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(54) **Title**: PROCESS FOR PREPARING (4S, 6S)-4-(ETHYLAMINO)-5,6-DIHYDRO-6-METHYL-4H-THIENO-[2,3-B]THIOPYRAN-2-SULFONAMIDE-7,7-DIOXIDE AND ITS INTERMEDIATES

(57) **Abstract**: Disclosed herein is an improved process for the preparation of (4S,6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7- dioxide (Dorzolamide) and its intermediates.

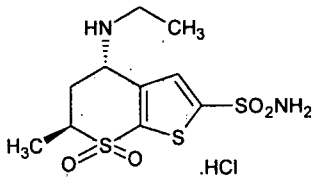
PROCESS FOR PREPARING (4S, 6S)-4-(ETHYLAMINO)-5,6-DIHYDRO-6-METHYL-4H-THIENO-[2,3-B]THIOPYRAN-2-SULFONAMIDE-7,7-DIOXIDE AND ITS INTERMEDIATES

Field of the Invention

The present invention relates to an improved process for preparing (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (Dorzolamide) and its intermediates.

Background of the Invention

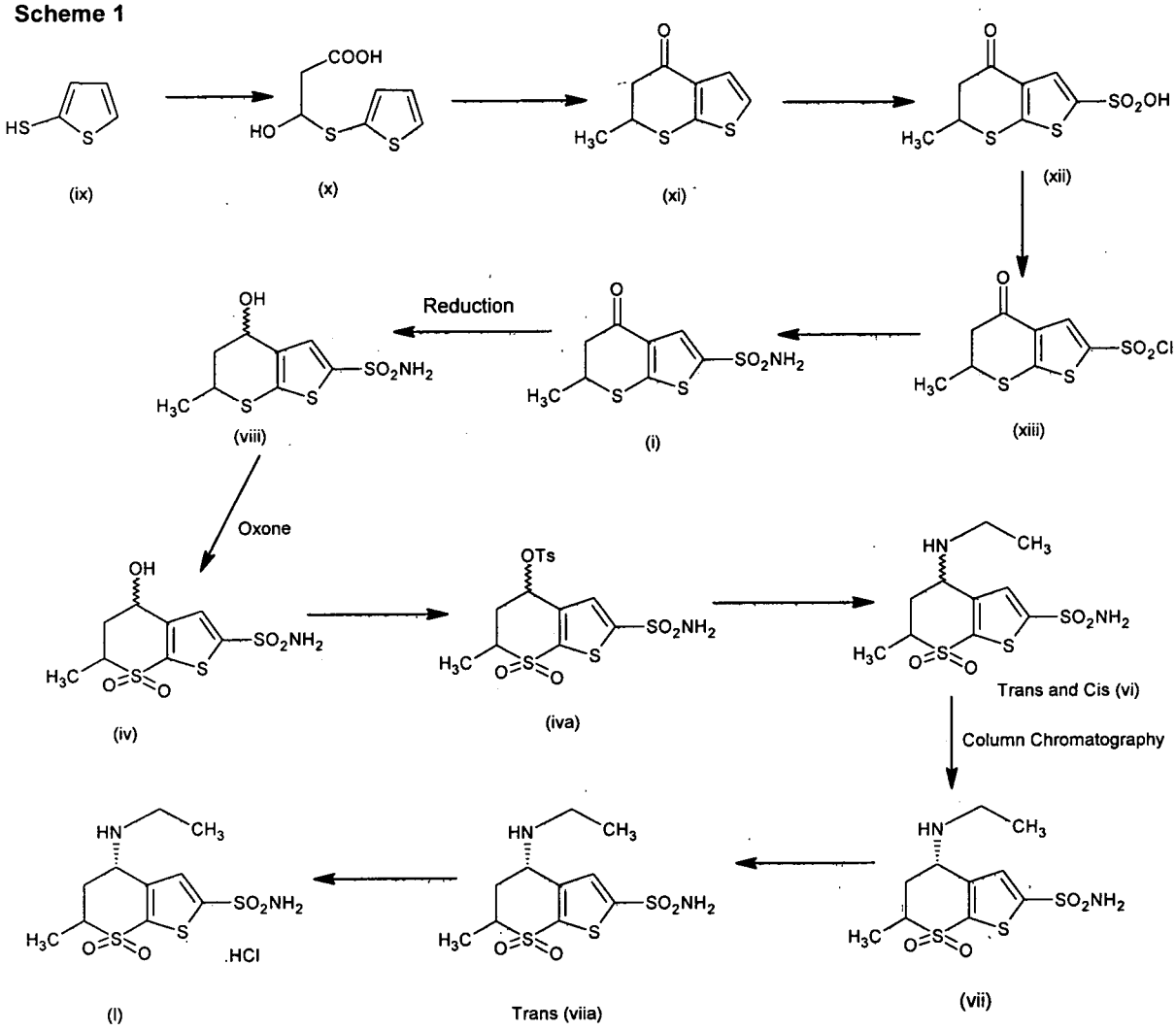
Dorzolamide, chemically known as (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide was first disclosed in US 4,797,413. The pharmaceutically acceptable salt of Dorzolamide is its hydrochloride salt. Dorzolamide HCl (I) is a carbonic anyhdrase inhibitor used for treating or ameliorating ocular hypertension.



Formula - I

US 4,797,413 discloses two schemes for making Dorzolamide as shown in Scheme 1 and Scheme 2. According to Scheme 1, Dorzolamide is prepared from Thiophene 2- thiol comprising reduction of keto sulfone at RT at overnight stirring followed by oxidation using oxone and final separation using column chromatography. Whereas in the other process Dorzolamide is prepared from aliphatic hydroxyl followed by separation of trans isomer.

Scheme 1


HS
S
(ix)
COOH
HO
S
S
(x)
O
H3C
S
S
(xi)
O
SO2OH
H3C
S
S
(xii)
O
SO2Cl
H3C
S
S
(xiii)
Reduction
O
SO2NH2
H3C
S
S
(i)
OH
SO2NH2
H3C
S
S
(viii)
Oxone
OH
SO2NH2
H3C
O=S=O
S
(iv)
OTs
SO2NH2
H3C
O=S=O
S
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HN
CH3
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H3C
O=S=O
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Trans and Cis (vi)
Column Chromatography
HN
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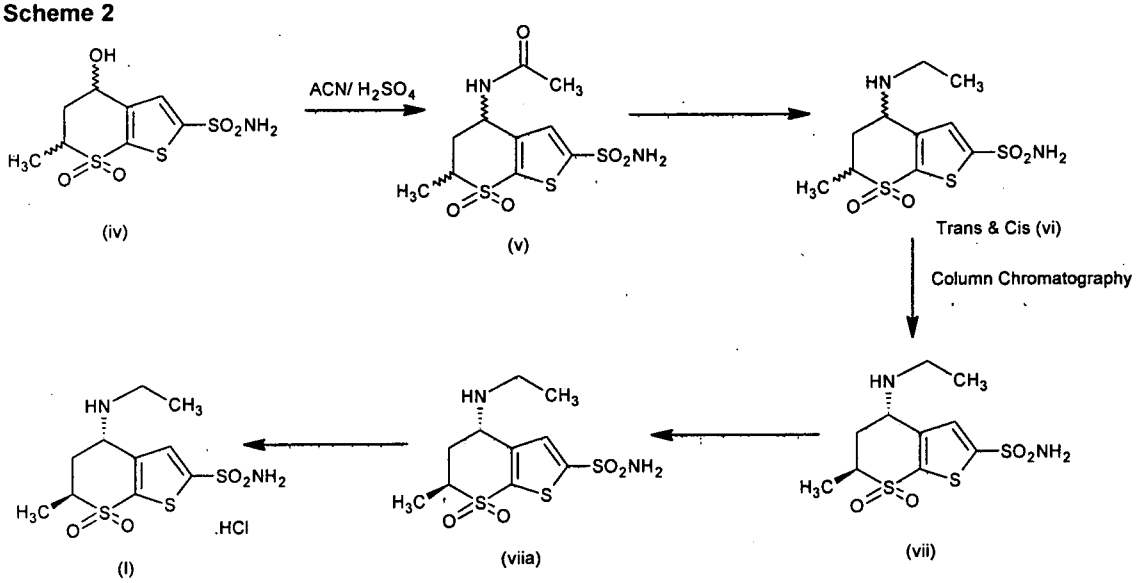
.HCl
(I)

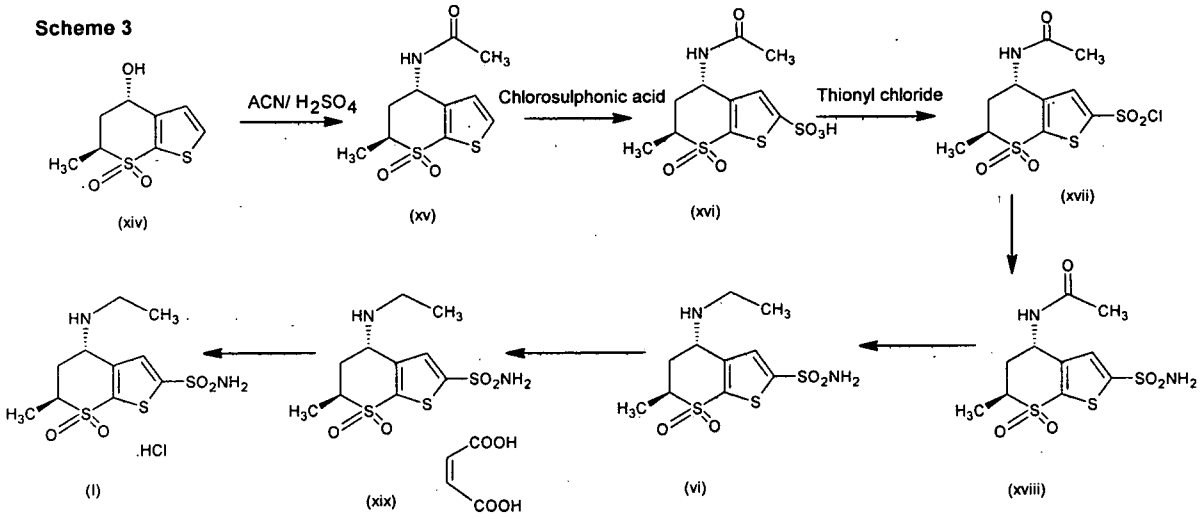
Scheme 2



The processes disclosed above are longer, multi step, involving use of oxone and column chromatography, which is not commercially feasible, whereas in Scheme 2 water is added into reaction mass consisting of concentrated sulfuric acid, which is a highly exothermic reaction.

US 5,688,968 discloses the process for preparation of dorzolamide from 4-hydroxy sulfone in seven steps as given in Scheme 3. The reaction involves Ritter reaction followed by formation of dorzolamide hydrochloride by using chlorosulphonic acid and thionyl chloride in a series of steps.

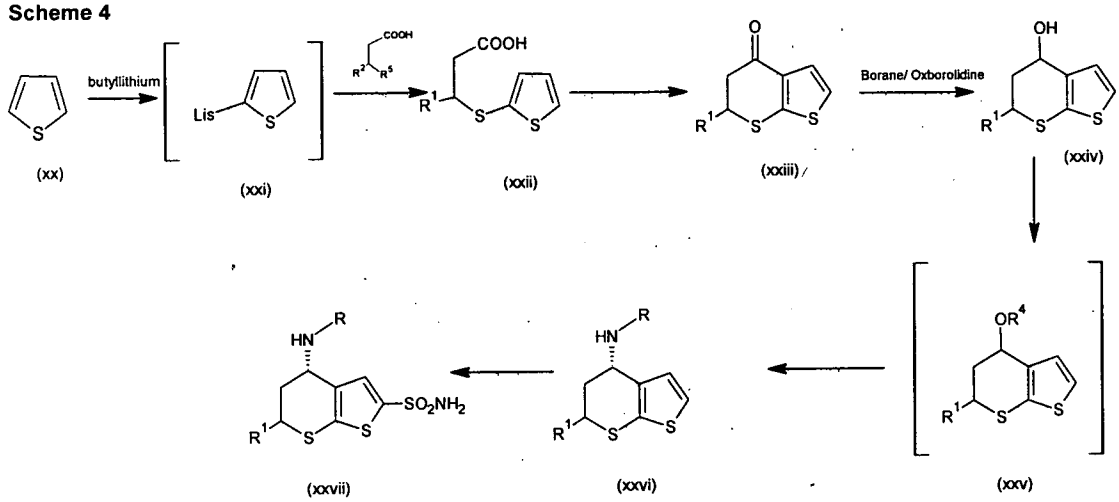
Scheme 3



The process uses chiral hydroxy sulfone as starting material, which is a costly reagent and involves use of chlorosulphonic acid and thionyl chloride, which are not industry friendly reagents.

US 5,157,129 discloses another alternate process for preparing dorzolamide as given in Scheme 4. The process involves thiophene as starting material which is converted to dorzolamide in 8 steps involving butyllithium for making the lithium salt of thiophene and borane in presence of oxoborolidine for reduction of keto (xxiii) form to hydroxy form (xxiv).

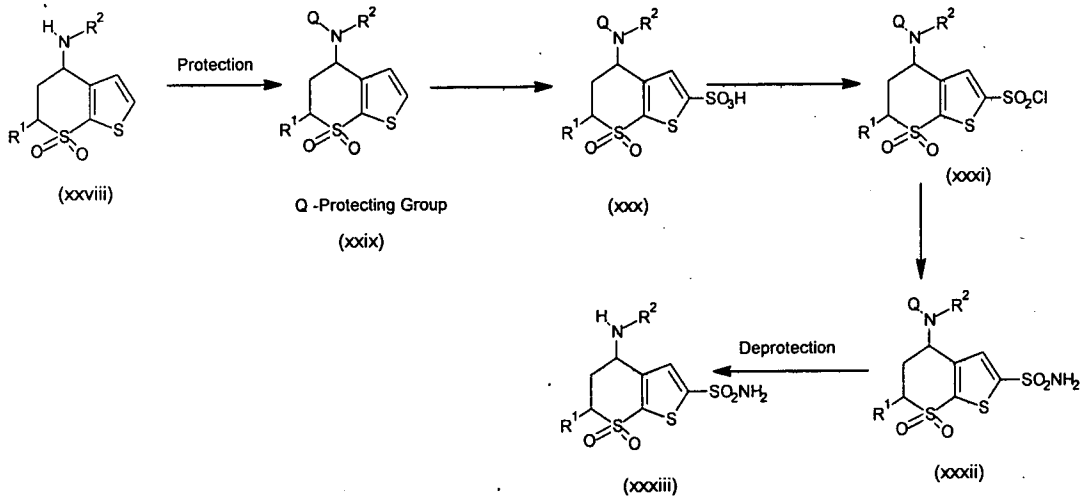
Scheme 4



The process involves butyllithium, which is a pyrophoric chemical and uses borane in presence of oxaborolidine catalyst, which is an expensive reagent to be used, thereby making the process unamenable for industrial scale production.

Another process of making dorzolamide is disclosed in US 7,030,250. The process as given in Scheme 5 involves protection of nitrogen by chloroacetyl chloride followed by a series of reactions to form final dorzolamide by deprotection of nitrogen.

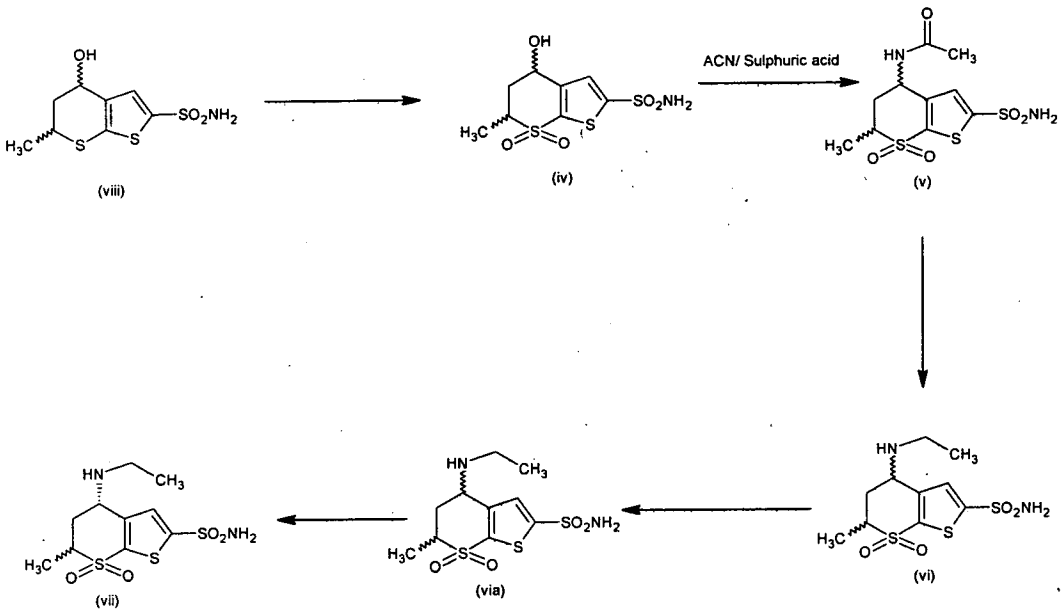
Scheme 5



The process uses advance intermediate (xxviii), which is a costly intermediate to start with and uses protection and deprotection steps, which affects the impurity profile of the final molecule.

PCT application WO 2008/135770 discloses another process for preparing dorzolamide as given in Scheme 6. The process involves oxidation of sulfide (viii) to sulfone (iv) and Ritter reaction to form dorzolamide.

Scheme 6



The use of gaseous ammonia to quench excess sulphuric acid is not advisable on industrial scale as gaseous ammonia is irritating to eyes, nose and throat. The reaction also involves unnecessary filtration of ammonium sulphate, thus formed.

In light of the foregoing discussion there still exists a need for an improved process for large scale production of dorzolamide that overcomes the drawbacks associated with the existing processes.

Objects and Summary of the Invention

The first object of the present invention is to prepare highly pure (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide by a simple commercial process.

Another object of the present invention is to prepare (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide by a novel process employing an intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide of formula (iv).

Yet another object of the present invention is to disclose a novel process for preparing said intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide of formula (iv).

Still another object of the present invention is to prepare (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride employing the said intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide of formula (iv) by using a simple, economic and industrially scalable process

Yet another object of the invention is to separate the cis isomer of (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide to maximize the yield of pure trans (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

The above and other objects of the present invention are further attained and supported by the following embodiments described herein. However, the scope of the invention is not restricted to the described embodiments herein after.

In accordance with one embodiment of the present invention, there is provided a process for preparing (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide comprising oxidizing 6-methyl-4-oxo-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide (ii) to give 6-methyl-4-oxo-5,6-

dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (iii), reducing 6-methyl-4-oxo-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (iii) to give 4-hydroxy-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (iv), reacting 4-hydroxy-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (iv) with acetonitrile in presence of acid to form N-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-yl)acetamide (v), followed by reducing the N-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-yl)acetamide (v) to give racemic mixture of 4-(ethylamino)6-methyl-5,6-dihydroxy dihydro-4H-thieno[2,3,b]thiopyran -2-sulfonamide-7,7-dioxide (vi) (Racemic dorzolamide), subsequently separating trans (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide from racemic (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (dorzolamide) by making acid addition salt with carboxylic acid and resolving with a suitable resolving agent to obtain pure trans (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (vii).

In accordance with another embodiment of the present invention, there is provided a novel process for synthesis of intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (hydroxy sulfone (iv)) from 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (keto sulfide (ii)). The reaction proceeds by oxidation of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (keto sulfide (ii)) to form 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (keto sulfone (iii)) followed by reduction to form 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iv) (hydroxy sulfone). The reaction may be done with or without isolating the intermediate 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (keto sulfone (iii)).

In accordance with still another embodiment of the present invention there is provided a process for preparing the intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iv) from 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (ii) comprising the steps of oxidizing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (ii) to give 6-methyl-4-oxo-

5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii) and reducing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii) to give 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iv).

In accordance with still another embodiment of the present invention, there is provided trans (-) Dorzolamide hydrochloride having a purity of at least 95%, preferably at least 97%, more preferably at least 99.5%.

Detailed Description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention discloses an improved process for preparing (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (dorzolamide) by a novel process employing an intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (hydroxy sulfone) (formula (iv)).

The improved process for preparing dorzolamide comprises the steps of:

a) oxidizing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (ii) to give 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii),

b) reducing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii) to give 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iv),

c) reacting 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide- 7,7-dioxide (iv) with acetonitrile in presence of acid to form *N*-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide (v),

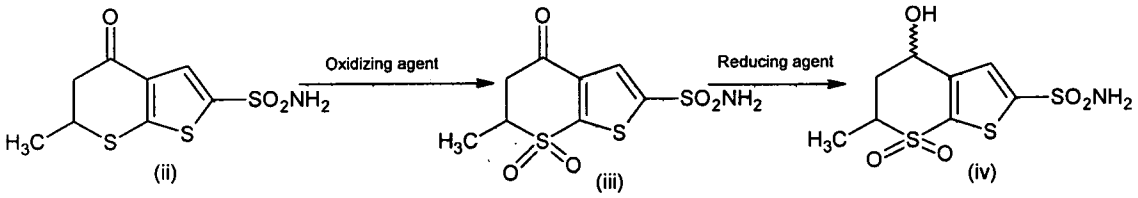
d) reducing *N*-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide (v) to give racemic mixture of 4-(ethylamino)6-methyl-5,6-dihydroxy dihydro-4H-thieno[2,3,b]thiopyran -2-sulfonamide-7,7-dioxide (vi) (racemic dorzolamide),

e) separating trans dorzolamide from racemic Dorzolamide by making acid addition salt with carboxylic acid, and

f) obtaining pure trans dorzolamide (vii) by resolving with a suitable resolving agent.

Further, the present invention provides a novel process for synthesis of the intermediate 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (hydroxy sulfone (iv)) from 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (keto sulfide (ii)). The reaction proceeds by oxidation of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (keto sulfide (ii)) to form 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (keto sulfone (iii)) followed by reduction to form 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (hydroxy sulfone (iv)).

The reaction may be done with or without isolating the intermediate 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (keto sulfone (iii)).



The oxidizing agent used for oxidation of (ii) to (iii) is selected from per acids such as peroxy benzoic acid, m-chloro per benzoic acid, peracetic acid, peroxytrifluoro acetic acid, perboric acid, performic acid, peroxy maleic acid, peroxy dichloro maleic acid, sodium hypchlorite and hydrogen peroxide. Preferably, the oxidizing agent is hydrogen peroxide. This oxidation is optionally catalyzed by using a salt of tungstic acid preferably, sodium tungstate.

Oxidation of keto sulfide (ii) to the keto sulfone (iii) thus preferably takes place in the presence of a solvent using hydrogen peroxide proceeds in good yield, particularly when the reaction is catalyzed by tungstic acid or sodium tungstate, preferably sodium tungstate. The use of hydrogen peroxide is industrially feasible as it is cheap, easily handled and non-polluting.

Solvents used for the above reaction are esters such as ethyl acetate, isopropyl acetate; alcohols like methanol, ethanol, n-propanol, isopropanol, butanol; ethers like diethylether, diisopropylether, tetrahydrofuran, 1,4-dioxan; chlorinated solvents like dichloromethane, chloroform, monochloro benzene; acids such as acetic acid, sulphuric acid, trifluoroacetic acid; hydrocarbons such as toluene, benzene, xylene and the mixtures thereof, preferably ethyl acetate. The advantage of using ethyl acetate is that it reduces the reaction time to about 1 hr. The excess peroxide left in the reaction mass is decomposed or quenched by using sodium sulphite, manganese dioxide, sodium bisulphate, sodium thiosulphite, preferably sodium sulphite, as against evaporation of reaction mass containing oxidant, as reported in the prior art. Thus, use of hydrogen peroxide reduces cost, simplifies work up and minimizes effluent disposal.

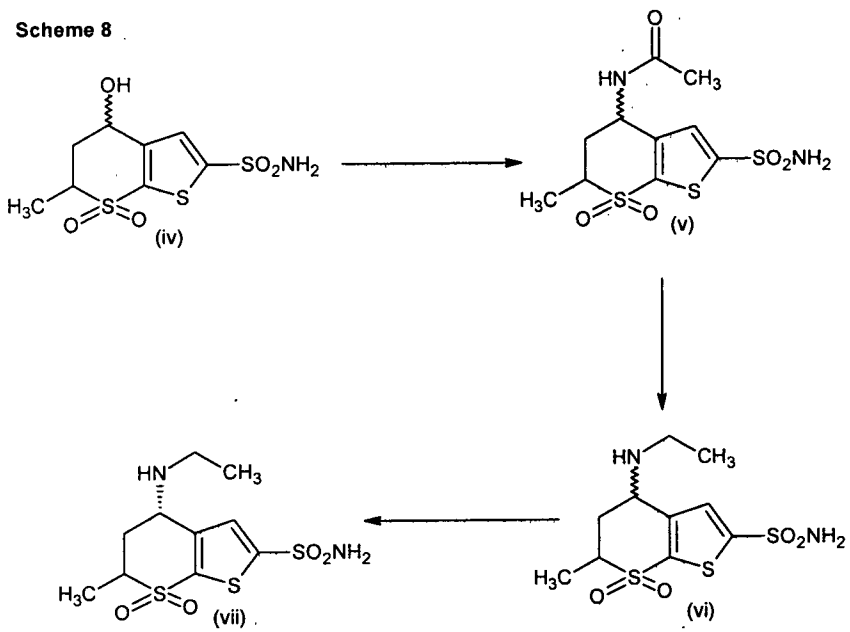
The reducing agent used in reduction of (iii) to (iv) is selected form groups of metal borohydride such as alkali and alkaline metal borohydrides i.e., sodium borohydride, lithium borohydride, potassium borohydride, preferably sodium borohydride.

A solvent is used in the reduction step and may be selected from protic solvents such as water, ethanol, methanol, isopropanol, n-propanol, butanol and mixture of alcohol with hydrocarbons and chlorinating solvents such as benzene, toluene, dichloromethane, mono chlorobenzene, esters with alcohols and mixture thereof.

The addition of borohydride is done in lots to avoid any effervescence formation and blurting out reaction mass. Excess borohydride is decomposed by using acids like acetic acid, hydrochloric acid, sulphuric acid, preferably acetic acid. Use of sodium borohydride is very feasible in the industry as it reduces cost, simplifies work up and minimizes effluent disposal.

The process of conversion of keto sulfide (ii) to hydroxy sulfone (iv) via keto sulfone (iii) may be preceded with or without isolating the intermediate keto sulfone (iii). The hydroxyl sulfonamide of formula (iv) may be converted to dorzolamide by using prior art methods. In accordance with the invention, the conversion of hydroxyl sulfone (iv) to dorzolamide is done by preparing acetamide sulfone of formula (v) by Ritter reaction as given in Scheme 8 with acetonitrile in presence of acid.

Scheme 8



The reaction is carried out in acetonitirile, which acts both as a solvent and as a reagent in presence of strong acid e.g., sulfuric acid. The process has an edge over the prior art:

a) The volume of sulphuric acid used is less than 7 moles.

b) The reaction is completed in 4-5 hrs.

Excess of sulphuric acid is quenched by using organic bases such as methylamine, ethylamine, triethylamine or inorganic bases such as aqueous ammonia, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, preferably aqueous ammonia. The acetamido sulfone (v) is then reduced to a mixture of cis and trans dorzolamide of formula (vi) using a suitable reducing agent selected from sodium borohydride or lithium aluminium hydride with borontrifluoride diethyl ether or borane methyl sulfide, preferably sodium borohydride with borontrifluoride diethylether. The product is obtained by retention of the cis-trans ratio.

Further, the separation of cis and trans isomers may be done by using a carboxylic acid selected from the group consisting of maleic acid, p-toluyl tartaric acid and p-hydroxy benzoic acid, preferably maleic acid. The racemic mixture may be treated with maleic acid to remove the cis isomer. Thus, the mixture of trans isomer and cis isomer of dorzolamide contains not more than 5% of cis isomer. The dorzolamide maleate thus

obtained is having trans content of at least 95%, preferably at least 97% and more preferably 99%.

The solvent used in reaction with a carboxylic acid may be selected from a group of alcohols, esters, hydrocarbons, ketones preferably, esters and more preferably, ethyl acetate either alone or in a mixture.

The acid addition salt is used for separation of cis and trans isomers thus, obtained which corresponds to carboxylic acid. The acid used for salt formation is selected from the group consisting of a carboxylic acid such as fumaric acid, maleic acid, benzoic acid, salicylic acid, p-toluyl tartaric acid and p-hydroxy benzoic acid or benzoic acid preferably maleic acid. The salt preparation is then carried out in the presence of organic solvent such as a ketone, ester, alcohol, aliphatic or aromatic hydrocarbon, or mixtures there of, particularly ethyl acetate.

The dorzolamide maleate thus obtained contains trans dorzolamide maleate having a percentage of cis isomer of below 1%.

The purification of trans Dorzolamide to get rid of cis Dorzolamide is carried out without using any organic solvent. The trans Dorzolamide thus, obtained is highly pure.

The salt of trans isomer is further purified by removing cis isomer as obtained above, in water, without using any organic solvent. Dorzolamide maleate crude is taken in about 10 volumes of water and heated to reflux and cooled to RT and filtered to get pure trans dorzolamide maleate.

The trans dorzolamide maleate thus formed may be converted to trans dorzolamide base (vi) by any of the conventional methods.

The trans dorzolamide base (vi) is then resolved using chiral resolving agents like di-p-toluyl-(L) tartaric acid. The solvents used is selected from polar protic or aprotic solvents or nonpolar solvents or mixtures thereof, preferably a mixture of polar protic and an aprotic solvent , most preferably a mixture of isopropanol and acetonitrile.

The salt of dorzolamide and resolving agent, for example dorzolamide di-p-toluyl-L-tartarate salt, is then converted to the hydrochloride salt by using hydrochloric acid gas in alcoholic solvent, preferably isopropanol, either by isolating the base or without isolating the base.

The following non-limiting examples illustrate specific embodiments of the present invention. They should not construe it as limiting the scope of present invention in any way.

The following examples justify the scope of the invention:

Example-1

Preparation of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide

A suspension of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (100 gms), 5 gms of sodium tungstate dihydrate in ethyl acetate (400 ml) and water (50 ml) were cooled to 20^{0}C. To the above cooled solution hydrogen peroxide was added over a period of 45 minutes by maintaining the temperature less than 20^{0}C. The reaction mass was stirred for 45-60 minutes. The reaction progress was monitored by TLC. The excess hydrogen peroxide was destroyed by adding the aqueous Na_2SO_3 and stirred for 30 minutes. The reaction mass was cooled to 10^{0}C, followed by filtration to get title compound (98 gms).

Example-2

Preparation of 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide

A suspension of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide (95 gms) in methanol (400 ml) was cooled to 10^{0}C and sodium borohydride (7.5 gms) was added in lots maintaining the temperature less than 20^{0}C. Reaction mass was stirred for another 30-45 minutes. The reaction progress was monitored by TLC. The reaction mass pH was adjusted to 5-6 using acetic acid. Solvent was distilled out from the reaction mass completely under vacuum. Water was added to the residue and stirred for 20-30 minutes and filtered to get the title compound (84 gms).

Example-3

Preparation of *N*-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide

To 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (200 gms) in acetonitrile (2000 ml) was added sulphuric acid 98% (300 ml) drop wise at 0-5^{0}C over a period of 45-60 minutes. The reaction mass was allowed to

warm to room temperature (25-30^{0}C) and stirred for 4 -5 hours. The progress of the reaction was monitored by TLC. Once the reaction was completed, the reaction mass was quenched in ice cold water (1400ml) below 10^{0}C. The reaction mass pH was adjusted to 7.0-8.0 using aqueous ammonia and stirred for 10 -15 minutes. The organic layer was separated from the reaction mixture, and distilled out the solvent completely under vacuum. Water was added to the resultant residue and stirred for 10 minutes. The title compound was isolated from the water by filtration (175 gms)

Example-4

Preparation of 4-(ethyl amino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide maleate salt

a) A suspension of *N*-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide (200 gms) in tetrahydrofuran 1000 ml was cooled to –5^{0}C and sodium borohydride (70 gms) was added portion wise over a period of 20-30 minutes by maintaining temperature less than 5^{0}C. Reaction mass was stirred for 15-20 minutes. Boron trifluoride diethyletherate (300ml) was added dropwise by maintaining the temperature below 5^{0}C over a period of 80-90 minutes. The reaction mass was stirred for 3-4 hours at room temperature. Reaction progress was monitored by HPLC. The reaction mass was cooled to 0^{0}C and 300 ml of methanol was added followed by 1M sulphuric acid (2000 ml). The reaction mass was stirred at 40-45^{0}C for 50-60 minutes. The organic solvent was distilled under reduced pressure. The reaction mass was cooled to 5-10^{0}C and pH adjusted to 7.0-8.0 using sodium hydroxide solution. The material was extracted twice with ethyl acetate (Chiral HPLC Purity 80:20). To this ethyl acetate solution 100 gms of maleic acid was added and the reaction mass was stirred for 2 hrs at reflux temperature. Cooled the reaction mass and filtered. The resultant crude maleate salt was purified with water to get rid of the cis isomer to obtain pure compound (Chiral HPLC: 99.9 : < 0.1:: Trans: Cis.).

b) The above obtained maleate salt was treated with sodium hydroxide solution pH 7.5-8.0) at room temperature for 25-30 minutes and filtered the reaction mass to get the racemic Dorzolamide. (115 gms) (Chiral HPLC purity 99.8 %:0.2% ::trans:cis).

Example-5

Preparation of Dorzolamide hydrochloride

a) A mixture of 4-(ethyl amino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (75 gms), isopropanol (600 ml) and acetonitrile (325 ml) was heated to 70^{0}C. Di-para toluoyl (L) tartaric acid (35.8 gms) was added at 70^{0}C. The reaction mass was refluxed for 1 hour and cooled to room temperature and stirred for 60-90 minutes. The taratrate salt of Dorzolamide was isolated by filtration and recrystallized in isopropanol andacetonitrile(34 gms).

trans(-) Dorzolamide di-p-toluoyl-L-taratrate >99.5%

trans (+) Dorzolamide di-p-toluoyl-L-taratrate <0.5% by HPLC

b) Dorzolamide di-p-toluyl L-tartate salt (28 gms) was taken into ethyl acetate (200 ml) and basified with sodium bicarbonate solution. Reaction mass was stirred for 15-20 minutes at room temperature and the layers were separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were distilled out completely under reduced pressure .The resultant residue was dissolved in methanol and treated with isopropanol/ hydrochloride and stirred for 40 minutes and filtered to get the title compound (18 gms).

Example-6

One pot synthesis of 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide

A suspension of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (100 gms), 5 gms of sodium tungstate dihydrate in ethyl acetate (400 ml) and water (50 ml) was cooled to 20^{0}C. To the above cooled reaction mass hydrogen peroxide was added over a period of 45 minutes by maintaining the temperature less than 20^{0}C. The reaction mass was stirred for 45-60 minutes. The reaction progress was monitored by TLC. The excess hydrogen peroxide was destroyed by adding the aqueous sodium sulphite and stirred for 30 minutes. Methanol (100 ml) was added to the above reaction mass and cooled to 10^{0}C. Sodium borohydride (7.5 gms) was added in lots by maintaining the temperature less than 20^{0}C. The reaction mass was stirred for 30-45 minutes, and the reaction progress was monitored by TLC. The reaction mass was kept at room temperature and separated the layers and extracted the aqueous layer twice with ethyl acetate. Combined organic layers and solvent was distilled out completely under

vacuum. Water was added to the resultant residue and stirred for 20-30 minutes and filtered the reaction mass to get the title compound (95 gms).

Certain modification and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.

We Claim:

1 A process for preparing (4S, 6S)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (Dorzolamide) comprising:

a) oxidizing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (ii) to give 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii);

b) reducing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii) to give 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iv);

c) reacting 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide- 7,7-dioxide (iv) with acetonitrile in presence of acid to form *N*-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide (v);

d) reducing *N*-(6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide (v) to give racemic mixture of 4-(ethylamino)6-methyl-5,6-dihydroxy dihydro-4H-thieno[2,3,b]thiopyran -2-sulfonamide-7,7-dioxide (vi) (Racemic Dorzolamide);

e) separating trans Dorzolamide from racemic Dorzolamide by making acid addition salt with carboxylic acid; and

f) obtaining pure trans Dorzolamide (vii) by resolving with a suitable resolving agent.

2. The process according to claim 1, wherein the oxidation is carried out using oxidizing agent selected from per acids consisting of peroxy benzoic acid, m-chloro per benzoic acid, peracetic acid, peroxytrifluoro acetic acid, perboric acid, performic acid, peroxy maleic acid, peroxy dichloro maleic acid and hydrogen peroxide.

3. The process according to claim 2, wherein the oxidizing agent is hydrogen peroxide.

4. The process according to claim 1, wherein the oxidation is optionally catalyzed by tungstic acid or a salt of tungstic acid.

5. The process according to claim 4, wherein the salt of tungstic acid is sodium tungstate.

6. The process according to claim 1, wherein the oxidation is carried out in presence of a solvent selected from the group consisting of esters such as ethyl acetate, isopropyl acetate; alcohols like methanol, ethanol, n-propanol, isopropanol, butanol; ethers like diethylether. diisopropylether, tetrahydrofuran, 1,4-dioxan; chlorinated solvents like dichloromethane, chloroform, monochloro benzene; acids such as acetic acid, sulphuric acid, trifluoroacetic acid; hydrocarbons such as toluene, benzene, xylene and a mixture thereof.

7. The process according to claim 6, wherein the solvent is ethyl acetate.

8. The process according to claim 1b, wherein the reduction is carried out using a reducing agent selected from metal borohydride such as sodium borohydride, lithium borohydride, potassium borohydride.

9. The process according to claim 8, wherein the reducing agent is sodium boro hydride.

10. The process according to claim 1b, wherein the reduction is carried out in presence of a solvent selected from the group of protic solvents such as water, ethanol, methanol, isopropanol, n-propanol, butanol; and mixture of alcohol with hydrocarbons and chlorinating solvents such as benzene, toluene, dichloromethane, mono chlorobenzene and mixture thereof.

11. The process according to claim 10, wherein the solvent is methanol.

12. The process according to claim 1b, wherein the reduction of 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide (iii) proceeds with or without isolating the same.

13. The process according to claim 3, wherein the process further comprises of optionally decomposing excess peroxide present in the reaction mass after the oxidation, by quenching the reaction mass in a solution of sodium sulphite, manganese dioxide, sodium bisulphate, sodium thiosulphite, preferably sodium sulphite.

14. The process according to claim 1, wherein the acid is sulphuric acid.

15. The process according to claim 14, wherein the sulphuric acid is neutralized by using organic bases such as methylamine, ethylamine, triethylamine or inorganic bases such as aqueous ammonia, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, preferably aqueous ammonia.

16. The process according to claim 1d, wherein the reduction is carried out using the reducing agent selected from sodium borohydride or lithium aluminium hydride with borontrifluoride diethyl ether or borane methyl sulfide, preferably sodium borohydride with borontrifluoride diethyl ether.

17. The process according to claim 1, wherein the carboxylic acid is selected from maleic acid, benzoic acid, fumaric acid, salicylic acid and p-hydroxy benzoic acid.

18. The process according to claim 17, wherein the carboxylic acid is maleic acid.

19. The process according to claim 1, wherein the acid addition salt is further purified in water.

20. The process according to claim 1, where in the resolving agent used is di-para toluoyl-L(-)- tartaric acid, D(+)-tartaric acid, D(+)- mandelic acid, preferably di-para-toluoyl-L(-) –tartaric acid.

21. The process according claim 1, wherein the resolution is carried out in a solvent selected from a polar protic or aprotic solvent or a nonpolar solvent or mixtures thereof.

22. The process according to claim 21, wherein the solvent used is a mixture of isopropanol and acetonitrile.

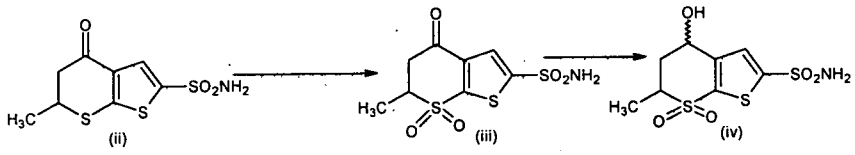
23. The process according to claim 1, wherein the Dorzolamide is further converted into hydrochloride salt using hydrochloric acid gas in alcoholic solvent.

24. The process according to claim 23, wherein the alcoholic solvent is isopropanol.

25. A process for preparing 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide of formula (iv) comprising:

a) oxidizing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide (ii) to give 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii); and

b) reducing 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii) to give 4-hydroxy-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iv).



26. The process according to claim 25, wherein the oxidation is carried out using oxidizing agent selected from group consisting of peroxy benzoic acid, m-chloro per benzoic acid, peracetic acid, peroxytrifluoro acetic acid, perboric acid, performic acid, peroxy maleic acid, peroxy dichloro maleic acid and hydrogen peroxide.

27. The process according to claim 26, wherein the oxidizing agent is hydrogen peroxide.

28. The process according to claims 25, wherein the oxidation is catalyzed by tungstic acid or a salt of tungstic acid.

29. The process according to claim 28, wherein the salt of tungstic acid is sodium tungstate.

30. The process according to claim 26, wherein the oxidation is carried out in presence of a solvent selected from the group of esters such as ethyl acetate, isopropyl acetate, alcohols like methanol, ethanol, n-propanol, isopropanol, butanol, ethers like diethylether, di-isopropylether, tetrahydrofuron, 1,4-dioxan, chlorinated solvents like dichloromethane, chloroform, monochloro benzene, acids such as acetic acid, sulphuric acid, trifluoroacetic acid, hydrocarbons such as toluene, benzene, xylene and the mixtures thereof.

31. The process according to claim 30, wherein the solvent is ethyl acetate.

32. The process according to claim 25, wherein the reduction is carried out using reducing agent selected from a group consisting of metal borohydride such as sodium borohydride, lithium borohydride, potassium borohydride, preferably sodium borohydride

33. The process according to claim 25, wherein the reduction is carried out in presence of a solvent selected from the group consisting of protic solvents such as water, ethanol, methanol, isopropanol, n-propanol, butanol, hydrocarbons and chlorinating solvents with alcohol such as benzene toluene, dichloromethane, mono chlorobenzene and mixture thereof.

34. The process according to claim 33, wherein the solvent is methanol.

35. The process according to claim 25, wherein the reaction proceeds with or without isolating 6-methyl-4-oxo-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide (iii).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 10/01973

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 335/04; C07D 335/06; C07D 495/00 (2010.01)
USPC - 549/23
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)
USPC: 549/23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/432

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: PGPB, USPT, USOC, EPAB, JPAB
Google: Scholar/patents: synthesis dorzolamide oxidation hydrogen peroxide sodium borohydride trans isomer sodium sulphite sulphuric acid ethyl acetate reduction sodium borohydride tartaric maleic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	WO 2008/135770 A2 (KANKAN et al.) 13 November 2008 (13.11.2008) pg 5, ln 3-6; pg 6; pg 8, ln 3-25; pg 9, 1-26; pg 10, ln 1-22; pg 11, ln 1-8; pg 12, ln 10-17; pg 17, ln 1-10; pg 21, ln 19-30	1-9, 13-32 ---------- 10-12, 33-35
Y	US 7,109,353 B2 (GURJAR et al.) 19 September 2006 (19.09.2006) col 6, ln 40-45; col 7, ln 1-10; col 8, ln 58-64	10-12, 33-35

☐ Further documents are listed in the continuation of Box C. ☐

* 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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"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	Date of mailing of the international search report
24 December 2010 (24.12.2010)	11 JAN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)