text{-[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino}-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxol-4-yl]oxy\}-1-ethanol of formula (XVI), and optionally isolating compound of formula (XVI);

   b) reacting compound of formula (XVI) of step (a) with a diazotizing agent in an acid and a solvent to prepare 2-\{([3aR,4S,6\text{aS},6\text{bS})-6-[7-chloro-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]-dioxal-4-yl]oxy\}-1-ethanol compound of formula (XVII);
c) reacting compound of formula (XVII) with trans-^R,2S)-2-(3,4-Difluorophenyl) cyclopropanamine or salt of formula (X) in a solvent, a base, and optionally in presence of a catalyst to produce 2-\{((3aR4S,6R6aS)-6-[7-\{((1R,2S)-2-(3,4-difluorophenyl)-cyclopropyl]mino\}-5-(propylthio)-3H-[1 ^.SJtriazolo^.S-o]pyrimidin-3-yl]-2,2-dimethyltetrahydro-3aH-cyclopenta [o][1 ,3]dioxal-4-yl]oxy)-1-ethanol of formula (XII);

d) deprotecting compound of formula (XII) using aqueous acid in a solvent to obtain ticagrelor of formula (I), and isolating compound of formula (I);

e) purifying ticagrelor of formula (I).

2. The process as claimed in claim 1, wherein the solvent used in step (a), (b), (c) and (d) may be same or different and is selected from the group consisting of esters selected from ethyl acetate, and isopropyl
acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons selected from toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride; dialkylformamides selected from dimethyl formamide; ethers selected from methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether, di-methyl ether, and methyl butyl ether; cyclic ethers selected from tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers selected from 2-methyl tetrahydrofuran; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones selected from acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides selected from dimethyl sulfoxide; dialkylacetamides selected from N,N-dimethyl acetamide; nitrites selected from acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide; water or mixtures thereof.

3. The process as claimed in claim 1, wherein the base used in step (a), and (c) may be same or different and is selected from the organic bases selected from group consisting of primary amines like methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethano); secondary amines selected from N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole, and methylethanolamine; tertiary amines selected from triethylamine, η,η-dimethy aniline, η,η-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, and N,N-dimethylethyl amine; tetraalkylammonium and phosphonium hydroxides; Metal Alkoxides and Amides; and Metal Silanoates; and inorganic bases selected from
group consisting of alkali metal carbonates selected from potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarbonates selected from sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides selected from sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal alkoxides selected from sodium methoxide, sodium ethoxide, and potassium tert butoxide; metal amides or liquor ammonia.

4. The process as claimed in claim 1, wherein the catalyst used in step (a) and (c) may be either same or different and is an organic, inorganic catalyst or phase transfer catalyst selected from 1, 8-Diazabicycloundec-7-ene (DBU); 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN); dimethylaminopyridine; alkali metal iodide selected from potassium iodide, lithium iodide and sodium iodide, iodine, p-toluene sulfonic acid, and tertiary alkyl ammonium halide.

5. The process as claimed in claim 1, wherein the diazotizing agent used in step (b) is selected from resin nitrite; metal nitrite selected from sodium nitrite, potassium nitrite, silver nitrite, aluminum nitrite, lithium nitrate, rubidium nitrite, and cesium nitrite; organic nitrites selected from isoamyl nitrite, isopentyl nitrite, and methyl nitrite.

6. The process as claimed in claim 1, wherein the acid used in step (b) is an organic acid selected from formic acid, acetic acid, propanoic acid, trifluoroacetic acid, perchloric acid, and paratoluene sulphonic acid.
7. The process as claimed in claim 1, wherein the aqueous acid used in step (d) is an organic acid selected from formic acid, acetic acid, propanoic acid, trifluoracetic acid, perchloric acid, oxalic acid, fumaric acid, maleic acid, and paratoluene sulphonlic acid or inorganic acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, hydrobromic acid in acetic acid, boron and trifluoride in ether.

8. The process as claimed in claim 1, wherein the isolation of compound of the formula (XVI) from reaction mass of step (a) comprises the steps of:
   i. extracting the compound of formula (XVI) from the reaction mass with solvent,
   ii. washing the organic layer of step (i) with water,
   iii. decolorizing the said organic layer of step (ii) with activated charcoal,
   iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (XVI),
   v. optionally, purifying the compound of formula (XVI) obtained in step (iv) by
      a. crystallization using solvent to obtain solid, or
      b. acid-base treatment to obtain solid, or
      c. crystallization in combination with acid-base treatment to obtain solid.

9. The process as claimed in claim 8, wherein the solvent used for extraction of the compound of formula (XVI) comprises of esters such as but not limited to ethyl acetate, isopropyl acetate, methyl acetate
and the like, aliphatic hydrocarbons such as but not limited to n-heptane, iso-octane, n-hexane, cyclohexane and the like, aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like, ethers such as but not limited to diisopropyl ether, diethyl ether and the like, cyclic ethers such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, and the like, alcohol such as but not limited to methanol, ethanol, isopropanol, iso-butanol and the like, ketone such as but not limited to acetone, ethyl methyl ketone and the like, nitriles, ionic liquids, halogenated aliphatic hydrocarbons such as but not limited to methylene dichloride, ethylene dichloride, chloroform and the like, or mixtures thereof.

10. The process as claimed in claim 1, wherein the isolation of compound of the formula (XVI) from reaction mass of the step (a) can also be performed by:
   i. isolating compound of formula (XVI) from the reaction mass;
   ii. drying the said compound of formula (XVI) obtained from step (i);
   iii. crystallizing the said dried compound of formula (XVI) using solvent to obtain purified compound of formula (XVI) as solid.

11. The process as claimed in claim 8 and 10, the solvent used for purification of compound of the formula (XVI) is selected from group consisting of esters selected from ethyl acetate, isopropyl acetate, and methyl acetate; aliphatic hydrocarbons selected from n-heptane, iso-octane, n-hexane, and cyclohexane; aromatic hydrocarbons selected from toluene, xylene, and naphthalene; ethers selected from diisopropyl ether, and diethyl ether; cyclic ethers selected from tetrahydrofuran, and 2-methyl tetrahydrofuran; alcohol selected from
methanol, ethanol, Isopropanol, and iso-butanol; ketone selected from acetone, and ethyl methyl ketone; nitriles, ionic liquids, halogenated aliphatic hydrocarbons selected from methylene dichloride, ethylene dichloride, and chloroform, or mixtures thereof.

12. The process as claimed in claim 1, wherein the isolation of compound of the formula (I) from reaction mass of step (d) comprises the steps of:
   i. extracting the ticagrelor compound of formula (I) from the reaction mass with solvent,
   ii. washing the organic layer of step (i) with water,
   iii. decolorizing the said organic layer of step (ii) with activated charcoal,
   iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),
   v. optionally, purifying the ticagrelor compound of formula (I) obtained in step (iv) by
      a. crystallization using solvent to obtain solid, or
      b. acid-base treatment to obtain solid, or
      c. crystallization in combination with acid-base treatment to obtain solid.

13. The process as claimed in claim 12, wherein the solvent used for extraction of ticagrelor compound of formula (I) comprises of esters selected from ethyl acetate, isopropyl acetate, and methyl acetate, aliphatic hydrocarbons selected from n-heptane, iso-octane, n-hexane, and cyclohexane, aromatic hydrocarbons selected from toluene, xylene, and naphthalene, ethers selected from di-isopropyl
ether, and diethyl ether, cyclic ethers selected from tetrahydrofuran, and 2-methyl tetrahydrofuran, alcohol selected from methanol, ethanol, isopropanol, and isooctanol, ketone selected from acetone, and ethyl methyl ketone, nitriles, ionic liquids, halogenated aliphatic hydrocarbons selected from methylene dichloride, ethylene dichloride, and chloroform, or mixtures thereof.

14. The process as claimed in claim 1, wherein the isolation of compound of the formula (I) from reaction mass of step (d) can also be performed by:
   i. isolating ticagrelor of formula (I) from the reaction mass;
   ii. drying the said ticagrelor of formula (I) obtained from step (i);
   iii. crystallizing the said dried ticagrelor compound of formula (I), using solvent to obtain purified compound of formula (I) as solid.

15. The process as claimed in claim 12 and 14, wherein the solvent used for purification of ticagrelor compound of formula (I) is selected from the group consisting of alkyl acetate selected from ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons selected from cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons selected from toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons selected from dichloromethane, chloroform, and ethylene dichloride; dialkylformamides selected from dimethyl formamide; ethers selected from methyl tertiary butyl ether, diisopropyl ether, di-ethyl ether, di-methyl ether, and methyl butyl ether; cyclic ethers selected from tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such selected from 2-methyl tetrahydrofuran; alcohols selected from methanol, ethanol, n-propanol, iso-propanol, n-
butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters; ketones selected from acetone, methyl ethyl ketone, and methyl isobutyl ketone; dialkylsulfoxides selected from dimethyl sulfoxide; dialkylacetamides selected from N,N,-dimethyl acetamide; nitrites selected from acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide and water or mixtures thereof.

16. The process as claimed in any of the preceding claims, wherein the process results less than about 0.20% of compound of formula IMP-1

\[\text{IMP-1}\]

17. A compound of formula (XVI);

\[\text{Formula (XVI)}\]

wherein said compound is crystalline in nature and is characterized by their X-ray diffraction (XRD) pattern as shown in figure 1.
**DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family annex.

**Date of the actual completion of the international search**

17 March 2014

**Date of mailing of the international search report**

03/04/2014

**Name and mailing address of the ISA/Office**

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Rudolf, Manfred
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