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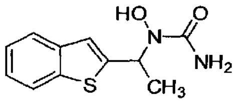
(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF (±)-1-(1-BENZO[B]THIEN-2-YLETHYL)-1-HYDROXYUREA



(I)

(57) Abstract: The present invention relates to an improved process for the preparation of (±)-1-(I -Benzo[b]thien-2-ylethyl)-1-hydroxyurea compound of formula 1.

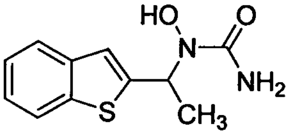
IMPROVED PROCESS FOR THE PREPARATION OF (±)-1-(1-BENZO-[B]THIEN-2-YLETHYL)-1-HYDROXYUREA

Related Application:

This application claims the benefit of priority of our Indian patent application number 2307/CHE/2009 filed on 23/09/2009 which is incorporated herein by reference.

Field of the Invention:

The present invention relates to an improved process for the preparation of (±)-1-(1-benzo-[b]thien-2-ylethyl)-1-hydroxyurea, which is commonly known as Zileuton and is represented by structural formula-1.



Formula-1

Zileuton is a potent leukotriene biosynthesis inhibitor. Leukotrienes have been implicated as important mediators of asthma, allergy, arthritis, psoriasis, and inflammation, and Zileuton which is an inhibitor of biosynthesis of leukotrienes offers treatment for leukotriene given mediated afflictions in man. Zileuton is commercially available under the brand name of “zyflo” and supplied as a tablet with different strengths.

Background of the Invention:

N-benzo[b]thienyl-N-hydroxyureas, as exemplified by N-(1-benzo[b]thien-2-ylethyl)-N-hydroxyurea (zileuton, U.S. Pat. No. 4,873,259) are potent leukotriene biosynthesis inhibitors. However, N-benzo[b]thienyl-N-hydroxyurea is difficult to prepare with required purity and yield, especially has proven to be a synthetic challenge commercially.

The synthesis of zileuton offers several illustrations of typical methods to prepare benzo[b]thienyl substituted N-hydroxyureas. In U.S. Pat. No. 4,873,259 a process is illustrated which involves reacting 2-acetylbenzo[b]thiophene with hydroxylamine to form the corresponding oxime. Then the oxime is reduced with an excess of reducing agent, generally borane-pyridine complex, to form 1-benzo[b]thien-2-ylethyl hydroxylamine. Finally, the hydroxylamine is reacted with trimethylsilyl isocyanate or sodium or potassium cyanate to form the corresponding N-hydroxyurea. Due to the safety considerations and cost involved several alternative preparations of N-(1-benzo[b]thien-2-ylethyl)-N-hydroxyureas have been devised.

One alternative process given in U.S. Pat. No. 4,873,259 involves reacting (1-benzo[b]thien-2-yl)-1-chloroethane with a nitrogen nucleophile. The nitrogen moiety is then converted to the N-hydroxyurea. However, direct displacement of chloride with hydroxylamine gives a mixture of N- and O-alkylation. Therefore, an O-protected hydroxylamine derivative such as O-benzylhydroxylamine is used as the nitrogen nucleophile. Then the product of the displacement reaction is deprotected to give 1-benzo[b]thien-2-ylethyl hydroxylamine. The hydroxylamine is then converted to the N-hydroxyurea as described above. The displacement has also been accomplished using Z-furfuraldehyde oxime and base to give the nitrone, which is hydrolyzed with acid or reacted with hydroxylamine to give 1-benzo[b]thien-2-ylethyl hydroxylamine. Other O-protected nitrogen nucleophiles such as O-protected hydroxyurea derivatives, for example O-(tetrahydropyran-2-yl)-N-hydroxyurea, have also been used to displace chloride. Removal of the oxygen protecting group provides the N-hydroxyurea.

Another process cited by A.O. Stewart and D. W. Brooks, in J. Org. Chem., 57 (18), 5020(1992) circumvents the conversion of the (1-benzo[b]thien-2-yl)-1-hydroxyethane to the corresponding chloride by using the Mitsunobu coupling. In this process (1-benzo[b]thien-2-yl)-1-hydroxyethane is reacted with N,O-bis(phenoxycarbonyl)hydroxyl amine, followed by aminolysis to obtain Zileuton. Mitsunobu reaction involves the use of diisopropyl azadicarboxylate which is highly toxic and hence not recommended for large scale production.

The processes described above require either many synthetic steps, and/or protection and deprotection of the hydroxylamine which is expensive and inefficient on a large scale. The pharmaceutical manufacturing industry still seeks a N-substituted-N-hydroxyurea synthesis that can be accomplished in a few steps with a minimum amount of expensive reducing agents or protecting groups.

The present invention provides an improved process for the preparation of zileuton which avoids all the above mentioned prior art problems

Brief Description of the Invention:

The first aspect of the present invention is to provide an improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) Treating 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2 with suitable reducing agent in a suitable solvent to provide 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3,
b) reacting alkyl or aryl chloroformate with hydroxylamine hydrochloride in presence of a suitable base in a suitable solvent to provide corresponding N-hydroxy carbamate, compound of general formula-4, which on in-situ reaction with the above compound of formula-3 in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy)carbamate, compound of general formula-5,
c) optionally purifying the compound of general formula-5 using a suitable solvent,
d) treating compound of general formula-5 with ammonia in a suitable solvent to provide zileuton, compound of formula-1.
e) optionally purifying the zileuton compound of formula-1 to get highly pure zileuton compound of formula-1.

The second aspect of the present invention is to provide an improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) reacting the compound of formula-3, with N-hydroxy carbamate, compound of general formula-4, in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy)carbamate, compound of general formula-5,
b) treating compound of general formula-5 with ammonia source to provide zileuton, compound of formula-1.

The third aspect of the present invention is to provide an improved process for the preparation of zileuton, compound of formula-1, which comprises of reacting the 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3, with N-hydroxyurea in the presence of suitable dehydrating agent in a suitable solvent to provide zileuton compound of formula-1.

The fourth aspect of the present invention is to provide an improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) Reacting 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2 with hydroxylamine to provide 1-(benzo[b]thiophen-2-yl)ethanone oxime compound of formula-7,
b) reducing the compound of formula-7 using borane-pyridine complex to provide N-(1-(benzo[b]thiophen-2-yl)ethyl)hydroxylamine compound of formula-8,
c) reacting the compound of formula-8, with urea in presence/absence of a suitable solvent to provide zileuton, compound of formula-1.

The fifth aspect of the present invention is to provide novel crystalline forms of zileuton and process for their preparation.

Advantages of the Present Invention:

- Provides an improved process for the preparation of Zileuton
- Provides a process with better yields and high purity of the intermediates, as well as zilueton.
- Avoids the use of toxic reagents like diisopropyl azadicarboxylate, sodium or potassium cyanate, triphosgene etc.
- Eco-friendly and cost effective process.

Brief Description of the Drawings:

Figure-1: Illustrates the powder X-ray diffractogram of crystalline Zileuton

Figure-2: Illustrates the IR spectrum of crystalline Zileuton

Figure-3: Illustrates the DSC thermogram of crystalline Zileuton

Figure-4: Illustrates the Zileuton morphology as seen through microscope.

Figure-5: Illustrates the powder X-ray diffractogram of crystalline zileuton

Detailed description of the invention:

Unless otherwise indicated, this disclosure uses definitions provided below. As used herein, the term "alkyl" refers to straight chain or branched hydrocarbon groups, generally having specified number of carbon atoms. A "C_{1-12} alkyl" refers to alkyl group having 1 to 12 carbon atoms. Examples of alkyl groups include, without limitation, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl,2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, n-hexyl and the like.

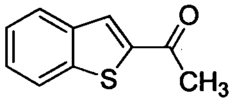
As used herein, the term "cycloalkyl" refers to saturated monocyclic and bicyclic hydrocarbon rings, generally having a specified number of carbon atoms that comprise the ring i.e C_{3-7} cycloalkyl refers to a cycloalkyl group having 3,4,5,6and 7 carbon atoms as ring members. Examples of monocyclic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of bicyclic cycloalkyl groups include without limitation, bicyclo[1.1.0]butyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.0]hexyl, bicyclo[3.1.0]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.0]heptyl and the like.

As used herein, the term "aryl-C_{1-6} alkyl" refers to an aryl group attached to the substrate through an alkyl group containing one to six carbon atoms. The term "aryl" refers to monovalent or divalent aromatic groups respectively including 5 and 6 membered monocyclic aromatic groups that contain zero to four heteroatom independently selected from nitrogen, oxygen and sulfur. Examples of monocyclic aryl groups include, without limitation, phenyl, pyrrolyl, pyranyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyradazinyl, pyrimidinyl, and the like. The aryl groups also include bicyclic groups, tricyclic groups etc including fused 5 and 6 membered rings described above. Examples of multicyclic aryl groups include, without limitation, naphthyl, biphenyl, anthracenyl, pyrenyl, carbazolyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzoimidazolyl, benzothiophenyl, quinolinyl, isoquinolinyl. indolyl, benzofuranyl, purinyl, indolizinyl and the like. The aryl groups may be attached to the substrate at any ring atom, unless such attachment would violate valence requirements.

Aryl groups may include one or more non hydrogen substituents unless such substitution would violate valence requirements. Useful substituents include, without limitation alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, halo, hydroxy, mercapto, nitro, amino, alkyl amino and the like.

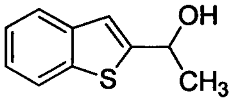
The first aspect of the present invention provides an improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) Treating 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2



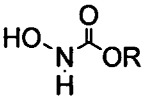
Formula-2

with a suitable reducing agent like sodium borohydride in alcohol solvent, to provide 1-(benzo[b]thiophen-2-yl) ethanol, compound of formula-3,



Formula-3

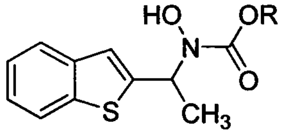
b) reacting the suitable chloroformate ester with hydroxylamine .hydrochloride in presence of a suitable base in a suitable solvent to provide corresponding N-hydroxy carbamate, compound of general formula-4,



Formula-4

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

which on in-situ reaction with the above compound of formula-3 in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate, compound of general formula-5,



Formula-5

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

c) optionally purifying the compound of formula-5 using a suitable solvent to provide the pure compound of formula-5,

d) treating compound of formula-5 with ammonia source in a suitable solvent to provide zileuton, compound of formula-1.

In the step a) the reduction of 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2 with sodium borohydride is carried out in alcohol solvent selected from methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol, preferably methanol.

In the step b) the suitable base used for the reaction of chloroformate ester with hydroxylamine hydrochloride is selected from a group consisting of alkali metal carbonates like sodium carbonate, potassium carbonate; or a alkali metal hydroxide like sodium hydroxide, potassium hydroxide; or alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate; or an organic base like triethylamine, tributylamine, diisopropylethlyamine in a solvent like diisopropylether, tetrahydrofuran, dimethylformamide, dimethoxy ethane, diethyl ketone, propyl acetate, butyl acetate, and propionitrile; and the like. The solvent used is selected from diethyl ether, tetrahydrofuran, dioxane, acetone, methyl ethyl ketone, ethyl acetate, acetonitrile, dimethyl formamide, dimethyl acetamide and dimethyl sulfoxidethe;

the condensation of 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3, with N-hydroxy carbamate, compound of general formula-4, is carried out in non polar aprotic solvent which includes but not limited to benzene, toluene, xylene, tetrahydofuran, 2-methyltetrahydrofuran, preferably toluene. The acid used is selected from an inorganic acid or organic acid. The inorganic acid is selected from a group consisting of but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like or lewis acids like aluminium chloride, aluminium bromide, ferric chloride, boron trifluoride, boron trichloride, stannous chloride, titanium tetrachloride and the like. The organic acid is selected from a group consisting of but not limited to acetic acid, trifluoroacetic acid, ethanoic acid, propionic acid, paratoluene sulfonic acid and the like.

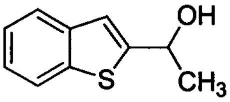
In the step c) the suitable solvent used for purification is selected from polar solvent like water;

In the step d) the source for ammonia includes ammonia gas, ammonium hydroxide, ammonium acetate, ammonium chloride, ammonium carbonate, methanolic ammonia, ethanolic ammonia and the like. The suitable solvent that can be used include, without limitation, aromatic hydrocarbon solvents like toluene, xylene; halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane and the like; alcoholic solvent like methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol; keto solvents like acetone, methyl ethyl ketone, diethyl ketone; ester solvents like ethyl acetate, propyl acetate and acetonitile.

In the step e) the suitable solvent used for purification is selected from ester solvents like ethylacetate, isoproylacetate or mixtures thereof.

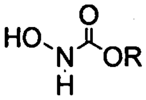
The second aspect of the present invention provides an improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) Reacting the compound of formula-3,



Formula-3

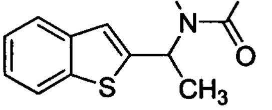
with N-hydroxy carbamate, compound of general formula-4,



Formula-4

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate, compound of general formula-5,



Formula-5

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

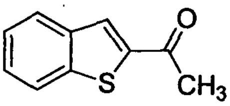
b) treating compound of general formula-5 with ammonia source to provide zileuton, compound of formula-1.

In the step a) the condensation of 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3, with N-hydroxy carbamate, compound of general formula-4, is carried out in non polar aprotic solvent which includes but not limited to benzene, toluene, xylene, tetrahydofuran, 2-methyltetrahydrofuran, preferably toluene. The acid used is selected from an inorganic acid or organic acid. The inorganic acid is selected from a group consisting of but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like or lewis acids like aluminium chloride, aluminium bromide, ferric chloride, boron trifluoride, boron trichloride, stannous chloride, titanium tetrachloride and the like. The organic acid is selected from a group consisting of but not limited to acetic acid, trifluoroacetic acid, ethanoic acid, propionic acid, paratoluene sulfonic acid and the like.

In the step b) the source for ammonia includes ammonia gas, ammonium hydroxide, ammonium acetate, ammonium chloride, ammonium carbonate, and the like. The suitable solvent that can be used include, without limitation, aromatic hydrocarbon solvents like toluene, xylene; halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane and the like; alcoholic solvent like methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol; keto solvents like acetone, methyl ethyl ketone, diethyl ketone; ester solvents like ethyl acetate, propyl acetate and acetonitrile.

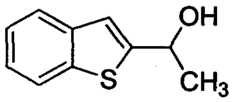
In a preferred embodiment of the present invention, the process for the preparation of zileuton comprises of the following steps,

a) Treating 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2



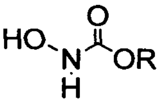
Formula-2

with sodium borohydride in methanol to provide 1-(benzo[b]thiophen-2-yl) ethanol, compound of formula-3,



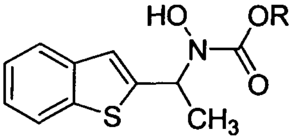
Formula-3

b) reacting the phenyl chloroformate with hydroxylamine hydrochloride in presence of sodiumbicarbonate in a mixture of water and tetrahydrofuran to provide phenyl N-hydroxy carbamate, compound of formula-4a,



Formula-4a

which on in-situ reaction with the compound of formula-3 in tolune and in presence of hydrochloric acid to provide phenyl 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate, compound of formula-5a,



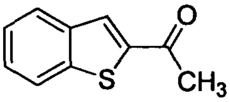
Formula-5a

c) purifying the compound of formula-5a using water to provide the pure compound of formula-5a,

d) treating compound of formula-5a with methanolic ammonia, followed by isolation of zileuton compound of formula-1 from toluene,

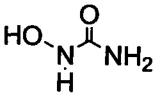
e) purifying the compound of formula-1 using ethylacetate to provide pure zileuton compound of formula-1.

The third aspect of the present invention provides an improved process for the preparation of zileuton, compound of formula-1, which comprises of reacting the compound 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3,



Formula-3

with N-hydroxyurea compound of formula-6,



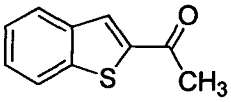
Formula-6

in the presence of suitable dehydrating agent in presence/absence of a suitable solvent to provide zileuton compound of formula-1.

The dehydrating agent used in the above reaction is preferably anhydrous zinc chloride. The reaction can also be performed in the presence of catalytic amount of water. The reaction can be carried out in absence of a solvent. But when the reaction is carried out in a solvent, the solvent is selected from aliphatic hydrocarbons like hexane, cyclohexane, petroleum ether; or aromatic hydrocarbons like xylene, toluene; or halogenated hydrocarbons like dichloromethane, chloroform, 1,2-dichloroethane and the like.

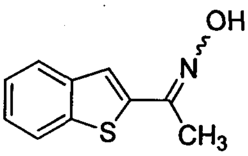
The fourth aspect of the present invention provides an improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps;

a) Reacting 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2



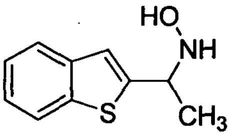
Formula-2

with hydroxylamine to provide 1-(benzo[b]thiophen-2-yl)ethanone oxime, compound of formula-7,



Formula-7

b) reducing the compound of formula-7 using borane-pyridine complex to provide N-(1-(benzo[b]thiophen-2-yl)ethyl)hydroxylamine compound of formula-8,



Formula-8

c) reacting the compound of formula-8, with urea in presence/absence of a suitable solvent to provide zileuton, compound of formula-1.

In step a) the condensation of 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2 with hydroxylamine is carried out in an alcoholic solvent like methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol, preferably ethanol.

In step b) the reduction of the 1-(benzo[b]thiophen-2-yl)ethanone oxime, compound of formula-7, with borane–pyridine complex the suitable solvent is an alcohol solvent selected from but not limited to methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol and the like preferably methanol.

Further the present invention provides a process for the purification of zileuton compound of formula-1, which comprises of the following steps,

a) dissolving zileuton in a suitable ester solvent such as ethyl acetate, isopropyl acetate or mixtures thereof at reflux temperature,
b) subjecting the solution to carbon treatment,
c) filtering the reaction through hyflow,
d) distilling off the solvent from the filtrate,
e) adding suitable ester solvent to the obtained residue,
f) heating the reaction mixture and stirring,
g) cooling the reaction mixture and stirring,
h) filtering the solid and washing with suitable solvent to provide pure zileuton compound of formula-1.

The fifth aspect of the present invention provides a novel crystalline form of zileuton. The novel crystalline form of the present invention is characterized by its X-ray diffractogram having characteristics peaks 2.81, 5.36, 10.10, 14.89, 15.97, 19.68 and 29.39 ± 0.2 degrees at 2θ as shown in figure-1, its Infra red spectrum showing characteristics peaks at 3463.9, 3323.3, 3270, 2988.8, 1657.8, 1470, 1367.6, 1153.4, 828.7 and 729 cm^{-1} as shown in figure-2 and its Differential Scanning Calorimetry showing endothermic peak at 159.42°C as shown in figure-3 and having rod shaped morphology as seen through microscope as shown in figure-4.

The present invention also provides another crystalline form of zileuton characterized by its powder X-ray diffractogram having peaks at 4.82, 9.61, 14.43, 15.42, 15.81, 19.25, 19.95, 20.64, 22.77, 29.05 and 31.29 ± 0.2 degrees 2θ as shown in figure-5.

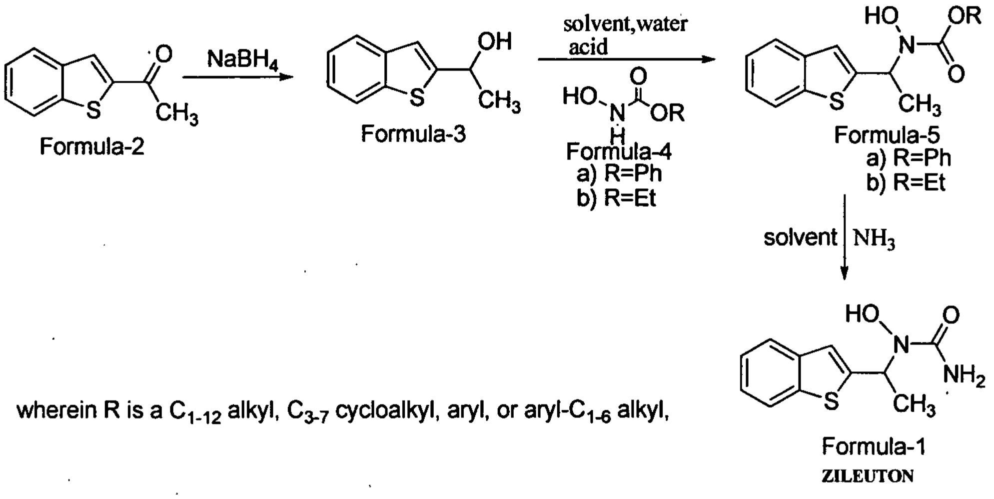
The present invention also provides a process for the preparation/purification of crystalline zileuton compound of formula-1, which comprises of the following steps,

a) dissolving zileuton in a suitable ester solvent such as ethyl acetate, isopropyl acetate or hydroxcarbon solvent like toluene, heptatne at reflux temperature,
b) subjecting the solution to carbon treatment,
c) filtering the reaction through hyflow,
d) distilling off the solvent from the filtrate,
e) adding suitable ester solvent to the obtained residue,
f) heating the reaction mixture to 50-70°C and stirring,
g) cooling the reaction mixture to 25-30°C then to 0-5°C and stirring,
h) filtering the solid and washing with suitable solvent to provide crystalline zileuton compound of formula-1.

Zileuton compound of formula-1 prepared as per the present invention having phenol content less than 3 ppm, preferably less than 1 ppm and more preferably substantially free of phenol.

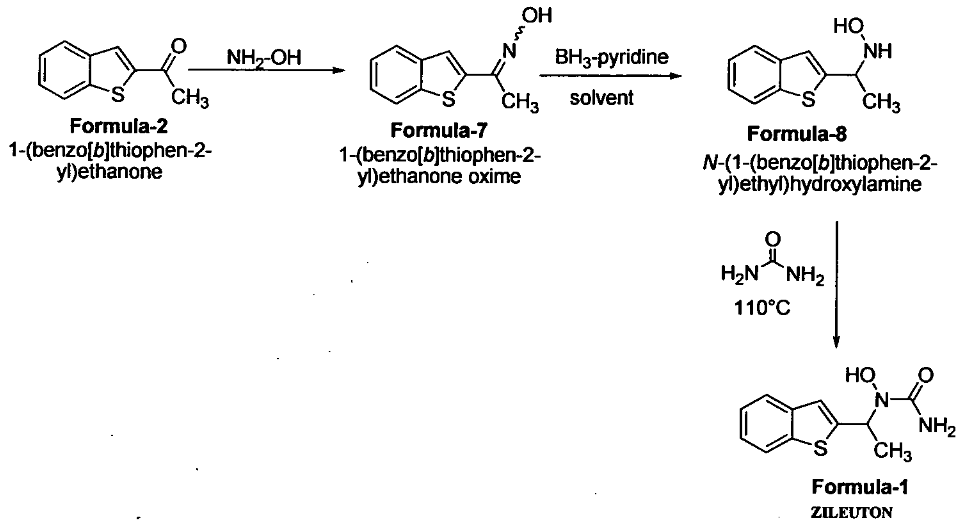
The present invention is schematically represented by the following schemes:

Scheme-1:



wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl, or aryl-C_{1-6} alkyl,

Scheme-2:



Zileuton prepared by the present invention can be further micronized or milled to get the desired particle size. Zileuton prepared as per the present invention is having mean particle size of 50 to 250 microns. Analysis of particle size distribution of zileuton was carried out using Malvern Mastersizer 2000.

N-(1-Benzo-[b]thien-2-ylethyl)urea (Impurity-A), 2-(Benzo[b]thien-2-oyl) benzo [b]thiophene (Impurity B), 1-Benzo-[b]thien-2-ylethanone (Impurity-C) are the impurities which are observed in the preparation of zileuton and are controlled well within the limits as per the ICH guidelines.

XRD analysis of Zileuton was carried out using SIEMENS/D-5000 X-Ray diffractometer using Cu, Ka radiation of wavelength 1.54 A° and continuous scan speed of 0.045°/min. FI-IR spectrum of Zileuton was recorded on Thermo model Nicolet-380 as KBr pellet. The thermal analysis of Zileuton was carried out on Waters DSC Q-10 model differential scanning calorimeter.

The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of 1-(benzo[b]thiophen-2-yl) ethanol (formula-3).

2-acetyl benzothiophene (formula-2) (50grams) was taken in methanol (200ml) and stirred for 15 min. The reaction mixture was cooled to 0-5°C and sodium borohydride (6.5grams) was added to it and stirred for 45 min at 0-5°C. Water (500ml) was added to the reaction mixture and stirred for 15 min. The temperature of the reaction mixture is raised to 25-30°C and extracted with dichloromethane. The solvent was distilled off under reduced pressure and n-heptane (25ml) was added to reaction mixture. It was stirred for 15 minutes and then the solvent was distilled off under the reduced pressure..The reaction mixture was cooled to 25-30°C, n-heptane (150ml) was added and further cooled to 0-5°C. It was stirred for one hour; the solid obtained was filtered, washed with chilled n-heptane (25ml) and dried to obtain the title compound.

Yield: 46 grams.

Example-2: Preparation of 1-(benzo[b]thiophen-2-yl) ethanol (formula-3).

2-acetyl benzothiophene (formula-2) (50grams) was taken in methanol (200ml) and stirred for 15 min. The reaction mixture was cooled to 0-5°C and sodium borohydride (6.5grams) was added to it and stirred for 45 min at 0-5°C. Water (500ml) was added to the reaction mixture and stirred for 15 min. The temperature of the reaction mixture is raised to 25-30°C and extracted with dichloromethane. The solvent was distilled off under reduced pressure and water (500ml) was added to reaction mixture. The pH of the reaction mixture was adjusted to 6.50 -7.5 with 20% hydrochloric acid and stirred for one and half hours at 25-30°C. The solid obtained was filtered, washed with chilled water (100ml) and dried to obtain the title compound.

Yield: 48 grams.

Example-3: Preparation of 1-(benzo[b]thiophen-2-yl) ethanol (formula-3).

2-acetyl benzothiophene (formula-2) (100 grams) was taken in methanol (400ml) and stirred for 15 min. The reaction mixture was cooled to 0-5°C and sodium borohydride (11.25 grams) was added to it lotwise and stirred for 45 min at 0-5°C. Solvent from the reaction mixture was distilled off completely under reduced pressure at below 55°C. Water (1000ml) was added to the reaction mixture at below 30°C. The pH of the reaction mixture was adjusted to 6.9 with aqueous hydrochloric acid and stirred for one and half hours at 25-30°C. The solid obtained was filtered, washed with chilled water and dried to obtain the title compound.

Yield: 98 grams.

Melting point: 58-65°C

Example-4: Preparation of phenyl hydroxycarbamate (formula-4a).

Hydroxylamine hydrochloride (44.4 grams), potassium carbonate (97.2 grams) was taken in diisopropylether (500 ml) and water (100 ml) was added to the reaction mixture. The reaction mixture was cooled to 5-10°C and a mixture of phenylchloro formate (100 grams) taken in diisopropyl ether (500 ml) was added to it. The temperature was raised to 25-30°C and stirred for 5 hours. The organic and aqueous layers were separated and the solvent was distilled off from the organic layer under reduced pressure. n-Heptane (50 ml) was added to obtained material, stirred for 5 minutes and then distilled off under the reduced pressure. The reaction mixture was cooled to 25-30°C and a mixture of n-heptane (500 ml) and diisopropylether (100 ml) was added to it. The solid obtained was filtered, and washed with n-heptane (100 ml) and dried to get the title compound.

Yield: 64 grams.

Example-5: Preparation of phenyl 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy) carbamate (formula-5a).

To 1-(benzo[b]thiophen-2-yl) ethanol (10 grams) (formula-3) taken in toluene (100 ml) added a mixture of phenyl hydroxycarbamate (14.6 grams), water (11 ml) and hydrochloric acid (17 ml). Heated the reaction mixture to 50-55°C and stirred for 5 hours. The reaction mixture was cooled to 10-15°C. The solid obtained was filtered and washed with toluene (10 ml). The wet material was taken in toluene (85 ml) and ethyl acetate (15 ml), heated to 65-70°C and stirred for 30 minutes. Cooled the reaction mixture to 10-15°C and stirred for 1 hour. The precipitated solid was filtered, washed with toluene (10 ml) and dried to get the title compound.

Yield: 12 grams.

Example-6: Preparation of phenyl 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy) carbamate (formula-5a).

Phenylchloro formate (100 grams) in tetrahydrofuran (200 ml) was added to a pre cooled mixture of hydroxylamine hydrochloride (44.7 grams), sodiumcarbonate (74.67 grams), water (50 ml) and tetrahydrofuran (200 ml) at 5-10°C. The temperature was raised to 25-30°C and stirred for 2 hours. The reaction mixture was filtered and washed the byproduct with tetrahydrofuran. The organic and aqueous layers from the filtrate was separated and distilled off the solvent from the organic layer under reduced pressure. The obtained residue was cooled to 20-25°C and 1-(benzo[b]thiophen-2-yl) ethanol (60 grams) (formula-3), toluene (600 ml) and 32% hydrochloric acid (102 ml) was added. The reaction mixture was heated to 50-55°C and stirred upto completion of the reaction at 50-55°C. the reaction mixture was cooled to 5-10°C and stirred for 3 hours. The solid obtained was filtered off, washed with toluene. Water (600 ml) was added to the obtained solid and stirred for an hour at 25-35°C. The solid obtained was filtered, washed with water and then dried to get the title compound.

Yield: 82 grams.

Melting Range: 137-140°C

Example-7: Preparation of Zileuton (formula-1).

Dissolved phenyl 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy)carbamate (5 grams) (formula-5a) in methanol (100 ml). The mixture was cooled to 5-10°C and ammonia gas was passed into the reaction mixture for 24 hours. The temperature of the reaction mixture was raised to 25-30°C. The solvent was distilled off under reduced pressure at 50°C. Toluene (5 ml) was added to obtain material and then distilled off under the reduced pressure. The reaction mixture was cooled to 25-30°C and toluene (25 ml) was added. Stirred for 45 minutes and filtered the precipitated solid. Washed with toluene (5 ml) and dried to obtain the title compound.

Yield: 2.5 grams.

Example-8: Preparation of Zileuton (formula-1).

Phenyl 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy)carbamate (100 grams) (formula-5a) and methanolic ammonia (2 Litres) was taken in a autoclave and stirred upto completion of the reaction at 25-35°C. The temperature of the reaction mixture was raised to 25-30°C. After completion of the reaction, the solvent was distilled off under reduced pressure at 50°C. Toluene (100 ml) was added to obtain material and then distilled off under the reduced pressure. The reaction mixture was cooled to 25-30°C, toluene (500 ml) was added and stirred for 2 hours. The solid was filtered off and washed with toluene then dried to get the title compound

Yield: 70 gram;

Melting Range: 146-150°C

Phenol content: 1.68 ppm

Particle Size Distribution:

D(0,1): 19.41 μm; D(0,5): 72.34 μm; D(0,9): 255.40 μm; D[4,3]: 108.39 μm

Example-9: Process for preparation/purification of crystalline Zileuton (formula-1).

A mixture was zileuton (100 grams) and ethyl acetate (2.5 litres) was heated to reflux temperature. The obtained solution was subjected to carbon treatment and then filtered through the hyflow. The solvent from the filtrate was distilled off completely under reduced pressure at below 50°C. The obtained residue was cooled to 25-35°C and ethylacetate (200 ml) was added to it. The reaction mixture was heated to 65-70°C and stirred for 10 mins. Cooling the reaction mixture to 25-30°C then stirred for 30 mins. The reaction mixture further cooled to 0-5°C and stirred for 2 hours. The solid obtained filtered off, wahed with ethyl acetate and then dried to get the title compound.

Yield: 78 grams

Phenol content: Not detected

Particle Size Distribution:

D(0,1): 12.13 μm; D(0,5): 50.65 μm; D(0,9): 198.31 μm; D[4,3]: 80.99 μm

Example-10: Ethyl 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy) carbamate (formula-5b).

Hydroxylamine hydrochloride (2 grams), potassium carbonate (4 grams) was taken in and water (10 ml) was added to the reaction mixture. The reaction mixture was cooled to 5-15°C and ethyl chloroformate (2.5 ml) was added to it. The temperature was raised to 5-15°C and stirred for 5 hours. The pH of the reaction mixture was adjusted to 3 with 6N hydrochloric acid and extracted with tetrahydrofuran. The solvent was distilled off under reduced pressure. Then reaction mixture was extracted with dichloromethane. The dichloromethane layer was dried over anhydrous sodium sulfate and then distilled off under the reduced pressure to obtain a residue. To the residue added water (2 ml) and hydrochloric acid and (3 ml) and 1-(benzo[b]thiophen-2-yl) ethanol (formula-3) (2 grams taken in 15 ml of toluene). The reaction mixture was heated to 50-55°C and stirred for 5 hours. And then it was cooled to 20-25°C, the organic and aqueous layers were separated. The organic layer was dried over anhydrous sodium sulfate and distilled off under reduced pressure to obtain the title compound as oil.

Yield: 2 grams

Example-11: Preparation of 1-(benzo[b]thiophen-2-yl) ethanone oxime (formula-7).

To a solution of 2-acetyl benzothiophene (10 grams) taken in methanol (100 ml) added hydroxyl amine hydrochloride (6 grams) and pyridine (100 ml).The reaction mixture was stirred for 1 hour at 25-30°C. The reaction was quenched with water (500 ml),and extracted with dichloromethane (100 ml). The organic layer was washed with water (200 ml). The solvent from the organic layer was distilled off under the reduced pressure. n-heptane (20 ml) was added to the reaction mixture and then distilled off under reduced pressure. n-heptane (50 ml)was added to the reaction mixture, cooled to 0-5°C and stirred 30 minutes. Filtered the precipitated solid, washed with n-heptane (20 ml) and dried it to obtain title compound.

Yield: 9.8 grams.

Example-12: Preparation of N-(1-(benzo[b]thiophen-2-yl)ethyl)hydroxylamine (formula-8).

1-(benzo[b]thiophen-2-yl)ethanone oxime (formula-7) (3.5 grams) was taken in ethanol (25 ml), cooled to 0-5°C and borane-pyridine (3.4 grams) was added to it very slowly. Hydrochloric acid (20%) in ethanol was added to the reaction mixture and the temperature was raised to 20-25°C stirred for 3 hours. The reaction mixture was cooled to 0-5°C and aqueous sodium bicarbonate solution (20 ml) was added slowly to the reaction mixture. The reaction mixture was extracted with dichloromethane (50 ml). The dichloromethane layer was washed with water and distilled off under reduced pressure. Diisopropyl ether (17.5 ml) was added to the reaction mixture, cooled to 0-5°C and stirred for 30 minutes. Filtered the obtain solid, washed with diisopropyl ether (7 ml) and dried to obtain title compound.

Yield: 2.6 grams.

Example-13: Preparation of Zileuton.

N-(1-(benzo[b]thiophen-2-yl)ethyl)hydroxylamine (1gram) (formula-8) was mixed with urea (0.6 grams) and then heated to 135-140°C for two hours. The reaction mixture was cooled to 25-30°C, and water (2 ml) and toluene (2 ml) was added to it. Stirred the reaction mixture for 30 minutes. Filtered the obtain precipitate, washed with toluene (2 ml) and dried to obtain title compound.

Yield: 0.2 grams.

Example-14: Preparation of Zileuton.

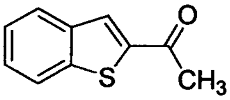
1-(benzo[b]thiophen-2-yl)ethanol (formula-3) (1 gram) was mixed with N-hydroxyurea (1 gram), anhydrous zinc chloride (0.7 grams) and then heated to 135-140°C for one hour. The reaction mixture was cooled to 25-30°C, and water (2 ml) and toluene (2 ml) was added to it .The reaction mixture was stirred for 30 minutes. Filtered the obtain precipitate, washed with toluene (2 ml) and dried to obtain title compound.

Yield: 0.6 grams.

We Claim:

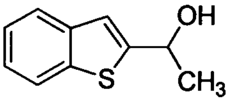
1) An improved process for the preparation of zileuton compound of formula-1, which comprises of the following steps;

   a) Treating 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2, with



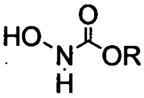
Formula-2

sodium borohydride in an alcohol solvent, to provide 1-(benzo[b]thiophen-2-yl) ethanol compound of formula-3,



Formula-3

   b) reacting the compound of formula-3, with N-hydroxy carbamate, compound of general formula-4,

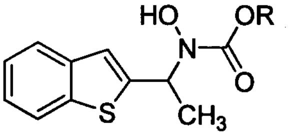


$HO\text{-}NH\text{-}C(O)OR$

Formula-4

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy)carbamate, compound of general formula-5,



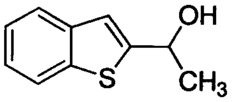
Formula-5

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

   c) treating compound of general formula-5 with a ammonia source to provide zileuton, compound of formula-1.

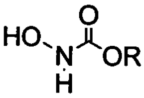
2) An improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) reacting the compound of formula-3,



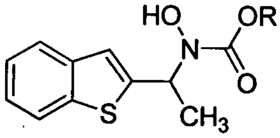
Formula-3

with N-hydroxy carbamate, compound of general formula-4,



Formula-4

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl, in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate, compound of general formula-5,



Formula-5

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

b) treating compound of general formula-5 with ammonia source to provide zileuton, compound of formula-1.

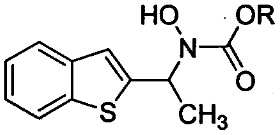
3) A process according to claim 1 and 2, wherein

i) the condensation of 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3, with N-hydroxy carbamate, compound of general formula-4, the solvent used is selected form a group of non polar aprotic solvents which includes but is not limited to benzene, toluene, xylene, tetrahydrofuran, 2-methyltetrahydrofuran, preferably toluene; and

ii) the condensation of 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3, with N-hydroxy carbamate, compound of general formula-4 the acid used is selected from either an inorganic acid or organic acid. The inorganic acid is selected from a group consisting of but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like or lewis acids like aluminium chloride, aluminium bromide, ferric chloride, boron trifluoride, boron trichloride, stannous chloride, titanium tetrachloride and the like. The organic acid is selected from a group consisting of but not limited to acetic acid, trifluoroacetic acid, ethanoic acid, propionic acid, paratoluene sulfonic acid and the like;

iii) The ammonia source used in the aminolysis of compound of general formula-5, is selected form a group includes ammonia gas, ammonium hydroxide, ammonium acetate, ammonium chloride, ammonium carbonate, and the like, and the suitable solvent that can be used includes, without limitation, aromatic hydrocarbon solvents like toluene, xylene; halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane and the like; alcoholic solvent like methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol; keto solvents like acetone, methyl ethyl ketone, diethyl ketone; ester solvents like ethyl acetate, propyl acetate and acetonitile.

4) A process for preparing zileuton, compound of formula-1, which comprises of treating the compound of general formula-5



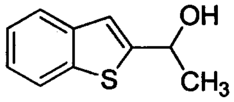
Formula-5

wherein R is methyl or phenyl,

with ammonia in an alcohol solvent to provide zileuton.

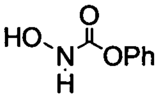
5) An improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) reacting the compound of formula-3,



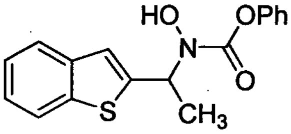
Formula-3

with phenyl N-hydroxy carbamate, compound of formula-4a,



Formula-4a

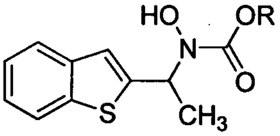
in toluene in the presence of hydrochloric acid to provide 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate, compound of formula-5a,



Formula-5a

b) treating compound of formula-5a with ammonia gas to provide zileuton, compound of formula-1.

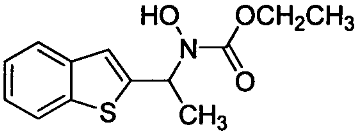
6) 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy)carbamates, compounds of general formula-5,



Formula-5

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl, with a proviso that R is not a phenyl group.

7) Ethyl 1-(benzo[b]thiophen-2-yl)ethyl(hydroxy) carbamate, compound of formula-5b.



Formula-5b

8) An improved process for the preparation of zileuton, compound of formula-1, which comprises of reacting the compound 1-(benzo[b]thiophen-2-yl)ethanol, compound of formula-3, with N-hydroxyurea in the presence of zinc chloride in presence/absence of a suitable solvent like hydrocarbon solvents or chloro solvents, to provide zileuton compound of formula-1.

9) An improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,
   a) Reacting 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2 with hydroxylamine to provide 1-(benzo[b]thiophen-2-yl)ethanone oxime, compound of formula-7,
   b) reducing the compound of formula-7 using borane-pyridine complex to provide N-(1-(benzo[b]thiophen-2-yl)ethyl)hydroxylamine compound of formula-8,
   c) reacting the compound of formula-8, with urea in presence/absence of a suitable solvent to provide zileuton, compound of formula-1.

10) Crystalline Zileuton characterized by any one of the following
   a) by its X-ray diffractogram having characteristics peaks at 2.81, 5.36, 10.10, 14.89, 15.97, 19.68 and 29. ± 0.2 degrees 2θ as shown in figure-1;
   b) by its Infra red spectrum showing characteristics peaks at 3463.9, 3323.3, 3270, 2988.8, 1657.8, 1470, 1367.6, 1153.4, 828.7 and 729 cm^{-1} as shown in figure-2;
   c) by its Differential Scanning Calorimetry showing endothermic peak at 159.42°C as shown in figure-3;
   d) having rod shaped morphology as seen through microscope as shown in figure-4.

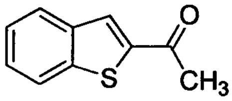
11) Crystalline Zileuton characterized by its X-ray diffractogram having characteristics peaks at 4.82, 9.61, 14.43, 15.42, 15.81, 19.25, 19.95, 20.64, 22.77, 29.05 and 31.29 ± 0.2 degrees 2θ as shown in figure-5.

12) A process for the purification/preparation of crystalline zileuton comprises of the following steps, which comprises of the following steps;
   a) dissolving zileuton in a suitable ester solvent such as ethyl acetate, isopropyl acetate or mixtures thereof or suitable hydrocarbon solvents such as toluene, heptanes or mixtures thereof at suitable temperature,
   b) subjecting the solution to carbon treatment,
   c) filtering the reaction through hyflow,
   d) distilling off the solvent from the filtrate,
   e) adding suitable ester solvent to the obtained residue,

f) heating the reaction mixture and stirring,
g) cooling the reaction mixture and stirring,
h) filtering the solid and washing with suitable solvent to provide crystalline zileuton compound of formula-1.

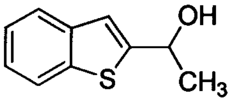
13) An improved process for the preparation of zileuton, compound of formula-1, which comprises of the following steps,

a) Treating 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2



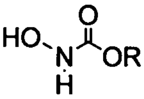
Formula-2

with a suitable reducing agent like sodium borohydride in a alcohol solvent, to provide 1-(benzo[b]thiophen-2-yl) ethanol, compound of formula-3,



Formula-3

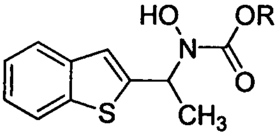
b) reacting the suitable chloroformate ester with hydroxylamine hydrochloride, in presence of a suitable base in a suitable solvent to provide corresponding N-hydroxy carbamate, compound of general formula-4,



Formula-4

wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

which on in-situ reaction with the compound of formula-3 in a suitable solvent in the presence of acid to provide 1-(benzo[b]thiophen-2-yl) ethyl (hydroxy)carbamate, compound of general formula-5,



Formula-5

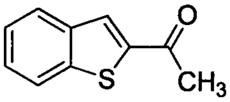
wherein R is a C_{1-12} alkyl, C_{3-7} cycloalkyl, aryl or aryl-C_{1-6} alkyl,

c) optionally purifying the compound of general formula-5 using a suitable solvent to provide the pure compound of formula-5,

d) treating compound of general formula-5 with ammonia source in a suitable solvent to provide zileuton, compound of formula-1.

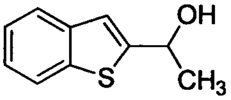
14) A process for the preparation of zileuton comprises of the following steps,

a) Treating 1-(benzo[b]thiophen-2-yl)ethanone compound of formula-2



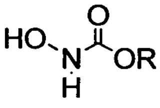
Formula-2

with sodium borohydride in methanol to provide 1-(benzo[b]thiophen-2-yl) ethanol, compound of formula-3,



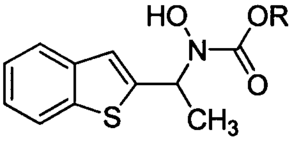
Formula-3

b) reacting the phenyl chloroformate with hydroxylamine hydrochloride in presence of sodiumbicarbonate in a mixture of water and tetrahydrofuran to provide phenyl N-hydroxy carbamate, compound of formula-4a,



Formula-4a

which on in-situ reaction with the compound of formula-3 in tolune and in presence of hydrochloric acid to provide phenyl 1-(benzo[b]thiophen-2-yl) ethyl(hydroxy)carbamate, compound of formula-5a,



Formula-5a

c) purifying the compound of formula-5a using water to provide the pure compound of formula-5a,

d) treating compound of formula-5a with methanolic ammonia, followed by isolation of zileuton compound of formula-1 from toluene,

e) purifying the compound of formula-1 using ethylacetate to provide pure zileuton compound of formula-1.

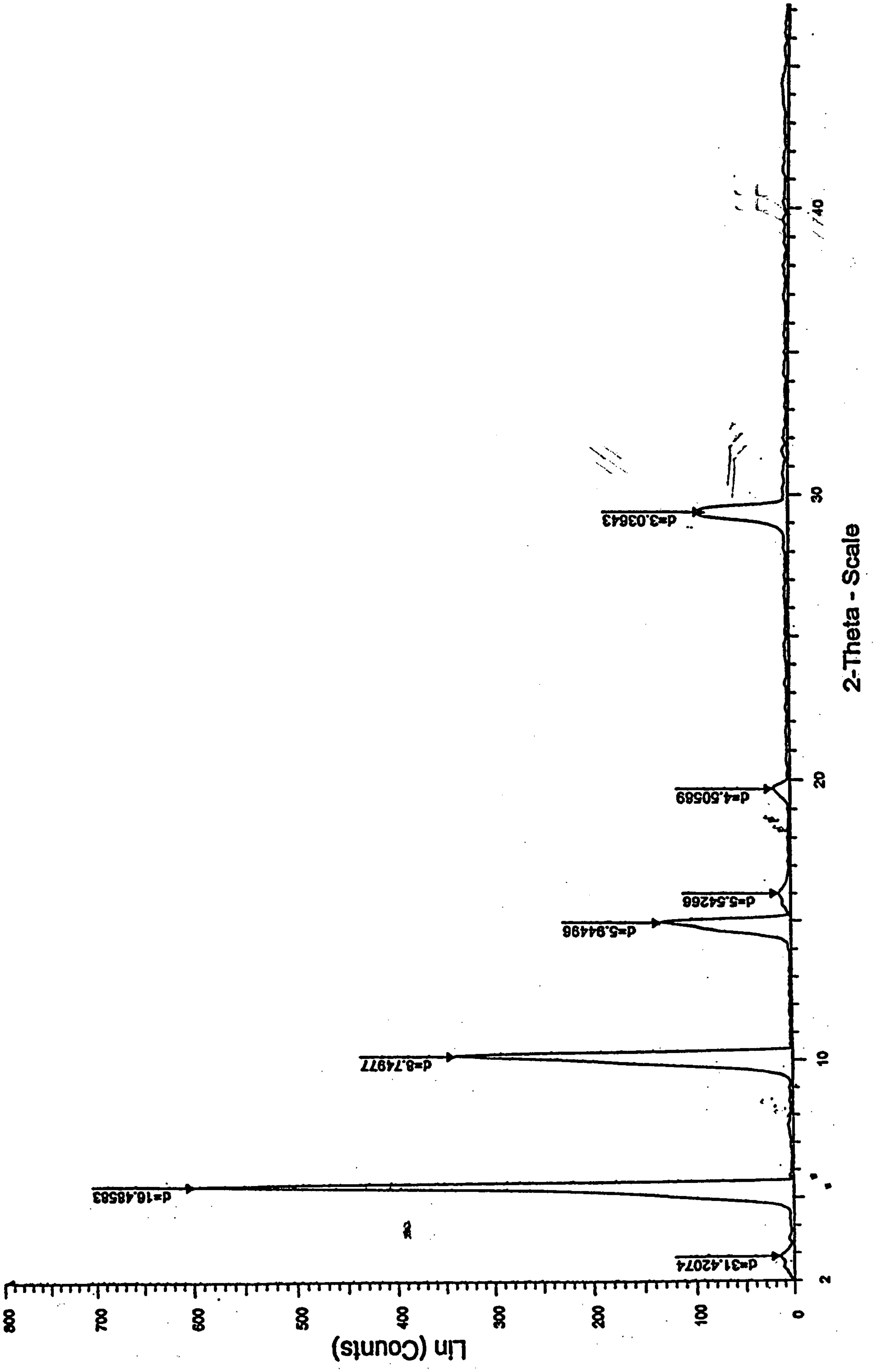
15) A process for the purification of zilueton, which comprises of the following steps,

   a) dissolving zileuton in a suitable ester solvent such as ethyl acetate, isopropyl acetate or mixtures thereof at reflux temperature,
   b) subjecting the solution to carbon treatment,
   c) filtering the reaction through hyflo ,
   d) distilling off the solvent from the filterate,
   e) adding suitable ester solvent to the obtained residue,
   f) heating the reaction mixture to 50-70°C and stirring,
   g) cooling the reaction mixture to 25-30C
   h) then cooling to 0-5 and stirring
   i) filtering the solid and washing with suitable solvent to provide crystalline zileton compound of formula-1.

16) Zileuton substantially free of phenol.

17) A process according to claim 13, 14 & 15, wherein the zileuton prepared is having purity greater than 99.5% by HPLC and substantially free of phenol.

18) A process according to claim 13, 14 & 15, wherein the zileuton obtained is having mean particle size of 50 to 250 microns.


Lin (Counts)
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100
200
300
400
500
600
700
800
2-Theta - Scale
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10
20
30
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d=18.48583
d=8.74977
d=5.94498
d=5.54266
d=4.50589
d=3.03643

Figure-1

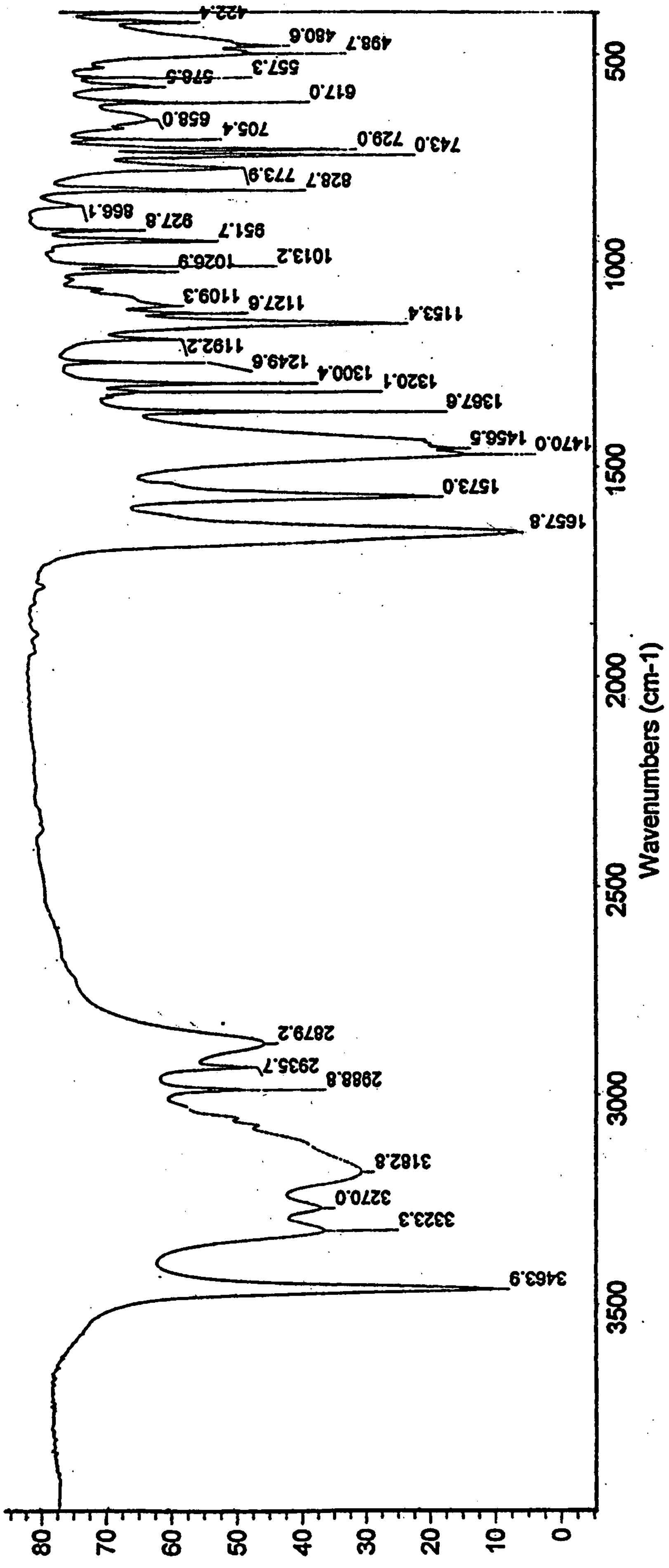
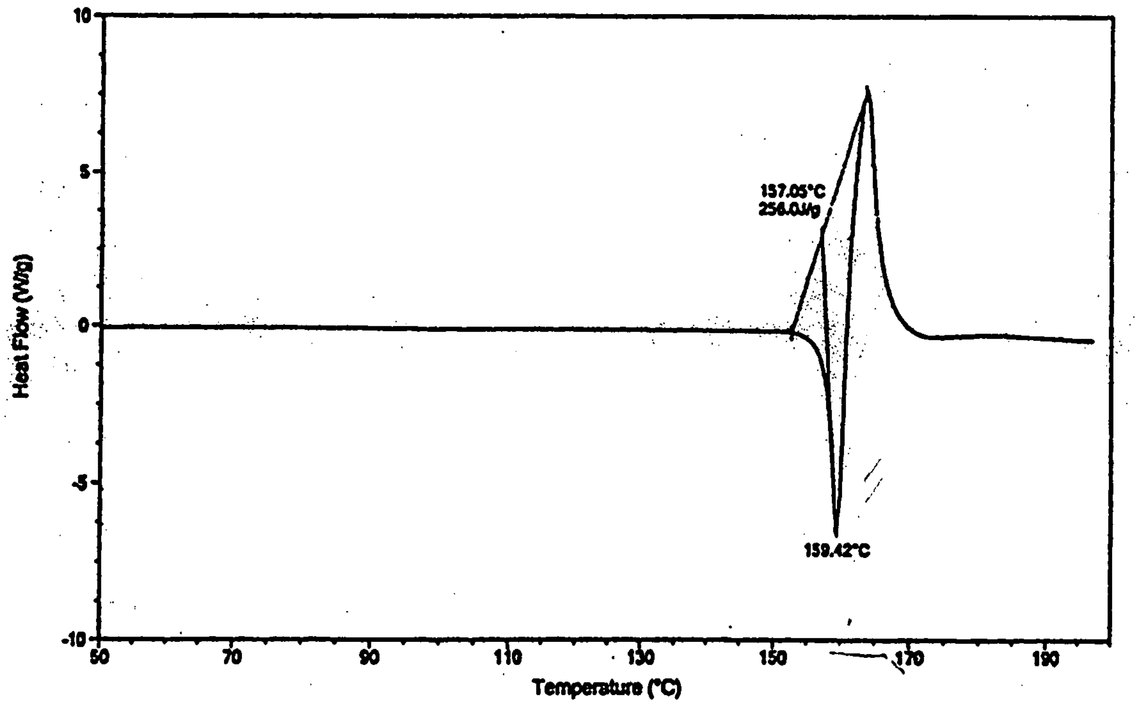

80
70
60
50
40
30
20
10
0
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3463.9
3323.3
3270.0
3182.8
2988.8
2935.7
2879.2
1657.8
1573.0
1470.0
1456.5
1367.6
1320.1
1300.4
1249.6
1192.2
1153.4
1127.6
1109.3
1026.9
1013.2
951.7
927.8
866.1
828.7
773.9
743.0
729.0
705.4
658.0
617.0
578.5
557.3
498.7
480.6
422.4

Figure-2


10
5
0
-5
-10
Heat Flow (W/g)
50
70
90
110
130
150
170
190
Temperature (°C)
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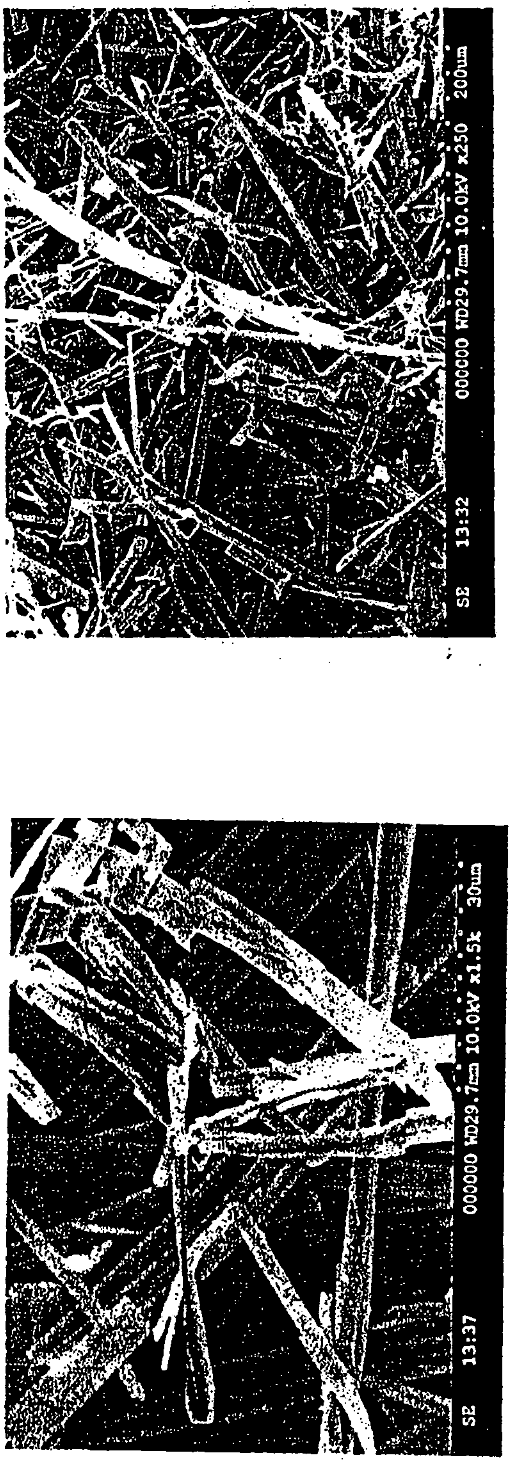
256.0J/g
159.42°C

Figure-3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SE 13:37 000000 WD29.7mm 10.0kV x1.5k 30um

Figure-4

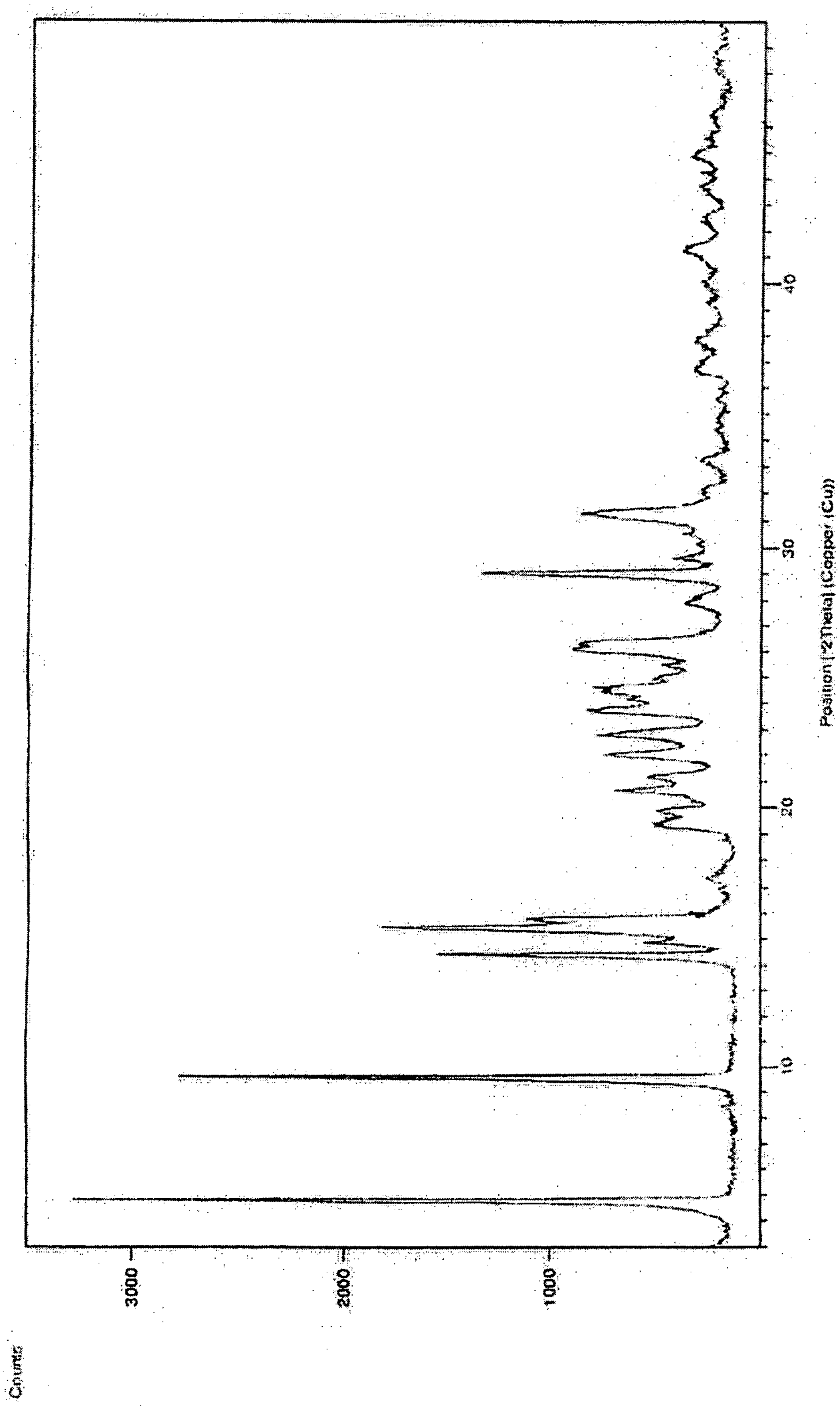

Figure-5