(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 July 2009 (09.07.2009)

PCT

(10) International Publication Number
WO 2009/084031 A2

(51) International Patent Classification:
C07C 255/43 (2006.01) *C07C 253/30* (2006.01)
C07C 205/22 (2006.01) *C07C 253/32* (2006.01)

(21) International Application Number:
PCT/IN2008/000806

(22) International Filing Date:
2 December 2008 (02.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2864/CHE/2007 3 December 2007 (03.12.2007) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2009/084031 A2

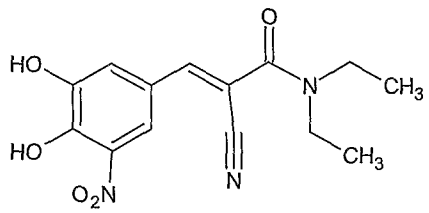
(54) Title: AN IMPROVED PROCESS FOR PREPARATION OF (2E)-2-CYANO-3-(3,4- DIHYDROXY-5-NITRO-PHENYL)N,N-DIETHYL-2-PROPENAMIDE POLYMORPHIC FORM A

(57) Abstract: The present invention relates to an improved, cost effective, eco-friendly and easy t handle process to manufacture substantially pure form of (2E)-2-Cyano-3-(3,4-dihydroxy-5 nitrophenyl)-N,N-diethyl-2-propenamide or (E)- N,N-diethyl-2-cyano-3-(3,4-dihyroxy-5 nitrophenyl)-acrylamide polymorphic form A commonly known as (E)-Entacapone represente by Formula I, using ammonium acetate as a base.

AN IMPROVED PROCESS FOR PREPARATION OF (2E)-2-CYANO-3-(3,4-DIHYDROXY-5-NITROPHENYL)-N,N-DIETHYL-2-PROPENAMIDE POLYMORPHIC FORM A

TECHNICAL FIELD OF INVENTION

The present invention relates to an improved, cost effective, eco-friendly and easy to handle process to manufacture substantially pure form of (2E)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide or (E)- N,N-diethyl-2-cyano-3-(3,4-dihyroxy-5-nitrophenyl)-acrylamide polymorphic form A commonly known as (E)-Entacapone represented by Formula I, using ammonium acetate as a base.



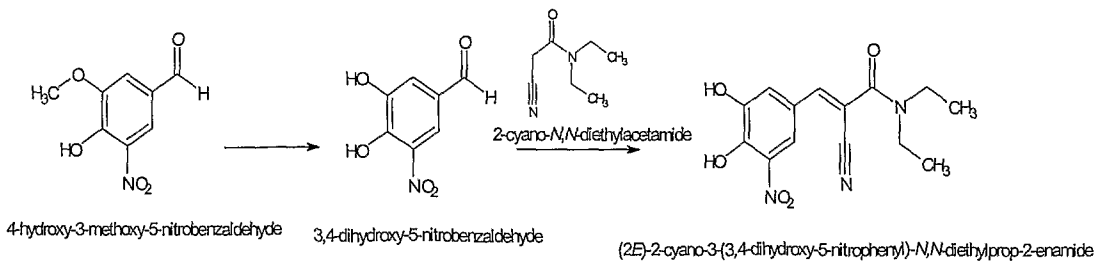
Formula I

BACKGROUND OF THE INVENTION

(2E)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide or Entacapone is a potent and specific peripheral catechol-O-methyltransferase (COMT) inhibitor and is used in the treatment of Parkinson's disease. This compound exists in two isomeric forms E & Z out of which E isomer being more pharmaceutically active. The Entacapone E isomer exists in five different polymorphic forms A, B, C, D and E.

The synthesis of entacapone was first described by Orion pharmaceutical in *US5963590* which involves conversion of 5-nitrovanillin to 3, 4-dihyroxy-5-nitrobenzaldehyde and condensation with N, N-diethyl-2-cyano acetamide in presence of piperdine acetate and dry ethanol to give racemic entacapone with 73% yield wherein the ration of E:Z isomer is 70%: 30%.

SCHEME I



4-hydroxy-3-methoxy-5-nitrobenzaldehyde 3,4-dihydroxy-5-nitrobenzaldehyde (2E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide

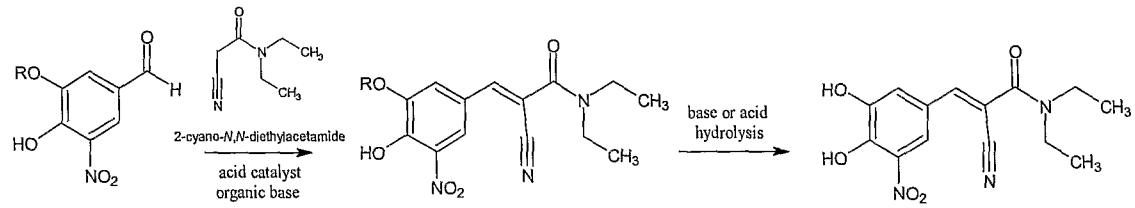
The '590 patent discloses racemic entacapone without describing the stereochemistry and polymorphic forms. Piperdine used as a base in this reaction, forms unwanted side products.

US5135950 discloses the process for preparation of E-isomer polymorphic form-A of entacapone by purification of the racemic form of entacapone obtained from '590 patent by treating with lower aliphatic carboxylic acid as acetic acid in presence of catalytic amount of hydrobromic acid to give the polymorphic form A of the E isomer of Entacapone with less than 0.1% of Z isomer.

The process of condensation disclosed in this invention is time consuming moreover the reported yield are very low 73% and the final E isomer is contaminated with the Z isomer is to 3%. The purification steps involved increases the process time and make this process commercially unviable for industrial production of entacapone.

WO2005063693 discloses the preparation of entacapone from 3-alkoxy-4-hydroxy-5-nitrobenzaldehyde described as alkoxy benzaldehyde with the acetamide derivative followed by dealkylation to give Entacapone.

SCHEME II



R=methyl or ethyl

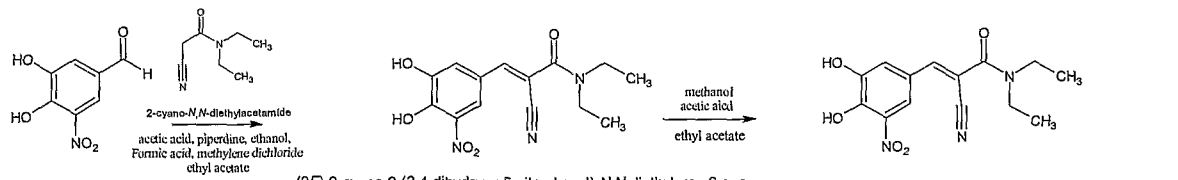
3-alkoxy entacapone

Entacapone

The process for the preparation of Entacapone, neither the isomerism nor the polymorphism have been discussed in this patent application, and also requires extra step of dealkylation of the 3-alkoxy entacapone which may also lead to lower yield and purity.

WO2005054950 discloses the preparation of Entacapone which process comprises condensing hydroxy nitrobenzaldehyde with acetamide derivative followed by extraction and purification with acid, different halogenated and alcoholic solvents like dichloromethane and methanol to give E-entacapone with less than 0.02 % of Z isomer.

SCHEME III



3,4-dihydroxy-5-nitrobenzaldehyde

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

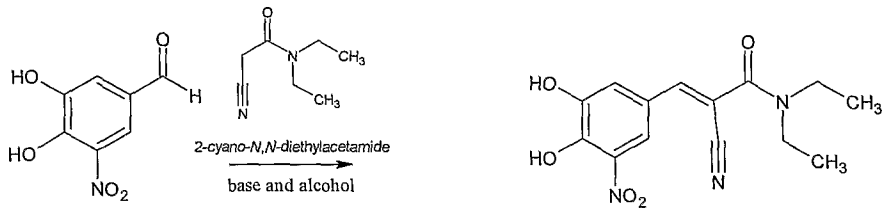
crude

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

The process involves lengthy workup and extra steps of acid and solvent purification making this process less attractive. Also this process is time consuming and the yield is also very low.

WO2005070881 (US20070004935) discloses the preparation of (E)-Entacapone by condensing 3, 4-dihyroxy-5-nitro-benzaldehyde with N, N-diethyl-2-cyano acetamide in presence of piperidine in an alcoholic solvent after which the reaction mixture is quenched in cold water and ethyl acetate followed by pH adjustment to 3.5-4.0 and the layers are separated .The organic layer was evaporated to get pure E isomer of entacapone as illustrated in Scheme IV below

SCHEME IV

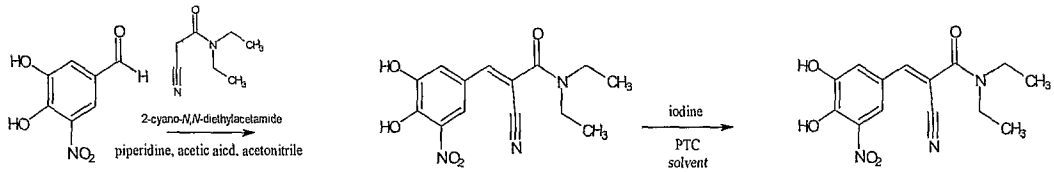


3,4-dihydroxy-5-nitrobenzaldehyde (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

The process is one pot synthesis of pure E isomer of entacapone, which involves lengthy work up and the product was isolated after evaporation of solvent which is not advisable on higher manufacturing scale. More over the compound is contaminated with Z isomer being at least 0.1%.

US200625877 (WO2007113845) discloses the preparation E-entacapone which involves condensation 3, 4-dihyroxy-5-nitro-benzaldehyde with N, N-diethyl-2-cyano acetamide in pyridine, acetic acid followed by treatment with halogen such as iodine added in presence of a phase transfer catalyst to give E-entacapone as illustrated below

SCHEME V



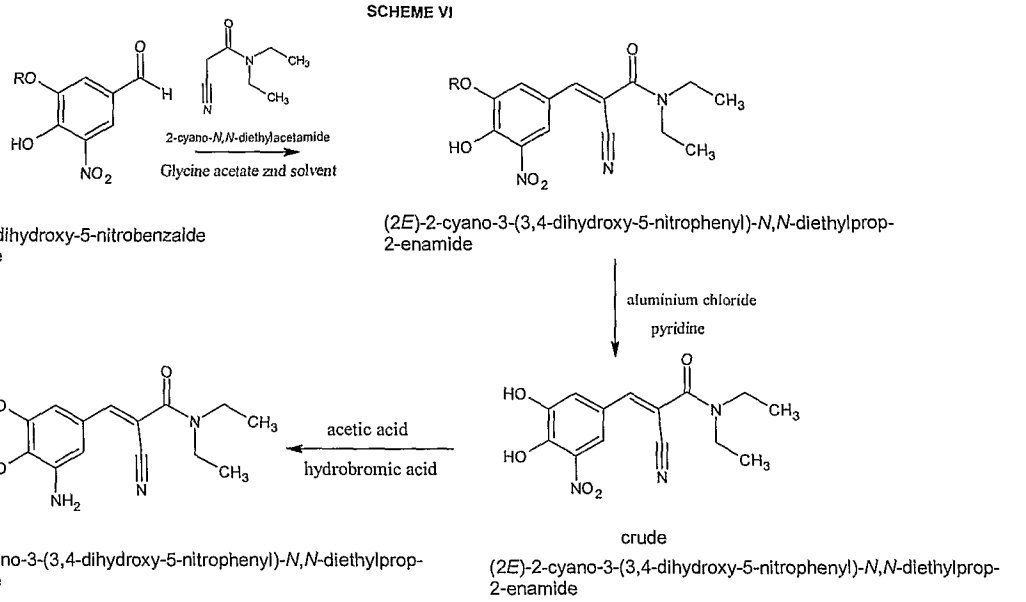
3,4-dihydroxy-5-nitrobenzaldehyde

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

WO2007094007 discloses the preparation E-entacapone which comprises condensation of 3-alkoxy-4-hyroxy-5-nitro-benzaldehyde with N,N-diethyl-2-cyano acetamide in the presence of glycine acetate and a solvent to give alkoxy Entacapone which is further dealkylated with aluminium chloride and pyridine to get crude entacapone which is further treated with acetic acid and catalytic amount of hydrobromic acid to give E-entacapone.

SCHEME VI



3,4-dihydroxy-5-nitrobenzaldehyde

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

crude (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

The invention uses glycine acetate which is expensive and commercially not viable at manufacturing scale, the invention also involves the extra step of dealkylation which causes extra time consumption and the yield is low and so the purity.

WO2007090923 discloses the preparation E-entacapone which comprises condensing 3,4-dihyroxy-5-nitro-benzaldehyde with N,N-diethyl-2-cyano acetamide in presence of C_{4-8} alcohol and in presence of base selected from methylamine hydrochloride, piperdine, N-methyl morpholine, pyridine and piperazine at a reduced pressure and at 70^0C, cooling and seeding the reaction with entacapone with 60% of E isomer further cooling and again seeding with Entacapone with 30% Z isomer further cooling to 5^0C during which time the product crystallises as racemic entacapone which is converted to pure E entacapone by known prior art methods. This method has significant drawback of cumbersome method of seeding the reaction mixture which is not possible for higher scale production, the base used in condensation forms unwanted impurities making the yields lower.

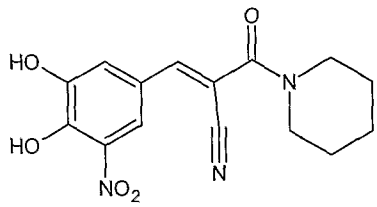
WO2007077572 discloses the preparation E-entacapone which comprises condensing 3,4-dihyroxy-5-nitro-benzaldehyde with N,N-diethyl-2-cyano acetamide in presence of piperdine, pyrolidine, diisopropyl amine and like and mixture of solvent selected from ether and hydrocarbon to give crude entacapone which is further purified in halogenated and further crystallised using suitable solvent. This process requires consequent purification and crystallisation which is time consuming and yields are also low, the base used in condensation forms unwanted impurities making the yields lower.

WO2005066117 discloses the preparation of different polymorphic forms C and D of E-Entacapone by condensing 3, 4-dihyroxy-5-nitro-benzaldehyde with N, N-diethyl-2-cyano

acetamide in presence of piperdine, N-methyl morpholine, pyridine and piperazine in an alcoholic solvent and further treating with proper acid or mixture of solvent to get the desired forms.

WO2005063696 by Cilag discloses the preparation of Entacapone by heating 3, 4-Dihyroxy-5-nitrobenzaldehyde with raw N,N-diethyl-2-cyano acetamide in presence of acetic acid and diethyl amine and toluene and by removing the water formed during reaction through azeotropic distillation. A significant drawback is large amount of solvent has to be used which is not feasible for a large scale production.

Most of the above disclosed invention utilizes piperdine as a base for the condensation which yields to unwanted impurity (2E)-3-(3, 4-dihydroxyphenyl)-2-(piperidin-1-ylcarbonyl)prop-2-enenitrile of Formula II and high cost of production



Formula II

so there is a continuing need for making a process which avoids the use of hazardous and expensive base as piperidine and a process that is easy to handle, eco-friendly, economical and yield gives better purity and good yield of the product.

SUMMARY OF THE INVENTION

The objective of the invention is to provide an improved process for the preparation of (2E)-2-Cyano-3-(3, 4-dihydroxy-5-nitrophenyl)-N, N-diethyl-2-propenamide or (E) Entacapone polymorphic form A of formula I which is substantially free from the (2E)-3-(3, 4-dihydroxyphenyl)-2-(piperidin-1-ylcarbonyl-) prop-2-enenitrile of formula II.

Another aspect of the present invention relates to the synthesis of E-entacapone which is simple, cost effective easy to handle and feasible at commercial or production scale with high purity and good yield.

Yet another object of the present invention relates to a process comprising

a) Reacting 3,4-dihyroxy-5-nitro-benzaldehyde with N,N-diethyl-2-cyano acetamide in the presence of anhydrous ammonium acetate and a suitable solvent to form racemic entacapone

b) Treating racemic entacapone with hydrogen bromide gas dissolved in suitable aliphatic carboxylic acid in to give crude (E)-entacapone polymorphic form A

c) Treating (E)-entacapone polymorphic form A first with an alcoholic solvent isolation of the product and further purification with a suitable ester to give pure polymorphic form A of E entacapone which is substaintially free from the compound of formula II.

In yet another embodiment of the present invention is to provide a process for preparation of E-entacapone free from the (2E)-3-(3,4-dihydroxyphenyl)-2-(piperidin-1-ylcarbonyl)prop-2-enenitrile impurity.

DETAILED DESCRIPTION OF THE FIGURES

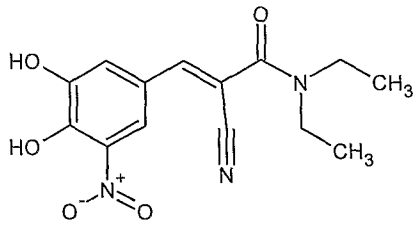
Figure I: XRD for polymorphic form A of E entacapone

Figure II: DSC for polymorphic form A of E entacapone

Figure III: IR Spectrum for polymorphic form A of E entacapone

DETAILED DESCRIPTION OF THE INVENTION

Accordingly the present invention relates to an improved process for the preparation of (2E)-2-Cyano-3-(3, 4-dihydroxy-5-nitrophenyl)-N, N-diethyl-2-propenamide of formula I



Formula I

which comprises

a) reacting 3,4-dihyroxy-5-nitrobenzaldehyde with N,N-diethyl-2-cyano acetamide in the presence of ammonium acetate and a suitable solvent selected from methanol, ethanol and isopropanol, most preferably ethanol to form racemic entacapone

b) treating racemic entacapone with hydrogen bromide gas dissolved in suitable aliphatic carboxylic acid in to give crude (E)-entacapone polymorphic form A

c) treating (E)-entacapone polymorphic form A first with an alcoholic solvent isolation of the product and further purification with a suitable ester to give pure polymorphic form A of E entacapone which is substantially free (means less than 0.1%) from compound of formula II.

The alcoholic solvent used in *step c*, are selected from isopropanol, ethanol or methanol most preferably isopropanol.

The ester solvent used for purification in the *step c* is selected from methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, butyl acetate, propylacetate; most preferably ethyl acetate.

The amount of hydrogen bromide used for the isomerisation of E & Z isomer to E-isomer of entacapone is 0.15-0.22 mole equivalent to that of the compound. This is to avoid the coloration of the final API which is caused because of less than 0.15 mole equivalent of hydrogen bromide and also to avoid the formation of decomposition of the compound which is caused due to use of more than 0.22 mole equivalent of hydrogen bromide.

The advantages of the present invention are

1. A process which is economical, eco-friendly, cost effective and industrially applicable
2. A process which does not employ hazardorus or corrosive reagents
3. Simple and easy handling process not extra care for temperature conditions required
4. Avoid the formation of impurity of Formula II obtained by using piperdine as base.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

EXAMPLES

1: Preparation of racemic 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide

3,4-dihydroxy-5-nitro-benzaldehyde (50g) and N,N-diethyl-2-cyano acetamide (99.4g) were taken together in dry ethanol (1000mL) and refluxed at 75-80°C for 15-20min. followed by the addition of ammonium acetate (27g) lot-wise over a period of 24hrs at every 2 hours of interval. After completion of reaction the content was cooled to room temperature and the ethanol was distilled off under vacuum. The residue was taken in dichloromethane (1000mL) and stirred for 15min at 25-30°C followed by the addition of purified water (1000mL) and stirred at 25-30°C for 1 hr. The layer if not cleared was filtered through hyflobed and washed with methylene chloride. The organic layer was separated and the aqueous layer was washed with dichloromethane twice. The organic layer were combined and treated with dilute hydrochloric acid 300mL (1:1 ratio of HCl and water). The organic layer was separated and treated with purified water to remove any undissolved impurities, the water treatment was repeated two to three times and further the organic layer was treated with activated carbon at 25-30 ° C and filtered. The filtrate distilled off under vacuum at 60°C and the residue was taken in ethyl alcohol at 25-30°C, stirred for 15-20min. and distilled off under vacuum at 35°C. To the residue was added purified water and the

stirred for 2 hrs at 25-30°C, filtered and washed with water and dried to obtain racemic 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide.(Dry Weight : 60g (72.20%), HPLC purity : 98.32%, E isomer (69.80%) and Z isomer (28.52%)

2: Preparation of Crude (2E)-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide polymorphic form A

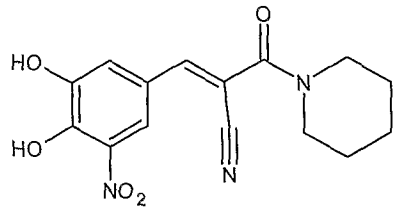
The compound (50 g) obtained from the example 1 above was taken in acetic acid (500 mL) at 25-30°C and heated to 70-75°C for complete dissolution. The reaction mass was treated with activated carbon (2.5 g) at 70-75°C for 15-30min and filtered. The filtrate was cooled to 25-30°C and to it was added hydrogen bromide dissolved in acetic acid (7.14 g). The reaction mass was heated to 70-75°C for complete dissolution and cooled to 20°C during which time the compound starts to crystallize, the reaction contents were further stirred for 20hrs for complete crystallization of the compound, filtered and dried at 55-60°C to get (2E)-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide polymorphic form A.(Dry weight : 40.5 g (81%), HPLC purity: 99.52% single individual impurity : 0.14%)

3: Purification of Crude (2E)-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide polymorphic form A

The compound (40g) obtained from the example 2 above was taken in isopropyl alcohol (200mL) and heated to reflux at 80-85°C for 2 hrs. The reaction contents was cooled to 25-30°C and stirred for 1 hr at 25-30°C, filtered and washed with isopropanol and dried. To this dried compound (38g) was charged ethyl acetate (115mL) and the content were refluxed at 72-78°C for 2 hrs, cooled and stirred at 25-30°C for 1 hr, filtered and dried under vacuum at 50-55°C to give 30 g of pure (2E)-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide polymorphic form A or (E) Entacapone polymorphic form A. Dry Weight : 36g (90.0%) and single individual impurity of 0.04%.

We Claim

1. An improved process for preparation of (2E)-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide polymorphic form A, which is substantially free from compounds of formula II and other impurities which comprises;
   (a) reacting 3,4-dihyroxy-5-nitrobenzaldehyde with N,N-diethyl-2-cyano acetamide in the presence of ammonium acetate and a suitable solvent to form racemic entacapone
   (b) treating racemic entacapone with catalytic amount of hydrogen bromide dissolved in a suitable aliphatic carboxylic acid in to give crude (E)-entacapone polymorphic form A
   (c) treating (E)-entacapone polymorphic form A first with an alcoholic solvent, isolating the product and further purifying with a suitable ester solvent to give pure polymorphic form A of E entacapone which is substantially free from compound of formula II.
2. An improved process for the preparation of racemic 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide or entacapone wherein the condensation of 3,4-dihyroxy-5-nitrobenzaldehyde with N,N-diethyl-2-cyano acetamide is carried out in the presence of ammonium acetate.
3. An improved process for the preparation of racemic 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide or entacapone wherein the isomerisation of E & Z isomer of Entacapone to E- isomer of Entacapone is done in the presence of 0.15-0.22 mole equivalent hydrogen bromide dissolved in suitable aliphatic carboxylic acid.
4. An improved process for the preparation of (E)-Entacapone polymorphic Form A wherein the crude polymorphic form A of (2E)-cyano-3-(3, 4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide is treated with an alcoholic solvent selected from isopropanol, ethanol or methanol most preferably isopropanol.
5. An improved process for the preparation of (E)-Entacapone polymorphic Form A wherein the crude polymorphic form A is purified using an ester selected from ethyl acetate and methyl acetate most preferably being ethyl acetate.
6. (E)-Entacapone polymorphic form A is substantially free from (2E)-3-(3,4-dihydroxyphenyl)-2-(piperidin-1-ylcarbonyl)prop-2-enenitrile of formula II



Formula II

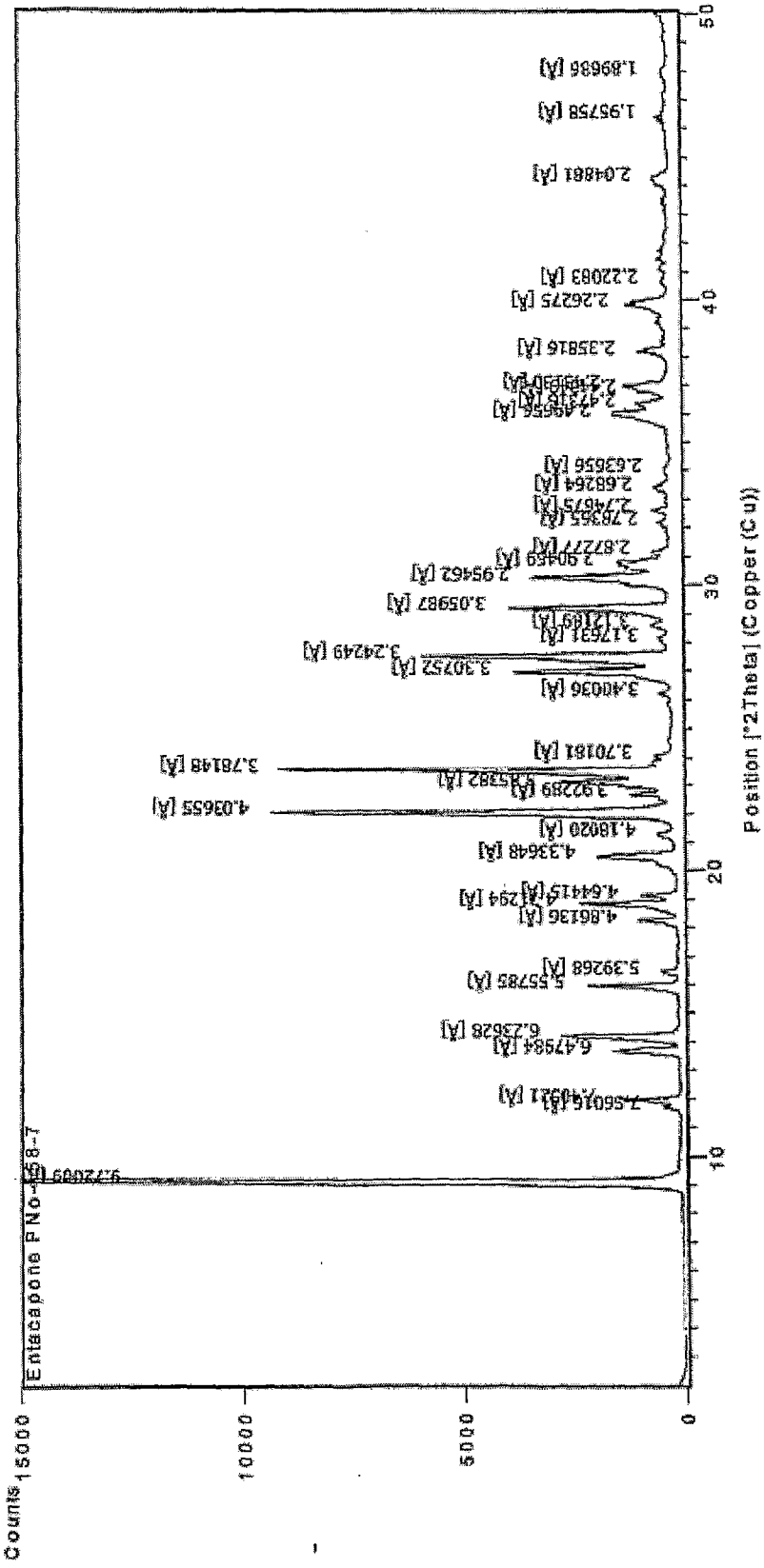


Figure I: XRD for polymorphic form A of E entacapone

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Area [cps*°2Th.]
9.0982	9.72009	100.00	90.03
11.7057	7.56016	1.89	1.71
11.9547	7.40321	6.39	4.60
13.6659	6.47984	6.96	6.27
14.2023	6.23628	12.31	13.29
15.9466	5.55785	9.43	8.49
16.4383	5.39268	1.71	2.46
18.2495	4.86136	4.07	4.39
18.8294	4.71294	10.19	14.68
19.1109	4.64415	3.83	4.14
20.4809	4.33648	8.16	14.69
21.2553	4.18020	1.85	3.34
22.0210	4.03655	41.90	60.36
22.6674	3.92289	4.61	4.15
23.0792	3.85382	12.10	13.07
23.5269	3.78148	40.89	51.54
24.0407	3.70181	2.10	2.27
26.2083	3.40036	1.31	1.42
26.9577	3.30752	16.52	23.80
27.5088	3.24249	25.95	32.71
28.0937	3.17631	1.24	2.68
28.5936	3.12189	2.06	2.96
29.1860	3.05987	16.93	15.24
30.2500	2.95462	14.48	10.43
30.7839	2.90459	5.60	4.04
31.1334	2.87277	1.87	2.69
32.1567	2.78365	1.00	2.16
32.6007	2.74675	1.64	2.36
33.4023	2.68264	1.56	2.25
34.0037	2.63656	0.48	1.38
35.9738	2.49656	5.68	8.19
36.3260	2.47316	3.05	4.40
36.7827	2.44349	2.98	3.21
36.9739	2.43130	4.60	3.31
38.1642	2.35816	2.96	1.60
39.8401	2.26275	3.44	8.67
40.6249	2.22083	0.32	0.68
44.2075	2.04881	1.47	5.30
46.3849	1.95758	0.81	3.52
47.9192	1.89686	0.52	3.08

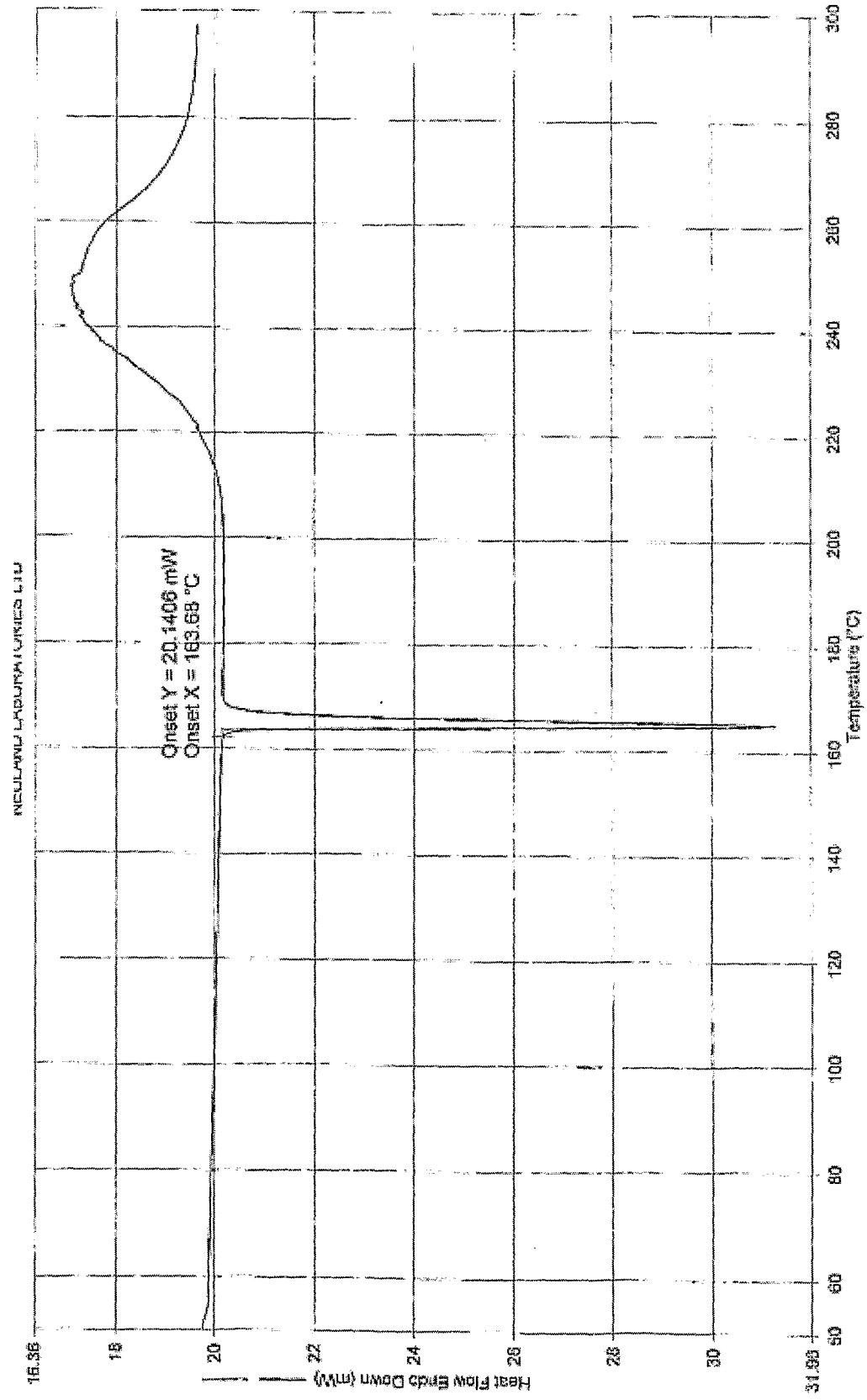


Figure II: DSC for polymorphic form A of E entacapone

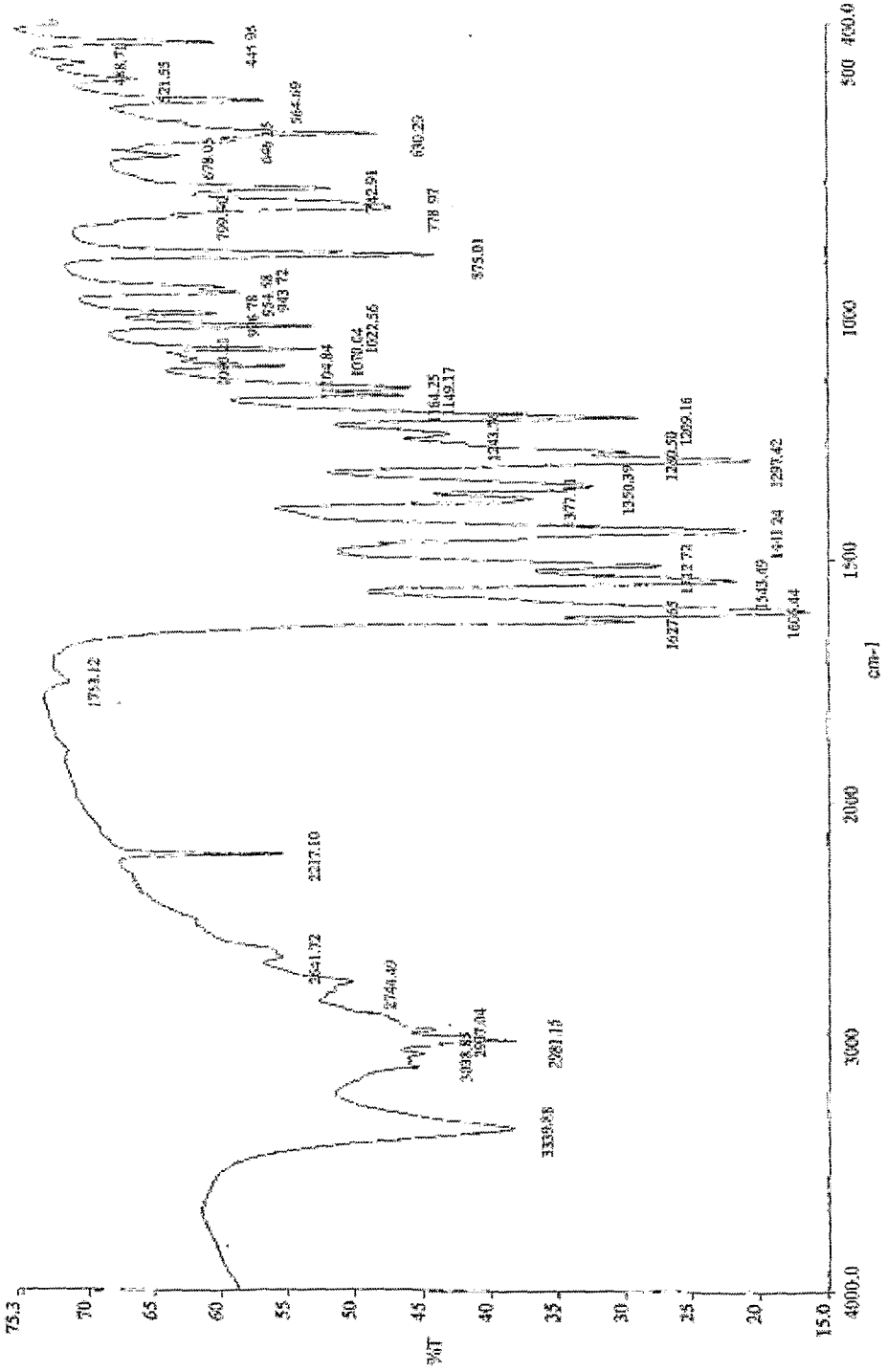


Figure III: IR of polymorphic form A of E-Entacapone for NLL's sample