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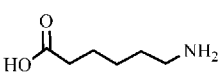
(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF 6-AMINOHEXANOIC ACID



(Formula-1)

(57) Abstract: The present invention relates to highly pure 6-aminohexanoic acid of formula-1 which is free of organic volatile impurities, caprolactam impurity and improved process for its preparation thereof. The present invention also relates to an improved process for the preparation of caprolactam of formula-2 which is used for the preparation of 6-aminohexanoic acid of formula-1.

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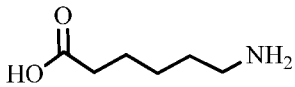
IMPROVED PROCESS FOR THE PREPARATION OF 6-AMINOHEXANOIC ACID

Related applications

This patent application claims the benefit of priority of Indian patent application number 201841029394 filed on 04th August 2018 which is incorporated herein by reference

Field of the invention

The present invention relates to highly pure 6-aminohexanoic acid of formula-1 and process for its preparation thereof.



(Formula-1)

The present invention also relates to an improved process for the preparation of caprolactam of formula-2 which is used for the preparation of 6-aminohexanoic acid of formula-1.

Background of the invention

6-Aminohexanoic acid is also known as aminocaproic acid, epsilon-aminocaproic acid or ε-aminocaproic acid. 6-Aminohexanoic acid is acts as an inhibitor of fibrinolysis which is approved with the brand name of AMICAR® with different dosage forms such as 500mg and 1gm as a tablet, 1.25gm/5ml as a syrup and 250mg/ml as an injectable injection. It is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt, hematological disorders and neoplastic diseases.

US patent document 7491520 B2 discloses a biochemical synthesis of 6-aminohexanoic acid from 6-aminohex-2-enoic acid using an enzymes having α,β-enoate reductase activity such as *Acremonium strictum*, *Clostridium tyrobutyricum*, *Moorella thermoacetica*, *Ochrobactrum anthropi,* or *Clostridium kluyveri.*

US patent document 8404465 B2 discloses a process for the preparation of 6-

aminohexanoic acid from Lysine using a microoganisam includes at least one nucleic acid encoding a polypeptide by catalyzation and the said process is schematically shown as follows:

Lysine → beta-lysine → 6-amino-3-oxohexanoic acid → 6-amino-3-hydroxyhexanoic acid → 6-aminohex-2-enoic acid → 6-aminohexanoic acid.

US patent document 9663805 B2 discloses a process for the preparation of 6-aminohexanoic acid from α-ketopimelic acid using a bio-catalyst comprising of two enzymes.

The main drawback of above disclosed prior art processes are involving the use of enzymes, microorganisms and biocatalysts which are highly expensive and also readily not available. Hence, these prior art processes are not viable for the industrial scale-up.

US patent document 8809581 B2 discloses a process for the preparation of 6-aminohexanoic acid comprising reaction of caprolactam with sodium hydroxide or potassium hydroxide and a solubility regulating agent to form an intermediate compound which is hydrogenated in presence of $Pd(OH)_2$ catalyst to produce 6-aminohexanoic acid.

The main drawback of above disclosed prior art process is the additional chemical reaction with solubility regulating agent and its hydrogenation reaction in the presence of $Pd(OH)_2$ catalyst which is expensive and causes for higher cost of the production of API. Hence, this prior art process is not eco-friendly and not suitable for industrial scale-up.

US patent document 9776953 B2 discloses a process for the preparation of 6-aminohexanoic acid comprising hydrolysis of caprolactam with hydrochloride and then tedious work up/azeotropic distillation with toluene followed by isolation/purification from isopropanol to get pure protic acid salts of 6-aminohexanoic acid which is further treating with an organic base in methanol followed by final purification from methanol, acetone in presence of seeds of 6-aminohexanoic acid.

The drawbacks of the above prior art process:

- Consumption of multiple organic solvents in the synthesis and purification of 6-aminohexanoic acid from caprolactam which is not eco-friendly in industrial scale preparations.
- Additional steps like isolation and purification of hydrochloride salt 6-aminohexanoic

acid as intermediate lengthen the process and also requires additional analytical tests.

6-Aminohexanoic acid has a maximum daily dose of about 24 gm. In view of this US FDA, EMA and other regulatory agencies issues guidelines to limit the chemical impurities, inorganic impurities, organic volatile solvents and other impurities in 6-aminohexanoic acid drug substance as much as possible.

In view of the above facts, there is still need to provide an improved process for the synthesis of highly pure 6-aminohexanoic acid of formula-1.

Advantages of the present invention:

- Highly pure 6-aminohexanoic acid of formula-1 obtained according to the present invention free of organic volatile impurities like n-pentane, cyclohexane, n-heptane, isopropanol, pentanol, benzene.
- Highly pure 6-aminohexanoic acid of formula-1 obtained according to the present invention contains less than 1100 ppm of organic volatile impurities.
- Highly pure 6-aminohexanoic acid of formula-1 obtained according to the present invention is substantially free of caprolactam impurity.
- Highly pure 6-aminohexanoic acid of formula-1 obtained according to the present invention is free of chloride content.
- Consumption of single organic solvent in the synthesis from caprolactam and until isolation/purification of 6-aminohexanoic acid which is eco-friendly in industrial scale preparations.
- Less number of synthetic steps to prepare pure 6-aminohexanoic acid, which leads to the consumption of less number of solvents, reagents, intermediates thereby reducing the formation of lesser pollutants making it eco-friendly and economically viable.

Brief description of the invention

In first embodiment, the present invention provides highly pure 6-aminohexanoic acid of formula-1 which is free of organic volatile impurities like n-pentane, cyclohexane, n-heptane, isopropanol, pentanol, benzene..

In second embodiment, the present invention provides highly pure 6-aminohexanoic acid of formula-1 substantially free of caprolactam impurity.

In third embodiment, the present invention provides highly pure 6-aminohexanoic

acid of formula-1 which is free of chloride impurity.

In fourth embodiment, the present invention provides an improved process for the preparation of 6-aminohexanoic acid of formula-1.

In fifth embodiment, the present invention provides an improved process for the preparation of highly pure 6-aminohexanoic acid of formula-1.

In sixth embodiment, the present invention provides an improved a process for the preparation of caprolactam of formula-2.

Brief description of the drawings

Figure-1: Illustrates the Powdered X-Ray Diffraction (PXRD) Pattern of crystalline form of 6-aminohexanoic acid obtained according to example-3.

Figure-2: Illustrates the Powdered X-Ray Diffraction (PXRD) Pattern of crystalline form of 6-aminohexanoic acid obtained according to example-6.

Detailed description of the invention

As used herein the term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; "ether solvents" such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol,

diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.

As used herein the term "suitable base" refers to inorganic bases like "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride, lithium hydride and the like; alkali metal amides such as sodium amide, potassium amide, lithium amide or mixtures thereof.

As used herein the term "suitable acid" refers to acid such as formic acid, acetic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, *p*-toluenesulfonic acid and the like.

As used herein the term "highly pure" refers to 6-aminohexanoic acid contains purity greater than about 99.90% by high performance liquid chromatography (HPLC) or greater than about 99.95% by HPLC or greater than about 99.98% by HPLC or greater than about 99.99% by HPLC.

As used herein the term "substantially free" in related to chemical compound as impurity refers to a content of less than about 0.05% or less than about 0.04% or less than about 0.03% or less than about 0.02% or less than about 0.01% or absent.

Free of chloride content herein refers to less than about 0.05% or absent.

As used herein the term "free" refers to 6-aminohexanoic acid contains less than 2000 ppm or 1000 ppm or 500 ppm or 100 ppm or 50 ppm or absent of organic volatile impurities such as n-pentane, cyclohexane, n-heptane, isopropanol, pentanol, benzene and the like.

The chemical compound as impurity is measured by high performance liquid chromatography (HPLC), organic volatile impurity is measured by gas chromatography (GC) and chloride content is measured by ion chromatography (IC).

In first embodiment, the present invention provides highly pure 6-aminohexanoic acid of formula-1 which is free of organic volatile impurities.

In one aspect of first embodiment provides highly pure 6-aminohexanoic acid of

formula-1 contains isopropanol organic volatile impurity less than about 1100 ppm.

In second embodiment, the present invention provides highly pure 6-aminohexanoic acid of formula-1 substantially free of caprolactam impurity.

In third embodiment, the present invention provides highly pure 6-aminohexanoic acid of formula-1 free of chloride content.

In fourth embodiment, the present invention provides an improved process for the preparation of 6-aminohexanoic acid of formula-1, comprising:

a) reacting the caprolactam with inorganic base in a solvent,
b) neutralizing the product obtained in step-a) with acid optionally in a organic solvent,
c) isolating 6-aminohexanoic acid of formula-1

In step-a) the inorganic base is selected form "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate and the like; prefarebly alkali metal hydroxides; in step-a) the solvent is polar protic solvent selected from water or alcohol solvents such as methanol, ethanol, n-propanol or isopropanol or mixtures thereof; prefarebly water; in step-b) the acid is selected from acetic acid, formic acid, propanoic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like; prefarebly acetic acid; in step-b) the suitable organic solvent is selected from alcohol solvents, hydrocarbon solvents, ether solvents, chloro solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof; prefarebly alcohol solvents; more prefarebly isopropanol; in step-c) the isolation is carried out by using crystallization, recrystallization or solvent and anti-solvent method using the solvent wherein, the solvent is water, polar protic solvent, anti-solvent is isopropanol and /or the isolation also carried out by the methods like distillation, decantation, filtration and then drying any other methods known in the art.

In the second aspect of fourth embodiment, the present invention provides an improved process for the preparation of 6-aminohexanoic acid of formula-1, comprising:

a) reacting the caprolactam with aqueous potassium hydroxide solution,
b) adding isopropyl alcohol and charcoal to the product obtained in step-a),
c) filtering the mixture obtained in step-b),

d) neutralizing the filtrate obtained in step-c) with acetic acid to provide 6-aminohexanoic acid.

In fifth embodiment, the present invention provides an improved process for the preparation of highly pure 6-aminohexanoic acid, comprising:

a) dissolving crude 6-aminohexanoic acid in water, organic solvent or mixtures thereof,
b) optionally filtering the mixture,
c) combining the filtrate obtained in step-a) or step-b) with anti-solvent to provide highly pure 6-aminohexanoic acid.

In step-a), the suitable organic solvent is same as defined hereinbefore; in step-a) the temperature is ranging from 25°C to reflux temperature of the solvent used; in step-c), the anti-solvent is selected from methanol, ethanol, isopropanol, n-propanol, n-butanol, chloroform and the like.

In the first aspect of fifth embodiment, the present invention provides 6-aminohexanoic acid of formula-1 having purity greater than about 99.90% by high performance liquid chromatography (HPLC). Prefarebly, about 99.98% by HPLC.

In sixth embodiment, the present invention provides a process for the preparation of caprolactam of formula-2, comprising:

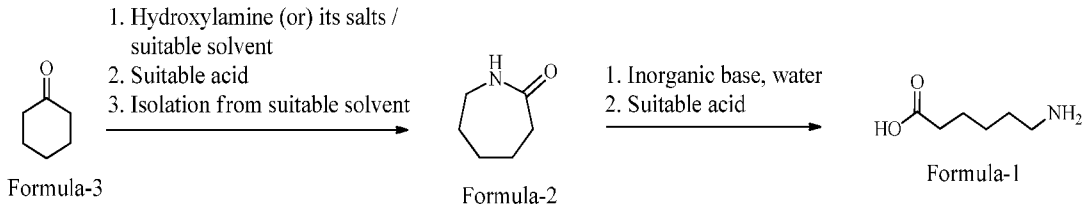
a) reacting the cyclohexanone with hydroxylamine or its salt in a suitable solvent,
b) *in-situ* treating the product obtained in step-a) with suitable acid to provide caprolactam of formula-2.

wherein in step-a) the hydroxylamine salt is selected from sulfate, hydrochloride, hydrobromide, hydroiodide and the like; the suitable solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof; in step-b) the acid is mineral acid such as sulfuric acid, nitric acid and the like or organic acid such as formic acid, acetic acid, methanesulfonic acid, p-toluenesulfonic acid, camphor sulfonic acid and the like.

In an aspect of the sixth embodiment, the caprolactam obtained by the present invention can be isolated by crystallization or recrystallization from the solvent wherein, the solvent is selected from hydrocarbon solvents, ether solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof, and/or the

isolation also carried out by the methods like distillation, decantation, filtration and then drying any other methods known in the art.

The process of the present invention can be represented schematically as follow:



Scheme-1

In another embodiment, the present invention provides pharmaceutical compositions comprising highly pure aminohexanoic acid of formula (1) and pharmaceutically acceptable excipient.

In yet another embodiment, composition comprising highly pure aminohexanoic acid of formula (1) and pharmaceutically acceptable excipient is formulated in a manner suitable for the route of administration to be used.

As used herein, the term "pharmaceutical compositions" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

6-Amino hexanoic acid obtained by the process of the present invention is analyzed by High Performance Liquid Chromatography (HPLC) by following conditions:

Apparatus: A liquid chromatographic system is equipped with variable wavelength UV detector; Column: Inertsil ODS-3V 250*4.6 mm, 5µm (or) equivalent; Column temperature: 40°C; Wave length: 210 nm; Injection volume: 20.0 µL; Elution: isocratic; Diluent: Milli-Q-water; Solution-A: weigh accurately about 0.55gr of sodium 1-heptanesulfonate and transfer into 600 mL of diluent. Mobile phase: Dissolve 10gr of monobasic potassium phosphate in 300 ml of solution-A and added 250 mL of methanol. H_3PO_4 was added to the mixture to adjust to a pH of 2.2 and diluted with Solution-A.

Caprolactam obtained by the process of the present invention is analyzed by Gas Chromatography (GC) under the following conditions:

Apparatus: A gas chromatographic system is equipped with FID; Column: DB-5 Capillary

column (or) equivalent; Length: 30 mts; ID: 0.53 mm; film thickness: 3.0µm; Injector temperature: 180°C; split ratio: 1:7; Injection volume: 0.0 µL; Diluent: methanol; Carrier gas: helium; hydrogen flow: 40 ml/min; air flow: 400 ml/min.

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: Process for the preparation of caprolactam

A mixture of cyclohexanone (50 gms), methanol (100 ml) and hydroxylamine sulfate (40 gms) were stirred for 10 hrs at 25-30°C. Distilled off the solvent completely from the reaction mixture. Sulfuric acid (127 gms) was slowly added to the above obtained compound and stirred for 2 hours at 45-50°C. Heated the reaction mixture to 65-70°C and stirred for 12 hrs. Cooled the reaction mixture to 0-5°C and basified with aqueous sodium hydroxide solution. n-Butanol (150 ml) was added to the reaction mixture at 25-30°C and stirred for 15 min. Separated the both organic and aqueous layers and extracted the aqueous layer with n-butanol. Combined the total organic layers and distilled off the solvent completely under reduced pressure followed by co-distillation with n-heptane. n-Heptane (100 ml) was added to the above obtained compound at 25-30°C and cooled the reaction mixture to 0-5°C and stirred for 2 hrs at the same temperature. Filtered the precipitated solid and washed with n-heptane and then dried to afford the title compound. (Yield: 60.7 gms)

Example-2: Process for the preparation of caprolactam

A mixture of cyclohexanone (100 gms), cyclohexane (100 ml) and hydroxylamine sulfate (100.35 gms) were stirred for 2 hrs at 25-30°C. Heated the reaction mixture to 45-50°C and added sulfuric acid (254 gms) and then stirred for 2 hours at same temperature. Heated the reaction mixture to 75-80°C and stirred for 12 hrs at same temperature. Basified the reaction mixture with aqueous sodium hydroxide solution at 10-15°C. n-Butanol (300 ml) was added to the above reaction mixture at 25-30°C and stirred for 15 min. Separated the both organic and aqueous layers and extracted the aqueous layer with n-butanol. Combined the total organic layers and dried over sodium sulfate. Distilled off the solvent completely

from the organic layer and then co-distilled with cyclohexane. Cyclohexane (200 ml) was added to the above obtained compound at 25-30°C and cooled the reaction mixture to 10-15°C and stirred for 2 hrs at the same temperature. Filtered the compound and washed with cyclohexane and then dried to afford the title compound.

(Yield: 81 gm, M.R: 69-72°C, Purity by GC: 99.96%)

Example-3: Process for the preparation of pure 6-aminohexanoic acid

Caprolactam (100 gms) was added to freshly prepared aqueous potassium hydroxide solution (56.5 gms of potassium hydroxide dissolved in 90 ml of water) at 25-30°C. Heated the reaction mixture to 90-95°C and stirred for 10 hrs at same temperature. Isopropanol (600 ml) and charcoal (5 gms) were added to the reaction mixture at 25-30°C and stirred for 30 min at same temperature. Filtered the reaction mixture through hy-flow bed and washed with isopropanol. The obtained filtrate again filtered through filter paper and washed with isopropanol. Acetic acid (85 ml) was added to the above obtained filtrate to neutralized the pH at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 3 hrs. Filtered the precipitated solid and then dried under reduced pressure.

The above obtained solid compound was added to water (94.5 ml) and isopropanol (220.5 ml) at 25-30°C and stirred for 10 min at same temperature. Heated the reaction mixture to 65-70°C and stirred for 30 min. Filtered the obtained solution through filter paper and washed with isopropanol. Isopropanol (504 ml) was added to the above filtrate at 25-30°C and stirred for 8 hrs at same temperature. Filtered the precipitated solid, washed with isopropanol and then dried to afford the title compound.

(Yield: 50 gms, M.R: 202-203°C, Purity by HPLC: 99.93%)

The PXRD pattern of the obtained compound is illustrated in figure-1.

Example-4: Process for the preparation of highly pure 6-aminohexanoic acid

Caprolactam (110 gms) was added to freshly prepared aqueous potassium hydroxide solution (62 gms of potassium hydroxide dissolved in 100 ml of water) at 25-30°C. Heated the reaction mixture to 90-95°C and stirred for 10 hrs at same temperature. Isopropanol (550 ml) and charcoal (5.5 gms) were added to the reaction mixture at 25-30°C and stirred for 30 min at same temperature. Filtered the reaction mixture through hy-flow bed and washed with isopropanol. Charcoal (5.5 gms) was added to the above obtained filtrate at 25-30°C and

filtered for particle free solution, washed with isopropanol. Mixture of acetic acid (95 ml) and isopropanol (110 ml) solution was added to the obtained filtrate to neutralized the pH at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 3 hrs. Filtered the reaction mixture and then dried under reduced pressure.

Water (95 ml) and isopropanol (220 ml) were added to above obtained compound at 25-30°C and stirred for 10 min at same temperature. Heated the reaction mixture to 65-70°C and stirred for 30 min. Filtered the obtained solution through filter paper and washed with isopropanol. Isopropanol (500 ml) was added to the obtained filtrate at 25-30°C and stirred for 8 hrs at same temperature. Filtered the precipitated solid, washed with isopropanol and then dried to afford the title compound.

(Yield: 66 gms, M.R: 202-203°C, Purity by HPLC: 99.98%; Caprolactam impurity: Not detected; 6-(6-aminohexanamido)hexanoic acid (also known as "Dimer impurity"): 0.02%).

Example-5: Process for the preparation of pure 6-aminohexanoic acid

Caprolactam (500 gms) was added to freshly prepared aqueous potassium hydroxide solution (280 gms of potassium hydroxide dissolved in 450 ml of water) at 25-30°C. Heated the reaction mixture to 90-95°C and stirred for 10 hrs at same temperature. Isopropanol (2.5 Lt) and charcoal (25 gms) were added to the reaction mixture at 25-30°C and stirred for 30 min at same temperature. Filtered the reaction mixture through hy-flow bed and washed with isopropanol. Mixture of acetic acid (425 ml) and isopropanol (500 ml) solution was added to the obtained filtrate to neutralized the pH. Cooled the reaction mixture to 0-5°C and stirred for 3 hrs. Filtered the precipitated solid, washed with isopropanol and then dried under reduced pressure for 6 hrs. Water (525 ml) and isopropanol (1255 ml) were added to the obtained material at 25-30°C and stirred for 10 min. Heated the reaction mixture to 65-70°C and stirred for 30 min. Filtered the reaction mixture and washed with pre-heated isopropanol. Cooled the filtrate to 25-30°C and slowly added isopropanol and stirred for 8 hrs. Filtered the precipitated solid, washed with isopropanol and then dried to afford title compound.

(Yield: 277 gms, caprolactam impurity: not detected, dimer impurity: 0.02%, purity: 99.98% by HPLC).

Example-6: Process for the preparation of highly pure 6-aminohexanoic acid

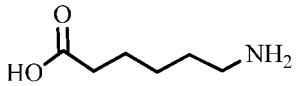
6-Aminohexanoic acid (250 gms) of example-5 was added to water (375 ml) and

isopropanol (875 ml) at 25-30°C and stirred for 10 min. Heated the mixture to 65-70°C and stirred for 30 min. Filtered the obtained mixture and washed with isopropanol. Isopropanol (2000 ml) was added to obtained material and stirred for 8 hrs, filtered the compound and washed with isopropanol. The obtained wet compound was dried at 60-65°C under vacuum for 18 hrs and cooled to 25-30°C and then milled to afford the title compound.
(Yield: 248.2 gms, caprolactam impurity: not detected, dimer impurity: 0.02%, acetic acid: less than 250 ppm; isopropyl alcohol: 1059 ppm, n-pentane: not detected; cyclohexane: below detection limit; n-heptane: less than LOQ; pentanol: not detected; benzene: not detected; purity: 99.98% by HPLC).

The PXRD pattern of obtained compound was illustrated in figure-2.

Claims:

1. Highly pure 6-aminohexanoic acid of formula-1 which is free of organic volatile impurities.

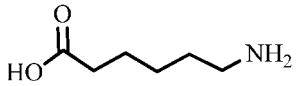


(Formula-1)

2. According to claim 1, organic volatile impurities are one or more selected from n-pentane, cyclohexane, n-heptane, isopropanol, pentanol, benzene.

3. According to claim 1, highly pure 6-aminohexanoic acid which contains isopropanol less than about 1100 ppm.

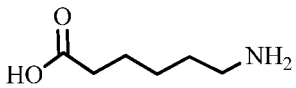
4. Highly pure 6-aminohexanoic acid of formula-1 substantially free of caprolactam impurity



(Formula-1)

5. Highly pure 6-aminohexanoic acid of claim 4, contains less than about 0.05% of caprolactam impurity.

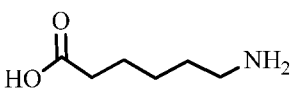
6. Highly pure 6-aminohexanoic acid of formula-1 is free of chloride content.



(Formula-1)

7. Highly pure 6-aminohexanoic acid of claim 6 contains less than 0.05% of chloride content.

8. A process for the preparation of 6-aminohexanoic acid of formula (1),



Formula (1)

comprising:

a) treating the caprolactam with an inorganic base in a solvent,

b) neutralizing the product obtained in step-a) with an acid optionally in an organic solvent,

c) isolating 6-aminohexanoic acid.

9. The process as claimed in claim 8, in step-a) an inorganic base is selected form "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate and the like; in step-a) the solvent is polar protic solvent selected from water or alcohol solvents such as methanol, ethanol, n-propanol or isopropanol or mixtures thereof; in step-b) the acid is selected from acetic acid, formic acid, propanoic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid; the organic solvent is selected from alcohol solvents, hydrocarbon solvents, ether solvents, chloro solvents, ketone solvents, nitrile solvents or mixtures thereof.

10. The process as claimed in claim 8, in step-a) an inorganic base is alkali metal hydroxides and solvent is water.

11. The process as claimed in claim 8, in step-b) the acid is acetic acid and an organic solvent is isopropanol.

12. The process as claimed in claim 8, in step-c) the isolation is carried out by using crystallization, recrystallization or solvent and anti-solvent method using the solvent wherein, the solvent is selected from polar protic solvent, anti-solvent is selected from alcohol solvents such as methanol, ethanol, n-propanol, isopropanol, chloroform and /or the isolation also carried out by the methods like distillation, decantation, filtration and drying.

13. The process as claimed in claim 8, in step-c) the isolation is carried out with water and

isopropanol.

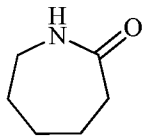
14. The process as claimed in claim 8, 6-aminohexanoic acid having purity greater than 99.95% by high performance liquid chromatography (HPLC).

15. The process as claimed in claim 1, preparation of highly pure 6-aminohexanoic acid, comprising:
    a) reacting caprolactam with aqueous potassium hydroxide solution,
    b) adding isopropyl alcohol and charcoal to the product obtained in step-a),
    c) filtering the mixture obtained in step-b),
    d) neutralizing the filtrate obtained in step-c) with acetic acid to provide 6-aminohexanoic acid.

16. A process for the preparation of highly pure 6-aminohexanoic acid, comprising:
    a) dissolving crude 6-aminohexanoic acid in water,
    b) optionally filtering the mixture,
    c) combining the filtrate obtained in step-b) with anti-solvent to provide pure 6-aminohexanoic acid.

17. The process as claimed in claim 16, wherein in step-c), the anti-solvent is selected from methanol, ethanol, isopropanol, n-propanol or n-butanol thereof.

18. A process for the preparation of caprolactam of formula-2,

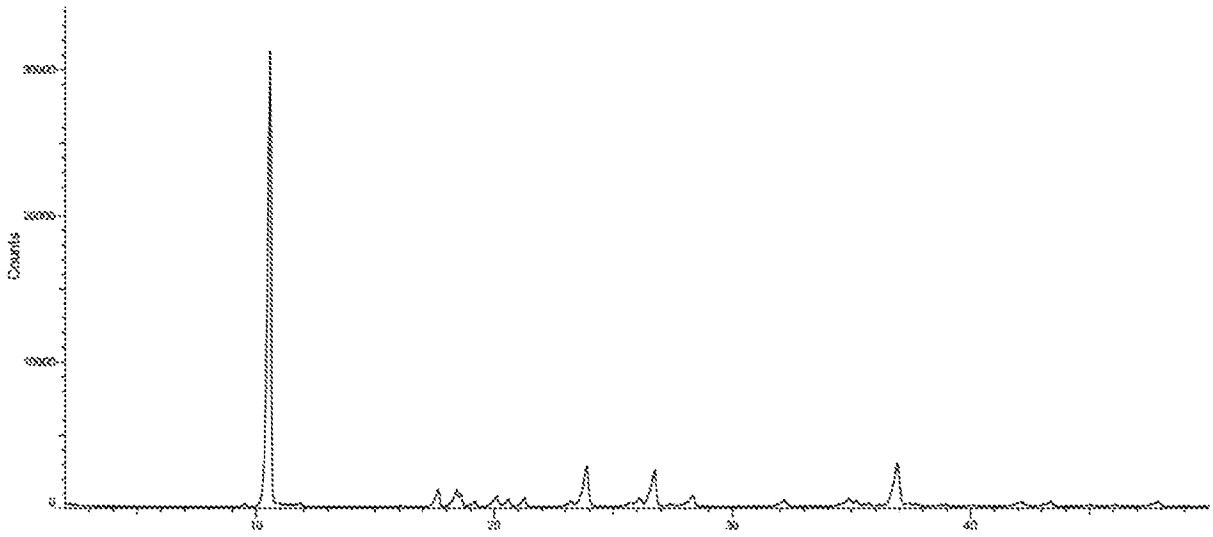


comprising:
a) reacting the cyclohexanone with hydroxylamine or its salt in a solvent,
b) *in-situ* treating the product obtained in step-a) with an acid to provide caprolactam.

19. The process as claimed in claim 18, wherein in step-a) the hydroxylamine salt is selected from sulfate, hydrochloride, hydrobromide, hydroiodide and the like; the solvent is

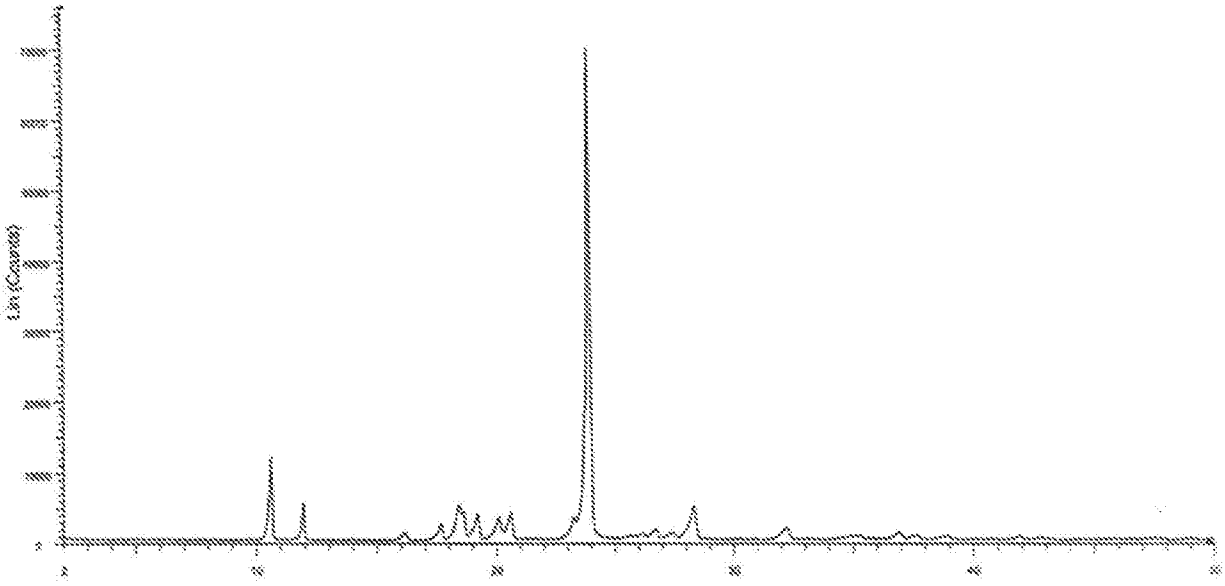
selected from hydrocarbon solvents, ether solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof; in step-b) the acid is mineral acid such as sulfuric acid, nitric acid and the like or organic acid such as formic acid, acetic acid, methanesulfonic acid, p-toluenesulfonic acid, camphor sulfonic acid and the like.

[1/1]



2-Theta-Scale

Figure-1



2-Theta-Scale

Figure-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050572

A. CLASSIFICATION OF SUBJECT MATTER
C07C227/22,C07C229/08,C07C227/40,C12P13/00 Version=2019.01

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)

C07C, C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5900482 A (MITSUBISHI CHEMICAL CORPORATION) 04 MAY 1999 (04.05.1999) *abstract; col.3, line 66- col.4, line 3; claim 8; col.5, lines 35-40; col.5, lines 49-56; claim 9* FAMILY: [NONE]	18-19
Y	CA 1256899 A (CONTINENTAL PHARMA INC) 04 JULY 1989 (04.07.1989) *scheme on pg. 23; claim 1; pg.8, paras 3-4*	8-15
Y	WO 1997010197 A1 (EMISPHERE TECHNOLOGIES, INC.) 20 MARCH 1997 (20.03.1997) *scheme on pg.9; example 2; example 3*	8-15
Y	US 8809581 B2 (SUNNY PHARMTECH INC) 19 AUGUST 2014 (19.08.2014) *example 5*	2-3,5,8-15
Y	DOLEŽAL, P., HRABÁLEK, A., & SEMECKÝ, V., (1993), "-AMINOCAPROIC ACID ESTERS AS TRANSDERMAL PENETRATION ENHANCING AGENTS", PHARMACEUTICAL	8-15

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19-11-2019	19-11-2019
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Vishakha Gupta Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050572

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	RESEARCH, 10(7), 1015-1019. *pg. 1015, 'Synthesis'*	
Y	GALAT, A., & MALLIN, S., (1946), "THE PREPARATION OF -AMINOCAPROIC ACID", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 68(12), 2729-2730. *pg. 2730, 'Experimental'*	8-15
X	US 20170036991 A1 (DIPHARMA FRANCIS SRL) 09 FEBRUARY 2017 (09.02.2017) *example 3;	1,4,6-7,16-17
Y	examples*	2-3,5,8-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050572

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I: Claims 1-7

These claims relate to pure 6-aminohexanoic acid of formula-1 which is free of organic volatile impurities or caprolactam impurity or chloride content.

Group II: Claims 8-15

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

These claims relate to a process for preparation of 6-aminohexanoic acid of formula-1 comprising the steps of treating caprolactam (2) with inorganic base, neutralizing the product and isolating 6-aminohexanoic acid.

Group III: Claims 16-17

These claims relate to a process for the preparation of pure 6-aminohexanoic acid comprising dissolving crude 6-aminohexanoic acid in water, optionally filtering and adding anti-solvent.

Group IV: Claims 18-19

These claims relate to a process for the preparation of caprolactam of formula-2 comprising reacting cyclohexanone with hydroxylamine or its salt in a solvent and treating with acid.

These groups of inventions are not so linked as to form a single general inventive concept as required under Rule 13.1 of PCT for the following reasons.

The special technical feature is an essential feature common to all embodiments of the claimed invention (and responsible for the inventive effect) and which defines a contribution with each of the claimed inventions over prior art (Rule 13.2 of PCT). Upon prior art search, it was found that 6-aminohexanoic acid and its synthesis from caprolactam is already known in the prior art. The only linking feature in the group of inventions is the compound 6-aminohexanoic acid or caprolactam which is already known. Hence, here it is considered that the common technical link in the above-mentioned groups is not novel. Therefore, the above-mentioned groups lack a common feature which could be regarded as the special technical feature providing unity to the claims. Consequently, the application may be objected for lacking unity 'a posteriori'.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2019/050572

Citation	Pub.Date	Family	Pub.Date
CA 1256899 A	04-07-1989	DE 3347867 A1	18-04-1985
WO 1997010197 A1	20-03-1997	US 6084112 A	04-07-2000
US 8809581 B2	19-08-2014	TW 201406708 A	16-02-2014
US 20170036991 A1	09-02-2017	IT UB20152961 A1	06-02-2017