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[Continued on next page]

(54) Title: AN IMPROVED PROCESS FOR PREPARATION OF TICAGRELOR AND INTERMEDIATES THEREOF

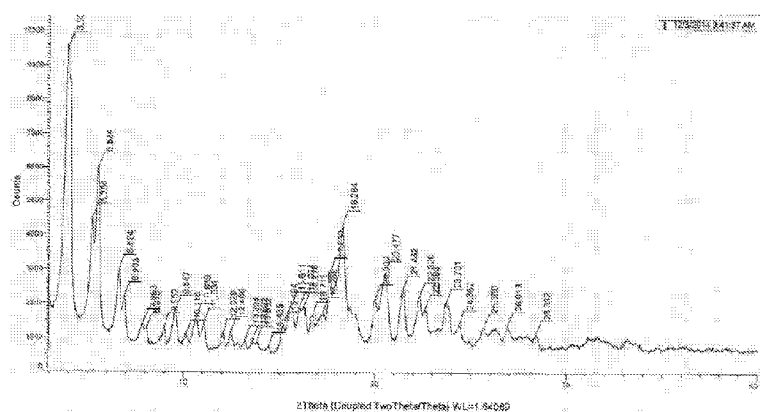


FIGURE-1

(57) Abstract: An improved, industrially viable, environment friendly and economically significant process for preparation of Ticagrelor is disclosed alongwith novel intermediates for the Ticagrelor synthesis.



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AN IMPROVED PROCESS FOR PREPARATION OF TICAGRELOR AND INTERMEDIATES THEREOF

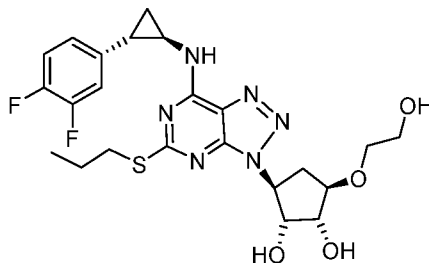
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FIELD OF INVENTION

The invention relates to an improved process for preparation of Ticagrelor. More particularly, the invention relates to an improved process which is industrially advantageous and economically significant for industrial scale preparation of Ticagrelor. The invention also provides novel intermediates for the synthesis of Ticagrelor.

BACKGROUND OF THE INVENTION

15 Ticagrelor is a platelet inhibitor used to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome and is chemically known as (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 represented by below formula-I.

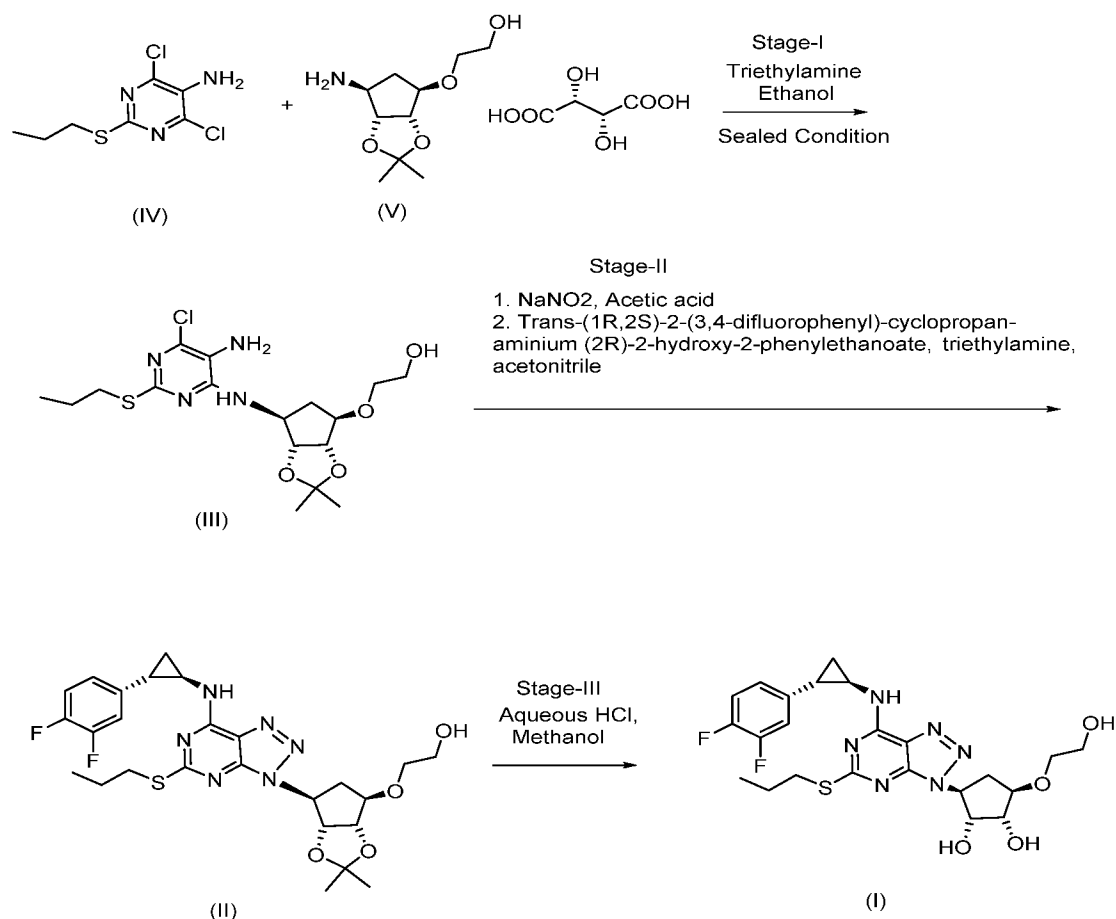


(I)

20

Ticagrelor was first disclosed in US Patent No. 6,525,060 (hereinafter referred as US'060). The process for the preparation of Ticagrelor in US'060 is lengthy and involves column chromatographic technique.

25 The Patent US 7,067,663 (hereinafter referred as US'663) discloses a process for the preparation of Ticagrelor as mentioned below:



The yield and purity of the intermediate resulted in Stage-I play a major role in the aforementioned process for the preparation of Ticagrelor.

- 5 To overcome this problem of the aforementioned process for the preparation of Ticagrelor, the Patent US 8,563,755 (hereinafter referred as US'755) employ oxalate salt or a dibenzoyl-L-tartrate salt of the (3aS,4R,6S,6aR)-6-(2-hydroxyethoxy)-2,2-dimethyltetrahydro-3aH-cyclopenta[d]-[1,3]dioxol-4-amine in the reaction of stage-I thereby enhancing the process efficiency and the purity of the resulted intermediate.

10

The PCT publication WO 20130150495 (hereinafter referred as WO'495) employ water, isoamyl alcohol and dimethyl sulfate as solvent for the reaction of stage-I to enhance purity of the Intermediate resulted in Stage-I.

- 15 The PCT publication WO 20140195861 (hereinafter referred as WO'861) discloses a process for purification of the intermediate resulted in Stage-I by the formation of an acid addition salt of this intermediate.

The PCT publication WO2014102830 (hereinafter referred as WO'830) discloses a purification process for the Intermediate resulted in Stage-I by ethyl acetate and n-heptane.

Further, the purification of the intermediates at each stage avoids carry over impurities at the last stage. There are no references in the prior arts for the crystallization of the Intermediate obtained in Stage-II. The Stage-III deprotection reaction to obtain Ticagrelor results in substantial racemization.

Hence there remains a need for an alternative improved process for the preparation of Ticagrelor that is commercially significant and friendly towards environment.

OBJECTS OF THE INVENTION

The primary object of the invention is to provide an improved process for preparation of Ticagrelor.

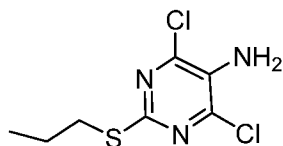
Another object of the invention is to provide an improved industrially viable, environment friendly and economically significant process for preparation of Ticagrelor.

A further object of the invention is to provide novel intermediates for the synthesis of Ticagrelor.

SUMMARY OF THE INVENTION

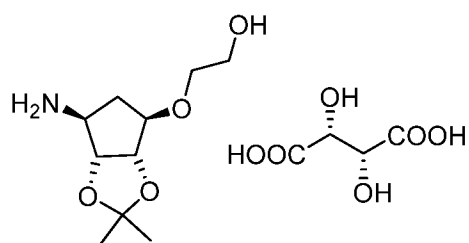
Accordingly, the present invention provides a process for the preparation of Ticagrelor comprising the steps of:

(a) reacting a compound-IV



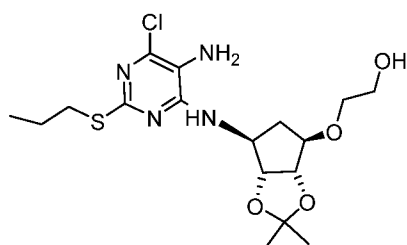
(IV)

with a compound-V



(V)

in presence of a base to obtain a compound-III

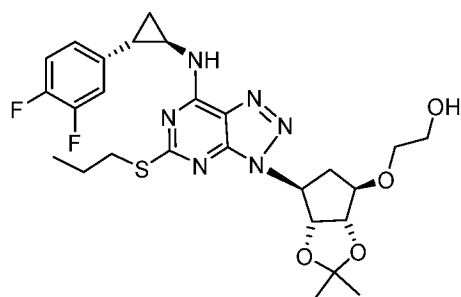


(III)

5 wherein, the reaction is carried out in absence of any solvent;

(b) treating the compound-III with sodium nitrite in acetic acid and then reacting the mass with trans-(1R,2S)-2-(3,4-Difluorophenyl)cyclopropanaminium (2R)-2-hydroxy-2-phenylethanoate to obtain a compound-II ;

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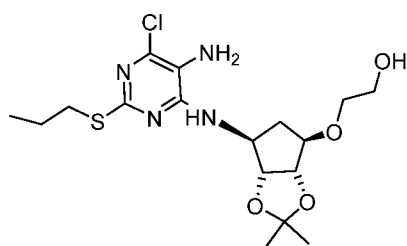


(II)

(c) deprotecting the compound-II in presence of pyridinium p-toluene sulphonate to obtain Ticagrelor.

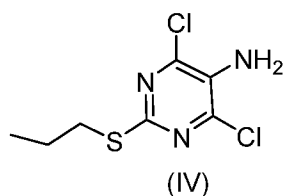
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In one aspect, the invention provides a process for the preparation of compound III



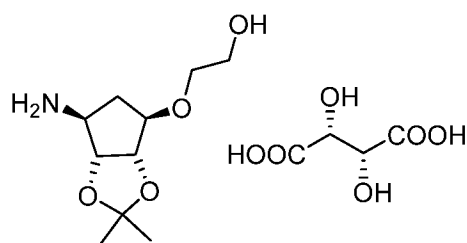
(III)

comprising the steps of reacting a compound-IV



(IV)

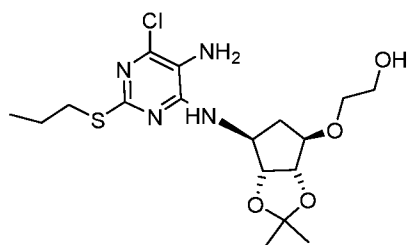
5 with a compound-V



(V)

in presence of a base, wherein the reaction is carried out in absence of any solvent.

10 In another aspect, the invention provides a process for purification of compound-III

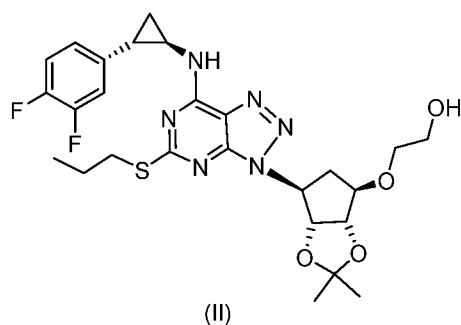


(III)

comprising the steps of :

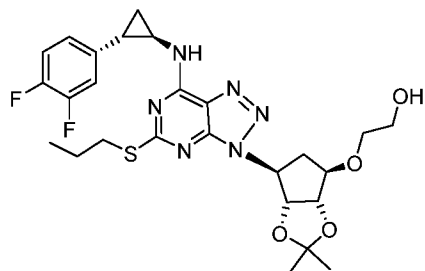
- 15 (i) dissolving the compound-III in a mixture of ethyl acetate and cyclohexane;
- (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
- (iii) filtering the solid.

In a further aspect, the invention provides a process for the preparation of Ticagrelor comprising the step of deprotecting a compound-II



5 in the presence of pyridinium p-toluene sulphonate.

In yet another aspect, the invention provides a process for purification of the compound-II



comprising the steps of:

- 10 (i) dissolving the compound-II in a solvent selected from the group of ether, aromatic hydrocarbon, saturated hydrocarbon or mixtures thereof;
- (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
- (iii) filtering the solid.

15

DESCRIPTION OF THE DRAWINGS

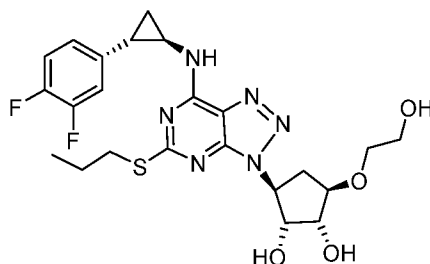
Figure-1: The PXRD of the 2-(((3aR,4S,6R,6aS)-6-((5-amino-6-chloro-2-(propylthio)pyrimidin-4-yl)amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-

20 yl)oxy)ethanol (III) resulted in Example-1(a)

Figure-2: The PXRD of the 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-dimethyl-tetrahydro-4H-cyclopenta[d][1,3]-dioxol-4-yl)oxy)-ethan-1-ol (II) resulted in Example-2

DETAILED DESCRIPTION OF THE INVENTION

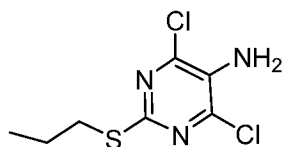
The present invention provides an improved process for the preparation of Ticagrelor represented by below formula-I



(I)

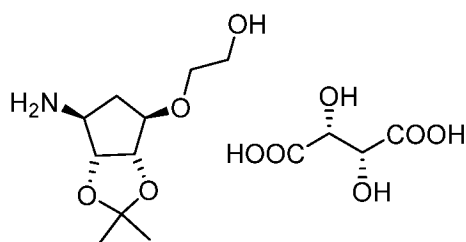
wherein, the process comprises the steps of:

(a) reacting a compound-IV



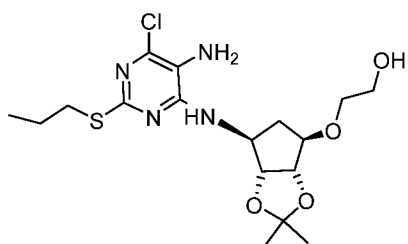
(IV)

with a compound-V



(V)

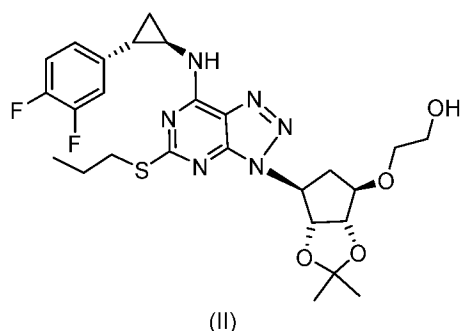
in presence of a base to obtain a compound-III



(III)

wherein the reaction is carried out in absence of any solvent;

(b) treating the compound-III with sodium nitrite in acetic acid and then reacting the mass with trans-(1R,2S)-2-(3,4-Difluorophenyl)cyclopropanaminium (2R)-2-hydroxy-2-phenylethanoate to obtain a compound-II ;



- 5 (c) deprotecting the compound-II in presence of pyridinium p-toluene sulphonate to obtain Ticagrelor.

The base employed in step-(a) of the above process may be an 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

10 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;

15 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,

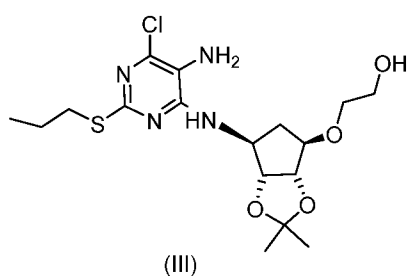
20 potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The solvent(s) used in step (b) and (c) of the above process is an organic solvent or its

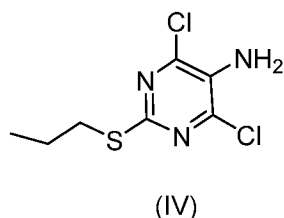
25 mixture thereof, said organic solvent is selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such 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.

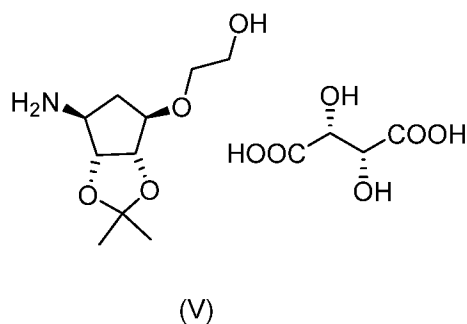
First embodiment of the present invention provides a process for preparation of a compound-III



comprising the step of reacting a compound-IV



with a compound-V

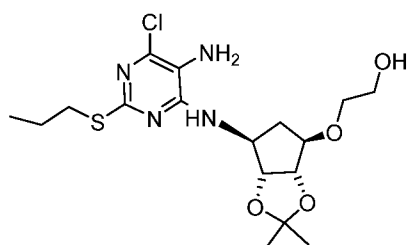


in presence of a base, wherein the reaction is carried out in absence of any solvent.

The base employed in the above embodiment may be an 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.

Second embodiment of the present invention provides a process for purification of the compound-III

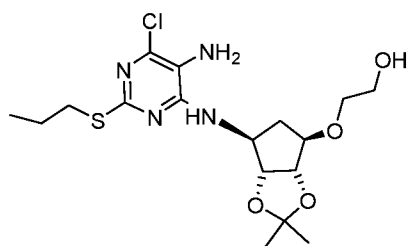


(III)

comprising the steps of:

- (i) dissolving the compound-III in a mixture of ethyl acetate and cyclohexane;
- (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
- (iii) filtering the solid.

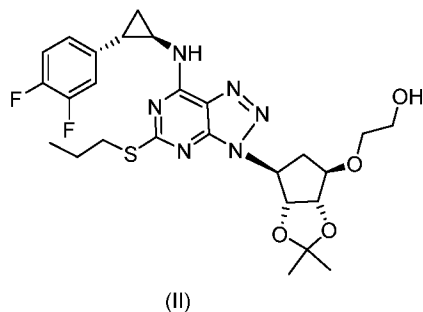
Third embodiment of the present invention provides a crystalline form of the compound-III



(III)

characterized by its X-ray diffraction (XRD) pattern as shown in figure 1.

Fourth embodiment of the present invention provides a process for purification of compound-II



5 comprising the steps of:

- (i) dissolving the compound-II in a solvent;
- (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
- 10 (iii) filtering the solid.

The solvent employed in the fourth embodiment above is selected from ethers, aromatic hydrocarbons, aliphatic hydrocarbons, preferably saturated aliphatic hydrocarbons or mixtures thereof.

15

Wherein, said ether(s) is selected from a group comprising of tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, tert-butyl methyl ether, diethyl ether, ethylene glycol dimethyl ether and diisopropyl ether.

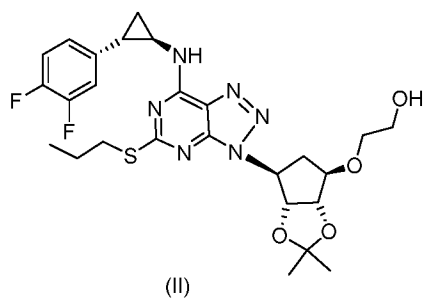
20 Said aliphatic hydrocarbon(s) is selected from a group comprising of octane, heptane, hexane and pentane.

Said aromatic hydrocarbon(s) is selected from a group comprising of toluene, xylenes and benzene.

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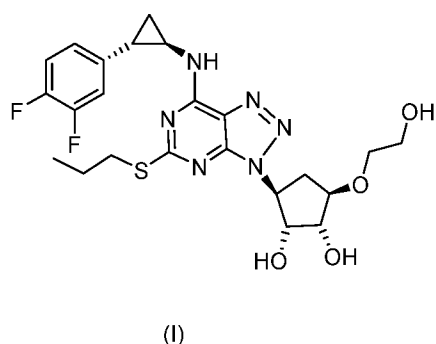
Preferably the solvent is diisopropyl ether or a mixture of toluene and heptane.

Fifth embodiment of the present invention provides a crystalline form of the compound-II

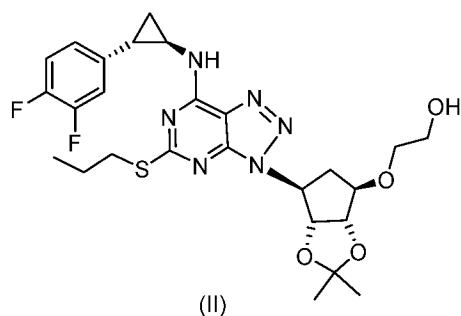


characterized by its X-ray diffraction (XRD) pattern as shown in figure 2

- 5 Sixth embodiment of the present invention provides a process for the preparation of Ticagrelor (I)



comprising the step of deprotecting a compound-II



- 10 in the presence of pyridinium p-toluene sulphonate.

The deprotection step in the sixth embodiment may be carried out in an organic solvent or the mixture thereof, said organic solvent is 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.

5

Seventh embodiment of the present invention provides a process for the purification of Ticagrelor comprising:

- (i) dissolving Ticagrelor in tetrahydrofuran;
- (ii) adding diisopropyl ether in the solution obtained in Step-(i);
- 10 (iii) maintaining the contents as obtained in step-(ii) till the formation of solid; and
- (iv) filtering the solid.

Eighth embodiment of the present invention provides a process for the purification of Ticagrelor comprising:

- 15 (i) dissolving Ticagrelor in a mixture of acetonitrile and isopropyl acetate;
- (ii) maintaining the contents as obtained in step-(i) till the formation of solid; and
- (iii) filtering the solid.

The present invention will now be further illustrated by the following examples, which are
20 not intended to be construed as limiting.

EXAMPLES

**Example-1: Preparation of 2-(((3aR,4S,6R,6aS)-6-((5-amino-6-chloro-2-(propylthio)-
25 pyrimidin-4-yl)amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-
yl)oxy)ethanol (III)**

To a mixture of diisopropylethylamine (1000 ml) and 4,6-dichloro-2-(propylthio)-pyrimidin-5-amine (200 gm), 2-(((3aR,4S,6R,6aS)-6-aminotetrahydro-2,2-dimethyl-4H-
30 cyclopenta[1,3]dioxol-4-yl]oxy)-ethanol.L-tartaric acid (340 gm) was added at 30°C and heated to a temperature of 128°C. The reaction mixture was maintained for 6 hours at 128°C. The progress of the reaction was monitored by HPLC. On completion of the reaction, the reaction mass was cooled to 75°C and distilled under vacuum to remove diisopropylethylamine. Methanol (300 ml) was added to the reaction mass at a temperature of

30°C followed by slowly addition of water (3000 ml) for 2 hours. The contents were then stirred for about 4 hours, filtered, washed with water (1200 ml) and dried. Yield: 1.5 gm

Example-1(a): Purification of 2-(((3aR,4S,6R,6aS)-6-((5-amino-6-chloro-2-(propylthio)-pyrimidin-4-yl)amino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)ethanol (III)

The solid resulted in example-1 (523 gm) was dissolved in ethylacetate (1000 ml) at a temperature of 30°C to get a clear solution. Activated carbon (40 gm) was added to the resulted solution and stirred for about 1 hour at 30°C. The contents were filtered through hyflo bed and the collected filtrate was distilled to obtain residue. The residue was mixed with a mixture of ethyl acetate (240 ml) and cyclohexane (2160 ml) at 50°C and stirred for about 1 hour to get a clear solution. The solution was then cooled to 30°C and stirred for about 1.5 hours at the same temperature. The solution was further cooled 10°C and maintained for about 2 hours. The resulted solid was filtered, washed with cyclohexane (400 ml) and dried in vacuum. Yield: 245 gm

Example-2: Preparation of 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-dimethyl-tetrahydro-4H-cyclopenta[d][1,3]-dioxol-4-yl)oxy)-ethan-1-ol (II)

Step-A: To a mixture of the compound obtained in example-1 (225 gm) and toluene (1125 ml), acetic acid (190 gm) was added at 30°C and cooled to a temperature of 3°C. Aqueous sodium nitrite solution was slowly added to the resultant mixture and maintained for about 1 hour at 3°C. The progress of the reaction was monitored by HPLC. On completion of the reaction, aqueous potassium carbonate solution was slowly added to the reaction mass and stirred at 5°C. The organic layer was separated from biphasic reaction mass and stored at 3°C.

Step-B: The compound (1R,2S)-2-(3,4-difluorophenyl)-cyclopropanaminium-(2R)-hydroxy (phenyl)ethanoate (188 gm) was added to aqueous potassium carbonate solution and stirred for about 30 minutes at 30°C. To this reaction mixture, the separated organic layer obtained in step-A and stirred for about 2 hours. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was allowed for layer separation and the organic layer was separated. The separated organic layer was washed with a mixture of

acetic acid, sodium chloride and water and with sodium chloride solution. The washed organic layer was distilled at about 53°C under vacuum to get a residue.

Step-C: The residue resulted in step-B was mixed with diisopropyl ether (2250 ml) and heated to 53°C. The contents were maintained for about 30 minutes at 53°C resulting in a solution. The obtained solution was cooled to 30°C, maintained for 3 hours and then the solution was further cooled to 3°C and maintained for 2 hours. The resultant solid was filtered, washed with a mixture of diisopropylether (45 ml) and cyclohexane (180 ml), washed with cyclohexane (225 ml) and dried under vacuum. Yield: 250 g

Example-2(b): Purification of 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-dimethyl-tetrahydro-4H-cyclopenta[d][1,3]-dioxol-4-yl)oxy)-ethan-1-ol (II) employing toluene and n-heptane

The residue resulted in Step-B of Example-2 (200 gm) was dissolved in toluene (400 ml) at 30°C to get a clear solution. The resultant clear solution was slowly added to n-heptane (2000 ml) and stirred for the 2 hours at 30°C till the formation of solid. The formed solid was filtered, washed with heptane (200 ml) and dried under vacuum. Yield: 139 gm

Example-3: Preparation of Ticagrelor (I)

A mixture of methanol (1000 ml), solid resulted in example-2 (200 gm), pyridinium p-toluene sulphonate (178 gm) and water (400 ml) was heated to 72°C and maintained for about 4 hours. The progress of the reaction was monitored by HPLC. On completion of the reaction, the reaction mixture was cooled to 30°C followed by the addition of water (1600 ml). The resultant reaction mass was maintained for about 4 hours. The solid thus obtained was filtered, washed with a mixture of methanol (133 ml) and water (266 ml), washed with water (400 ml) and dried. Yield: 350 gm

Example-4: Purification of Ticagrelor (I)

Crude Ticagrelor (160 gm) was dissolved in tetrahydrofuran (800 ml) at 30°C. Activated carbon (32 gm) was added to the obtained solution and stirred for about 45 minutes at 30°C.

The resulted contents were filtered through hyflo bed and the filtrate was distilled under vacuum at 42°C to get a residue. The residue was mixed with tetrahydrofuran (480 ml) and stirred for about 15 minutes to get a clear solution. To this clear solution diisopropyl ether (1120 ml) was slowly added and maintained the contents for about 2.5 hours at 30°C. The contents were then cooled to 12°C and maintained for about 1.5 hours at 12°C. The resultant solid was filtered, washed with a mixture of tetrahydrofuran (48 ml) and diisopropyl ether (112 ml), then washed with chilled diisopropyl ether (160 ml) and dried under vacuum. Yield: 133 gm

10 **Example-5: Purification of Ticagrelor (I)**

Crude Ticagrelor (130 gm) was mixed with isopropyl acetate (832 ml) and acetonitrile (468 ml). The contents were then heated to 53°C and maintained for about 45 minutes. The resulted contents are cooled to 30°C and stirred for about 3.5 hours till the formation of solid. Then the contents were cooled 12°C and stirred for about 2.5 hours. The resulted solid was filtered, washed with a mixture of isopropyl acetate (83 ml) and acetonitrile (46 ml), washed with cyclohexane (130 ml) and dried. Yield: 116 gm

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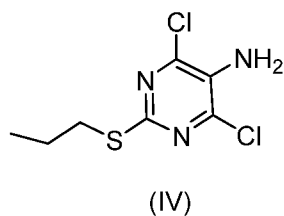
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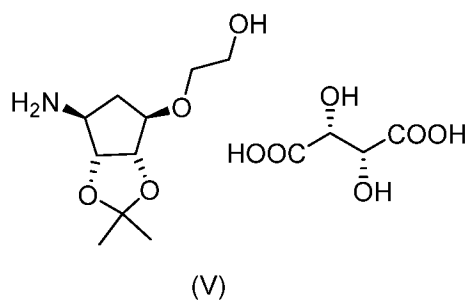
We Claim:

1. A process for the preparation of Ticagrelor comprising the steps of:

5 (a) reacting a compound-IV

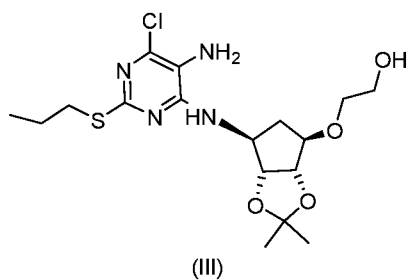


with a compound-V



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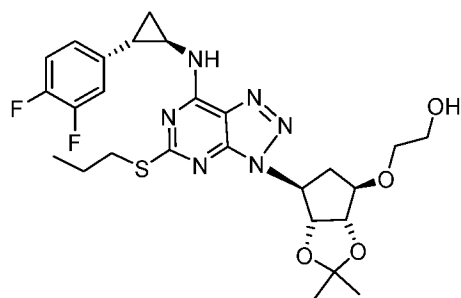
in presence of a base to obtain a compound-III



wherein the reaction is carried out in absence of any solvent;

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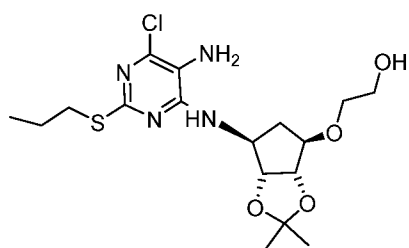
(b) treating the compound-III with sodium nitrite in acetic acid and then reacting the mass with trans-(1R,2S)-2-(3,4-Difluorophenyl)cyclopropanaminium (2R)-2-hydroxy-2-phenylethanoate to obtain a compound-II ;



(II)

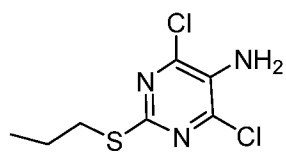
(c) deprotecting the compound-II in presence of pyridinium p-toluene sulphonate to obtain Ticagrelor.

5 2. A process for the preparation of a compound III



(III)

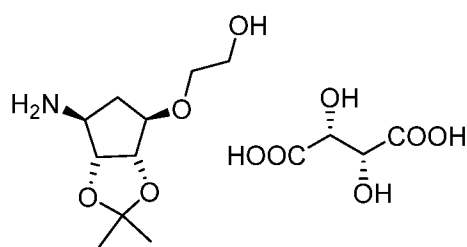
comprising the step of reacting a compound-IV



(IV)

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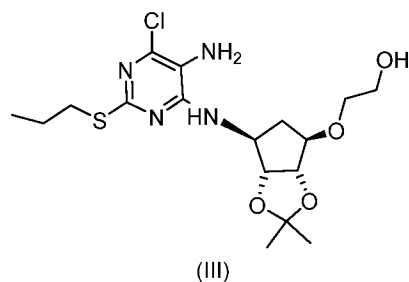
with a compound-V



(V)

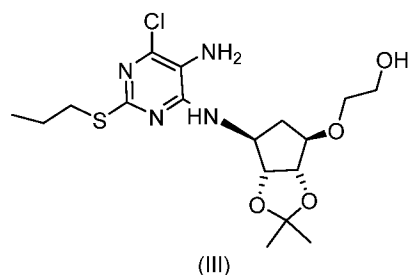
15 in presence of a base, wherein the reaction is carried out in absence of any solvent.

3. A crystalline form of compound-III



5 characterized by the X-ray diffraction (XRD) pattern shown in figure 1.

4. A Process for the purification of compound-III



10 comprising the steps of:

- (i) dissolving the compound-III in a mixture of ethyl acetate and cyclohexane;
- (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
- (iii) filtering the solid.

15 5. A process for the purification of Ticagrelor comprising:

- (i) dissolving Ticagrelor in tetrahydrofuran;
- (ii) adding diisopropyl ether in the solution obtained in Step-(i);
- (iii) maintaining the contents as obtained in step-(ii) till the formation of solid; and
- (iv) filtering the solid.

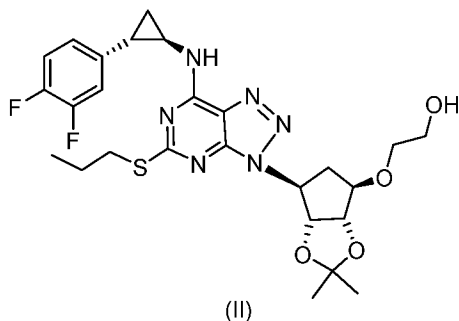
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6. A process for the purification of Ticagrelor comprising:

- (i) dissolving Ticagrelor in a mixture of acetonitrile and isopropyl acetate;
- (ii) maintaining the contents as obtained in step-(i) till the formation of solid; and
- (iii) filtering the solid.

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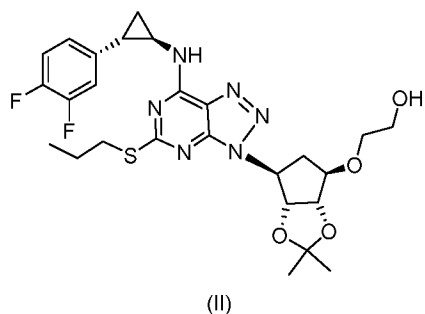
7. A process for the preparation of Ticagrelor comprising the step of deprotecting a compound-II



in the presence of pyridinium p-toluene sulphonate.

5

8. A Process for the purification of compound-II



10 comprising the steps of:

- (iv) dissolving the compound-II in a solvent;
- (v) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
- (vi) filtering the solid.

15

9. The process as claimed in claim 8, wherein the solvent is selected from the group comprising of ether, aromatic hydrocarbon, saturated hydrocarbon or mixtures thereof.

10. The Process as claimed in claim 8, wherein the purification of the compound-II comprises the steps of:

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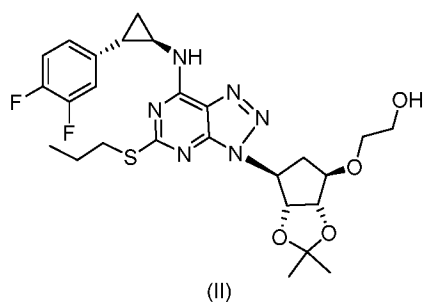
- (i) dissolving the compound-II in diisopropyl ether;
- (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and

(iii) filtering the solid.

11. The Process as claimed in claim 8, wherein the purification of the compound-II comprises the steps of:

- 5 (i) dissolving the compound-II in toluene and heptane;
 (ii) maintaining the contents of the solution obtained in step-(i) till the formation of solid; and
 (iii) filtering the solid.

10 12. A crystalline form of compound-II



characterized by the X-ray diffraction (XRD) pattern as shown in figure 2.

15

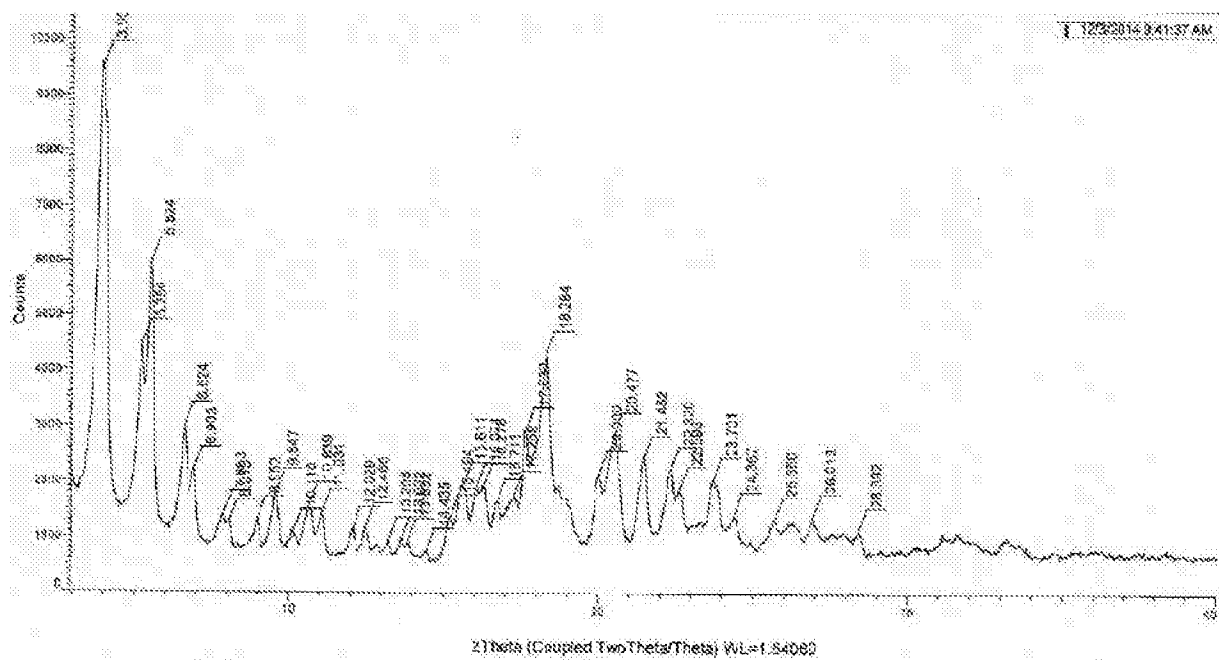


FIGURE-1

