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(54) Title: PROCESS FOR THE PREPARATION OF CLOPIDOGREL BISULPHATE FORM I

(57) Abstract: The invention relates to a process for the preparation of crystalline form-I of S- (+)-clopidogrel bisulphate.



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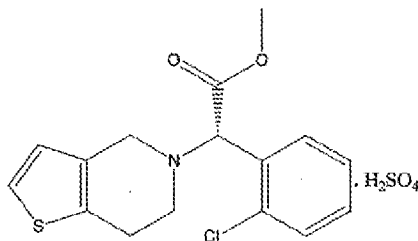
Process for the preparation of Clopidogrel bisulphate form I

Field of invention

The present invention relates to a process for the preparation of (+)-(S)- α -(2-chlorophenyl)-6, 7-dihydrothieno [3, 2-C] pyridine-5(4H)-acetic acid methyl ester and its salt of formula I, commonly known as clopidogrel bisulphate. The present invention further provides a process for the isolation of S-(+)-clopidogrel camphor sulphonic acid salt. The present invention further provides a process for the preparation of crystalline form-I of S-(+)-clopidogrel bisulphate with high chiral purity.

Background of invention

(+)-(S)- α -(2-chlorophenyl)-6, 7-dihydrothieno [3, 2-C] pyridine-5(4 H)-acetic acid methyl ester is marketed as hydrogen sulphate salt and is known as Clopidogrel bisulphate and has the following structure.



Compound I

S-(+)-Clopidogrel bisulphate

Clopidogrel bisulphate is an antiplatelet agent. Clopidogrel's platelet inhibiting activity makes it an effective drug for reducing the incidences of ischemic stroke, heart attacks or claudication due to vascular disease such as atherosclerosis. By inhibiting platelet aggregation the chances of arterial blockages is reduced, thus preventing strokes and heart attacks.

Recent studies have shown that clopidogrel is more effective in blocking platelet aggregation than aspirin and does not have any gastrointestinal side effects. Clopidogrel is administered as the bisulphate salt. Both the racemic form and the S-isomer are known

in the art. The S-enantiomer of clopidogrel is particularly preferred since it is the pharmaceutically active compound.

US patent no. 4,847,265 (the '265 patent) discloses clopidogrel bisulphate and discloses the process for the synthesis of clopidogrel. Clopidogrel bisulphate form I, is prepared by reaction of clopidogrel with concentrated sulphuric acid using acetone as solvent.

US patent no. 6,429,210 (the '210 patent) discloses that clopidogrel bisulphate can exist in two polymorphic forms (designated as Form I and Form II) and provides characterization of the polymorphs.

U.S. Patent No. 6,429,210 (the '210 patent) describes, however, that clopidogrel bisulphate can exist in different polymorphic crystalline forms which differ from each other in terms of stability, physical properties, spectral characteristics and the process by which the different polymorphic crystalline forms are prepared. In addition, a method of preparing the novel polymorph sulfate is disclosed in the '210 patent. According to the '210 patent, the powder of crystalline form II is more compact and much less electrostatic than crystalline form I and may, hence, have better formulation processability. In particular, clopidogrel bisulfate in its polymorphic crystalline form II is thermodynamically more stable than crystalline form I. As such thermodynamic stability results in a delay of decomposition of medicines over time, Plavix®, which is commercially available clopidogrel bisulfate, contains crystalline form II, according to the '210 patent, as the active ingredient.

EP 281459 (the '459 patent) teaches the isolation of the two isomers of clopidogrel base using optically active acid such as camphor sulphonic acid in solvents like acetone, followed by successive recrystallization of the salt until a product with constant rotatory power was obtained.

PCT patent publication WO2004/020443 discloses a process to produce clopidogrel bisulphate form I from a solvent selected from the series of C₁-C₅ alcohols or their esters, optionally mixtures of alcohols and esters. The process involves dissolving clopidogrel freebase in solvents like isopropyl alcohol and/or butyl acetate, cooling the

mixture, adding sulphuric acid and inoculating the mixture with form I of clopidogrel bisulphate.

PCT patent publication WO2005/012300 discloses a process to produce clopidogrel bisulphate form I by using a single solvent preferably ethyl acetate. PCT patent publication WO2007/017886 describes a process for the preparation of (S)-(+)-clopidogrel bisulphate form I from form II without affecting the chiral purity using C₁ to C₄ alcohol as solvent.

PCT patent publication WO2005/104663 describes a one pot process for the manufacture of Clopidogrel. PCT patent publication WO 2002/059128 describes a novel process for the synthesis of (S)-(+)-clopidogrel bisulphate form I.

Prior art describes various processes for the synthesis of S-(+)-clopidogrel bisulphate. However, there is a need for a process for the manufacture of S-(+) isomer of clopidogrel bisulphate that would avoid the transfer and handling of oily and lachrymatory intermediates. Further, a rugged process for the formation of Form I of clopidogrel bisulphate is desirable.

Object of Invention

The main objective of the present invention is to provide an efficient and cost effective process to prepare (S)-(+)-clopidogrel bisulphate form I which is easy to carry out on industrial scale.

In particular, the process of the present invention provides a method which is most suitable for application on an industrial scale due to the more direct, high yield, main reaction and use of chemicals which are more environmentally friendly than prior art processes.

Another objective of the present invention is to prepare and isolate S-(+)-clopidogrel camphor sulphonic acid salt.

Another objective of the present invention is to provide (S)-(+)-clopidogrel bisulphate form I in high purity and yield without affecting the chiral purity.

Summary of the invention

The present invention provides a process for the isolation of S-(+)-clopidogrel camphor sulphonic acid salt, a compound of formula [F] comprising,

- a) reacting alpha -bromo -O-chloro phenyl acetic acid methyl ester, a compound of formula [A] with 4,5,6,7-tetrahydrothieno[3,2,c] pyridine, a compound of formula [D] in the presence of toluene and triethylamine to form racemic alpha (2-chlorophenyl)-6,7-dihydrothieno[3,2-C]pyridine-5(4 H)-acetic acid methyl acetate [clopidogrel base], a compound of formula [E],
- b) resolving racemic clopidogrel base, a compound of formula [E] using levo camphor sulphonic acid monohydrate to obtain S-(+)-clopidogrel camphor sulphonic acid salt, a compound of formula [F] in the presence of acetone.

The present invention further provides a process for the preparation of crystalline form-I of S-(+)-clopidogrel bisulphate, a compound of formula I comprises,

- a) dissolving S-(+)-clopidogrel camphor sulphonic acid salt, a compound of formula [F], in a mixture of aqueous sodium bicarbonate and ethyl acetate,
- b) separating organic (ethyl acetate) and aqueous layers,
- c) washing aqueous layer with ethyl acetate,
- d) distilling off organic layer (ethyl acetate) to obtain S-(+)- clopidogrel base, a compound of formula [G],
- e) dissolving S-(+)- clopidogrel base, a compound of formula [G] in acetone,
- f) adding conc.sulphuric acid,
- g) distilling off acetone partially to obtain viscous residue,
- h) adding n-butyl acetate or methoxy propyl acetate and S-(+)- clopidogrel bisulphate form-I seed under stirring at room temperature to obtain crystalline form-I of S-(+)-clopidogrel bisulphate, a compound of formula I

The present invention also provides a process for the preparation of crystalline form-I of S-(+)-clopidogrel bisulphate, a compound of formula I by the displacement reaction of S-(+)-clopidogrel camphor sulphonic acid salt (F) comprises,

- a) slurring S-(+)-clopidogrel camphor sulphonic acid salt, a compound of formula [F], in n-butyl acetate or methoxy propyl acetate at room temperature,
- b) adding conc.sulphuric acid and S-(+)-clopidogrel bisulphate form-I seed under stirring at room temperature to obtain crystalline form-I of S-(+)-clopidogrel bisulphate, a compound of formula I.

Brief description of figures

Figure 1 represents powder X- ray diffraction pattern of S-(+) - clopidogrel bisulphate form I

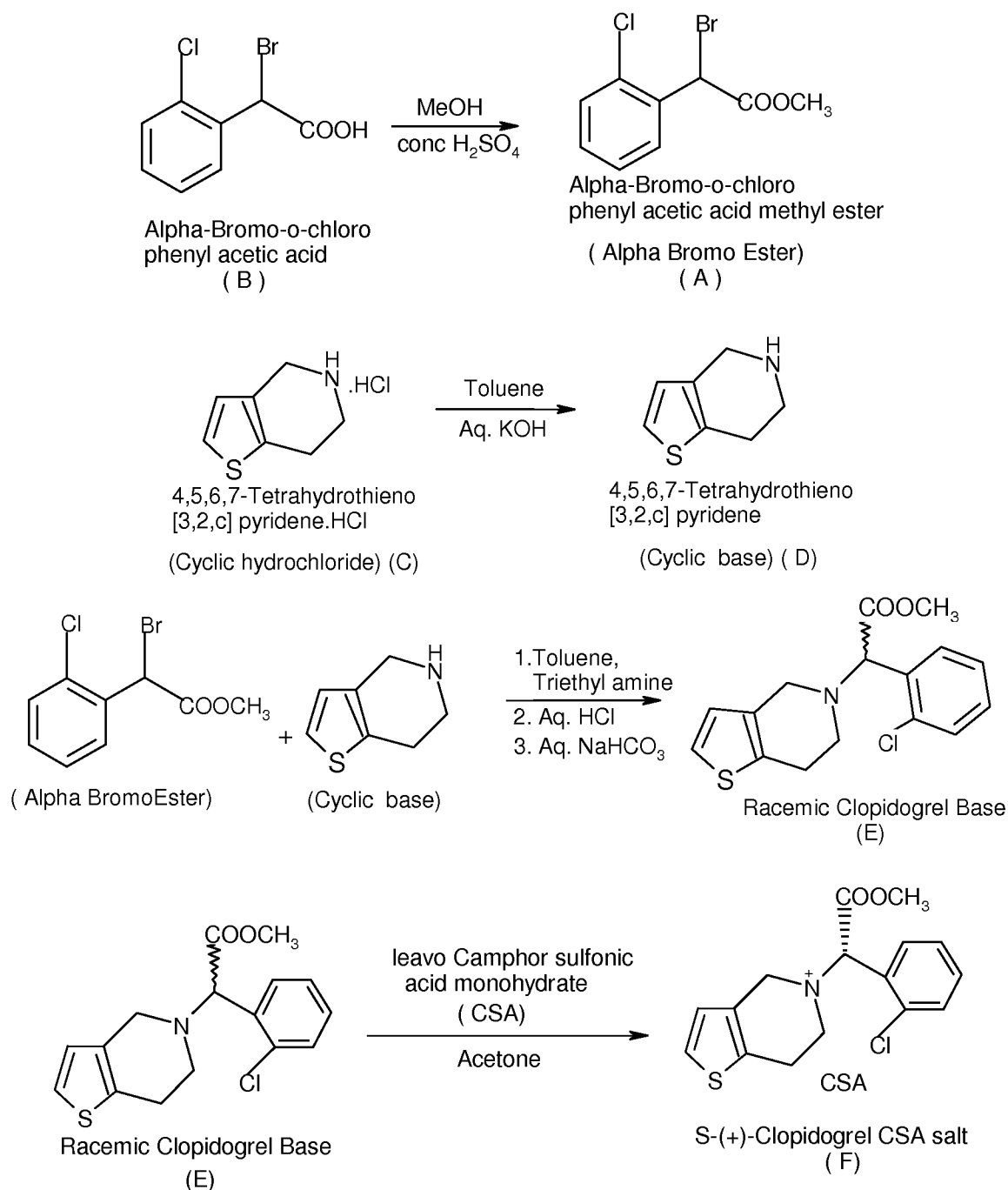
Figure 2 represents Differential scanning calorimeter thermograph of S-(+) - clopidogrel bisulphate form I

Detailed Description of the Invention

According to the one aspect of the present invention, there is provided a process for the preparation of (+)-(S)-alpha-(2-chlorophenyl)-6, 7-dihydrothieno [3, 2-C] pyridine-5(4H)-acetic acid methyl ester and its salt of formula I, commonly known as clopidogrel bisulphate. According to another aspect of the present invention, there is provided a process for the isolation of S-(+)-clopidogrel camphor sulphonic acid salt. According to yet another aspect of the present invention there is provided a process for the preparation of crystalline form-I of S-(+)-clopidogrel bisulphate with high chiral purity. According to yet another aspect of the present invention there is provided a process for the preparation of crystalline form-I of S-(+)-clopidogrel bisulphate with high chiral purity by the displacement reaction of S-(+)-clopidogrel camphor sulphonic acid salt in a suitable organic solvent.

The present invention can be illustrated in best possible manner as shown in scheme 1 below:

Scheme I



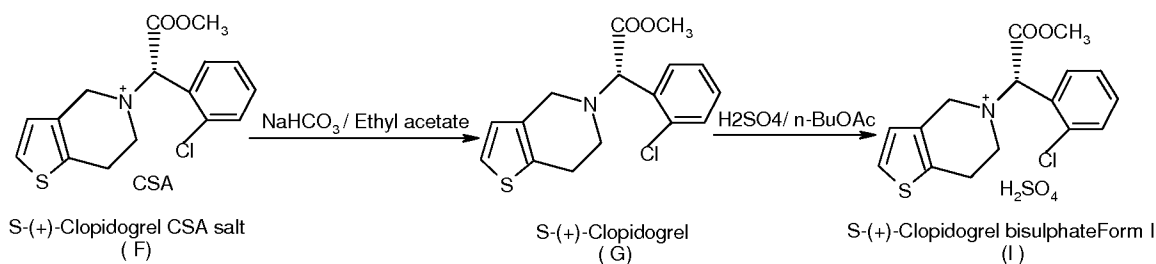
According to the present invention alpha bromo ortho-chloro phenyl acetic acid methyl ester (A) was prepared from alpha bromo ortho-chloro phenyl acetic acid (B). The

reaction was carried out in methanol and extracted in toluene. The final product alpha bromo o-chloro phenyl acetic acid methyl ester (A) was obtained in Toluene.

According to another aspect of the present invention 4,5,6,7-tetrahydrothieno [3,2,c] pyridine (D) was obtained from 4,5,6,7-tetrahydrothieno[3,2,c]pyridine hydrochloride (C). This reaction is carried out in toluene and the final product is obtained as a solution in Toluene which is taken for further reaction.

4, 5, 6, 7-tetrahydrothieno [3, 2, c] pyridine (D) and alpha bromo ortho-chloro phenyl acetic acid methyl ester (A) are reacted in presence of a base in toluene, followed by complete distillation of toluene to get racemic clopidogrel base (E). Finally acetone is added to racemic clopidogrel base (E) and distilled off completely to ensure the absence of toluene traces to yield racemic clopidogrel base (E) as an oil. The preparation of racemic clopidogrel base reaction is carried out in a single solvent namely toluene and thus avoids the transfer and handling of oily and lachrymatory intermediates. Further, the racemic clopidogrel base (E) is reacted with levo- rotatory camphorsulfonic acid in acetone to form S-(+) clopidogrel camphorsulfonic acid salt (F)

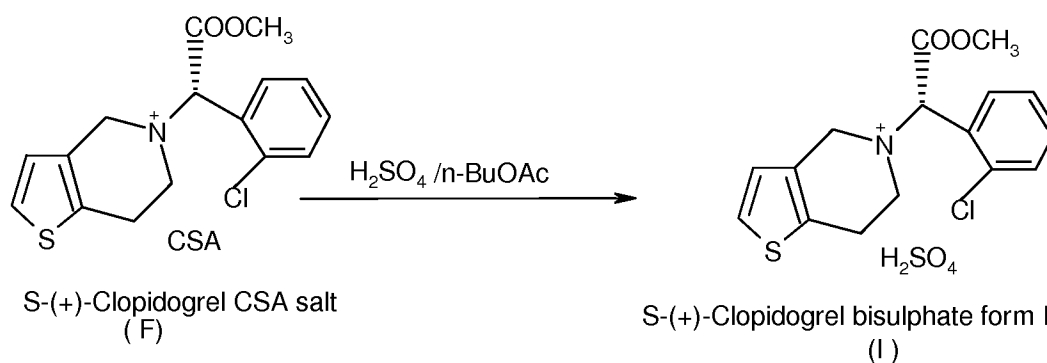
S - (+) clopidogrel camphorsulfonic acid salt obtained via above mentioned process was then converted to the S - (+) clopidogrel free base (G) using sodium bicarbonate solution and ethyl acetate. S - (+) clopidogrel free base (G) was obtained by distilling the ethyl acetate layer.



S - (+) clopidogrel free base (G) was then dissolved in acetone followed by the addition of concentrated sulfuric acid to form the bisulphate salt. In order to obtain form I of S-

(+) clopidogrel bisulphate (I), the acetone was distilled off partly followed by the addition of n-butyl acetate and seed of Form I of S- (+) clopidogrel bisulphate.

The preparation of S-(+)-clopidogrel bisulphate form I (I) from the enantiomerically pure clopidogrel is a simple procedure which involves basification of S-(+) - clopidogrel camphorsulfonic acid salt (F) with aqueous sodium bicarbonate and ethyl acetate as solvent. The isolated base (G) is further treated with concentrated sulphuric acid using acetone as solvent followed by partial removal of acetone. Addition of n-butyl acetate and seeding with form I results in the precipitation of the desired form I of clopidogrel bisulphate.



According to yet another aspect of the present invention there is provided a process for the preparation of crystalline form-I of S-(+)-clopidogrel bisulphate (I) with high chiral purity by the displacement reaction of S-(+)-clopidogrel camphor sulphonic acid salt (F) in a suitable organic solvent

A suitable organic solvent for this step includes, for example, n-butyl acetate and methoxy propyl acetate or a mixture thereof.

In one particular embodiment, the process of the present invention produces clopidogrel bisulphate form-I (I) in crystalline form. This crystalline form of clopidogrel bisulphate form-I (I) was characterized by an X-ray powder diffraction pattern. An example of one X-ray diffraction analysis is shown in Figure 1, and the characteristic 2-theta values (in degrees) in the X-ray diffractogram are shown in Table 1.

Table 1 (Clopidogrel bisulphate form-I)

Diffraction angles (2θ,°)	Intensity(I/I₀)
23.3018	100
25.6092	35.2
20.6852	30.1
23.9658	16.87
23.5053	16.22
9.323	14.95
14.9497	13.44
15.6188	12.9
29.0064	12.78
19.0941	12.65

The differential scanning calorimetry (DSC) thermogram was recorded on TAQ1000 instrument with 10°/min heating rate in a nitrogen atmosphere, having empty pan as a reference with closed system. The differential scanning calorimetry (DSC) thermogram of crystalline form of clopidogrel bisulphate form – I (I) is shown in Figure 2.

Unless defined otherwise, 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.

The invention is further described by reference to the following examples which set forth in detail the preparation of compounds and compositions of the present invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention. The examples that follow illustrate the present invention and are not intended to limit the scope of the invention as described hereinabove.

EXAMPLES

Example 1

Preparation of Alpha Bromo O-Chloro phenyl acetic acid methyl ester (A)

100 gm of alpha bromo O-chloro phenyl acetic acid (B), methanol (365 ml) and concentrated sulphuric acid (54.5 gm) were charged in a reaction vessel at 25-30° C and the reaction mixture was then heated to reflux. The reflux was maintained at 65-66 ° C for 7 hours. The formation of alpha bromo O-chloro phenyl acetic acid methyl ester was monitored on TLC. After the formation of alpha bromo O-chloro phenyl acetic acid methyl ester the reaction mixture was distilled at 50-55° C under vacuum. Water was added to the concentrated mass and the aqueous layer was extracted twice with toluene (175ml). The toluene layer was distilled under vacuum to get the concentrated mass of alpha bromo o-chloro phenyl acetic acid methyl ester.

Yield: 97.8 gm,

% Yield: 93

Preparation of 4, 5, 6, 7-tetrahydrothieno [3, 2, c] pyridine [D]

70 gm of 4, 5, 6, 7-tetrahydrothieno [3, 2, c] pyridine hydrochloride [C], toluene (245 ml), water (70ml) and potassium hydroxide (24.5 gm) were charged in a reaction vessel. The reaction mixture was stirred at 25-30° C and the layers were separated. The aqueous layer was extracted with toluene (145 ml) at 25-30° C. The toluene layer was distilled at 50-55° C to get the concentrated mass as oil.

Yield: 53.5 gm,

% yield: 96.5

Preparation of S-(+)-Clopidogrel Camphor sulfonic acid salt [F]

52.2 gm of 4, 5, 6, 7-tetrahydrothieno [3, 2, c] pyridine [D], 90 gm alpha bromo o-chloro phenyl acetic acid methyl ester [B], triethyl amine (44.6 gm) and toluene (270 ml) were charged in a 2 liter round bottom flask at 25-30° C and the reaction mixture was heated to reflux. The reflux was maintained for 3 hours. Water (150 ml) was added to the

reaction mixture at 25-30 °C. Separate organic (toluene) and aqueous layers. Water (90 ml) was added to the toluene layer followed by the addition of aqueous hydrochloric acid (4.8 ml). Separate organic (toluene) and aqueous layers. Wash organic layer (toluene) with 10% solution of sodium bicarbonate. The toluene layer was distilled under vacuum to get racemic clopidogrel base (E) as oily residue (102 gm). Leavo- camphor-10-sulfonic acid (34.4 gm) and acetone (396 ml) was charged in the 2 liter round bottom flask containing clopidogrel base at 25-30° C. The reaction mixture was heated to 50-55° C under stirring and maintained for 1 hour. The reaction mixture was cooled to 25-30° C under stirring and S-(+) clopidogrel camphor sulphonic acid salt (0.1 gm) was added as a seed. This reaction mixture was stirred at 25-30° C for 24 hours and filtered at 25-30° C. S-(+)-clopidogrel camphor sulfonic acid salt [F] obtained was washed twice with Acetone (50ml) and was dried in the oven at 50-55 ° C. S-(+)-clopidogrel camphor sulfonic acid salt [F] may be purified if required in acetone or in a mixture of acetone and IPA to obtain the desired enantiomeric purity.

Yield: 72 to 82 gms

% Yield: 65-75

Clopidogrel bisulphate form I [I]

18.2 gm of S-(+) clopidogrel camphor sulphonic acid salt [F] and ethyl acetate (55ml) were charged in a 250 ml four necked round bottom flask and solution was stirred at room temperature for 10-15 minutes. A solution containing sodium bicarbonate (9.65 gm) and water (150 ml) was added to 250 ml four necked round bottom flask. Separate organic and aqueous layer. The aqueous layer was washed with ethyl acetate (2X100ml). Separate ethyl acetate layer and was distilled on a rotavapor to obtain S-(+) clopidogrel (10 gm). This was then dissolved in 50 ml acetone, 2.76 gm of concentrated sulphuric acid was added, and solution was stirred at 30-32 ° C for 30 minutes. The acetone was then distilled out on a rotavapor until 45 ml of acetone was removed. To the viscous residue n-butyl acetate (50 ml) and S-(+) clopidogrel bisulphate form I seed (0.25 g) were added and was stirred at 30-32° C. 100 ml of N-butyl acetate was added to the stirred solution and was further stirred at 30-32° C for 5 hours. The precipitated salt was then filtered and dried under vacuum for 24 hours.

Yield: 11.7 gms

% Yield: 85

Clopidogrel bisulphate form I [I]

18.2 gm of S-(+) clopidogrel camphor sulphonic acid salt [F] and ethyl acetate (55ml) were charged in a 250 ml four necked round bottom flask and solution was stirred at room temperature for 10-15 minutes. A solution containing sodium bicarbonate (9.65 gm) and water (150 ml) was added to 250 ml four necked round bottom flask. Separate organic and aqueous layer. The aqueous layer was washed with ethyl acetate (2X100ml). Separate ethyl acetate layer and was distilled on a rotavapor to obtain S-(+) clopidogrel (10 gm). This was then dissolved in 50 ml acetone, 2.76 gm of concentrated sulphuric acid was added, and solution was stirred at 30-32 ° C for 30 minutes. The acetone was then distilled out on a rotavapor until 45 ml of acetone was removed. To the viscous residue methoxy propyl acetate (50 ml) and S-(+) clopidogrel bisulphate form I seed (0.25 g) were added and was stirred at 30-32° C. 100 ml of methoxy propyl acetate was added to the stirred solution and was further stirred at 30-32° C for 5 hours. The precipitated salt was then filtered and dried under vacuum for 24 hours.

Yield: 7.5 – 10 gms

% Yield: 55-75

Clopidogrel bisulphate form I [I]

10 gm of S-(+) clopidogrel camphor sulphonic acid salt [F] and n-butyl acetate (100ml) were charged in a 250 ml four necked round bottom flask and solution was stirred at room temperature for 10-15 minutes. A mixture of 50 ml of n-butyl acetate and 1.75 gm of concentrated H₂SO₄ were added in a 250 ml four necked round bottom flask over a period of 30 minutes followed by the addition of S-(+) clopidogrel bisulphate form I seed (0.25 g) under stirring at 30-32° C for 24 hours. The precipitated salt was then filtered and dried under vacuum for 24 hours.

Yield: 4 gm

% Yield: 55

Clopidogrel bisulphate form I [I]

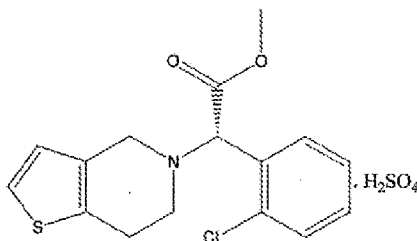
10 gm of S-(+) clopidogrel camphor sulphonic acid salt [F] and methoxy propyl acetate (50ml) were charged in a 250 ml four necked round bottom flask and solution was stirred at room temperature for 10-15 minutes. A mixture of 50 ml of methoxy propyl acetate and 1.75 gm of concentrated H_2SO_4 were added in a 250 ml four necked round bottom flask over a period of 30 minutes followed by the addition of S-(+) clopidogrel bisulphate form I seed (0.25 g) under stirring at 30-32° C for 24 hours. The precipitated salt was then filtered and dried under vacuum for 24 hours.

Yield: 3.8 gm

% Yield: 50 % of theory

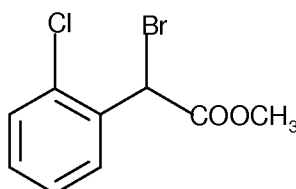
Claims:

- 1) A process for the preparation of crystalline S-(+)-clopidogrel bisulphate form-I of Formula I comprising the steps of:

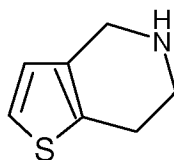


Formula I

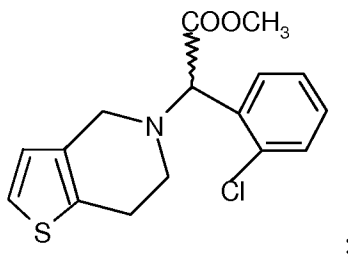
- a. reacting alpha-bromo-O-chloro phenyl acetic acid methyl ester of formula [A]



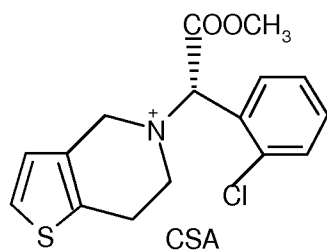
with 4,5,6,7-tetrahydrothieno[3,2,c] pyridine of formula [D]



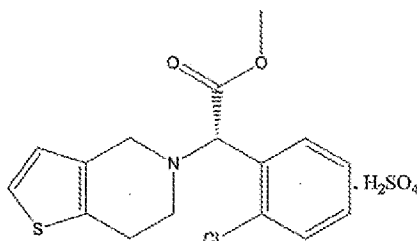
in the presence of toluene and triethylamine to form racemic alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-C]pyridine-5(4 H)-acetic acid methyl acetate of formula [E]



- b. resolving the compound of formula [E] using levo camphor sulphonic acid monohydrate in the presence of acetone to yield a compound of formula [F] ;

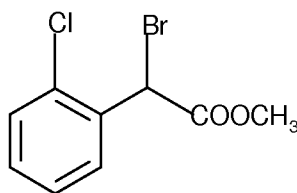


- c. slurring the compound of formula F in an organic solvent at 30-32°C;
 - d. adding concentrated sulphuric acid to the slurry of step (c) and subsequent seeding with the compound of formula I under stirring at 30-32°C to yield the compound of formula I.
- 2) The process according to claim 1 wherein the organic solvent in 1(c) is an aliphatic ester.
 - 3) The process according to claim 2 wherein the aliphatic ester is selected from n-butyl acetate, methoxy propyl acetate or a mixture thereof.
 - 4) A process for the preparation of crystalline S-(+)-clopidogrel bisulphate form-I of Formula I comprising the steps of:

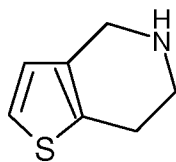


Formula I

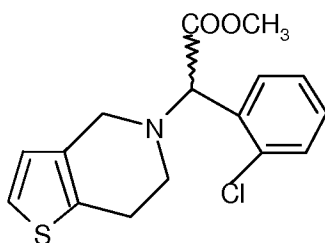
- a) reacting alpha -bromo -O-chloro phenyl acetic acid methyl ester of formula [A]



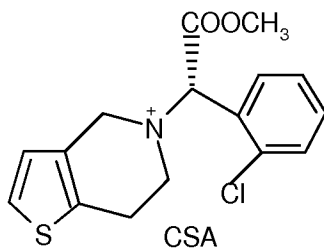
with 4,5,6,7-tetrahydrothieno[3,2,c] pyridine of formula [D]



in the presence of toluene and triethylamine to form racemic alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-C]pyridine-5(4 H)-acetic acid methyl acetate of formula [E] ;

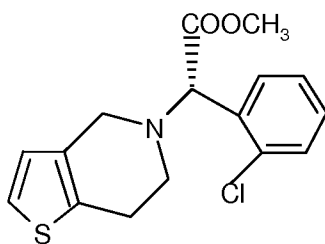


- b) resolving the compound of formula [E] using levo camphor sulphonic acid monohydrate in the presence of acetone to yield a compound of formula [F];
- c) extracting the compound of formula [F]



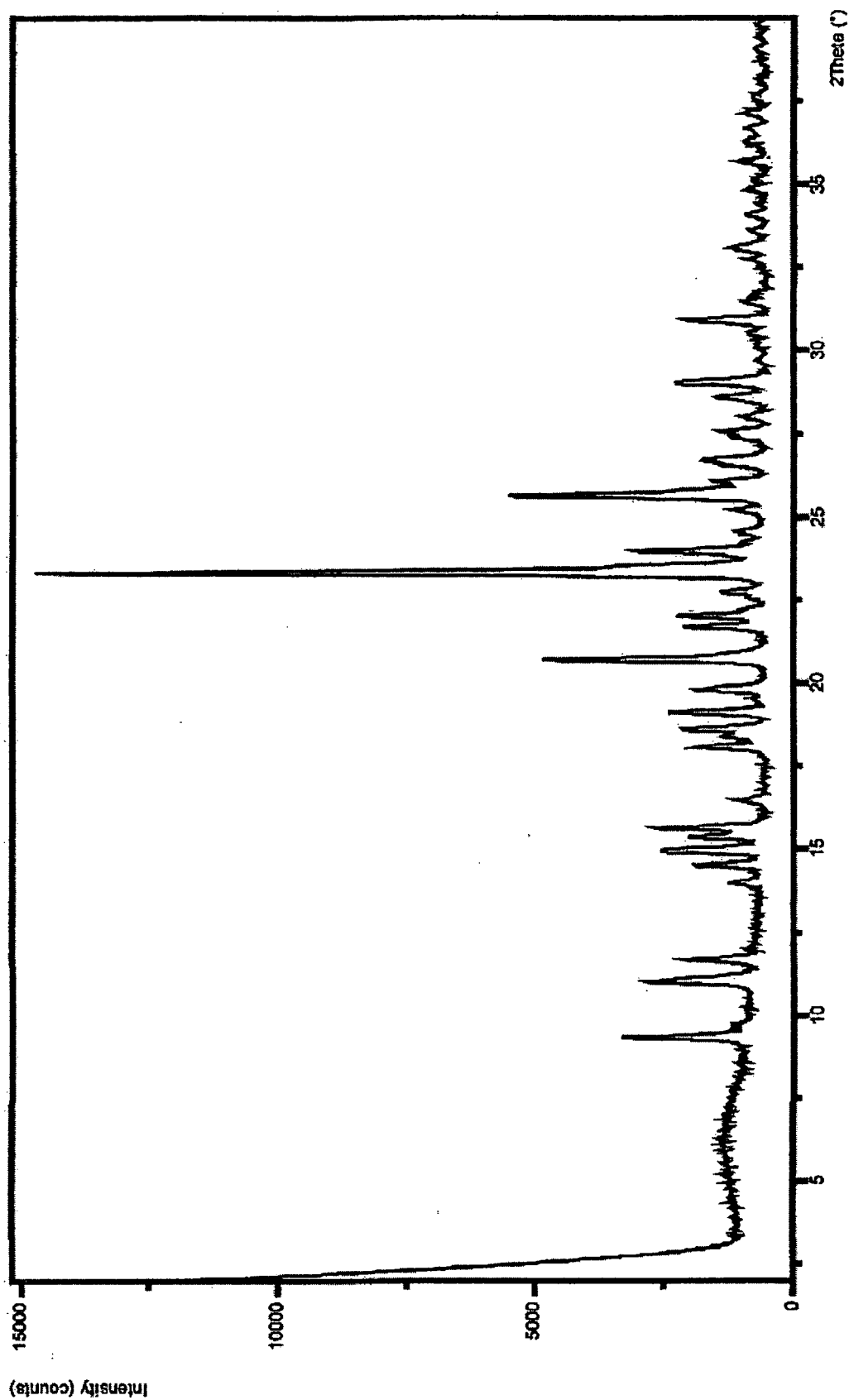
in ethyl acetate in the presence of aqueous sodium bicarbonate;

- d) separating and distilling out ethyl acetate from step c to obtain S-(+)- clopidogrel base of formula [G] ;



- e) dissolving the compound of formula [G] in acetone followed by the addition of concentrated sulphuric acid;
- f) distilling out acetone partially to obtain a viscous residue;

- g) adding an organic solvent to the above mass followed by seeding with the compound of formula I under stirring at 30-32°C to yield the compound of formula I.
- 5) The process according to claim 4 wherein the organic solvent in 4 (g) is an aliphatic ester.
- 6) The process according to claim 5 wherein the aliphatic ester is selected from n-butyl acetate, methoxy propyl acetate.
- 7) Crystalline S-(+)-clopidogrel bisulphate form-I prepared by the process claimed in claim 1 and claim 4.
- 8) Crystalline S-(+)-clopidogrel bisulphate form-I according to claim 7 with characteristic powder X-ray diffraction (PXRD) with diffraction angle (2θ) at 23.3018° and exothermic thermal event in differential scanning calorimetry (DSC) at about 179.96°C.

*Fig 1*

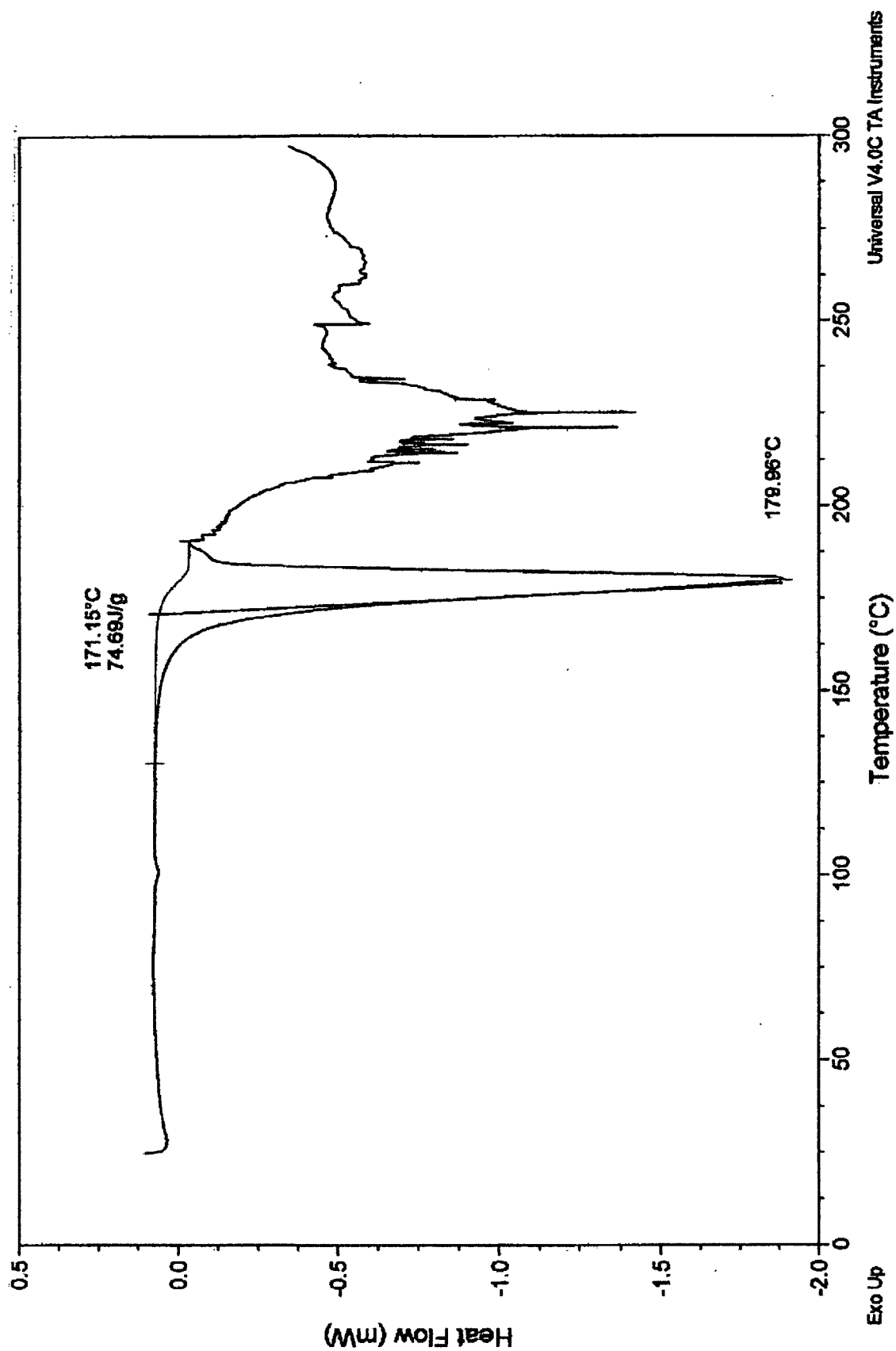


Fig 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/066866

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 6 429 210 B1 (BOUSQUET ANDRE [FR] ET AL) 6 August 2002 (2002-08-06) figure 1	7,8
Y	US 4 529 596 A (AUBERT DANIEL [FR] ET AL) 16 July 1985 (1985-07-16) cited in the application	1-6
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X	column 8, paragraph D	7,8
	-/--	

☒ 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

19 February 2009

Date of mailing of the international search report

27/02/2009

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Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/066866

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	claim 1 -----	7,8

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International application No

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