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(54) Title: PROCESS FOR THE PREPARATION OF CLOPIDOGREL AND SALTS THEREOF

(57) Abstract: The present invention relates to an improved process for the preparation of Clopidogrel, and pharmaceutical acceptable salts thereof, and in particular to a cost-effective process for large scale production of highly pure Clopidogrel besylate.



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PROCESS FOR THE PREPARATION OF CLOPIDOGREL AND SALTS THEREOF

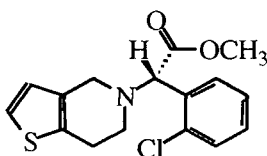
TECHNICAL FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of thieno[3, 2-c]pyridine derivatives, such as Clopidogrel and pharmaceutically acceptable salts thereof and in particular to a cost-effective process for large scale production of thieno[3, 2-c]pyridine derivatives, such as optically pure Clopidogrel besylate and pharmaceutical preparations containing said compounds.

BACKGROUND OF THE INVENTION

Thieno[3, 2-c]pyridines are a class of adenosine diphosphate (ADP) receptor inhibitors used as anti-coagulants in the pharmaceutical industry, such as Clopidogrel.

Clopidogrel is chemically designated as methyl (S)-2-(2-chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-c] pyridin-5(4H)-yl) acetate and is presented by the chemical structure of Formula I.



Formula I

Clopidogrel is a known anti-thrombotic agent with therapeutic activity of preventing platelet aggregation and is useful in reducing the frequency of thrombotic events, such as strokes or ischaemic attacks, in patients with established vascular disease. Clopidogrel is a more effective and well-tolerated platelet aggregation inhibiting agent as compared to other antiplatelet agents, such as Aspirin and Ticlopidine.

The molecule of Formula I has one optically active center. Clopidogrel is used in the form of its dextro-rotary enantiomer, also known as the (S)-enantiomer. The levo-rotary enantiomer, also known as the (R)-enantiomer, is not only inactive but also less tolerated and therefore, a cost-effective process for the manufacture of Clopidogrel in the form of the single dextro-rotary enantiomer is needed.

Various methods are already known for the preparation of Clopidogrel or salts thereof due to its useful properties. Prior art processes for the preparation of Clopidogrel or salts thereof present disadvantages of non-satisfactory yield of the product. Moreover, many of these prior art processes utilize hazardous material and large amount of organic solvents, which are not suitable for large scale industrial production.

Clopidogrel and its salts and methods for the preparation thereof were first disclosed in EP-B-0 099 802, wherein Clopidogrel is obtained in racemic form by reacting methyl 2-halo-o-chlorophenyl acetate with 4, 5, 6, 7-tetrahydrothieno[3, 2-c]pyridine.

EP-B-0 281 459 discloses a process for the preparation of the desired dextro-rotary enantiomer by fractional crystallization using levo-rotary camphor-10-sulfonic acid. However, this method

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utilizes DMF as reaction media, which is expensive and highly toxic, and the yield of the product is low.

WO-A-2006/137628 discloses a process for the preparation of clopidogrel, which comprises preparation of ($\pm$)-2-(2-chlorophenyl)-6, 7-dihydro-4H-thieno[3, 2-c]pyridine-5-acetic acid by the reaction of 4,5,6,7-tetrahydrothieno[3, 2-c]pyridine hydrochloride and 2-bromo-(2-chlorophenyl)acetic acid and optical resolution of the resulted carboxylic acid intermediate using optically active amines. According to this process, the formation of the (+)-2-(2-chlorophenyl)-6, 7-dihydro-4H-thieno[3, 2-c]pyridine-5-acetic acid ammonium salt requires long period of reaction time to be completed.

WO-A-2008/018779 discloses a process for the preparation Clopidogrel comprising optically resolving 2-(2-chlorophenyl)-6, 7-dihydro-4H-thieno[3, 2-c]pyridine-5-acetic acid intermediate using (+)-cinchonine and recycling the unwanted levo-rotary enantiomer by racemization. According to this document, in order to isolate the desired compound from the reaction mixture solvent extraction is carried out several times using a large amount of organic solvents.

Although each of the above patents represents an attempt to overcome the use of costly and hazardous material, there still exists a need for a cost-effective process for large scale production which provides higher yield with improved quality.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an improved process for the preparation of Clopidogrel or pharmaceutically acceptable salts thereof, which overcomes the deficiencies of the prior art and results to a cost effective production without sacrificing the yield and quality of the product.

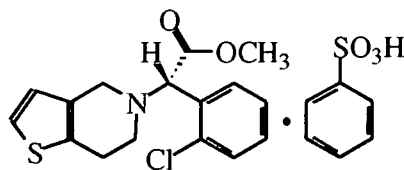
Another object of the present invention is to provide an improved method for the preparation of Clopidogrel or salts thereof or its derivatives by selecting the appropriate reactants, catalysts, solvent systems and conditions used during the organic reactions, so that the purity and yield of the reaction are increased and the presence of any contaminants and formed by-products is minimized.

Further object of the present invention is to provide an improved method for the preparation of Clopidogrel or salts thereof, or its derivatives, by reducing the reaction time and using milder and safer reaction conditions that helps protect the environment and the personnel.

Yet another object of the present invention is to provide an improved method for the preparation of Clopidogrel or salts thereof, or its derivatives by using novel intermediate which plays an important role in improving the chemical and optical purity of the product.

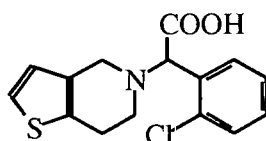
In accordance with the above objects of the present invention, a process for the preparation of Clopidogrel or pharmaceutically acceptable salts thereof, or its derivatives such as Clopidogrel besylate of Formula II, is provided comprising the following steps:

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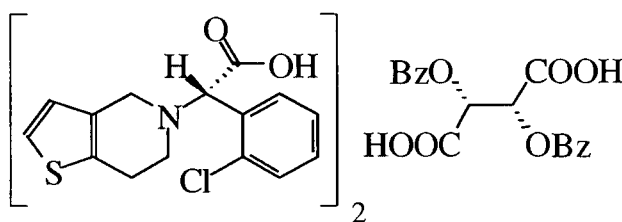
Formula II

- (i) providing 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid of Formula III by condensation of 4, 5, 6, 7-tetrahydrothieno[3, 2-c]pyridine hydrochloride with 2-bromo-2-(2-chlorophenyl)acetic acid in water;



Formula III

- (ii) optical resolution of the obtained 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid of Formula III, using di-O-benzyl-L-tartaric acid and obtaining the dextro-rotary enantiomer (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV;



Formula IV

- (iii) conversion of the obtained (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV, into clopidogrel or pharmaceutically acceptable salts thereof, such as Clopidogrel besylate of Formula II; and
- (iv) de-salting the remaining material from the optical resolution process of step (ii) and racemization to obtain compound of Formula III with chiral purity less than 60%.

According to another embodiment of the present invention, the use of compound of Formula IV is provided for the preparation of clopidogrel or pharmaceutically acceptable salts thereof. Preferred embodiments of the present invention are set out in dependent claims 2 to 14.

Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

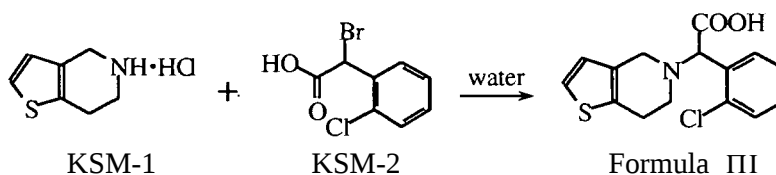
The present invention relates to an improved process for the preparation of Clopidogrel and pharmaceutically acceptable salts thereof or its derivatives, which is characterized by

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substantially shorter reaction time, milder and safer reaction conditions, without sacrificing the yield and quality of the product and low cost of reactants and reagents.

According to the present invention, the process for the preparation of Clopidogrel and pharmaceutically acceptable salts thereof, or its derivatives comprises the following stages:

Stage-I: Preparation of 2-(2-chlorophenyl)-2-(6, 7-dihydrothieno[3, 2-c]pyridine-5(4H)-yl)acetic acid of Formula III using water as reaction media.



Stage I comprises a condensation reaction of 4, 5, 6, 7-tetrahydrothieno[3, 2-c]pyridine hydrochloride (KSM-1) and 2-bromo-2-(2-chlorophenyl)acetic acid (KSM-2), wherein said reaction is carried out in water at room temperature and in absence of any organic solvent. The product is isolated from the reaction mixture simply by adjusting the pH value and precipitation. The average yield of this reaction is 97%.

Three different batches of the obtained compound of Formula III have been analyzed and Table 1 summarizes the content of impurities and the purity of the product obtained according to the process of Stage-I of the present invention.

Table 1: Impurities content and purity of the compound of Formula III obtained according to the process of Stage-I

	Batch 1 (%)	Batch 2(%)	Batch 3(%)
Imp.1	0.025	0.031	0.031
Imp.2	0.018	0.039	0.056
Imp.3	N.D.	N.D.	N.D.
Imp.4	0.006	0.007	0.007
Imp.5	0.136	0.147	0.106
Imp.6	0.017	N.D.	0.026
Imp.8	0.042	0.038	0.059
Imp.9	0.032	0.063	0.034
Purity	99.56	99.41	99.50

Wherein, imp. 1 is 2-(2-chlorophenyl)acetic acid; imp. 2 is 2-(2-chlorophenyl)-2-hydroxyacetic acid; imp. 3 is 2-(thiophen-2-yl)ethanamine; imp. 4 is 2-bromo-2-(2-chlorophenyl) acetic acid; imp. 5 is 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride; imp. 6 is 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride; imp. 8 is 5, 5-Dimethyl hydantoin; and imp. 9 is 2-(2-chlorophenyl)-2-(2-(thiophen-2-yl)ethylamino) acetic acid.

Data is obtained by high-performance liquid chromatography (HPLC) measurements, wherein the conditions of the HPLC measurements are the following:

Column: BDS-Hypersils C8 (50 x 4.6mm, 5um)

Mobile phase: A) buffer (2.7g KH₂PO₄ in 1L of water, pH = 5.0); B) acetonitrile

Flow rate: 0.8 mL/min

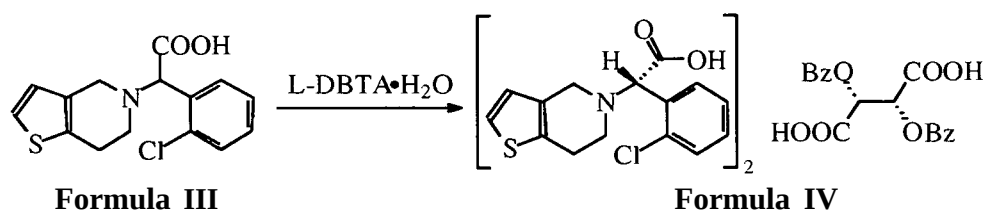
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Detector: UV set at 220nm

Temperature: 30°C

5 Run time: 80 min

10 **Stage-II:** Optical resolution of 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4 *H*)-yl)acetic acid of Formula III using di-O-benzyl-L-tartaric acid to obtain the dextro-rotary enantiomer represented by Formula IV.



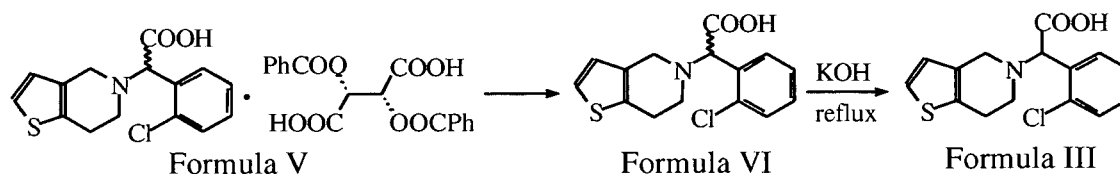
15 According to the present invention an improved process for optical resolution of 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4 *H*)-yl)acetic acid of Formula III using L-di-O-benzoyl tartaric acid monohydrate is provided. The resolution is carried out in ethanol media. The obtained product is isolated from the reaction mixture by precipitation. Yield of this process is in the range of 53.2% to 59.7%, and the chemical purity of the obtained product is not less than 99.5%.

20 The process of optical resolution of 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-yl)acetic acid of Formula III, according to the present invention is significantly more efficient, as the reaction is completed in a much shorter period of time than the prior art processes by using less costly and less hazardous materials.

25 Further, the process of the present invention provides product in higher yield with higher purity.

In addition, the process according to the present invention also comprises a step of recycling the unwanted enantiomer (compound of Formula V), to compound of Formula III by racemization, as depicted in Scheme below.

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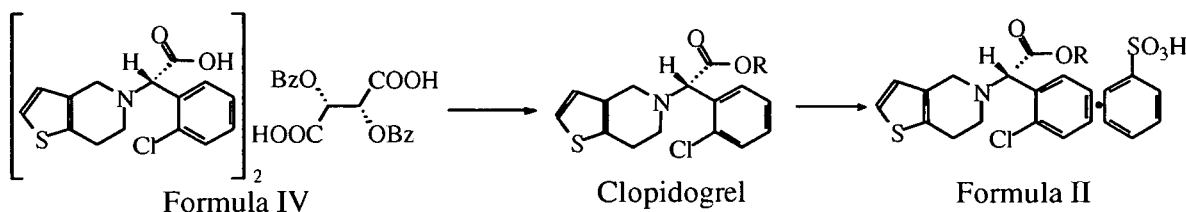


35 The mother liquid from the optical resolution step, which comprises compound of Formula V, is recovered and de-salted. The de-salting procedure is carried out by extraction using ethyl acetate and water under acidic conditions. The organic layer containing mainly L-di-O-benzoyl tartaric acid is discarded. The aqueous layer containing compound of Formula VI is racemized using a strong inorganic base, such as KOH. The racemization is carried out in a high pressure reactor at a temperature above the boiling point of water, which is used as the reaction media. Chiral purity is the percentage area of the S-enantiomer peak in the HPLC chromatogram. The reaction according to said process is completed in about 24 hours.

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Stage-III: Conversion of the (5)-(o-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV into clopidogrel or pharmaceutically acceptable salts thereof, such as Clopidogrel besylate of Formula II.



According to Stage III of the process of the present invention, the (S)-(o-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV is de-salted and esterified with methanol to obtain clopidogrel. The de-salting process is carried out by participation between ethyl acetate and water under acidic conditions. The aqueous layer containing (5)-(o-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid is back extracted using ethyl acetate at pH between 3.5 and 4.0. The (5)-(o-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid thus obtained is dissolved in methanol and treated with thionyl chloride under argon atmosphere and is subjected to further work-up to obtain the highly pure Clopidogrel.

The Clopidogrel thus obtained is converted into the pharmaceutically acceptable salt thereof, such as Clopidogrel besylate of Formula II. The salt is formed in a mixture of isopropanol and *tert-butyl* methyl ether. Recrystallization of Clopidogrel besylate in the same solvent pair provides final product with chemical purity >99.5% and chiral purity >99.7%

The process of the present invention will be demonstrated in more details with reference to the following examples, which are provided by way of illustration only and should not be construed as a limit to the scope of the reaction in any manner.

Example 1: Preparation of 2-(2-chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-c] pyridin-5(4H)-yl)acetic acid

600 ml de-mineralised water and 100 g 4,5,6,7-tetrahydrothieno [3,2-c]pyridine hydrochloride (0.57 mol) are charged into a 2L 3-neck round-bottom flask at 25-35°C under stirring. 182 ml aqueous NaOH solution (50% w/v, 2.28 mol) are added slowly and the reaction mass is stirred for 5-15 minutes at a temperature of about 25 to 35°C. The reaction mixture is cooled to below 20°C, 135g of 2-bromo-2-(2-chlorophenyl) acetic acid are added slowly, while maintaining the temperature below 20°C (external cooling is required due to the addition of the acid, which is exothermic). The reaction mixture is stirred for 4-6 hours, keeping the temperature at 22-27°C. The 135g of 2-bromo-2-(2-chlorophenyl) acetic acid have been calculated based on pure actual material after LOD and purity by HPLC correction, wherein the actual load of this material should be calculated as: Quantity for Loading = 135 x [1 + (100-96.4) % + 5.5%] = 147.3 g

After the completion of the reaction, 50 ml ethyl acetate and 200 ml de-mineralised water are added to the reaction mixture, 90-100 ml HCl (37%, w/v) are added dropwise over a period of 30-60 minutes under stirring till the pH is within the range of 3.5 - 4.5, while maintaining the temperature from about 20 to 30°C. The mixture is stirred for additional 90-180 minutes at

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temperature from about 20 to 30°C. The mass is filtered under reduced pressure and the surface of the glassware is rinsed with 100 ml de-mineralised water. The wet cake is suck-dried for 45 to 60 minutes and transferred into a 2L round-bottom flask, 300ml de-mineralised water are added and the mixture is stirred for 60 to 120 minutes. The mass is filtered under reduced pressure. The solid is washed with 100 ml de-mineralised water and dried in the vacuum to provide 165 to 185g of 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl) acetic acid.

Example 2: Preparation of (S)-2-(2-chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-c] pyridin-5(4H)-yl) acetic acid L-DBTA salt

800 ml ethanol (96%, v/v) and 100 g 2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetic acid (0.32mol) are charged into a 2L 3-neck round-bottom flask under stirring. The reaction mass is heated to temperature from about 65 to 75°C. 42.8 g L-Dibenzoyl tartaric acid monohydrate (0.1lmol) is added under stirring at temperature from about 65 to 75°C. The reaction mass is stirred at temperature from about 65 to 75°C for 10-20 minutes. If necessary, the mass is filtered while hot under vacuum to remove the insoluble particles.

The clear solution is heated under stirring at temperature from about 65 to 75°C. Then it is gradually cooled to temperature from about 22 to 27°C over a period of 120 to 180 minutes and stirring is continued for additional 120 to 180 minutes at this temperature while precipitation starts at about 38 to 45°C. The precipitated solid is filtered in Buchner funnel under reduced pressure and sucked dry in the vacuum pump for 45 to 60 minutes. The wet cake is transferred into a 1L round-bottom flask and 300 ml ethanol (96%, v/v) is added.

The mixture is stirred for 60 to 120 minutes at temperature from about 22 to 27°C then filtered in Buchner funnel under reduced pressure. The wet cake is dried under vacuum to provide 57 to 64g (S)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetic acid L-DBTA salt.

Example 3: Preparation of (S)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetic acid besylate crude

100g (S)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid L-DBTA salt are charged into a 3-neck 2L round-bottom flask. 550 ml ethyl acetate and 550 ml de-mineralised water are added into the mixture. Then 100ml HCl (37%, w/v) are added slowly under stirring. The aqueous layer is collected and mixed with 690 ml ethyl acetate. 94 ml aqueous NaOH solution (50%, w/v) is added under stirring until pH becomes 3.5 to 4.0. The aqueous layer is back extracted with 690 ml ethyl acetate and repeat with 450 ml ethyl acetate. The three organic layers are combined and dehydrated over 40 g sodium sulfate anhydrous. The solid is filtered off under vacuum and the filtrate is evaporated to dryness. The residue is dissolved in 170 ml methanol and the solvent is evaporated to dryness. The residue is dissolved in 95 ml methanol and the solvent is evaporated again to dryness. This residue is dissolved in 500 ml methanol and Argon atmosphere is applied. 45 ml thionyl chloride (SOCl₂) are added at temperature from about 20 to 25°C. The mixture is heated at temperature from about 55 to 60°C for 8 hours under stirring. The progress of the reaction is monitored by in process high-performance liquid chromatography (HPLC).

When the reaction is completed, the reaction mixture is evaporated to dryness. The yellow oily residue is dissolved in 100 ml toluene and the solvent is evaporated to dryness. 135 ml aqueous NaOH solution (10%, w/v) is added to the residue, followed by 330 ml de-mineralised water and

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1000 ml toluene. The pH of the aqueous layer is adjusted to pH 6.5 to 7.5. The organic layer is collected and back washed with 165 ml de-mineralised water and then 165 ml brine.

The organic layer is dried over 30g sodium sulfate anhydrous. The solid is filtered off and the filtrate is evaporated to dryness.

The light brown oil is dissolved in 30 ml isopropanol and the solvent is evaporated to dryness. 180 ml isopropanol are added to the light brown oil. The mixture is heated to a temperature of about 35 to 40°C and then 22.5 g benzenesulfonic acid are added and heated further to temperature from about 50 to 55°C. After benzenesulfonic acid is completely dissolved, 40 ml *tert*-butylmethyl ether are added and the mixture is stirred at temperature from about 50 to 55°C until a clear solution is formed. Then the mixture is cooled gradually to temperature about 25 to 30°C. At this temperature 50 mg (S)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetic acid besylate pure are added as seed and the mixture is stirred at this temperature for 4 hours. The mixture is filtered under reduced pressure. The wet cake thus obtained is spray-washed with 20 ml $\frac{1}{2}$ *tert*-butylmethyl ether and suck-dried for an hour to obtain 48 to 56 g white powder.

Example 4: Preparation of (S)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetic acid besylate pure

100g crude Clopidogrel besylate are charged into a 1L 3-neck round-bottom flask and 300 ml isopropanol are added. The mixture is heated to temperature about 55 to 60°C under stirring until a clear solution is formed. This solution is filtered while hot and reheated to temperature of about 55 to 60°C. Then 100 ml *tert*-butyl methyl ether is added and the mixture is stirred until a clear solution is formed. The mixture is cooled gradually to temperature from about 25 to 30°C over 50 to 60 minutes, and stirred at this temperature for 3 hours. The mixture is filtered under vacuum and the wet cake is spray-washed with 100 ml *tert*-butyl methyl ether. The product is suck-dried to obtain 85 to 95g of the title compound as white powder.

Example 5: Racemisation of the (R)-2-(2-chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-c] pyridin-5(4H)-yl) acetic acidL-DBTA salt

The solvent of the mother liquid obtained according to the resolution process as described in Example 2 is evaporated under reduced pressure at temperature about 40°C till dry. To the foam residue, which contains about 60g of levo-rotary enantiomer of the carboxylic acid intermediate for Formula III, 540ml water and 540 ml ethyl acetate are charged under stirring. About 4 to 6ml HCl solution (37% w/v) are added slowly till pH value equals to about 1. An additional quantity of 12 to 15 ml HCl (37%, w/v) is added to dissolve the gummy solids in the biphasic mass. The mixture is stirred for 15 to 30 minutes. Then the layers are allowed to settle and separate. The organic layers containing mainly L-Dibenzoyl tartaric acid are discarded.

The aqueous layer is concentrated (about 324 ml of water is removed). About 32g potassium hydroxide (KOH) are added at temperature from about 20 to 30°C till the pH value is within 13 to 14. The reaction mixture is heated in a 2-L-glass high pressure reactor at oil bath temperature 130°C for about 25 to 35 hours, till chiral purity becomes about 50 to 55%. Upon completion of the racemization, the reaction mixture is cooled to temperature from about 20 to 30°C. 25 ml isopropanol are charged under stirring. About 20 ml HCl (37%, w/v) are added dropwise till the pH value is about 3.5 to 4.5, while the temperature is maintained from about 20 to 30°C (use external cooling if required), and stirring is continued for about 60 to 90 minutes. The

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5 precipitated solid is filtered under reduced pressure and suck-dried in the vacuum pump for 30-45 minutes. The wet cake is transferred into a 2L round-bottom flask and 400 ml de-mineralised water is charged. The mixture is stirred for 60 to 90 min at temperature from about 25 to 30°C.

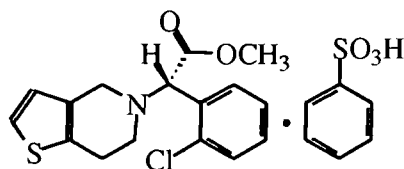
10 Then the mixture is filtered in Buchner funnel under reduced pressure. The wet cake is suck-dried for 45-60 minutes. The wet cake is again transferred into a 2L round-bottom flask and 200 ml isopropanol are charged. The mixture is heated under stirring at temperature from about 50 to 60°C for 30 to 60 minutes. The mass is cooled to temperature from about 10 to 15°C over a period of 120 to 180 minutes. The mixture is filtered under reduced pressure and the wet cake is suck-dried in the vacuum pump for 30 to 45 minutes. 30 to 40g 2-(2-chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-*c*] pyridin-5(4*H*)-yl) acetic acid are obtained.

15 The present invention describes a large-scale manufacturing process for the preparation of Clopidogrel, and pharmaceutically acceptable salts thereof, in particular Clopidogrel besylate with improved quality at relative low production cost compared to the known prior art processes, wherein the reactions are carried out in low-toxic media, such as water and ethanol, with the average yield of 47.2% without recycling and 60% with recycling.

20 It should be noted that while the present invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made in the invention without departing from the spirit and scope thereof, as defined in the appended claims.

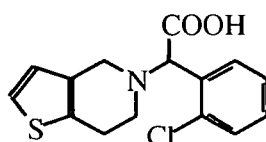
CLAIMS

1. A process for the preparation of clopidogrel or pharmaceutically acceptable salts thereof, such as Clopidogrel besylate of Formula II, which comprises



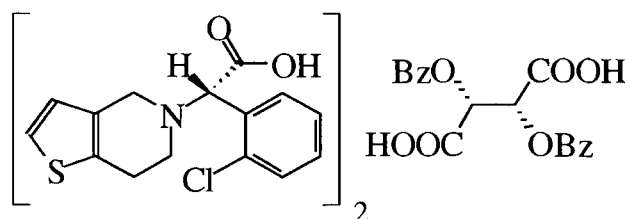
Formula II

- (i) providing 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4H)-yl)acetic acid of Formula III by condensation of 4, 5, 6, 7-tetrahydrothieno[3,2-c]pyridine hydrochloride with 2-bromo-2-(2-chlorophenyl)acetic acid in water;



Formula III

- (ii) optical resolution of the obtained 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4H)-yl)acetic acid of Formula III, using di-O-benzyl-L-tartaric acid and obtaining the dextro-rotary enantiomer (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4H)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV;



Formula IV

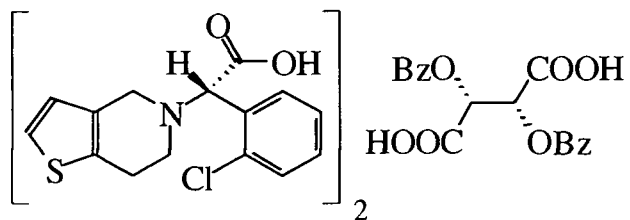
- (iii) conversion of the obtained (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4H)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV, into clopidogrel or pharmaceutically acceptable salts thereof, such as Clopidogrel besylate of Formula II; and

- (iv) de-salting the remaining material from the optical resolution process of step (ii) and racemization to obtain compound of Formula III with chiral purity less than 60%.

2. The process according to claim 1, wherein the condensation of 4, 5, 6, 7-tetrahydrothieno[3, 2-c]pyridine hydrochloride with 2-bromo-2-(2-chlorophenyl)acetic acid of step (i) is carried out in water under basic conditions.
5
3. The process according to claim 1, wherein the condensation of 4, 5, 6, 7-tetrahydrothieno[3, 2-c]pyridine hydrochloride with 2-bromo-2-(2-chlorophenyl)acetic acid of step (i) is carried out in water under basic conditions at room temperature, preferably from about 22°C to 27°C.
10
4. The process according to claim 1, wherein the 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid of Formula III obtained from step (i) is obtained by adjusting the pH value of the reaction mass and isolating the precipitated material.
15
5. The process according to claim 1, wherein the optical resolution process of step (ii) is carried out in ethanol media.
6. The process according to claim 1, wherein the (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV of step (ii) is obtained by fractional crystallization.
20
7. The process according to claim 1, wherein the conversion of (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid L-di-O-benzoyl tartaric acid salt of Formula IV of step (iii) is achieved through esterification.
25
8. The process according to claim 7, wherein the esterification is performed by dissolving the compound of (S)- 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3, 2-c]pyridine-5(4*H*)-yl)acetic acid in methanol and thionyl chloride is added thereto.
30
9. The process according to claim 8, wherein the esterification reaction is carried out under argon atmosphere.
10. The process according to claim 1, wherein the Clopidogrel obtained in step (iii) is converted into Clopidogrel besylate of Formula II by treating Clopidogrel with benzensulfonic acid.
35
11. The process according to claim 10, wherein the Clopidogrel besylate of Formula II is recrystallized in a mixture of isopropanol and ½*ri*-butyl methyl ether.
40
12. The process according to claim 1, wherein the de-salting process of step (iv) is carried out by extraction using ethyl acetate and water.
13. The process according to claim 1, wherein the racemization process of step (iv) is performed in water under basic conditions.
45
14. The process according to claim 1, wherein the racemization process of step (iv) is performed in a high pressure reactor.
50

15. Use of compound of Formula IV for the preparation of Clopidogrel or pharmaceutical acceptable salts thereof according to claim 1.

5



Formula IV

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/004240

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D495/04

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	examples 3C, 4C, 4D, 5A, 6-11 page 5 page 9	1-14
Y	wo 2006/137628 AI (HANMI PHARM IND CO LTD [KR] ; KIM EUN SOOK [KR] ; KIM HEE CHEOL [KR] ; KW) 28 December 2006 (2006-12-28) cited in the appli cation	1-14
A	Pages 5-7 and exampl es 1-5 , 7-9, 11 Page 6 scheme 3 and lines 27-30 ----- .-/-- .	15

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

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

29 September 2010

Date of mailing of the international search report

05/10/2010

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Authorized officer

Lecai Ilon , Jennifer

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/004240

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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	[KR]; KIM NAM HO [KR]; LEE JIN YOUNG [KR];	
	KIM JAE) 14 February 2008 (2008-02-14)	
A	Scheme 5 page 9	15
	examples 1-8	

Y	EP 2 107 061 A1 (KRKA TOVARNA ZDRAVIL D D	1-14
	NOVO [SI]) 7 October 2009 (2009-10-07)	
A	example 5	15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/004240

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