

Clopidogrel Bisulfate (Cas No 120202-66-6)

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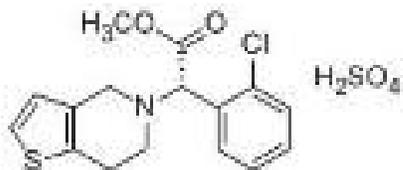


Raw Material / Chemicals Index

Taj Pharmaceuticals Ltd.

Clopidogrel Bisulfate

Cas Number 120202-66-6



Product	Clopidogrel Bisulfate
CAS number	120202-66-6
Chemical Name:	Clopidogrel hydrogen sulfate; (S)-(+)-Methyl 2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate hydrogen sulfate, Clopidogrel bisulfate, FORM 1, I
Synonym	Clopidogrel bisulfate, FORM 1, I, Clopidogrel hydrogen sulfate; (S)-(+)-Methyl 2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate hydrogen sulfate
Molecular Formula	C16H16ClNO2S.H2SO4
Molecular Weight	419.03

**Specifications
Packing**

Clopidogrel bisulfate, FORM 1, I complies as per USP
Export worthy packing

Description : white or almost white powder ; smell-less, soluble in water, methyl alcohol, grain alcohol and glacial acetic acid, bit soluble in acetone or chloroform, almost not soluble in ethyl acetate ; soluble in 0.1 mol/L HCL solution.

Specific optical rotation : +52°~+56°

Assay : 98.5%~101.5%

Origin: INDIA

Specifications:

Appearance: White or off-white powder

Assay (Dry basis): 97.00% ~ 101.50%

Solubility: Soluble in water, methanol, ethanol, acetic acid and 0.1N HCl, very slightly soluble in acetone and chloroform, practically insoluble in ethyl acetate.

Identification

1. IR absorption spectrum should be accordance with that of the reference standard

2. HPLC

3. Sulfate test

Related Substances (HPLC)

Impurity A: NMT 0.20%

Impurity B: NMT 0.30%

Impurity C: NMT 1.00%

Other Single Impurity: NMT 0.10%

Total Impurities: NMT 1.50%

Loss on Drying: NMT 0.50%

Residue on Ignition: NMT 0.10%

PH: 1.5 ~ 2.5

Heavy Metals: NMT 20ppm

Executive standard : USP28

Package : 25kg /drum ; or packed according to your requirements

Production capacity : 100kg/month

FIELD OF THE INVENTION

The present invention relates to a novel process for the manufacture of blood-platelet aggregation inhibiting agent. In particular, the present invention is directed to a process for the manufacture of Methyl-()-(S)- α -(2-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-- 5(4H)-acetate bisulfate Form-I of Formula:

PRESENT INVENTION

The present invention relates to a novel process for the preparation of Clopidogrel bisulfate or the bisulfate of methyl-()-(S)- α -(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2,-c]p- yridine-5-acetate. More particularly, the invention relates to a novel process for the preparation of Clopidogrel bisulfate Form-1 having Formula:

##STR00002##

Single solvent like isopropyl alcohol, isopropyl ether, 2-butanol etc. afforded mixture of Form-I and Form-II as evidenced by IR and XRD values. Even using seeded crystals of pure Form-I in acetone afforded only ()-(S)-Clopidogrel bisulfate Form-II.

It is observed that ethyl acetate is the solvent of choice for getting ()-(S)-Clopidogrel bisulfate Form-I in good yield and highly pure form. The Form-I of Clopidogrel bisulfate is well characterized by IR and XRD. These values are identical with the reported values of Form-I (reported in U.S. Pat. No. 6,429,210 B1). HPLC purity of Clopidogrel bisulfate Form-I prepared using ethyl acetate solvent is found more than 99%. An increase in melting point is observed in our process, i.e., 198 to 200° C. in comparison to 181.2° C. disclosed in U.S. Pat. No. 6,429,210 B1. The increase in melting point indicates higher purity of Form-I from what is reported in the "210" patent.

The present process for the manufacture of Clopidogrel bisulfate in an ester solvent, more specifically in ethyl acetate consumes less time than other solvent combinations reported in the prior art. It is also observed that the yield and purity of the Form-I is 88% and 99%, respectively. The obtained yield and purity of the Form-I by this process is better than reported in prior art. The specific rotation $[\alpha]_{D20}$ of the Clopidogrel bisulfate Form-I is observed at 55.16° at a concentration of 1.61 gm/100 ml methanol. Clopidogrel bisulfate is characterized by ¹H NMR, ¹³C NMR, mass and CHN analyses. The ()-(S)-Clopidogrel bisulfate Form-I is confirmed on the basis of IR, XRD and melting point analyses. These values are tabulated as follows. For comparison purpose the values of Form-II are also given in the table.

IR, XRD, HPLC purity, melting point and Specific Rotation of ()-(S)-Clopidogrel bisulfate Form-I and Form-II are tabulated as follows:

TABLE-US-00001 TABLE Comparative analytical data of ()-(S)-Clopidogrel bisulfate Form-I and Form-II. Sr. ()-(S)-Clopidogrel ()-(S)-Clopidogrel No. Analysis bisulfate Form-I bisulfate Form-II 1. IR 2987, 1753, 1222, 2551, 1497, 1189 1175,841 cm⁻¹ and 1029 cm⁻¹ 2. XRD 9.60, 8.13, 5.80, 10.04, 6.86, 6.49, 4.95, 4.80, 4.31, 5.66, 5.01, 4.80, 3.86, 3.83, 4.11, 3.87, 3.74, 3.8, 3.49 d(A°) 3.6 0 d(A°) 3. HPLC Purity 99.96% 99.94% 4. Melting Point 198-200° C. 176-178° C. 5. Specific Rotation 55.16° 55.10° (c = 1.68% in methanol)

Form-I obtained by this process is found to be stable and does not convert to any other forms.

Apart from all these technical and economical advantages of the process according to the invention, excellent yields and very good quality of the desired product, viz., Clopidogrel bisulfate Form-I is obtained. The process is suitable for industrial scale.

The following example illustrates the invention more clearly, without limiting its scope.

Examples

The following examples illustrate the invention, but is not limiting thereof.

Preparation of ()-(S)-Clopidogrel Bisulfate Form-I

(a) Resolution of ()-(S)-Clopidogrel

Racemic Clopidogrel base 12 gm (0.037 mole) (prepared according to procedure described in U.S. Pat. No. 4,529,596) is dissolved in acetone (100 ml) and to it at 20° C. a solution of L-camphor-10-sulphonic acid, 5.196 gm (0.037 mole) in 20 ml acetone is added drop-wise. The mixture is heated at reflux temperature for 7 to 8 hours and then cooled to room temperature. The mixture is seeded with ()-(S)-Clopidogrel-camphor-sulfonate salt (2.5% of the weight of base), stirred at room temperature for 10-12 hours. The product is filtered under suction to get ()-(S)-Clopidogrel-camphor-sulfonate salt and washed with acetone which yielded 5.20 gm of product. The ()-(S)-Clopidogrel is characterized on the basis of specific rotation based on literature and $[\alpha]_{D20}$ of ()-(S)-Clopidogrel is found 24.70° at a concentration of 1.68 gm/100 ml methanol. The 5.20 gm of the above compound is treated with minimum amount of water and made alkaline with sodium bicarbonate at 5° C., the obtained mixture is extracted in dichloromethane and subsequently removal of the solvent provided oily ()-(S)-Clopidogrel in 4.92 gm yield and 99.96% pure form based on HPLC.

The structure of the ()-(S)-Clopidogrel has been assigned on the basis of spectral values like ¹H NMR, ¹³C NMR and specific rotation etc.

(b) ()-(S)-Clopidogrel bisulfate Form-I

()-(S)-Clopidogrel, 4.50 gm (0.0139 mole) is dissolved in ethyl acetate 50 ml and seeded with ()-(S)-Clopidogrel bisulfate Form-I (2.5% of the weight of base). During stirring Conc. sulfuric acid 1.50 gm (0.015 mole) is added at room temperature. After complete addition the reaction slurry is heated at reflux for 1 hour. Then it is stirred at room temperature for 1 hour. The product is then filtered under suction and washed with ethyl acetate followed by drying under vacuum at 60 to 70° C. for 6-8 hours. After complete drying, 4.0 gm ()-(S)-Clopidogrel bisulfate Form-I is obtained in having 99.96% purity and $[\alpha]_D^{20} = 51.16^\circ$ at a concentration of 1.61 gm/100 ml methanol.

The ()-(S)-Clopidogrel bisulfate Form-I is characterized by ¹H NMR, ¹³C NMR, mass and CHN analyses. The Form-I of ()-(S)-Clopidogrel bisulfate has been confirmed on the basis of IR, XRD and melting point etc.

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