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(71) Applicant: **BRAWN LABORATORIES LTD** [IN/IN]; C-64, First Floor, Lajpat Nagar -1, New Delhi, Delhi 110024 (IN).

(72) Inventors: **GUPTA, Surinder Mohan**; 151, Narmada Apartments, Alaknanda, Pocket - D, New Delhi, Delhi 110019 (IN). **KUMAR, Ajay**; 1766, Sector 10, Gurugram, Haryana, Gurugram 122001 (IN). **GUPTA, Kush**; 38 Gulmohar Marg, DLF Phase 2, Gurugram, Haryana, Gurugram 122002 (IN). **GUPTA, Nitin**; 38 Gulmohar Marg, DLF Phase 2, Gurugram, Haryana, Gurugram 122002 (IN). **GUPTA, Love**; 38 Gulmohar Marg, DLF Phase 2, Gurugram, Haryana, Gurugram 122002 (IN).

(74) Agent: **JADHAV, Mahesh**; Garima Gupta Associates, C 64 Lajpat Nagar -1 Delhi, Delhi 110024 (IN).

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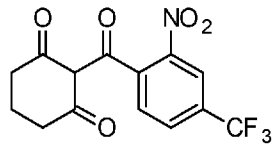
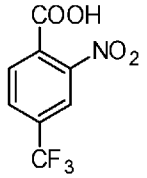
(54) Title: PROCESS FOR THE PREPARATION OF NITISINONE

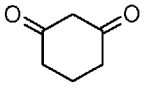
(57) Abstract: Disclosed herein is a process for the preparation of Nitisinone of formula (1) which comprises reacting 2-nitro-4-(trifluoromethyl) benzoic acid of formula (2) with cyclohexane-1,3-dione of formula (3) in the presence of a base, and a coupling agent.



Formula (1)



Formula (2)



Formula (3)

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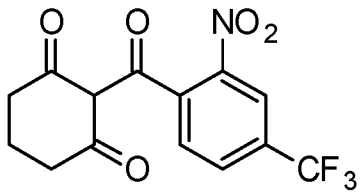
PROCESS FOR THE PREPARATION OF NITISINONE

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of Nitisinone of formula 1.



Formula (1)

BACKGROUND OF THE INVENTION

Nitisinone is a hydroxyphenyl-pyruvate dioxygenase inhibitor. It is indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1). Chemically, it is known as 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione.

Several processes have been reported for the preparation of Nitisinone for example, in U.S. Patent No. 4,695,673; 4,774,360; 5,006,158 5,550,165; 5,728,889; 9,783,485; 10,328,029; U.S. Patent Publication No. 2016/0324785; Indian Patent Application No. 201611023671; 201841016377, the contents of which are hereby incorporated as reference in their entirety. These processes require multiple steps or complicated purification processes such as chromatography and therefore inevitably lead to poorer yields or purity.

There is still a need for an improved and simplified process for the preparation of Nitisinone or salts thereof, which can reduce the burden of isolating, crystallizing, and purifying the intermediate compound(s), and thus minimize production time, provide high yield and is convenient to operate on a commercial scale and also, a

need for a process that leads to formation of Nitisinone with an improved yield and purity, and in particular by avoiding use of toxic, hazardous and corrosive chemicals such as phosphorus oxychloride, thionyl chloride etc.

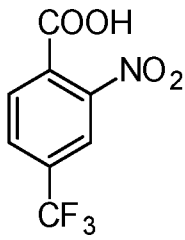
The present invention is associated with these advantages and enables practical and efficient manufacture of Nitisinone. Added advantages of the present invention are cost effectiveness, readily accessible raw materials, less hazardous reaction conditions, and simple work up procedures which all make the process more robust and cost-efficient.

The impurities associated to nitisinone can be either derived from the starting materials themselves (i.e., Formula (2) and Formula (3)) or obtained as side products during the process of synthesis and/or under storage conditions (i.e., Formula (4)) and are the following:

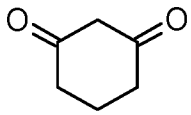
2-nitro-4-(trifluoromethyl)benzoic acid of formula (2),

cyclohexane-1,3-dione of formula (3), and

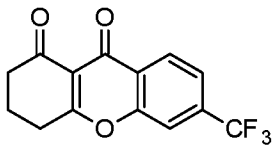
6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4).



Formula (2)



Formula (3)



Formula (4)

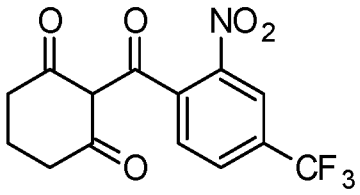
Impurities in nitisinone, or any active pharmaceutical ingredient ("API"), are undesirable and, in extreme cases, might even be harmful to a patient being treated with a dosage form containing the API.

The purity of an API produced in a manufacturing process is critical for commercialization. The product of a chemical reaction is rarely a single compound with sufficient purity to comply with pharmaceutical standards. Side products and by-products of the reaction and adjunct reagents used in the reaction will, in most cases, also be present in the final product. At certain stages during processing of an API, it must be analyzed for purity, typically, by high performance liquid chromatography ("HPLC") or thin-layer chromatography ("TLC"), to determine if it is suitable for continued processing and, ultimately, for use in a pharmaceutical product.

As known by those skilled in the art, the management of process impurities is greatly enhanced by understanding their chemical structures and synthetic pathways and by identifying the parameters that influence the amount of impurities in the final product. Extensive experimentation has been carried out by the present inventors. As a result, the present inventors found an improved method for the preparation of nitisinone which is substantially free of formula (2) and formula (4), by controlling critical process parameters. The nitisinone made by the process of the present invention is suitable for commercial scale production.

SUMMARY OF THE INVENTION

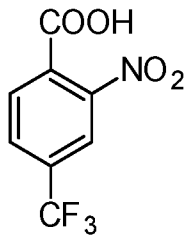
In one aspect, the present invention provides a process for the preparation of Nitisinone of formula (1).

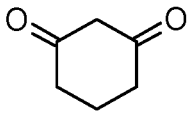


Formula (1)

The process comprises:

reacting 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) with cyclohexane-1,3-dione of formula (3)





Formula (2) Formula (3)

in the presence of a base, and a coupling agent to obtain Nitisinone of formula (1).

In another general aspect, the present invention provides a process for the preparation of nitisinone substantially free of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2), and 6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4) in an amount of 0.001% or less as determined by HPLC method.

In yet another general aspect, the present invention provides a process for the preparation of nitisinone substantially free of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2), and 6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4) undetectable as determined by HPLC method.

BRIEF DESCRIPTION OF THE DRAWINGS

A SKILLED PERSON WILL UNDERSTAND THAT THE DRAWINGS, DESCRIBED BELOW, ARE FOR ILLUSTRATION PURPOSES ONLY. THE DRAWINGS ARE NOT INTENDED TO LIMIT THE SCOPE OF THE PRESENT INVENTION IN ANY WAY.

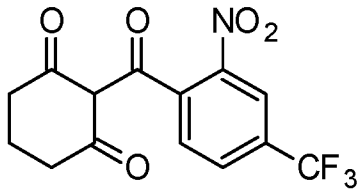
FIG. 1 SHOWS AN X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF NITISINONE AS OBTAINED BY THE PROCESS ACCORDING TO THE PRESENT INVENTION, AS DISCLOSED HEREIN IN EXAMPLE 1.

DETAILED DESCRIPTION OF THE INVENTION

The term "about", as used herein, when used along with values assigned to certain measurements and parameters means a variation of up to 10% from such values, or in case of a range of values, means up to a 10% variation from both the lower and upper limits of such ranges.

Use of exemplary language, such as "for example", "such as", and the like, is merely intended to better illustrate the invention and does not indicate a limitation on the scope of the invention unless so claimed.

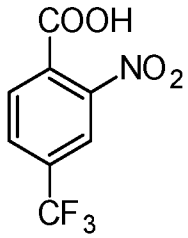
In one aspect, the present invention provides a process for the preparation of Nitisinone of formula (1)



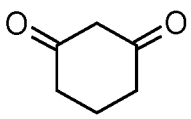
Formula (1)

which comprises:

reacting 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) with cyclohexane-1,3-dione of formula (3)



Formula (2)



Formula (3)

in the presence of a base, and a coupling agent to obtain Nitisinone of formula (1).

The 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) may be obtained by any of the methods known in the art including those described in U.S. Patent No. 4,868,333.

In one embodiment of this aspect, the base includes, for example an amine, an inorganic base or ammonia.

Examples of amines include triethylamine, N-methyl morpholine, N,N-dimethyl benzyl amine, pyridine, picoline, and lutidine.

The inorganic base may be an alkali metal carbonate, bicarbonate or hydroxide. Examples of alkali metal carbonates include lithium carbonate, potassium carbonate and sodium carbonate. Examples of alkali metal bicarbonates include potassium bicarbonate and sodium bicarbonate. Examples of alkali metal hydroxides include potassium hydroxide and sodium hydroxide.

Preferably, the base is an amine. More preferably, the base is triethylamine.

In another embodiment of this aspect, the amount of base used with respect to 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) is between 0.9 to 4 molar equivalents, more preferably between 1 to 2 molar equivalents, even more preferably between 1.1 to 1.3 molar equivalents, and most preferably about 1.2 molar equivalents.

In another embodiment of this aspect, the coupling agent includes, for example a carbodiimide, a 1,1′-carbonyl compound, or a mixture thereof. Preferably, the coupling agent is selected from 1,3-dicyclohexylcarbodiimide (DCC); 1,1′-carbonyldiimidazole (CDI); N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC . HCl); 1,3-diisopropylcarbodiimide (DIC); or a mixture thereof.

Preferably, the coupling agent is N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC . HCl)

In another embodiment of this aspect, the amount of coupling agent used with respect to 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) is between 0.5 to 5 molar equivalents, more preferably between 0.9 to 2 molar equivalents, even more preferably between 0.95 to 1.25 molar equivalents, and most preferably about 1.05 molar equivalents.

In another embodiment of this aspect, the reaction may be carried out in the presence of a catalyst. In another embodiment, the reaction may be carried out in the presence of a catalytic amount of a source of cyanide. Preferably, the cyanide sources are cyanohydrins of methyl alkyl ketones having from C_1-C_4 carbon atoms in the alkyl groups, such as acetone or methyl isobutyl ketone cyanohydrins; cyanohydrins of benzaldehyde or of C_2-C_5 aliphatic aldehydes such as acetaldehyde, propionaldehyde; alkali metal cyanides such as sodium and potassium cyanide; zinc cyanide; trimethyl silyl cyanide. Among cyanohydrins, the preferred cyanide source is acetone cyanohydrin.

The cyanide source may be used in as little as about 0.1 mole equivalent to produce an acceptable rate of reaction on a small scale. Larger scale reactions give more reproducible results with slightly higher catalyst levels of about 0.12 to about 1 mole equivalent. Generally, about 0.001 to 1.5 mole % of the cyanide source is preferred.

In yet another embodiment of this aspect, the reaction may be carried out in the presence of a solvent. There are no specific limitations with respect to the organic solvent employed in the reaction, so far as the solvent does not participate in the reaction. The solvent includes, for example, water, alcohols, such as, methanol, ethanol, n-propanol, 2-propanol, n-butanol, 2-butanol; aromatic hydrocarbon, such as, benzene, toluene, and xylene, substituted toluenes, substituted xylenes; halogenated

hydrocarbons, such as, dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform, carbon tetrachloride; ethers, such as, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dioxane, tetrahydrofuran; ketones, such as, acetone, methyl ethyl ketone, methyl isobutyl ketone; alkyl acetate, such as, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate; alkyl nitriles, such as, acetonitrile, propionitrile; amides, such as, N,N-dimethylformamide; dimethyl sulfoxide. The solvents may be employed singly or in combination.

Preferably, the solvent is halogenated hydrocarbon. More preferably, the solvent is dichloromethane.

In yet another embodiment of this aspect, 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) and cyclohexane-1,3-dione of formula (3) can be taken in the mole ratio of about 1:0.9 to about 1:1.5, preferably, about 1:1 to about 1:1.2, more preferably, about 1:1.05.

In yet another embodiment of this aspect, the reaction can be carried out in one-pot.

In yet another embodiment of this aspect, the temperature at which the reaction of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) with cyclohexane-1,3-dione of formula (3) may be carried out may range from about -20°C to about 120°C, for example from about 0°C to about 40°C or from about 20°C to about 35°C. In particular, it may be carried out at a temperature from about 25°C to about 30°C.

In yet another embodiment of this aspect, the process involves addition of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2), cyclohexane- 1,3-dione of formula (3), triethylamine (base), in dichloromethane (solvent) in optional order of succession at a temperature of about 25°C to 30°C, optionally under stirring, and

maintaining at a temperature of about 25 to 30°C for about 0.5 hours, followed by the addition of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride [EDC . HCl] (coupling agent), and acetone cyanohydrin (catalyst), in optional order of succession at a temperature of about 25°C to 30°C, optionally under stirring, and maintaining at a temperature of about 25 to 30°C for about 2 to 3 hours, to obtain nitisinone, and the isolation of the nitisinone involves common isolation techniques such as one or more of washing, crystallization, precipitation, cooling, filtration, filtration under vacuum, decantation and centrifugation, or a combination thereof.

In yet another embodiment of this aspect, the Nitisinone obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum, dried at 50-55°C in hot air oven and/or in a Fluid Bed Drier.

In another embodiment, the Nitisinone of formula (1) obtained may have X-Ray powder diffraction (XRPD) pattern as shown in FIG. 1 and the 2 theta values (main values) provided in Table 1.

2θ values
7.415
13.718
14.510
14.708
14.807
15.764
16.787
17.315
18.206
22.166

22.331
22.892
23.552
23.849
25.235
25.697
29.723
30.251
31.835
37.412
37.841
38.699
39.161
45.233

In another general aspect, the present invention provides a process for the preparation of nitisinone substantially free of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2), and 6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4) in an amount of 0.001% or less as determined by HPLC method.

In yet another general aspect, the present invention provides a process for the preparation of nitisinone substantially free of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2), and 6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4) as determined by HPLC method.

While the present invention has been described in terms of its specific aspect, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

In the following section, the aspect is described by way of examples to illustrate the processes of the invention. However, these do not limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

EXAMPLES

EXAMPLE 1: PROCESS FOR THE PRERPATIN OF NITISINONE

2-Nitro-4-(trifluoromethyl)benzoic acid (5.0 g), Triethylamine (2.57 g) and then, Cyclohexane-1,3-dione (2.50 g) were added into Dichloromethane (50 ml) at 25-30°C and maintained at 25-30°C for 30 minutes. N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride [EDC. HCl] (3.46 g) was added to the mixture at 25-30°C in one lot. Acetone cyanohydrin (0.18 g) was added at 25-30°C, and the mixture was maintained at 25-30°C for 2-3 hours. Purified water (50 ml) was charged at 25-30°C. The mixture was stirred and settled for 15 minutes. The aqueous layer was separated, and washed with methylene dichloride (25 ml). The aqueous layer was cooled to 15-20°C and concentrated hydrochloric acid (5 ml) was charged slowly over 15-20 minutes. The mixture was maintained at 25-30°C for 30 minutes and distilled below 40°C under vacuum to completely remove methylene dichloride. Acetonitrile (25 ml) was added with the residue at 25-30°C and heated at 45-50°C for 30 minutes. Purified water (30 ml) was added at 45-50°C, slowly over 30 minutes. The mixture was maintained at 45-50°C for 30 minutes and then cooled to 25-30°C for 2 hours. The solid obtained was filtered, washed with purified water (5 ml), suck dried under vacuum and dried at 50-55°C in hot air oven.

Yield (%): 48.6%

Purity (%): 99.98% (by HPLC)

2-nitro-4-(trifluoromethyl)benzoic acid of formula (2): ND (by HPLC)

6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4): ND (by HPLC)

(ND = Not Detected)

EXAMPLE 2: PROCESS FOR THE PRERPATION OF NITISINONE

2-Nitro-4-(trifluoromethyl)benzoic acid (5.0 g), Triethylamine (2.57 g) and then, Cyclohexane-1,3-dione (2.50 g) were added into Dichloromethane (50 ml) at 25-30°C and maintained at 25-30°C for 30 minutes. N,N'-Dicyclohexylcarbodiimide-[DCC] (4.6 g) was added to the mixture at 25-30°C in one lot. Acetone cyanohydrin (0.18 g) was added at 25-30°C, and the mixture was maintained at 25-30°C for 2-3 hours. Purified water (50 ml) was charged at 25-30°C. The mixture was stirred and settled for 15 minutes. The aqueous layer was separated, and washed with methylene dichloride (25 ml). The aqueous layer was cooled to 15-20°C and concentrated hydrochloric acid (5 ml) was charged slowly over 15-20 minutes. The mixture was maintained at 25-30°C for 30 minutes and distilled below 40°C under vacuum to completely remove methylene dichloride. Acetonitrile (25 ml) was added with the residue at 25-30°C and heated at 45-50°C for 30 minutes. Purified water (30 ml) was added at 45-50°C, slowly over 30 minutes. The mixture was maintained at 45-50°C for 30 minutes and then cooled to 25-30°C for 2 hours. The solid obtained was filtered, washed with purified water (5 ml), suck dried under vacuum and dried at 50-55°C in hot air oven.

Yield (%): 46.4%

Purity (%): 99.97% (by HPLC)

2-nitro-4-(trifluoromethyl)benzoic acid of formula (2): ND (by HPLC)

6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4): ND (by HPLC)

(ND = Not Detected)

EXAMPLE 3: PROCESS FOR THE PRERPATIN OF NITISINONE

2-Nitro-4-(trifluoromethyl)benzoic acid (5.0 g), Triethylamine (2.57 g) and then, Cyclohexane-1,3-dione (2.50 g) were added into Dichloromethane (50 ml) at

25-30°C and maintained at 25-30°C for 30 minutes. N,N'-carbonyldiimidazole-[CDI] (3.61 g) was added to the mixture at 25-30°C in one lot. Acetone cyanohydrin (0.18 g) was added at 25-30°C, and the mixture was maintained at 25-30°C for 2-3 hours. Purified water (50 ml) was charged at 25-30°C. The mixture was stirred and settled for 15 minutes. The aqueous layer was separated, and washed with methylene dichloride (25 ml). The aqueous layer was cooled to 15-20°C and concentrated hydrochloric acid (5 ml) was charged slowly over 15-20 minutes. The mixture was maintained at 25-30°C for 30 minutes and distilled below 40°C under vacuum to completely remove methylene dichloride. Acetonitrile (25 ml) was added with the residue at 25-30°C and heated at 45-50°C for 30 minutes. Purified water (30 ml) was added at 45-50°C, slowly over 30 minutes. The mixture was maintained at 45-50°C for 30 minutes and then cooled to 25-30°C for 2 hours. The solid obtained was filtered, washed with purified water (5 ml), suck dried under vacuum and dried at 50-55°C in hot air oven.

Yield (%): 47.1%

Purity (%): 99.96% (by HPLC)

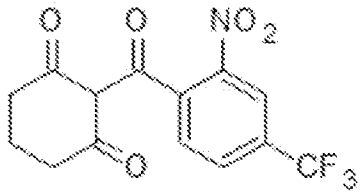
2-nitro-4-(trifluoromethyl)benzoic acid of formula (2): ND (by HPLC)

6-(trifluoromethyl)-3,4-dihydro-1H-xanthene-1,9(2H)-dione of formula (4): ND (by HPLC)

(ND = Not Detected)

CLAIMS:

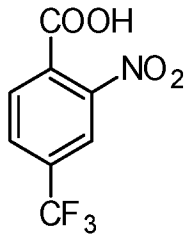
1. A process for the preparation of Nitisinone of formula (1)



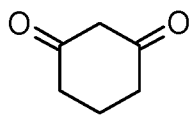
Formula (1)

which comprises:

reacting 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) with cyclohexane-1,3-dione of formula (3)



Formula (2)



Formula (3)

in the presence of a base, and a coupling agent to obtain Nitisinone of formula (1).

2. The process as claimed in claim 1, wherein the base is selected from a group comprising an amine, an inorganic base or mixtures thereof.

3. The process as claimed in claim 1, wherein the base is triethylamine.

4. The process as claimed in claim 1, wherein the coupling agent is selected from a group comprising a carbodiimide, a 1,1′-carbonyl compound, or a mixture thereof.

5. The process as claimed in claim 1, wherein the coupling agent is N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC.HCl).

6. The process as claimed in claim 1, wherein the reaction is carried out in the presence of a catalyst.

7. The process as claimed in claim 6, wherein the catalyst is acetone cyanohydrin.

8. The process as claimed in claim 1, wherein the reaction is carried out in the presence of a solvent selected from a group comprising of water, methanol, ethanol, n-propanol, 2-propanol, n-butanol, 2-butanol, benzene, toluene, and xylene, dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform, carbon tetrachloride, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dioxane, tetrahydrofuran, acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate; acetonitrile, propionitrile, N,N-dimethylformamide; dimethyl sulfoxide or any mixtures thereof.

9. The process as claimed in claim 8, wherein the solvent is dichloromethane.

10. The process as claimed in claim 1, wherein the reaction is carried out at a temperature of about -20°C to about 120°C.

11. The process as claimed in claim 10, wherein the reaction is carried out at a temperature of about 20°C to about 35°C.

12. The process as claimed in claim 1, the process comprises addition of 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2), cyclohexane-1,3-dione of formula (3), triethylamine, N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride [EDC . HCl], and acetone cyanohydrin, in dichloromethane at a temperature of about 25°C to 30°C,
wherein,
the amount of triethylamine used with respect to 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) is about 1.2 molar equivalent,
the amount of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride [EDC . HCl] used with respect to 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) is about 1.05 molar equivalent,
the amount of acetone cyanohydrin used with respect to 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) is about 0.1 molar equivalent,

the mole ratio between 2-nitro-4-(trifluoromethyl)benzoic acid of formula (2) and cyclohexane-1,3-dione is about 1 : 1.05 molar equivalent.

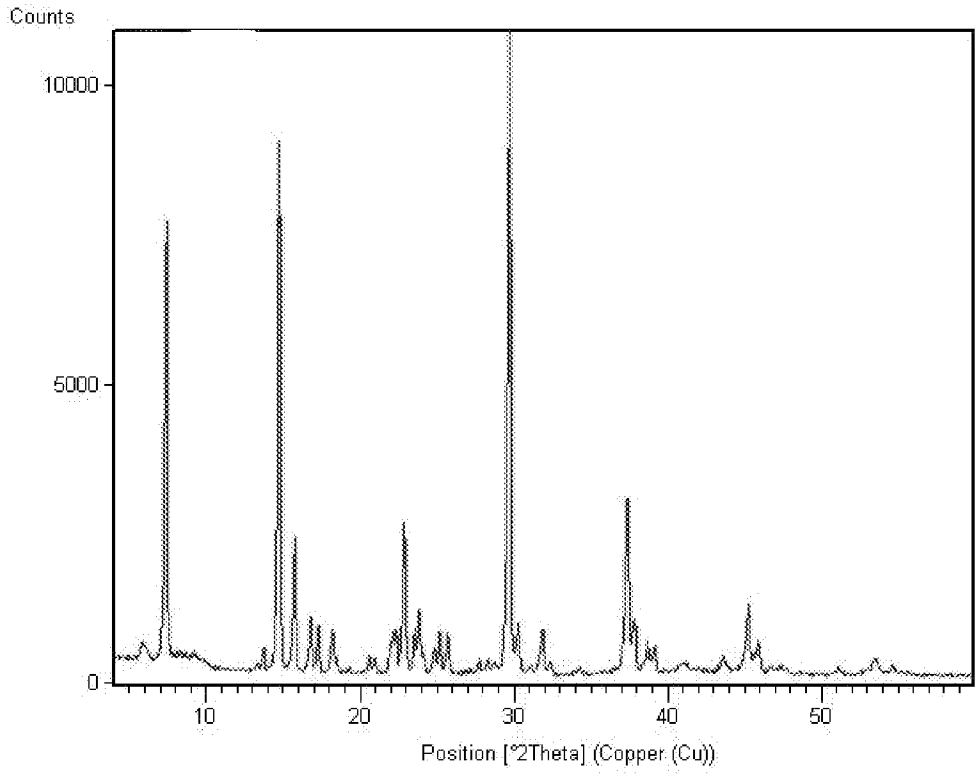


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2022/050879

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/122,A61K31/122,C07C201/12,C07C205/46 Version=2023.01

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)

A61K, C07C

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

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

PatSeer, 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.
Y	IN201841016377 A; (BIOPHORE INDIA PHARMACEUTICALS PVT. LTD [IN]); 11 SEPTEMBER 2020; (cited in the application) Pages 6-8; claims 1-10	1-12
Y	WO1993000080 A1; (IMPERIAL CHEMICAL INDUSTRIES PLC [GB]); 7 JANUARY 1993 Example 1	1-12
Y	CN102976948 A; (ZHENGZHOU DAMING MEDICINE SCIENCE & TECHNOLOGY CO LTD); 20 MARCH 2013 Abstract; claim 1	1-12
Y	US9783485 B1; (DIPHARMA S A [CH]); 10 OCTOBER 2017; (cited in the application) Abstract; column 5, lines 31-60	1-12

☐ 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
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13-01-2023	13-01-2023
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Sateesh Kumar Meena Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2022/050879

Citation	Pub.Date	Family	Pub.Date
WO 1993000080 A1	07-01-1993	AU 1986092 A	25-01-1993
		CA 2072047 A1	25-12-1992
		DE 69228813 T2	05-08-1999
		EP 0591275 A1	13-04-1994
		JP 3130935 B2	31-01-2001
		US 5550165 A	27-08-1996
US 9783485 B1	10-10-2017	US 2018148402 A1	31-05-2018
		US 10093610 B2	09-10-2018