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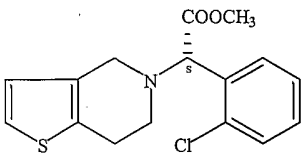
(54) **Title:** A PROCESS FOR PREPARATION OF CLOPIDOGREL



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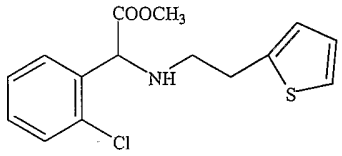

(4)

(57) **Abstract:** The present invention provides a process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula (4), or a salt thereof comprising, (a) resolving racemic α-[(2-thien-2-yl)ethylamino]-a-(2-chlorophenyl)methylacetate, a compound of formula 1 or a salt thereof to obtain S-isomer of a compound of formula (1) or a salt thereof and R-isomer of formula (1) or a salt thereof, (b) racemizing the R-isomer of formula 1 or a salt thereof to obtain a racemic compound of formula (1) and optionally converting it into a salt thereof, (c) optionally repeating steps 'a' and 'b', (d) converting the S-isomer of compound of formula (1) obtained in step 'a' to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl) acetate.

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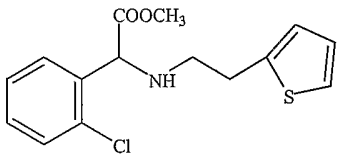
A PROCESS FOR PREPARATION OF CLOPIDOGREL

The present invention relates to a process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate or a salt thereof. The International Non-Proprietary name (INN) of the compound is Clopidogrel. Particularly, the present invention provides a convenient process for optical resolution of a key intermediate for clopidogrel and recycling of the undesired isomer thereof through racemisation and its subsequent resolution to obtain the desired isomer, that is converted to clopidogrel.

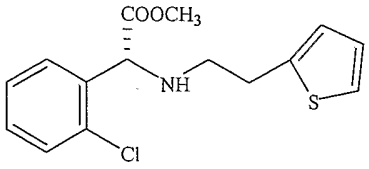
The present invention also provides a process of improving the yield of the S-isomer of α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, a compound of formula 1.



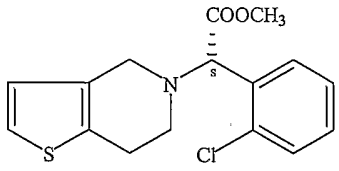
Formula 1

BACKGROUND OF THE INVENTION

The optically active compound of formula 1 i.e. the S-isomer of compound of formula 1 is used as an intermediate for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, bearing the International Non-Proprietary name (INN) Clopidogrel. Clopidogrel has the absolute configuration S and is a commercially significant drug with excellent antithrombotic and platelet aggregation inhibiting activity disclosed in United States Patent no. 4,847,265.

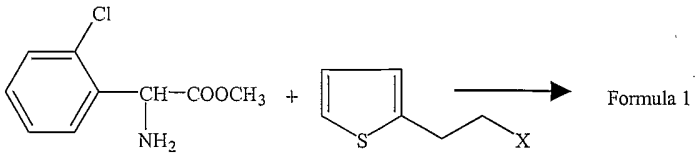


Formula 1(S-isomer)



Formula 4

The United States Patent No. 5,204,469 incorporated herein by reference, teaches that racemic compound of formula 1 can be prepared by reaction of methyl α-amino(2-chlorophenyl)acetate of formula 5 with a thienyl derivative of formula 6 according to the reaction scheme 1:



Formula 5 Formula 6

Scheme 1

in which X is a halogen atom or a sulphonate group RSO_2O- in which R is a C1-C4 alkyl group or a phenyl group, optionally substituted.

Example 3(b) of United States Patent No. 5,204,469 exemplifies resolution of racemate of the compound of formula 1 by employing (+)-tartaric acid. The resultant (+)-tartrate salt is required to be recrystallised four times from isopropanol to provide finally the required dextrorotatory product i.e. the (+)-tartrate salt of compound of formula 1. The rotatory power of the corresponding free base is mentioned as +99.76°C. Also, this prior art does not provide any method for converting the isomeric mixture or any other derivatives thereof remaining in the mother liquor to the racemic compound of formula 1, which can be recycled and subsequently resolved to obtain the desired isomer.

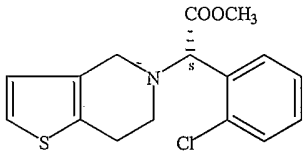
The PCT publication WO 04/013147 teaches a process for obtaining S-clopidogrel by resolving racemic clopidogrel using (-)-camphor sulphonic acid and racemization of R-clopiodogrel isomer by reacting with a base. It does not teach resolution of intermediate compounds or racemization of unwanted isomer thereof.

It is the objective of the present invention to develop a simple process whereby the unwanted isomers or derivatives/by-products of compound of formula 1 that may be generated during resolution of compound of formula 1 can be converted to racemic compound of formula 1 and recycled to produce the desired dextrorotatory isomer represented by a compound of formula 1, which is then converted to clopidogrel.

Surprisingly, we have found that by controlling the key parameters like concentration, agitation and cooling in a controlled manner of the reaction mass during the resolution process provides the desired isomer, i.e. (+)-enantiomer of the tartrate salt of the compound of formula 1 in a single operation directly from the reaction mixture avoiding repetitive crystallisations. The other isomer of the compound of formula 1 and derivatives thereof remain in the mother liquor in the form of an enantiomerically enriched mixture of the isomers or salt thereof, which can be converted to racemic compound of formula 1 by following the process of the present invention, which can then be further recycled.

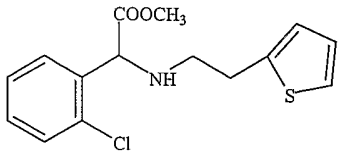
SUMMARY OF THE PRESENT INVENION

The present invention provides a process for preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,



Formula 4

(a) resolving racemic α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, a compound of formula 1 or a salt thereof



Formula 1

to obtain S-isomer of a compound of formula 1 or a salt thereof and R-isomer of formula 1 or a salt thereof,

(b) racemizing the R-isomer of formula 1 or a salt thereof to obtain a racemic compound of formula 1 and optionally converting it into a salt thereof,

(c) optionally repeating steps 'a' and 'b',

(d) converting the S-isomer of compound of formula 1 obtained in step 'a' to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl) acetate.

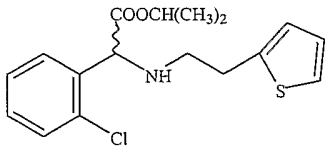
DETAILED DESCRIPTION OF THE INVENTION

The R-isomer compound of formula 1 as used herein represents the compound of formula 1 wherein R-isomer of the compound of formula 1 may be present as a major compound and S-isomer of the compound of formula 1 may be present as a minor compound.

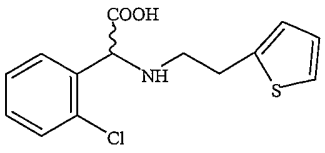
In one embodiment resolution of compound of formula 1 is carried out by resolving a racemic compound of formula 1 or a salt thereof by reacting with L-(+)-tartaric acid in isopropanol. Preferably, the ratio of racemic compound of formula 1:L-(+)-tartaric acid is 1:0.85 moles.

In second embodiment racemization of the R-isomer compound of formula 1 or a salt thereof is done in methanol in presence of sodium methoxide to obtain racemic compound of formula 1.

After resolution of compound of formula 1 to isolate the S-isomer of compound of formula 1, the R-isomer of formula 1, remaining in the mother liquor may contain impurity of ester derivative or a salt thereof, represented by a compound of formula 2 and/or impurity of an acid derivative or a salt thereof, represented by a compound of formula 3.



Formula 2

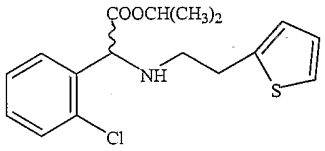


Formula 3

The mother liquor after resolution of compound of formula 1, can be concentrated to remove the solvent and the concentrated residue then subjected to racemization. This concentrated isomeric residue may contain the mixture of R-isomer of compound of formula 1 in about 30 to about 70%, the compound of formula 2 in about 5 to about 30% and the compound of formula 3 in about 5 to about 25% wt/wt.

In a preferred embodiment the racemization of the R-isomer of formula 1 may be carried out by treatment in methanol with sodium methoxide. Preferably, the ratio of sodium methoxide:L-(+)-tartaric acid is 1.5:1 moles. The role of a reagent like sodium methoxide being neutralization of any excess tartaric acid, and to provide a basic pH to reaction mass for racemization process.

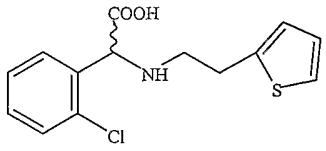
In third embodiment of the process of the present invention the R-isomer of formula 1 contains an impurity of ester derivative or a salt thereof, represented by a compound of formula 2,



Formula 2

and the said impurity reacts with methanol in presence of sodium methoxide to form a racemic compound of formula 1.

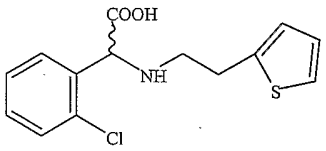
In fourth embodiment of the process of the present invention the R-isomer of formula 1 contains an impurity of acid derivative or a salt thereof, represented by a compound of formula 3,



Formula 3

and wherein subsequent to racemization, the reaction mixture is acidified for e.g. by treatment with methanolic HCl, wherein the compound of formula 3 reacts with methanol to form a racemic compound of formula 1. Preferably, it is carried out at temperature between the range of 0°C to 40°C.

In fifth embodiment of the process of the present invention the R-isomer of formula 1 contains an impurity of acid derivative or a salt thereof, represented by a compound of formula 3,



Formula 3

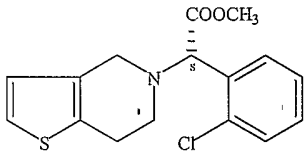
and wherein subsequent to racemization, the reaction mixture is treated with thionyl chloride wherein the compound of formula 3 reacts with methanol to form a racemic compound of formula 1. Preferably, it is carried out at temperature between the range of 0°C to 40°C.

In a preferred embodiment, the racemization of the R-isomer of formula 1 or a salt thereof may be carried out with a reagent such as sodium methoxide in presence of methanol wherein the R-isomer rich compound of formula 1 and if present the compound of formula 2 are converted to a racemic compound of formula 1, optionally followed by treatment with methanol preferably in presence of thionyl chloride wherein a compound of formula 3 is converted to a racemic compound of formula 1. If desired, the treatment with methanol and thionyl chloride can be carried out first wherein a compound of formula 3 is converted to a racemic compound of formula 1 and then the treatment with the reagent in methanol. On treatment with the reagent such as sodium methoxide in

methanol the R-isomer compound of formula 1 is converted to a racemic compound of formula 1 and the compound of formula 2 if present is also converted to a racemic compound of formula 1, simultaneously.

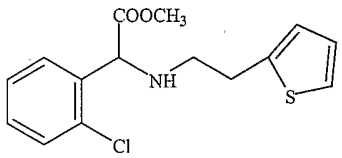
Preferably, the treatment of the R-isomer compound of formula 1 and if present the compound of formula 2 and/or 3 in methanol with sodium methoxide is carried out at temperature between the range of 25°C to 80°C.

In one aspect the present invention provides a process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,



Formula 4

(a) racemizing the R-isomer of α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, a compound of formula 1 or a salt thereof



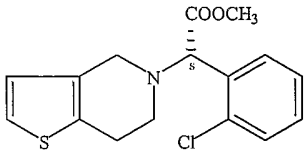
Formula 1

to obtain a racemic compound of formula 1,

(b) resolving the racemic compound of formula 1 to obtain S-isomer of compound of formula 1,

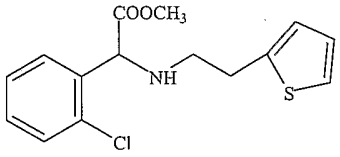
(c) converting the S-isomer of compound of formula 1 to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate.

In another aspect the present invention provides a process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,

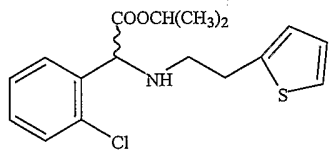


Formula 4

(a) reacting a compound of formula 2 with methanol in presence of sodium methoxide to obtain a racemic compound of formula 1,



Formula 1

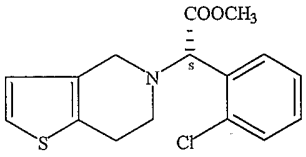


Formula 2

(b) resolving the racemic compound of formula 1 to obtain S-isomer of compound of formula 1,

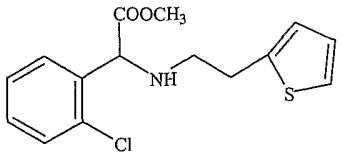
(c) converting the S-isomer of compound of formula 1 to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate.

In yet another aspect the present invention provides a process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,

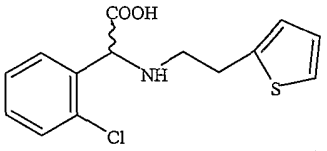


Formula 4

(a) reacting a compound of formula 3 with methanol to obtain a racemic compound of formula 1,



Formula 1

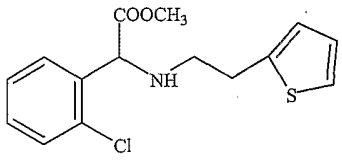


Formula 3

(b) resolving the racemic compound of formula 1 to obtain S-isomer of compound of formula 1,

(c) converting the S-isomer of compound of formula 1 to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate.

In still another aspect, the present invention provides a process of increasing the yield of the S-isomer of α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, a compound of formula 1,



Formula 1

comprising,

(a) resolving a racemic compound of formula 1 or a salt thereof to obtain S-isomer of a compound of formula 1 or a salt thereof and a R-isomer compound of formula 1 or a salt thereof,

(b) racemizing the R-isomer compound of formula 1 or a salt thereof to obtain a racemic compound of formula 1 and optionally converting it into a salt thereof

(c) repeating steps 'a' and 'b'.

The present invention provides a process for the preparation of S-isomer of (+)-α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, the compound of formula 1 or a salt thereof comprises the steps of ,

1) treating the racemic compound of formula 1 with L(+)-tartaric acid in isopropanol as the reaction solvent,

2) cooling the resultant solution in the reaction solvent in a controlled manner, comprising the steps of

i) cooling the solution gradually to ambient temperature under slow stirring,

ii) maintaining the solution at ambient conditions for about 2 to about 24 hours,

iii) cooling the solution gradually to about 0 to about 5°C

iv) raising the temperature of the solution gradually to about 15-20°C

3) isolating the (+)-tartrate salt of the S-isomer of compound of formula 1, from the reaction solvent

4) obtaining the S-isomer of compound of formula 1 from the (+)-tartrate salt of the compound of formula 1 in a known manner, if desired converting the S-isomer of compound of formula 1 to an acid addition salt thereof.

It is advantageous to have the concentration of the racemic compound of formula 1, which is to be resolved with L(+)-tartaric acid in isopropanol as the reaction solvent, in about 6.5-7% wt/vol.

In a preferred embodiment, after the resolution of the racemic compound of formula 1 with L(+)-tartaric acid in isopropanol, cooling the resultant isopropanol solution in a controlled manner may comprise the steps of,

i) cooling the solution gradually to 30-35°C over the period of 1 to 2 hours under slow stirring, and optionally seeding with a crystal of (+)-tartrate salt of the dextrorotatory compound of formula 1,

ii) maintaining the solution at 30-35°C for about 18 to about 20 hours,

iii) cooling the solution gradually to about 0 to about 5°C over a period of about 3 to 4 hours and maintaining the temperature for about 1 to about 2 hours,

iv) raising the temperature of the solution gradually to about 15-20°C over a period of about 2 hours and maintaining the temperature for about 3 to about 4 hour.

In a particularly preferred embodiment the resolution of compound of formula 1 to obtain S-isomer of (+)-α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, the compound of formula 1 is carried out by reacting the racemic compound of formula 1 with L-(+)-tartaric acid, in isopropanol solvent. To the isopropanol solution of a free base of racemic compound of formula 1, L(+)-tartaric acid is added at about 30°C under stirring, then the temperature of the reaction mixture is raised to about 50°C to about 55°C and maintained at about 65°C to about 70°C for a period of about 2 hours. The reaction mixture is gradually cooled to about 30°C to about 35°C over a period of about 1 to about 2 hours and optionally seeded with (+)-tartrate salt of dextrorotatory compound of formula 1 and stirred at 30-35°C for a period of about 18 to about 20 hours. The reaction mixture is gradually cooled to 0-5°C over a period of about 3 to 4 hours and stirred further at this temperature for about 1-2 hours. The temperature of the reaction mixture is gradually raised to about 15-20°C over a period of about 2 hours and stirred further at this temperature for about 3-4 hours. The resultant solid is filtered at 15-20°C and washed with chilled isopropanol at about 5°C and dried to obtain (+)-tartrate salt of the desired compound of formula 1. The filtrate rich in undesired isomer and containing its derivatives/by-products is subjected to racemization and recycled.

The isolated (+)-tartrate salt of the compound of formula 1 can be converted to the free base of S-(+)-isomer of compound of formula 1 in a known manner. The S-(+)-isomer of compound of formula 1 can be converted to a salt thereof by treatment with an acid in a known manner, for example to HCl salt thereof

The resultant S-isomer of compound of formula 1 or an acid addition salt thereof prepared by the process of the present invention can be converted to dextrorotatory isomer of clopidogrel or a salt thereof by a known process in the art. For example, by a process described in United States Patent No. 5,204,469, incorporated herein by reference, by reacting with a formylating agent, followed by cyclisation in presence of an acid.

The following examples are given by way of illustration only and not to be construed as limiting.

5

EXAMPLES

EXAMPLE 1

Preparation of α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate hydrochloride-

In (750 ml) acetonitrile at about 30-35°C, (150g) DL-2-(2-chlorophenyl)glycine methyl ester is added followed by addition of (191 g) 2(2-thiophene)ethanol tosylate, (76g) sodium bicarbonate and (12.5g) potassium iodide. The reaction mixture is refluxed at about 80°C under vigorous stirring for 24 hours, (12.5g) potassium iodide is added and refluxed further for 24 hours. The solvent is distilled off completely under vacuum at 45-50°C and the residual mass is degassed at 50-55°C under vacuum for 30 minutes. It is dissolved in (2250ml) ethyl acetate at 30-35°C and (750ml) water is added. The upper product enriched layer is washed with aq NaCl 10% soln and cooled to 0-5°C. To this ethyl acetate layer is added con HCl acid (110 ml con HCl acid in 210ml of chilled water) at 0-5°C with stirring and maintain for 2 hours. The product is filtered and washed with chilled ethyl acetate (2x150ml) and sucked to dryness. The product cake is washed with (2x150ml) hexane and suck to maximum dryness and dried at 45-55°C. (175g)

EXAMPLE 2

Resolution of DL-α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate hydrochloride –

The compound (140g) α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate hydrochloride prepared above is added to (560ml) water at 30-35°C, followed by (560ml) dichloromethane and reaction mixture stirred at 30-35°C for 15 minutes. The reaction mixture basified with gradual addition of (~70g) sodium carbonate solid until pH of the aq layer is 7.5-8.0. The lower product enriched methylene chloride layer is separated. The aq layer is extracted with (2x280ml) methylene chloride and the combined organic extract is washed with water at 30-35°C. The methylene chloride layer is dried and distilled out completely under vacuum at 30-35°C and degassed at 35-40°C under high

vacuum to obtain thick syrupy mass of free base of α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl)methylacetate (116-120g).

The above obtained free base is dissolved in (1.74lit) isopropanol at 30-35°C and (51.3g) L(+)-tartaric acid is added to it at 30-35°C under stirring. The temp of the reaction mixture is raised to 50-55°C then maintained at 65-70°C for 2 hours. The reaction mixture is gradually cooled to 30-35°C over a period of 1-2 hrs and the reaction mixture is seeded with (+)-α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl)methylacetate tartrate and stirred further for 18-20 hours at 30-35°C. The reaction mixture is gradually cooled to 0-5°C over a period of 3-4 hours and stirred further for 1-2 hours at 0-5°C. Then temp of reaction mixture is gradually raised to 15-20°C over a period of 2 hours and stirred at 15-20°C for 3-4 hours. The product, (S)-(+)-α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl)methylacetate tartrate is filtered at 15-20°C and washed with (120ml) chilled isopropanol and suck dried (46gm), $[\alpha]_D$=+88° (temperature 20°C, c=1, methanol). The mother liquor is preserved for further processing and is subjected to treatment as in Example 3$.

Table I summarises results observed for three experiments on resolution carried out as in Example 2.

No.	Input*	Output**	Rotation observed#
1	50g	22.7g	+ 88.19°
2	50g	20.0g	+ 88.61°
3	50g	19.8g	+ 89.02°

*racemic -α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate free base

**(+)-α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate tartrate

temperature 20°C, c=1, methanol

EXAMPLE 3

Recycling of (R)-enriched isomer of α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate/compound of formula 2/Compound of formula 3 to racemic α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate –

The $mother liquor (~14.5lit) resulting from the example 2 is subjected to distillation to remove solvent completely under vacuum at 45-50°C to obtain (~1kg) residue. To this

residue (5lit) methanol is added at 30°C and stirred to obtain a clear solution. To this solution, sodium methoxide solution (1lit, ~30%w/v) is added with stirring at 30°C. The reaction mixture is refluxed at 65-70°C and maintained for 2-3 hours and then cooled to 5-10°C. Methanolic HCl (1.43lit, 15-20%w/v) is added to it with stirring at temperature between 5-15°C. To this reaction mixture (5ml) N,N-dimethylformamide at 5-15°C is added followed by gradual addition of (555ml) thionyl chloride over a period of 2-3 hours by maintaining the reaction temperature between 5-15°C. Temperature is gradually raised to 30-35°C over 1-2 hours without external heating and reaction is maintained at 30-35°C for 12-15 hours. The solvent is distilled out from the reaction mixture under vacuum at 45-50°C to obtain a thick stirable suspension. To the reaction mixture at 30-35°C (5lit) DM water and (2lit) ethyl acetate is added and the reaction mass is stirred at 30°C for 1 hour. The reaction mass is basified by gradual addition of (~700ml) aqueous ammonia (25% w/v) at 15-20°C until the pH of the reaction mixture is 9-9.5, it is stirred for 15-20 minutes. The upper product enriched organic layer is separated. The aqueous layer is extracted with (2lit) ethyl acetate at 30°C. The combined organic layers are washed with aqueous NaCl (2% w/v) at 30°C. Ethyl acetate (3lit) is added to the product enriched organic layer and cooled to 5-10°C. Concentrated HCl acid (330ml) is added to it at 5-10°C and stirred for 2 hours. The crystallized product, racemic α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl) methylacetate hydrochloride is filtered and washed with chilled ethyl acetate (2x500ml) and suck dried. (0.38-0.42 kg).

EXAMPLE 4

Preparation of S-(+)-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2,c]-5-pyridyl-methylacetate bisulphate (clopidogrel bisulphate)-

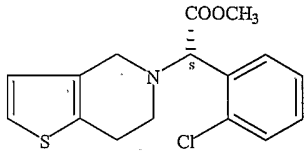
The (+)-tartrate salt of α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl)methylacetate prepared as in Example 2 above is converted to free base and then to its HCl salt. To this (+)-α-[(2-thien-2-yl)-ethylamino]-α-(2-chlorophenyl)methylacetate HCl salt in methanol at 30-32°C is added aq formaldehyde 37-41% solution and temp is raised to 55°C and maintained for 3-4 hours. The reaction mixture is cooled to about 30°C and water and methylene chloride are added to it. The quenched reaction mass is stirred at 30°c for 15 minutes and basified by gradual addition of sodium bicarbonate until pH of aqueous layer

is 7.5-8.0. The aqueous layer is extracted with methylene chloride and combined organic extracts are washed with water at about 30°C. The methylene chloride layer is charcolised, filtered and solvent is completely distilled out at 35-40°C under vacuum and degassed at 35-40°C under high vacuum to obtain thick syrupy mass of free base of clopidogrel.

The clopidogrel free base is dissolved in acetone at about 30°C and cooled to 15-20°C and aq. H_2SO_4 acid (90%) is added maintaining the temp at 15-20°C. the temp of the reaction mix is raised to 50-55°C and maintained for 2 hrs. The reaction mixture is cooled to 40-45°C and solvent is distilled out under vacuum to get thick white slurry. It is cooled to about 30°C and acetone is added to it. The suspension is cooled to 0-5°C and maintained for 2 hrs. The product is filtered and washed with chilled acetone, followed by n-hexane and suck dried. The product is dried at about 30°C under vacuum. $[\alpha]_D$=+56° (temperature 20°C, c=1, methanol).

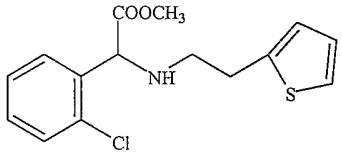
We claim:

1. A process for preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,



Formula 4

(a) resolving racemic α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, a compound of formula 1 or a salt thereof



Formula 1

to obtain S-isomer of a compound of formula 1 or a salt thereof and R-isomer of formula 1 or a salt thereof,

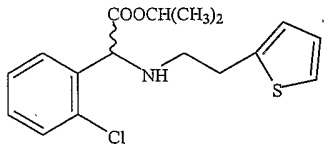
(b) racemizing the R-isomer of formula 1 or a salt thereof to obtain a racemic compound of formula 1 and optionally converting it into a salt thereof,

(c) optionally repeating steps 'a' and 'b',

(d) converting the S-isomer of compound of formula 1 obtained in step 'a' to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl) acetate.

2. The process as claimed in claim 1, wherein the racemization of the R-isomer of formula 1 is done in methanol in presence of sodium methoxide.

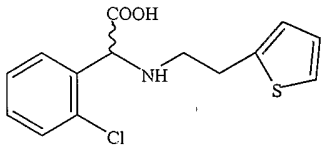
3. The process as claimed in claim 2, wherein the R-isomer of formula 1 contains an impurity of ester derivative or a salt thereof, represented by a compound of formula 2,



Formula 2

and the said impurity reacts with methanol to form a racemic compound of formula 1.

4. A process as claimed in claim 2, wherein the R-isomer of formula 1 contains an impurity of acid derivative or a salt thereof, represented by a compound of formula 3,

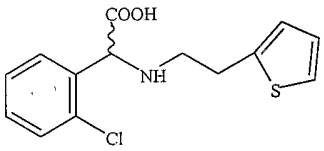


Formula 3

and wherein subsequent to racemization, the reaction mixture is acidified wherein the compound of formula 3 reacts with methanol to form a racemic compound of formula 1.

5. The process as claimed in claim 4, wherein the reaction mixture is acidified by treatment with methanolic HCl.

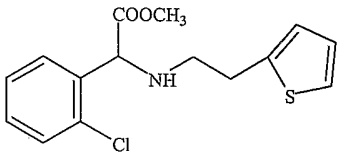
6. A process as claimed in claim 2, wherein the R-isomer of formula 1 contains an impurity of acid derivative or a salt thereof, represented by a compound of formula 3,



Formula 3

and wherein subsequent to racemization, the reaction mixture is treated with thionyl chloride wherein the compound of formula 3 reacts with methanol to form a racemic compound of formula 1.

7. A process for preparation of S-isomer of α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl) methylacetate, a compound of formula 1 or a salt thereof



Formula 1

comprising,

1) treating the racemic compound of formula 1 with L(+)-tartaric acid in isopropanol as the reaction solvent,

2) cooling the resultant solution in the reaction solvent in a controlled manner, comprising the steps of

   i) cooling the solution gradually to ambient temperature under slow stirring,

   ii) maintaining the solution at ambient conditions for about 2 to about 24 hours,

   iii) cooling the solution gradually to about 0 to about 5°C,

   iv) raising the temperature of the solution gradually to about 15-20°C,

3) isolating the (+)-tartrate salt of the S-isomer of compound of formula 1, from the reaction solvent,

4) obtaining the S-isomer of compound of formula 1 from the (+)-tartrate salt of the compound of formula 1 in a known manner, if desired converting the S-isomer of compound of formula 1 to an acid addition salt thereof.

8. The process as claimed in claim 7, wherein cooling the resultant solution in the reaction solvent in a controlled manner, comprising the steps of

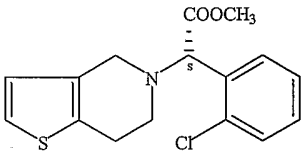
i) cooling the solution gradually to 30-35°C over the period of 1 to 2 hours under slow stirring, and optionally seeding with a crystal of (+)-tartrate salt of the dextrorotatory compound of formula 1,

ii) maintaining the solution at 30-35°C for about 18 to about 20 hours,

iii) cooling the solution gradually to about 0 to about 5°C over a period of about 3 to 4 hours and maintaining the temperature for about 1 to about 2 hours,

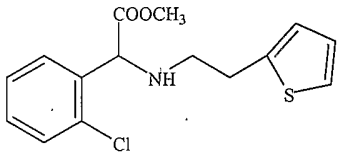
iv) raising the temperature of the solution gradually to about 15-20°C over a period of about 2 hours and maintaining the temperature for about 3 to about 4 hour.

9. A process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,



Formula 4

(a) racemizing the R-isomer of α-[(2-thien-2-yl)ethylamino]-α-(2-chlorophenyl)methylacetate, a compound of formula 1 or a salt thereof



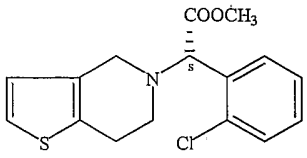
Formula 1

to obtain a racemic compound of formula 1,

(b) resolving the racemic compound of formula 1 to obtain S-isomer of compound of formula 1,

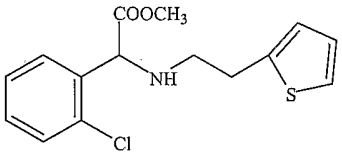
(c) converting the S-isomer of compound of formula 1 to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate.

10. A process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,

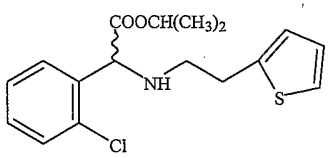


Formula 4

(a) reacting a compound of formula 2 with methanol in presence of sodium methoxide to obtain a racemic compound of formula 1,



Formula 1

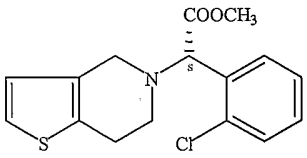


Formula 2

(b) resolving the racemic compound of formula 1 to obtain S-isomer of compound of formula 1,

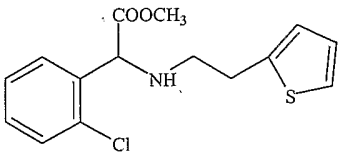
(c) converting the S-isomer of compound of formula 1 to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate.

11. A process for the preparation of S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate, a compound of formula 4, or a salt thereof comprising,

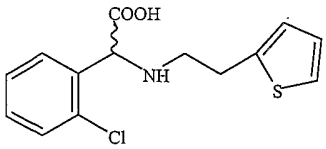


Formula 4

(a) reacting a compound of formula 3 with methanol to obtain a racemic compound of formula 1,



Formula 1



Formula 3

(b) resolving the racemic compound of formula 1 to obtain S-isomer of compound of formula 1,

(c) converting the S-isomer of compound of formula 1 to S-isomer of methyl α-(4,5,6,7-tetrahydro-5-thieno[3,2-c]pyridyl)(2-chlorophenyl)acetate.