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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
24 December 2008 (24.12.2008)

(10) International Publication Number
WO 2008/155777 A2

(51) **International Patent Classification:** **Not classified**

(21) **International Application Number:**
PCT/IN2008/000279

(22) **International Filing Date:** 2 May 2008 (02.05.2008)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
1164/MUM/2007 18 June 2007 (18.06.2007) IN

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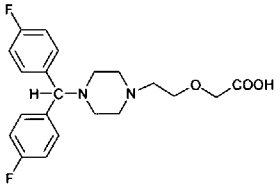
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, 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, 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:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U))*

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

(54) Title: PROCESS FOR PREPARING EFLETRIZINE



(I)

(57) Abstract: A new process for preparing Efletrizine or its pharmaceutically acceptable salts thereof is disclosed. The present invention also relates to the process of preparation of novel intermediate thereof in crystalline form. The present invention further provides the process for preparation of substantially pure 2-{-2-[4-(bis(4-fiourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid dihydrochloride. 2-{-2-[4-(bis(4-flourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid commonly known as efletrizine and represented by Formula (I). Efletrizine is useful as therapeutic agents for the treatment of allergic diseases and other disorders.

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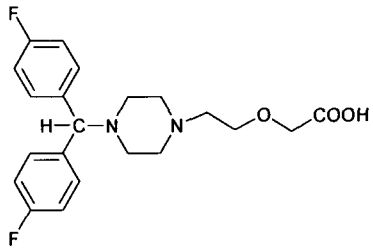
PROCESS FOR PREPARING EFLETRIZINE

FIELD OF INVENTION

The present invention relates to a new process for preparing Efletrizine or its pharmaceutically acceptable salts thereof. The present invention also relates to the process of preparation of novel intermediate thereof in crystalline form. The present invention further provides the process for preparation of substantially pure 2-{-2-[4-(bis(4-flourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid dihydrochloride.

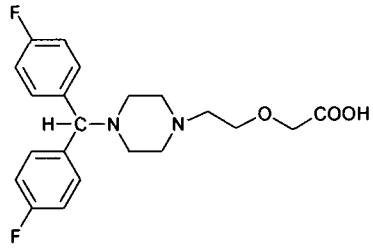
2-{-2-[4-(bis(4-flourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid commonly known as efletrizine and represented by Formula I. Efletrizine is useful as therapeutic agents for the treatment of allergic diseases and other disorders.



(I)

BACKGROUND OF THE INVENTION

Efletrizine is chemically known 2-{-2-[4-(bis(4-flourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid of Formula I, have been proven useful as therapeutic agents for the treatment of allergic diseases and other disorders.



(I)

Efletrizine is a substituted benzhydrylpiperazine derivative encompassed within general formula (I) of European patent No. 0058146. It has been demonstrated to have antiallergic and antihistaminic properties and has been suggested for the treatment of seasonal and perennial allergic rhinitis.

Efletrizine has been found to possess excellent antihistaminin properties. It belongs to the pharamcological class of second generation histamine Hi-receptor antagonists and shows in vitro high affinity and selectivity for Hi-receptors. Efletrizine

is useful as an antiallergic, antihistaminic, bronochodilator and antispasmodic agent. Recent clinical studies have shown the utility of efletrizine when administered in the form of a nasal spray for the treatment of allergic rhinitis and rhino-conjunctivities (J.F Dessanges et.al. *Allergy and Clin. Immunol .News* (1994), Suppl. No. 2, abstract 1864; C. De Vos et al., *Allergy and Clin. Immunol News* (1994), Suppl. No. 2, abstract 428). Another recent clinical pharmacological study has shown that efletrizine gives unexpectedly good results in the treatment of urticaria, atopic dermatitis ad pruritis.

DESCRIPTION OF PRIOR ART

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of the common general knowledge in the field.

Efletrizine is encompassed within the general formula of European patent No. 0 058 146 and may be prepared according to the general process described in this patent. Said process for the synthesis of 2-{-2-[4-(bis(4-flourophenyl-)rnethyl)-l-piperazinyl]ethoxy} acetic acid derivatives comprises reacting a l-(diphenylmethyl)-piperazine derivative with methyl(2-chloroethoxy)acetate or 2-(2-chloroethoxy)acetamide to form a methyl 2-{-2-[4-(diphenylmethyl)-l-piperazinyljethoxy} acetate or a 2-{-2-[4-(diphenylmethyl)-l-piperazinyl]ethoxy} acetamide, respectively. Thus formed methyl ester or acetamide is then subjected to basic hydrolysis followed by acidification and isolation of the free carboxylic acid. This material is then transformed into its dihydrochloride salt.

Processes for preparing efletrizine or a pharmaceutically acceptable salt thereof have been described in International patent applications WO 99/28310, WO 97/37982 and WO 03/09849.

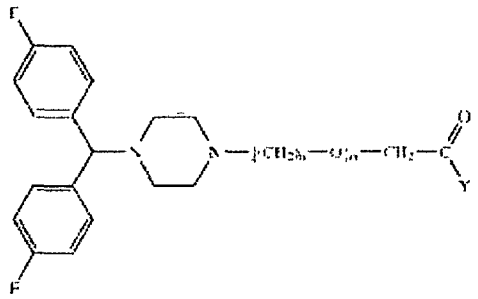
International patent application WO 99/28310 and European patent application number EP 0919550 A1 describe pseudopolymorphic forms of efletrizine dihydrochloride.

WO 2006/050909 A1 discloses an amorphous form of efletrizine dihydrochloride obtained by freeze-drying. The patent also discloses various solvate form of efletrizine dihydrochloride characterized by x-ray powder diffraction.

U.S. Patent 6,335,331 B2 discloses the pseudopolymorphic forms of efletrizine dihydrochloride characterized by x-ray powder diffraction pattern and their process of preparation. Thus, US '331 B2 provides two pseudopolymorphic forms, namely anhydrous efletrizine dihydrochloride and efletrizine dihydrochloride monohydrate.

The anhydrous efletrizine dihydrochloride is designated as "Form A" and efletrizine dihydrochloride monohydrate is designated as "Form B".

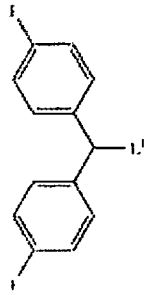
US 2004/0254375 A1 discloses a new process for the synthesis of 2-{-2-[4-(bis(4-flourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid and their corresponding salt forms is provided. In particular, it discloses the process for the manufacture of 2-{-2-[4-(bis(4-flourophenyl-)methyl)-l-piperazinyl]ethoxy} acetic acid, amides and related derivatives of the general formula (A) below.



(A)

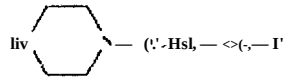
as well as non-toxic; pharmaceutically acceptable salts and mixtures thereof, characterized by

(a) reacting compound of formula (B)



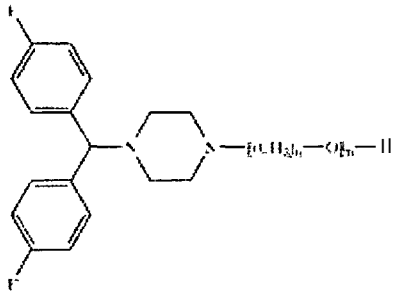
(B)

wherein L' represents a leaving group, with a compound of formula (C)



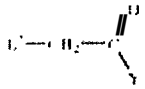
(C)

(b) reacting corresponding compound of formula (D)



(D)

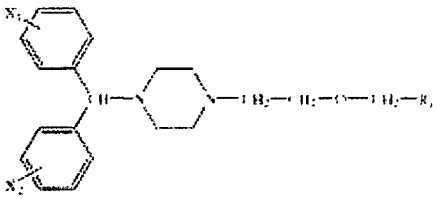
with a compound of formula (E)



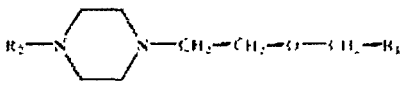
(E)

wherein L^2 represents a leaving group and Y in the presence of an inert solvent and a proton acceptor.

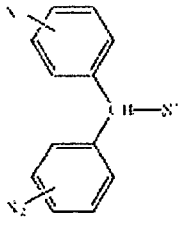
US 6,255,487 B1 discloses the process for preparing [2-(1-piperazinyl)ethoxy]methyl compounds of general formula A' which comprises reacting a substituted [2-(1-piperazinyl)ethoxy]methyl compound of formula B' with a diphenyl halide of formula C



(A')



(B')



(C')

The above known processes in the prior art make use of hazardeous reagents and non-ecofriendly.

There is a desire for an alternative economical and high yielding process for the synthesis of efletrizine dihydrochloride with novel intermediates.

OBJECTS OF INVENTION:

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

It is another object of the present invention to provide simple, cost effective, non-hazardeous, ecofriendly and high yielding process for preparation of efletrizine dihydrochloride.

It is still another object of the present invention to provide a new and improved process for preparation f efletrizine dihydrochloride or its pharmaceutically acceptable salts thereof.

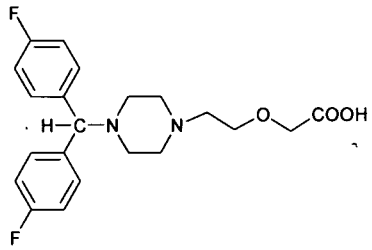
It is still another object of the present invention to provide crystalline intermediates for preparation of crystalline efletrizine dihydrochloride.

It is yet another object of the present invention to provide crystalline efletrizine dihydrochloride having particle size D_{50} less than or equal to 250 μm.

It is yet another object of the present invention to provide crystalline efletrizine dihydrochloride having purity greater than about 99% by area percentage of HPLC and having dimer impurity less than about 0.1% by area percentage of HPLC. The total impurities are less than about 0.4% by area percentage of HPLC.

SUMMARY OF THE INVENTION:

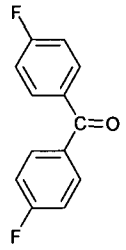
According to the present invention, there is provided a process for the preparation of Eflitrizine of the formula (I) or its non-toxic pharmaceutically acceptable salts thereof



(I)

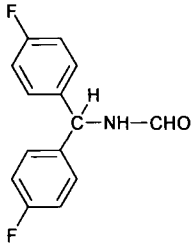
which comprises steps of

a) reacting 4,4'-diflourobenzophenone of formula (II),



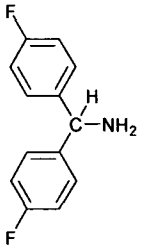
(H)

with ammonium formate in a suitable organic solvent to give N-(bis(4-fluorophenyl)methyl)formamide of formula (III);



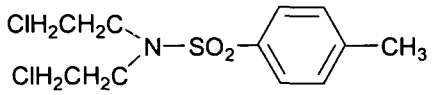
(III)

b) hydrolyzing N-(bis(4-fluorophenyl)methyl)formamide of formula (III) to obtain bis(4-fluorophenyl)methanamine of formula (IV) or its salts in presence of suitable reagent;



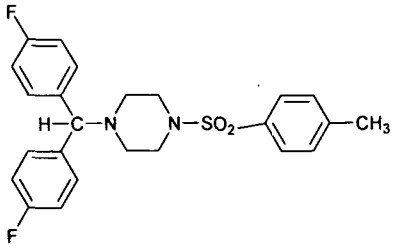
(IV)

c) reacting bis(4-fiuorophenyl)methanamine of formula (IV) with compound of formula (V)



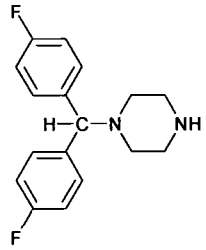
(V)

in suitable organic solvent to give compound of formula (VI);



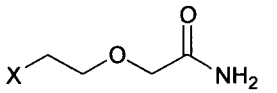
(VI)

d) reacting compound of formula (VI) with suitable reagent in presence of acid to give l-(bis(4-fluorophenyl)methyl)piperazine formula (VII);



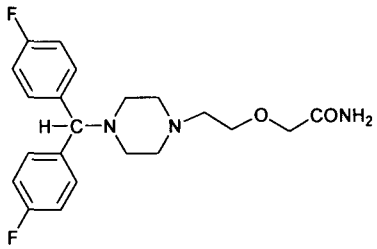
(VII)

e) reacting l-(bis(4-fiuorophenyl)methyl)piperazine formula (VII) with amide of formula (VIII)



(VIII)

where X represents leaving group such as OTs, OMs, Cl, F or Br etc., preferably Cl, to prpvide compound of formula (IX)



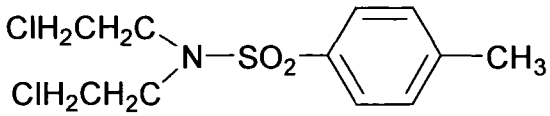
(IX)

f) treating compound of formula (IX) with mineral acid provide Eflitrizine of formula (I)

g) optionally converting the compound of formula (I) to its non-toxic pharmaceutically acceptable salts thereof.

According to the present invention, Efletrizine hydrochloride can be in the form of Anhydrous Form A or monohydrate form.

The present invention, further provides the process for the preparation of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V), which is a key intermediate for the preparation of Eflitrizine



(V)

which comprises reacting bis(2-chloroethyl amine) HCl with a base to obtain bis(2-chloroethyl amine), which is subsequently treated with p-toluenesulphonyl chloride in presence of base to obtain N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V). N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V) is isolated by the conventional method.

According to the still further aspect of the present invention, there is provided crystalline form of intermediates of formula (III) and formula (VI).

Preferably, the compound of formula (I) or its pharmaceutically acceptable salts i.e. efletrizine dihydrochloride monohydrate in crystalline form is having particle size D50 less than or equal to 250 μm.

Preferably, the compound of formula (I) or its pharmaceutically acceptable salts i.e. efletrizine dihydrochloride monohydrate in crystalline form is substantially pure having purity greater about 99% by area percentage of HPLC and having dimer impurity less than about 0.1% by area percentage of HPLC. The total impurities is less than about 0.4% by area percentage of HPLC is also within the scope of the present invention.

According to further aspect of the present invention, the compound of formula (I) or its pharmaceutically acceptable salts i.e. efletrizine dihydrochloride anhydrous in crystalline form is substantially pure having purity greater about 99% by area percentage of HPLC and having dimer impurity less than about 0.1% by area percentage of HPLC. The total impurities is less than about 0.4% by area percentage of HPLC is also within the scope of the present invention.

BRIEF DISCRIPTION OF DRAWINGS

A preferred embodiment of the invention will now be described, by way of examples only, with reference to the accompanying drawings in which:

FIG.l is a differential scanning calorimetry (DSC) thermogram of compound of formula (III)

FIG.2 is powder X-ray diffraction pattern of compound of formula (III)

FIG.3 is an FTIR spectrum of compound of formula (III).

FIG.4 is a differential scanning calorimetry (DSC) thermogram of compound of formula (IV)

FIG. 5 is powder X-ray diffraction pattern of compound of formula (IV)

FIG.6 is an FTIR spectrum of compound of formula (IV)

FIG. 7 is a differential scanning calorimetry (DSC) thermogram of compound of formula (VI).

FIG. 8 is powder X-ray diffraction pattern of compound of formula (VI)

FIG.9 is an FTIR spectrum of compound of formula (VI).

FIG. 10 is a differential scanning calorimetry (DSC) thermogram of efletrizine dihydrochloride monohydrate

FIG.l 1 is powder X-ray diffraction pattern of efletrizine dihydrochloride monohydrate

FIG. 12 is an FTIR spectrum of efletrizine dihydrochloride monohydrate

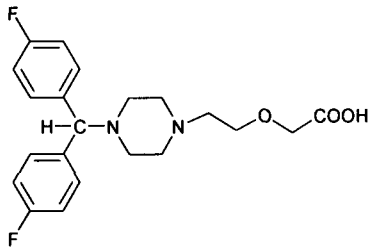
FIG. 13 is a differential scanning calorimetry (DSC) thermogram of efletrizine dihydrochloride anhydrous

FIG. 14 is powder X-ray diffraction pattern of efletrizine dihydrochloride anhydrous

FIG. 15 is an FTIR spectrum of efletrizine dihydrochloride anhydrous

DETAILED DESCRIPTION OF THE INVENTION

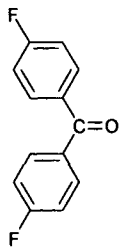
The present invention provides a process for the preparation of Eflitrizine of the formula (I) or its non-toxic pharmaceutically acceptable salts thereof



(I)

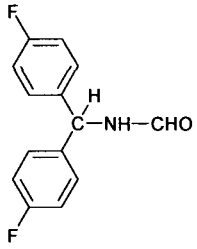
which comprises steps of

a) reacting 4,4'-diflourobenzophenone of formula (II),



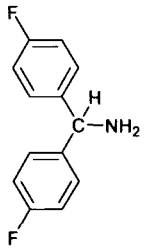
(H)

with ammonium formate in a suitable organic solvent to give N-(bis(4-fluorophenyl)methyl)formamide of formula (III);



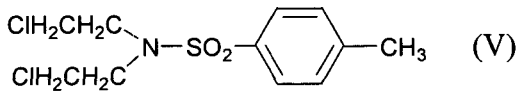
(III)

b) hydrolyzing N-(bis(4-fluorophenyl)methyl)formamide of formula (III) to obtain bis(4-fluorophenyl)methanamine of formula (IV) or its salts in presence of suitable reagent;



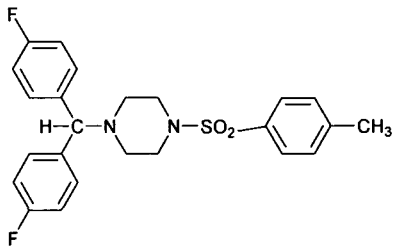
(IV)

c) reacting bis(4-fluorophenyl)methanamine of formula (IV) with compound of formula (V)



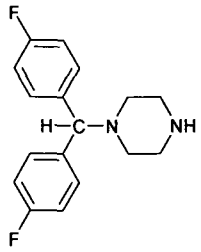
(V)

in suitable organic solvent to give compound of formula (VI);



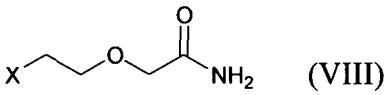
(VI)

d) reacting compound of formula (VI) with suitable reagent in presence of acid to give l-(bis(4-fluorophenyl)methyl)piperazine formula (VII);



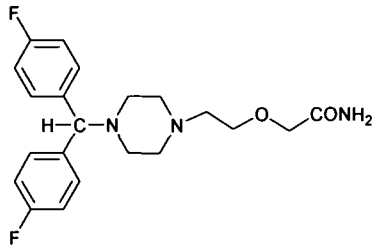
(VII)

e) reacting l-(bis(4-fluorophenyl)methyl)piperazine formula (VII) with amide of formula (VIII)



(VIII)

where X represents leaving group such as OTs, OMs, Cl, F or Br etc., preferably Cl, to provide 2-(2-(4-(bis(4-fluorophenyl)methyl)piperazin- 1-yl)ethoxy)acetamide compound of formula (IX)



(IX)

f) treating compound of formula (IX) with mineral acid provide Eflitrizine of formula (I)

g) optionally converting the compound of formula (I) to its non-toxic pharmaceutically acceptable salts thereof.

Accordingly, 4,4'-diflourobenzophenone of formula (II) is reacted with ammonium formate in a suitable organic solvent to give N-(bis(4-fluorophenyl)methyl)formamide of formula (III). The suitable organic solvent as used in step (a) is polar solvent. Preferably selected from amides like formamide, dimethyl formamide, sulfoxides like dimethyl sulfoxides, preferably formamide. The reaction of 4,4'-diflourobenzophenone of formula (II) with ammonium formate is carried out at ambient temperature to the reflux temperature. Preferably, reaction step (a) is carried out at about 100^0C to $25O^0$C, preferably $15O^0$C to 200^0C, most preferably 175°C to $18O^0$C.

Thus, obtained N-(bis(4-fluorophenyl)methyl)formamide of formula (III) is hydrolyzed in suitable solvent to provide bis(4-fluorophenyl)methanamine of formula (IV) or its salt such as hydrochloride by using suitable reagent

The suitable reagents for hydrolysis as mentioned is step (b) may be selected from the group of inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid. The reaction is preferably carried out in water or water miscible solvent such as alcohols like methanol, isopropanol, ethanol, n-propanol, butanol.

The hydrolysis reaction is preferably carried out at temperature about 75^0C to 150^0C, preferably $9O^0$C to 120^0C, most preferably 95°C to 100^0C.

Bis(4-fluorophenyl)methanamine of formula (IV) is condensed with compound of formula (V) in suitable organic solvent, wherein organic solvent selected from, but not limited to, members from the classes: ketonic solvents such as acetone, ethylmethyl ketone, methyl isobutyl ketone and the like; ether solvents such as diethyl ether, dimethyl ether, di-isoopropyl ether, methyltertiarybutyl ether, tetrahydrofuran, 1,4-dioxane and the like; hydrocarbon solvents such as toluene, xylene and the like; nitrile solvents such as acetonitrile, propionitrile and the like; halogenated solvents such as dichloromethane, 1,2-dichloromethane, chloroform, carbon tetrachloride and the like; aprotic polar solvents such as dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide, Ci-C_4 alcohols like methanol, ethanol, propanol, isopropanol, butanol, preferably methanol and the like; or mixtures of any two or more thereof in various proportions

The reaction is carried out in presence of suitable base preferably but not limited to sodium hydroxide, potassium hydroxide, sodium ethoxide, potassium ethoxide, sodium methoxide, potassium methoxide, amines such as ammonia, methyl amine, ethyl amine, tri ethyl amine, diethyl amine, isopropyl amine, diisopropyl amine or mixtures thereof.

The condensation reaction as mentioned in step (c) is preferably carried out at temperature about 50^0C to 200^0C, preferably 100^0C to $15O^0$C, most preferably 125°C to 130^0C. The compound of formula (VI) is isolated by gradual cooling is at room temperature initially followed by chilling to 0^0C to 5^0C.

The compound of formula (VI) is converted to l-(bis(4-fluorophenyl)methyl)piperazine formula (VII) using hydroxy acid like p-hydroxy benzoic acid in presence of HBr in acetic acid reagent.

The reaction step (d) is carried out at O^0C $5O^0$C, preferably 45°C to 47^0C.

l-(bis(4-fluorophenyl)methyl)piperazine formula (VII) reacted with amide of formula (VIII) in presence of base to obtain 2-(2-(4-(bis(4-fluorophenyl)methyl)piperazin- 1-yl)ethoxy)acetamide of formula (IX).

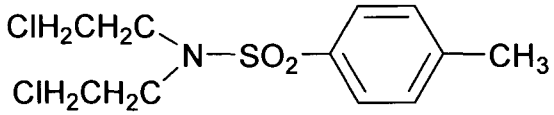
The base can be used in the reaction is selected from inorganic base or organic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, potassium tert-butoxide, tri ethyl amine, diisopropyl amine and the like.

The reaction is preferably carried out in polar solvent such as alcohols like methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, water and the like or mixtures thereof.

2-(2-(4-(bis(4-fluorophenyl)methyl)piperazin- 1-yl)ethoxy)acetamide is converted to Eflitrizine by treatment with mineral acid. The preferred mineral acid is selected from Hydrochloric acid, sulfuric acid, hydrobromic acid, nitric acid, phosphoric acid. The preferred acid is hydrochloric acid.

Thus obtained Eflitrizine of formula (I) is further converted its non-toxic pharmaceutically acceptable salts and hydrates thereof. Preferably, Thus, the obtained compound of formula (I) can be converted to efletrizine dihydrochloride monohydrate or efletrizine dihydrochloride anhydrous being characterized by their X-ray powder diffraction patterns and DSC as depicted in the respective figures.

The present invention further provides the process for the preparation of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V), which is a key intermediate for the preparation of Eflitrizine

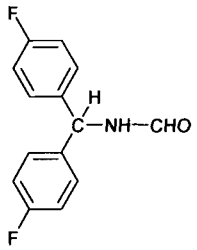


(V)

which comprises reacting bis(2-chloroethyl amine) HCl with a base to obtain bis(2-chloroethyl amine), which is subsequently treated with p-toluenesulphonyl chloride in presence of base to obtain N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V). N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V) is isolated by the conventional method.

Base can selected from like sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, organic bases like isopropyl amine, diisopropyl amine, triethylamine, ammonia, pyridine etc. preferably inorganic base like sodium hydroxide.

There is provided N-(bis(4-fluorophenyl)methyl)formamide of formula (III) in its crystalline form and having powder X-ray diffraction pattern as depicted in FIG.2 is another most preferred embodiment of the present invention.



(III)

Crystalline N-(bis(4-fluorophenyl)methyl)formamide of formula (III) is being characterized by differential scanning calorimeter profile as depicted in FIG.l and having endothermic peak at 117.20^{0}C.

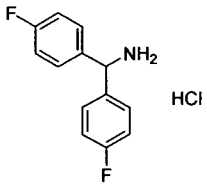
Crystalline N-(bis(4-fluorophenyl)methyl)formamide of formula (III) is being characterized by powder X-ray diffraction pattern having characteristic peaks at 2Θ (±0.2) values 7.7°, 11.1°, 15.5°, 21.1° and 25.2°.

Furthermore, the crystalline N-Formyl-N-(4,4'-diflourobenzhydraryl) of formula (III) is being characterized by powder X-ray diffraction pattern peaks at 2θ(±0.2) values 7.7°, 8.9°, 11.1°, 15.5°, 16.0°, 18.5°, 19.3°, 20.1°,21.1°, 21.5°, 22.4°, 23.4°, 24.5°, 25.2°, 27.0°, 28.9° and 31.3°.

Crystalline N-(bis(4-fluorophenyl)methyl)formamide of formula (III) is being characterized by FTIR spectrum as depicted in FIG. 3 with characteristics peaks at about 3278, 1658, 1602, 1390, 833 and 732 cm^{-1}.

Furthermore, the crystalline N-(bis(4-fluorophenyl)methyl)formamide of formula (III) is being characterized by FTIR spectrum with peaks at about 3278, 2889, 1658, 1602, 1531, 1390, 1228, 1159, 1101, 1033, 1014, 893, 833, 813, 732 and 557 cm^{-1}.

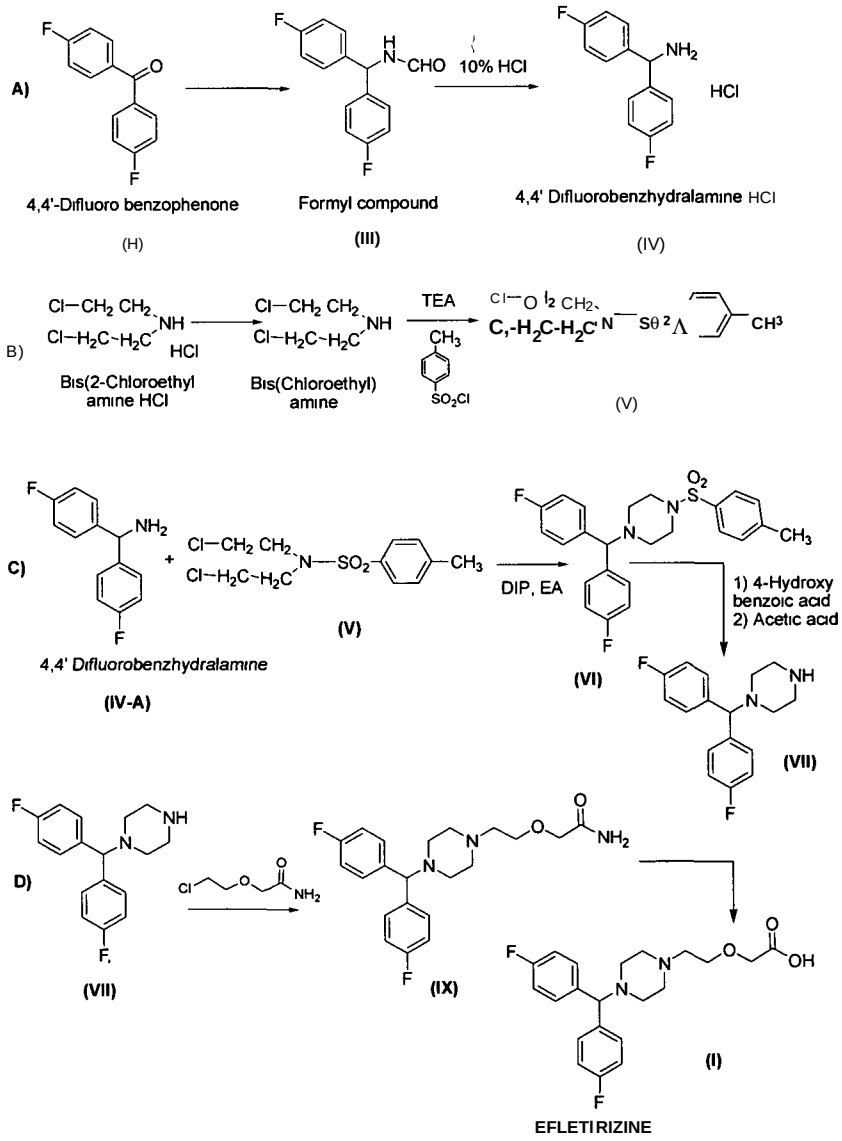
A crystalline bis(4-fiuorophenyl)methanamine hydrochloride of formula (IVa) is being characterized by x-ray powder diffraction as depicted in FIG. 4 is also the scope of the present invention.



(IVa)

A crystalline bis(4-fluorophenyl)methanamine hydrochloride of formula (IVa), is being characterized by differential scanning calorimeter profile as depicted in FIG. 5 and having endothermic peak at about 277.1°C.

According to the present invention, the process for the preparation of Eflitrizine dihydrochloride is shown in below mentioned scheme for illustration only.



SCHEME - 1

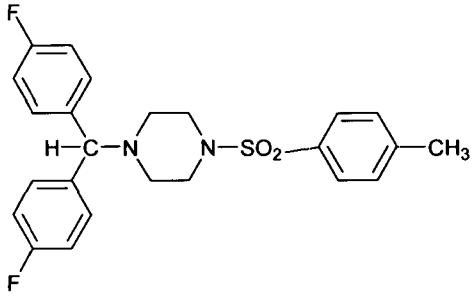
A crystalline bis(4-fluorophenyl)methanamine of formula (IV), is being characterized by x-ray powder diffraction pattern having characteristic peaks at 2Θ (±0.2) values 7.4°, 15.1°, 19.8° and 25.0°.

Furthermore, crystalline bis(4-fluorophenyl)methanamine of formula (IV) characterized by x-ray powder diffraction pattern having peaks at 2Θ(±0.2) values 7.4°, 10.8°, 13.6°, 15.1°, 16.6°, 18.6°, 19.8°, 22.0°, 22.7°, 24.0°, 25.0°, 26.6°, 27.9°, 29.5°, 30.5° and 31.6°.

A crystalline bis(4-fluorophenyl)methanamine of formula (IV), is being characterized by FTIR spectrum as depicted in FIG. 6 with peaks at about 2962, 2908, 1602, 1514, 1244 and 553 cm^{-1}.

Furthermore, the crystalline bis(4-fiuorophenyl)methanamine of formula (IV) is being characterized by FTIR spectrum with peaks at about 2962, 2908, 2040, 1602, 1514, 1425, 1382, 1244, 1193, 1165, 1120, 1014, 835, 775, 721, 586 and 553 cm^{-1}.

A crystalline l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI) is being characterized by x-ray powder diffraction as depicted in FIG. 7 is also the scope of the present invention.



(VI)

A crystalline compound l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI), is being characterized by differential scanning calorimeter profile as depicted in FIG. 8 and having endothermic peak at about 196.9 ^0C.

A crystalline compound l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI), is being characterized by x-ray powder diffraction pattern having characteristic peaks at 2Θ(±0.2) values 6.2°, 12.5, 15.3, 16.0° and 22.3°.

Furthermore, crystalline compound l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI), characterized by x-ray powder diffraction pattern having peaks at 20 (±0.2) values 6.2°, 9.1, 12.5°, 14.3°, 15.3, 16.0, 17.7°, 18.0°, 18.6°, 19.6°, 20.4°, 21.0°, 22.3°, 23.5°, 24.7, 25.7, 26.5, 27.0, 27.5 and 30.1°.

A crystalline compound l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI), is being characterized by FTIR spectrum as depicted in FIG. 9 with peaks at about 2989, 1896, 1600, and 584 cm^{-1}.

Furthermore, the crystalline compound l-(bis(4-fiuorophenyl)methyl)-4-tosylpiperazine (VI) is being characterized by. FTIR spectrum with peaks at about 2989, 2816, 1896, 1780, 1600, 1502, 1456, 1328, 1220, 1172, 1060, 1006, 937, 829, 788, 732, 650, 621, 584, 518, and 443 cm^{-1}.

In the processes of the invention, the monohydrate of efletrizine dihydrochloride is substantially pure having purity greater than about 99% by area percentage of HPLC, preferably purity greater than about 99.6% by area percentage of HPLC. In the processes of the invention, the monohydrate of efletrizine dihydrochloride may contain less than or about 0.4% total impurities and having not detectable level of dimer impurity at RRT 3.80 as measured by area percentage of HPLC.

In the processes of the invention, the anhydrate of efletrizine dihydrochloride is substantially pure having purity greater than about 99% by area percentage of HPLC, preferably purity greater than about 99.6% by area percentage of HPLC. In the processes of the invention, the anhydrate of efletrizine dihydrochloride may contain less than or about 0.4% total impurities and having not detectable level of dimer impurity at RRT 3.80 as measured by area percentage of HPLC.

It is also the scope of the present invention to provide a crystalline efletrizine dihydrochloride monohydrate having particle size D_{50} less than or equal to 400 μm as measured by Malvern light scattering instrument, preferably less than or equal to 250 μm, more preferably less than or equal to 200 μm, most preferably less than or equal to 175 μ*m* as measured by Malvern light scattering instrument and being characterized by x-ray powder diffraction pattern as depicted in FIG. 11.

A crystalline efletrizine dihydrochloride monohydrate as disclosed herein above is being characterized by differential scanning calorimetry profile as depicted in FIG. 10 and having endothermic peak at 160.22^{0}C.

A crystalline efletrizine dihydrochloride monohydrate is characterized by powder x-ray diffraction pattern having characteristic peaks at 2Θ(±0.2) values 7.3°, 10.3°, 17.7° and 24.5° and as shown in FIG.l 1

Furthermore, crystalline efletrizine dihydrochloride monohydrate is characterized by powder x-ray diffraction pattern having peaks at 2Θ(±0.2) values 7.3°,

10.3°, 10.6°, 15.6°, 17.7°, 18.8°, 19.4°, 20.3°, 20.8°,21.5°, 22.1°, 22.4°, 24.5°, 25.8°, 26.6° and 29.2°.

A crystalline efletrizine dihydrochloride monohydrate is also characterized by FTIR spectrum as depicted in FIG. 12 with peaks at about 3398, 2922, 1712, 1512, 1120, 869 and 574 cm^{-1}.

Furthermore, crystalline efletrizine dihydrochloride monohydrate is characterized by FTIR spectrum with peaks at about 3398, 2922, 2357, 1712, 1604, 1512, 1433, 1313, 1232, 1163, 1087, 995, 902, 869, 792, 651 and 574 cm^{-1}.

It is also the scope of the present invention to provide a crystalline efletrizine anhydrous having particle size D_{50} less than or equal to 400 µm as measured by Malvern light scattering instrument, preferably less than or equal to 350 µm, more preferably less than or equal to 250 µm, most preferably less than or equal to 225 µm as measured by Malvern light scattering instrument and being characterized by x-ray powder diffraction pattern as depicted in FIG. 14.

It is also the preferred embodiment of the present invention that efletrizine dihydrochloride monohydrate is having moisture content of about 3.75%

A crystalline efletrizine dihydrochloride anhydrous as disclosed herein above is being characterized by differential scanning calorimetry profile as depicted in FIG. 13 and having endothermic peak at about 226^0C.

A crystalline efletrizine dihydrochloride anhydrous is characterized by powder x-ray diffraction pattern having characteristic peaks at $2\Theta(\pm 0.2)$ values 13.6°, 14.8°, 18.4° and 25.0° and as shown in FIG. 14

Furthermore, crystalline efletrizine dihydrochloride anhydrous is characterized by powder x-ray diffraction pattern having peaks at $2\Theta(\pm 0.2)$ values 8.2°, 13.6°, 14.8°, 18.4°, 20.7°, 22.9°, 23.9°, 25.0°, 26.6°, 28.2°, 30.1°, 30.7°, 31.3° and 32.2°.

A crystalline efletrizine dihydrochloride anhydrous is also characterized by FTIR spectrum as depicted in FIG. 15 with peaks at about 2949, 1749, 1514, and 829 cm^{-1}.

Furthermore, crystalline efletrizine dihydrochloride anhydrous is characterized by FTIR spectrum with peaks at about 2949, 2418, 2349, 1749, 1604, 1514, 1454, 1352, 1230, 1166, 1138, 1055, 920, 829 and 576 cm^{-1}.

It is also the preferred embodiment of the present invention that efletrizine dihydrochloride anhydrous is having moisture content of about 0.13%

The Impurity Profile Determination of Efletrizine dihydrochloride comprised testing a sample using HPLC. Typically, the HPLC testing parameters included a column of Grace Vydac 5 μm 4.6*250 mm (or equivalent column) at a temperature of 40^0C and eluted with a two solvent system. A first reservoir, Reservoir A, contained 0.01M potassium hydrogen phosphate, 1-octane sulfonic acid, adjusted to pH 3.0 with H_3PO_4, and a second reservoir, Reservoir B, contained acetonitrile. The gradient was as follows: at the initial time, 65% Reservoir A and 35% Reservoir B; time 15.0 min 65% Reservoir A and 35% Reservoir B; and at time 25.0 min 35% Reservoir A and 65% Reservoir B, and at time 50.0 min 35% Reservoir A and 65% Reservoir B, and at time 55.0 min 65% Reservoir A and 35% Reservoir B, and at time 70.0 min 65% Reservoir A and 35% Reservoir B. The system equilibrated further for 10 min and a flow rate of 1.3 mL/min. The detector was set for 220 nm. The sample volume was 20 μL and the diluent was acetonitrile: water 50:50. As commonly known by the skilled artisan, the mobile phase composition and flow rate may be varied in order to achieve the required system suitability.

The sample was prepared by weighing accurately about 10 mg of Efletrizine dihydrochloride sample in a 20 ml amber volumetric flask. Dissolving the sample with 10 ml of acetonitrile and diluting to the desired volume with water.

Thereafter, the freshly prepared sample was injected. The sample solutions were injected into the chromatograph and the chromatogram of sample was continued up to the end of the gradient. Thereafter, the areas for each peak in each solution was determined using a suitable integrator. The calculations were obtained using the following formula:

Impurity Profile Determination

$$\% \text{ impurity} = \frac{\text{area impurity in sample}}{\text{Total area}} \times 100$$

Although the invention has been described with reference to a specific examples, it will be appreciated by those skilled in the art that the invention can be embodied in many other forms.

The process of the present invention will be explained in more detail with reference to the following examples, which are provided by way of illustration only and should not be constructed as limit to the scope of the claims in any manner.

Example-1 : Preparation of N-(bis(4-fluorophenyl)rnethyl)formamide of formula (III)

4,4'-difluorobenzophenone (100 gm, 0.458 mole) (II), Ammonium Formate (232 gm, 3.67 mole) were taken in 56 mL of foramide in RBF. The reaction mixture was heated slowly to 175^{0}C to 18O^{0}C within 3 hours and maintained for 6-7 hours. The reaction mass was quenched in 400 mL of water within 1 hour and stir for 30 min. The product was filtered and suck dried. The product was washed with water and suck dried. The product was dried in oven at 5O^{0}C to 55^{0}C to N-(bis(4-fiuorophenyl)methyl)formamide of formula (III).

Example-2: preparation of bis(4-fluorophenyl)methanamine hydrochloride of formula (IVa)

N-(bis(4-fluorophenyl)methyl)formamide (III). (100 gm, 0.405 mole) and Cone. HCl (700 mL) were taken in RBF and heated at 95°C to 100^{0}C. The reaction mass was cooled upto room temperature and further chilled to O^{0}C to 5^{0}C and stirred for 1 hour. The product was filtered and washed with toluene. The wet-cake was taken in 400 mL of toluene and stirred for 1 hour at room temperature. The product was filtered and washed with toluene and suck dried. The wet-cake was further dried at 75^{0}C to 8O^{0}C to give bis(4-fiuorophenyl)methanamine hydrochloride of formula (IVa).

Example-3: Preparation of bis(4-fluorophenyl)methanamine of formula (IV)

bis(4-fluorophenyl)methanamine hydrochloride of formula (IVa) (100 gm, 0.391 mole) was taken in 800 mL of water and stirred for 10 min. 25% NaOH solution was added till alkaline pH 12. Methylene dichloride (500 mL) was added and the reaction mass was stirred for 15 min. The layers were separated. The aqueous layer was extracted with 300 mL of methylene dichloride. The organic layer was washed with 300 mL of water and layers were separated. The organic layer was treated with sodium bisulfate and filtered. The methylene dichloride was distilled atmospherically and finally under vacuum to remove the traces of methylene dichloride to give bis(4-fluorophenyl)methanamine of formula (IV).

Example-4: Preparation of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V)

N, N'-Bis (2-chloroethyl)amine hydrochloride (112.5 gm, 0.63 mole), methylene dichloride (800 mL) and triethylamine (182 mL) were taken in RBF. Freshly prepared solution of p-toluene sulfonyl chloride (100 gm, 0.524 mole) in methylene dichloride (400 mL) was added slowly within 1 hour at room temperature. After

addition is completed the reaction mixture was heated to reflux at 40°C to 43°C for 6 hours. The reaction mass was cooled to room temperature. The organic solution was washed with water and stirred for 15 minutes. The layers were separated. The organic layer was washed with mixture of 1:9 HCl and water. Further organic layer of methylene dichloride was treated with sodium bisulfate and filtered. The methylene dichloride was distilled atmospherically and finally under vacuum to remove the traces of methylene dichloride. The residue was treated with 600 rnL of hexane and stirred at room temperature. The isolated precipitates were stirred for L hour, filtered, suck dried and washed with hexane. The product thus obtained was air dried to give N,N-bis(2-chloroethyl)-4-methy lbenzenesulfonamide of formula (V).

Example-5: Preparation of l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI)

4,4'-diflourobenzyhydrarylamine (100 gm, 0.456 mole) were taken in 100 mL of diisopropyl ethyl amine. N,N-bis(2-chloroethyl)-4-methylbenzenesulfonarnide of formula (V) (135 gm, 0.456 mole) in 100 mL of diisopropyl ethyl amine was added to it and the reaction mass was stirred for 10 min. The reaction mixture was heated to reflux temp at 125°C to 127°C for 17 to 18 hours and cooled to 75°C. 400 mL of methanol was added and refluxed at 65°C to 70°C for 1 hour. The reaction mixture was cooled to room temperature and chilled to 0°C to 5°C with stirring for 3 hours. The product was filtered, suck dried and washed with 100 mL of chilled methanol. The product was dried at 50°C to 55°C to give l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI)

Example-6: Preparation of l-(bis(4-fluorophenyl)methyl)piperazine formula (VII)

The solution of hydrobromic acid acetic acid (550 mL) was prepared and chilled to 0°C to 5°C. 4-hydroxy benzoic acid (152.8 gm, 1.107 mole) was added to the above solution. l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI) (100 gm, 0.226 mole) was added slowly at same temperature. The reaction mass was treated with 50 mL HBr in acetic acid and stirred for 30 min. The reaction mixture was gradually heated at 45°C to 47°C within 1 hour to 1.5 hour and stirred for 4 hours at same temperature. The reaction mass was cooled to room temperature and treated with 1000 mL of water with stirring for 1 hour. The product was filtered and washed with water. The product was suck dried. The aqueous filtrate was extracted with toluene. Further 1000 mL of toluene was added to aqueous filtrate. 50% NaOH solution was added to it till the alkaline pH 9 to 10. The layers were separated. The aqueous layer was again extracted with toluene

500 mL. The organic layer of toluene, acetic acid (100 mL) solution in (642.5 niL) of water was added. The separated aqueous layer was washed with toluene. The organic layer was treated with Na_2SO_4. The toluene was distilled under vacuum at 50^0C to 55^0C. Excess of toluene was further co-distilled with hexane (100 mL). The product was washed with water and suck dried followed by drying at 50^0C to 55^0C to give 1-(bis(4-fluorophenyl)methyl)piperazine formula (VII).

Example-7: Preparation of 2-(2-(4-(bis(4-fiuorophenyl)methyl)piperazin-l-yl)ethoxy)acetamide of formula (VIII)

4,4'-diflourobenzyl piperazine (100 mg, 0.346 mole), 2-(2-chloroethoxy) acetamide (95.15 gm, 0.692 mole) and sodium carbonate (73.35 gm) were taken in RBF. Xylene 400 mL was added to the reaction mass and stirred for 10 min. The reaction mass was heated at 120^0C to 125°C for about 11-13 hours. The product was filtered and washed with toluene. The filtrate was cooled to 20^0C to 25^0C. Dilute HCl (66.09 mL make upto 725 mL) was added and stirred for 30 minutes at room temperature. The layers were separated. The aqueous layer was washed with toluene 600 mL. The separated aqueous layer was treated with IN 725 mL of NaOH and stirred for 10 minutes. 600 mL of methylene dichloride was added. The layers were separated and aqueous layer was extracted with 400 mL of methylene dichloride. The combined methylene dichloride was washed with 400 mL of water. The methylene dichloride was distilled out atmospherically at 50^0C to 55°C further under vacuum to remove the traces. Diisopropyl ether (200 mL) was added and distilled out under vacuum at 50^0C. Further diisopropyl ether (500 mL) was added , stirred at 50^0C to 55^0C and cool to room temperature. The product was filtered and suck dried followed washing with diisopropyl ether. The product was finally dried at 50^0C to 55^0C for 12 hours to get 2-(2-(4-(bis(4-fluorophenyl)methyl)piperazin- 1-yl)ethoxy)acetamide (VIII)

Example-8: Preparation of EFLETRIZINE DIHYDROCHLORIDE MONOH YDRATE

2-(2-(4-(bis(4-fiuorophenyl)methyl)piperazin- 1-yl)ethoxy)acetamide (VIII) (100 gm) and 230 mL of water were taken at room temperature. 30% HCl (290 gm) was added within 10 minutes. The reaction mass was heated upto 65^0C and stirred for 1 hour. Cooled to 0^0C and stirred for 3 hours and 30 minutes. The product thus obtained was filtered and washed with dil HCl solution. The product was suck dried to obtain wet-cake. The wet-cake was treated with 489.1 mL of water at room temperature and heated to 60^0C to get clear solution. The solution was treated with toluene and layers

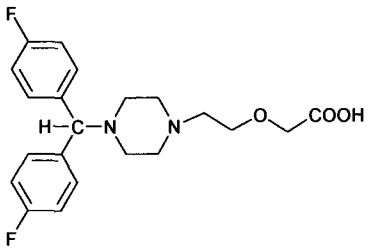
were separated. Aqueous layer was treated with charcoal and stirred for 30 min. The aqueous layer was cooled upto room temperature and acidified with 714.95 gm of Cone. HCl and chilled to 0^0C with stirring for 4 hours. The product was filtered and washed with 86.95 mL chilled HCl and suck dried. The compound was further dried at 50^0C to 55^0C temperature to give Efletrizine dihydrochloride monohydrate. The samples were analyzed by HPLC. The fractions with a purity of ≥ 99.0% were pooled. In the pooled fractions the HPLC purity was about ≥ 99.7%.

Example-9: Preparation of EFLETRIZINE DIHYDROCHLORIDE ANHYDROUS

Efletrizine dihydrochloride monohydrate (100 gm) was taken in 300 mL of methylethyl ketone. The reaction mixture was refluxed to the reflux temperature of the solvent to get clear solution. The product was cooled to room temperature. The product thus obtained was filtered, washed with methyl ethyl ketone and dried at 50^0C to 55°C to obtain Efletrizine dihydrochloride anhydrous. The samples were analyzed by HPLC. The fractions with a purity of ≥ 99.0% were pooled. In the pooled fractions the HPLC purity was about ≥ 99.7%.

Claims:

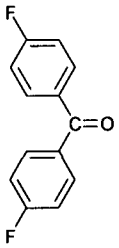
1. A process for the preparation of Efletrizine of the formula (I) or its non-toxic pharmaceutically acceptable salts thereof



(I)

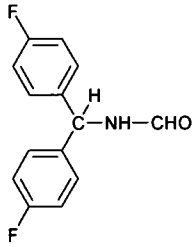
which comprises steps of

a) reacting 4,4'-diflourobenzophenone of formula (II),



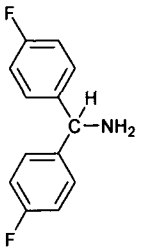
(II)

with ammonium formate in a suitable organic solvent to give N-(bis(4-fluorophenyl)methyl)formamide of formula (III);



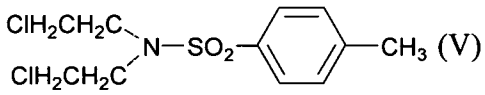
(III)

b) hydrolyzing N-(bis(4-fluorophenyl)methyl)formamide of formula (III) to obtain bis(4-fluorophenyl)methanamine of formula (IV) or its salts in presence of suitable reagent;



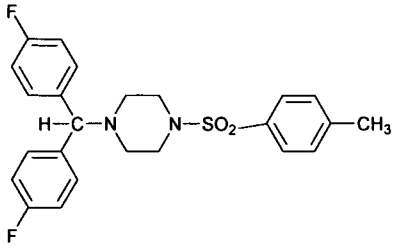
(IV)

c) reacting bis(4-fluorophenyl)methanamine of formula (IV) with compound of formula (V)



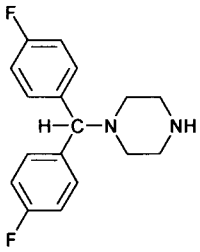
(V)

in suitable organic solvent to give compound of formula (VI);



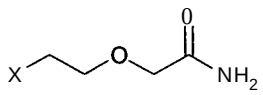
(VI)

d) reacting compound of formula (VI) with suitable reagent in presence of acid to give l-(bis(4-fluorophenyl)methyl)piperazine formula (VII);



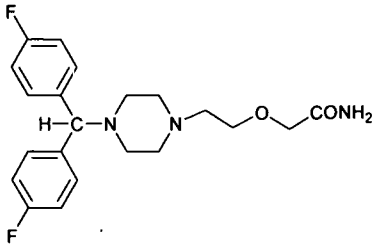
(VII)

e) reacting l-(bis(4-fluorophenyl)methyl)piperazine formula (VII) with amide of formula (VIII)



(VIII)

where X represents leaving group such as OTs, OMs, Cl, F or Br etc., preferably Cl, to provide compound of formula (IX)



(IX)

f) treating compound of formula (IX) with mineral acid provide Efletrizine of formula (I)

g) optionally converting the compound of formula (I) to its non-toxic pharmaceutically acceptable salts thereof.

2. The process as claimed in claim 1, wherein suitable organic solvents used in step (a) is a polar solvent selected from amides like formamide, dimethyl formamide, sulfoxides like dimethyl sulfoxides, preferably formamide.

3. A process as claimed in claim 1 or 2, wherein step (a) is carried out at temperature in the range of about 100^0C to 250^0C, preferably $15O^0$C to 200^0C, most preferably 175°C to l80°C.

4. A process as claimed in any preceding claim wherein acid used in step (b) is selected from inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid.

5. A process as claimed in any preceding claim wherein base used in step (c) is selected from sodium hydroxide, potassium hydroxide, sodium ethoxide, potassium ethoxide, sodium methoxide, potassium methoxide, amines such as ammonia, methyl amine, ethyl amine, tri ethyl amine, diethyl amine, isopropyl amine, diisopropyl amine or mixtures thereof.

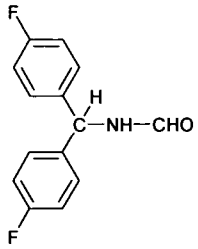
6. The process as claimed in any preceding claim wherein suitable organic solvent in step (c) is selected from members from the classes: ketonic solvents such as acetone, ethylmethyl ketone, methyl isobutyl ketone and the like; ether solvents such as diethyl ether, dimethyl ether, di-isoopropyl ether, methyltertiarybutyl ether, tetrahydrofuran, 1,4-dioxane and the like; hydrocarbon solvents such as toluene, xylene and the like; nitrile solvents such as acetonitrile, propionitrile and the like; halogenated solvents such as dichloromethane, 1,2-dichloromethane, chloroform, carbon tetrachloride and the like; aprotic polar solvents such as dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide and the like; or mixtures of any two or more thereof in various proportions.

7. A process as claimed in claim 6, wherein the suitable organic solvent is methylene dichloride.

8. The process as claimed in any preceding claim wherein said hydroxy acid in step (d) is p-hydroxy benzoic acid.

9. A process as claimed in in any preceding claim wherein suitable reagent in step (d) is HBr in acetic acid.

10. The process as claimed in any preceding claim wherein base in step (e) is selected from inorganic base or organic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, potassium tert-butoxide, tri ethyl amine, diisopropyl amine and the like.
11. A process as claimed in any preceding claim wherein mineral acid in step (f) is Hydrochloric acid, sulfuric acid, hydrobromic acid, nitric acid, phosphoric acid. The preferred acid is hydrochloric acid.
12. A process as clamed in any preceding claim wherein said Efletrizine is converted to efletrizine dihydrochloride monohydrate.
13. A process as clamed in any preceding claim wherein said Efletrizine is converted to efletrizine dihydrochloride anhydrous.
14. Efletrizine dihydrochloride monohydrate prepared by the process as claimed in any preceding claim which is substantially pure having purity greater than or equal to about 99% by area percentage of HPLC.
15. Efletrizine dihydrochloride monohydrate as claimed in claim 14, wherein the purity is greater than or equal to about 99.6% by area percentage of HPLC.
16. Efletrizine dihydrochloride monohydrate in a solid state having less than or of about 0.4% total impurities as measured by area percentage of HPLC.
17. Efletrizine dihydrochloride in a solid state, wherein the monohydrate does not have detectable level of dimer impurities when measured by HPLC at RRT 3.80.
18. Efletrizine dihydrochloride anhydrous prepared by the process as claimed in any preceding claim which is substantially pure having purity greater than 99% by area percentage of HPLC.
19. Efletrizine dihydrochloride anhydrous as claimed in claim 18, wherein the purity is greater than or equal to about 99.6% by area percentage of HPLC.
20. Efletrizine dihydrochloride anhydrous in a solid state having less than or of about 0.4% total impurities as measured by area percentage of HPLC.
21. Efletrizine dihydrochloride in a solid state, wherein the anhydrate does not have detectable level of dimer impurities when measured by HPLC at RRT 3.80.
22. A compound N-(bis(4-fluorophenyl)methyl)formamide of formula (III)



23. A compound N-(bis(4-fluorophenyl)methyl)formamide of formula (III)as claimed in claim 22, which is crystalline in nature being characterized by x-ray powder diffraction as depicted in FIG 2.

24. A crystalline compound N-(bis(4-fluorophenyl)methyl)formamide of formula (III) as claimed in claim 22, being further characterized by differential scanning calorimety profile as depicted in FIG.l and having endothermic peak at about 117.2^{0}C.

25. A crystalline compound N-Formyl-N-(4,4'-diflourobenzhydraryl) of For N-(bis(4-fluorophenyl)methyl)formamide of formula (III) as claimed in claim 22, being characterized by x-ray powder diffraction pattern having characteristic peaks at 2Θ (±0.2) values 7.7°, 11.1°, 15.5°, 21.1° and 25.2°.

26. A crystalline compound N-(bis(4-fluorophenyl)methyl)formamide of formula (III) as claimed in claim 22, characterized by FTIR spectrum as depicted in FIG 3 with characteristic peaks at about 3278, 1658, 1602, 1390, 833 and 732 cm^{-1}.

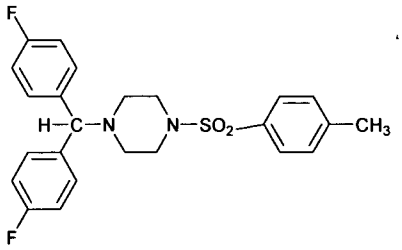
27. A crystalline bis(4-fiuorophenyl)methanamine hydrochloride of formula (IVa) characterized by x-ray powder diffraction as depicted in FIG-5.

28. A crystalline bis(4-fluorophenyl)methanamine hydrochloride of formula (IVa) as claimed in claim 27, being characterized by differential scanning calorimety profile as depicted in FIG-4 and having endothermic peak at about 227. 1^{0}C.

29. A crystalline bis(4-fluorophenyl)methanamine hydrochloride of formula (IVa) as claimed in claim 31, being characterized by x-ray powder diffraction pattern having characteristic peaks at 2θ(±0.2) values 7.4°, 15.1°, 19.8° and 25.0°.

30. A crystalline bis(4-fluorophenyl)methanamine hydrochloride of formula (IVa) as claimed in claim 31, being characterized by FTIR spectrum as depicted in FIG-6 with peaks at about 2962, 2908, 1602, 1514, 1244 and 553 cm-1.

31. A compound l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI)



(VI)

32. A compound l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI) as claimed in claim 31, is crystalline in nature being characterized by x-ray powder diffraction as depicted in FIG 8.

33. A crystalline l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI)as claimed in claim 31, being further characterized by differential scanning calorimety profile as depicted in FIG.7 and having endothermic peak at 196.93°C.

34. A crystalline l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI) as claimed in claim 31, being characterized by x-ray powder diffraction pattern having characteristic peaks at 20 (±0.2) values 6.2°, 12.5, 15.3, 16.0° and 22.3°.

35. A crystalline l-(bis(4-fluorophenyl)methyl)-4-tosylpiperazine (VI) as claimed in claim 31, characterized by FTIR spectrum as depicted in FIG-9 with characteristic peaks at about 3278, 1658, 1602, 1390, 833 and 732 cm^{-1}.

36. A crystalline Efletrizine dihydrochloride monohydrate having particle size D_{50} is less than or equal to 400 μm, as measured by Malvern light scattering instrument.

37. A crystalline efletrizine dihydrochloride monohydrate as claimed in claim 36, wherein particle size D_{50} is less than or equal to 250 μm as measured by Malvern light scattering instrument.

38. A crystalline efletrizine dihydrochloride monohydrate as claimed in claim 36, wherein particle size D_{50} is less than or equal to 175 μm as measured by Malvern light scattering instrument.

39. A crystalline Efletrizine dihydrochloride anhydrous having particle size D_{50} is less than or equal to 400 μm, as measured by Malvern light scattering instrument.

40. A crystalline efletrizine dihydrochloride anhydrous as claimed in claim 39, wherein particle size D_{50} is less than or equal to 250 μm as measured by Malvern light scattering instrument.

41. A crystalline efletrizine dihydrochloride anhydrous as claimed in claim 40, wherein particle size D_{50} is less than or equal to 175 μm as measured by Malvern light scattering instrument.

42. Efletrizine dihydrochloride monohydrate in crystalline form being characterized by at least one of:

a) differential scanning calorimetry having endotherm at 160.22^{0}C as depicted in FIG-10;

b) X-ray powder diffraction pattern having characteristic peaks from atleast one of 7.3°, 10.3°, 17.7° and 24.5° as depicted in FIG-1 1; and

c) FTIR Spectrum having characteristic peaks at 3398, 2922, 1712, 1512, 1120, 869 and 574 cm-1 as depicted in FIG-12.

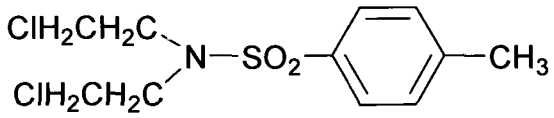
43. Efletrizine dihydrochloride anhydrous ins crystalline form being characterized by at least one of:

a) differential scanning calorimetry having endotherm at 226.22^{0}C as depicted in FIG-13;

b) X-ray powder diffraction pattern having characteristic peaks from atleast one of 13.6°, 14.8°, 18.4° and 25.0° as depicted in FIG-14; and

c) FTIR Spectrum having characteristic peaks at 2949, 1749, 1514, and 829 cm-1 as depicted in FIG- 15.

44. A process for the preparation of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V),



(V)

which comprises reacting bis(2-chloroethyl amine) HCl with a base to obtain bis(2-chloroethyl amine), which is subsequently treated with p-toluenesulphonyl chloride in presence of base to obtain N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide of formula (V).

45. A process as claimed claim 44, wherein said base is selected from the group of inorganic bases like sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate; or organic bases like isopropyl amine, diisopropyl amine, triethylamine, ammonia, pyridine etc.

46. The process as claimed in claim 45, wherein the base is triethyl amine.

47. The process as claimed in claim 44, wherein suitable organic solvent can be selected from members from the classes: ketonic solvents such as acetone,

ethylmethyl ketone, methyl isobutyl ketone and the like; ether solvents such as diethyl ether, dimethyl ether, di-isoopropyl ether, methyltertiarybutyl ether, tetrahydrofuran, 1,4-dioxane and the like; hydrocarbon solvents such as toluene, xylene and the like; nitrile solvents such as acetonitrile, propionitrile and the like; halogenated solvents such as dichloromethane, 1,2-dichloromethane, chloroform, carbon tetrachloride and the like; aprotic polar solvents such as dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide and the like; or mixtures of any two or more thereof in various proportions.

48. The process as claimed in claim 47, wherein said organic solvent is methylene dichloride.

FIG. 1

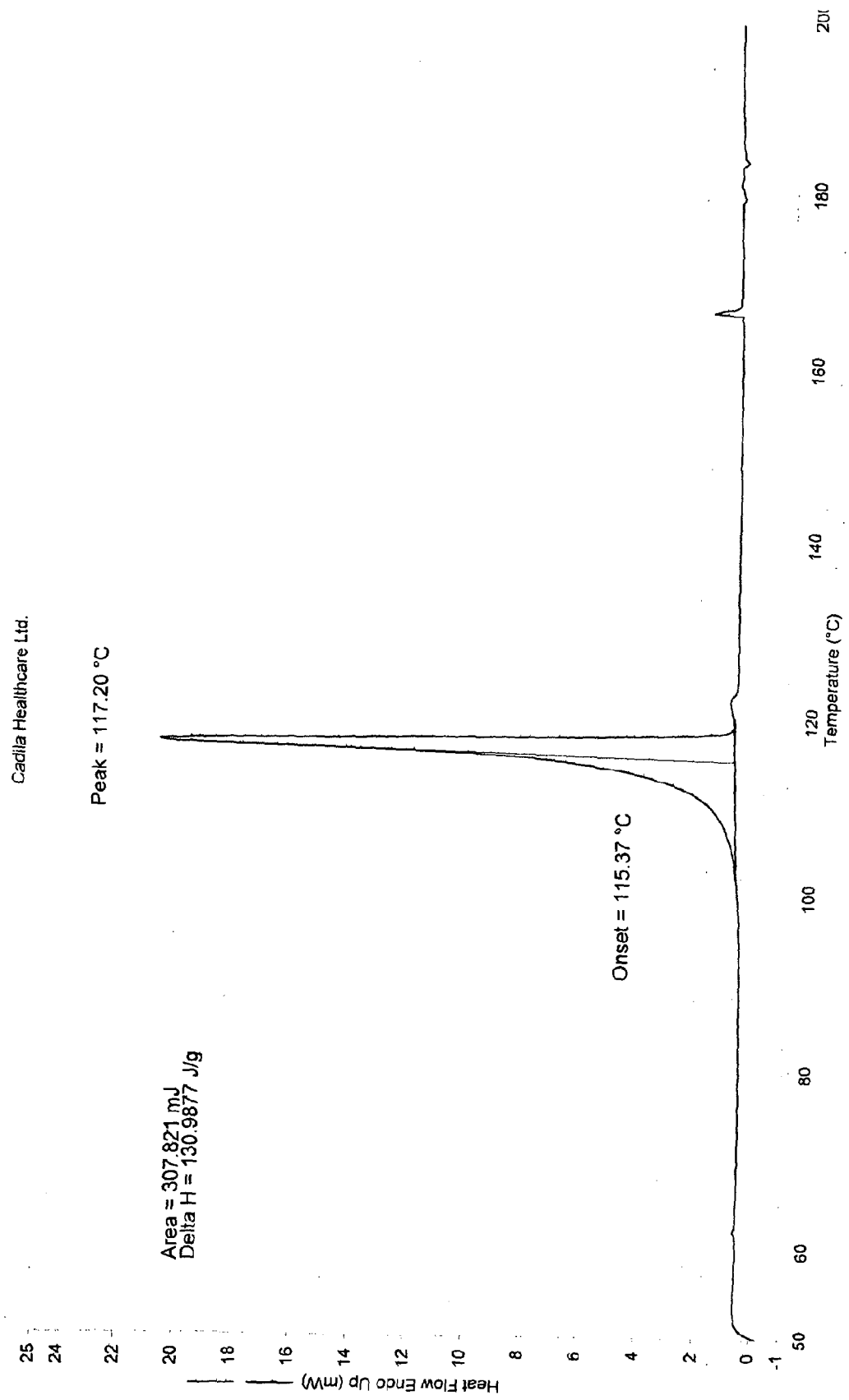
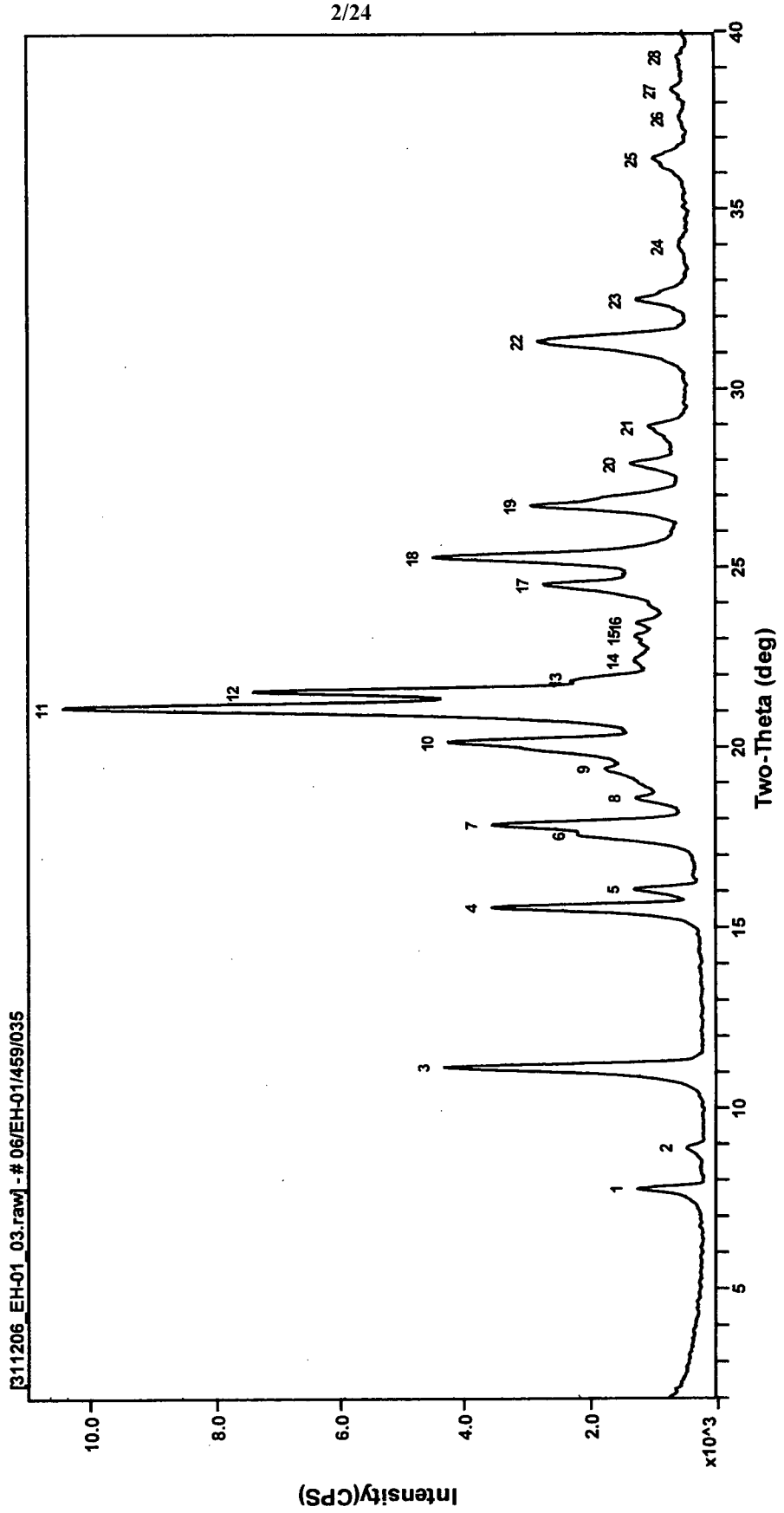

Cadila Healthcare Ltd.
Peak = 117.20 °C
Area = 307.821 mJ
Delta H = 130.9877 J/g
Onset = 115.37 °C
Heat Flow Endo Up (mW)
Temperature (°C)

FIG. 2


[311206_EH-01_03.raw] - # 06/EH-01/459/035
Intensity(CPS)
x10^3
10.0
8.0
6.0
4.0
2.0
Two-Theta (deg)
5
10
15
20
25
30
35
40
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15/6
17
18
19
20
21
22
23
24
25
26
27
28

[311206_EH-01_03.raw] - # 06/EH-01/459/035 **Peak Search Report**

SCAN: 2.0/40.0/0.02/0.4(sec), Cu(40kV,40mA), I(cps)=10452, 12/31/06 12:44

PEAK: 23-pts/Parabolic Filter, Threshold=3.0, Cutoff=0.1%, BG=3/1.0, Peak-Top=Summit

NOTE: Intensity = CPS, 2T(0)=0.0(deg), Wavelength to Compute d-Spacing = 1.54056Å (Cu/K-alpha1)

#	2-Theta	d(Å)	BG	Height	Height%	Area	Area%	FWHM
1	7.760	11.3829	214	1238	11.8	13395	6.4	0.222
2	8.900	9.9281	199	460	4.4	4720	2.2	0.307
3	11.159	7.9222	215	4306	41.2	64265	30.5	0.267
4	15.560	5.6901	294	3531	33.8	48906	23.2	0.257
5	16.060	5.5143	333	1287	12.3	12281	5.8	0.219
6	17.541	5.0517	496	2139	20.5	31903	15.1	0.330
7	17.840	4.9677	541	3530	33.8	64965	30.8	0.369
8	18.578	4.7721	880	1259	12.0	3651	1.7	0.164
9	19.399	4.5719	1137	1747	16.7	21648	10.3	0.603
10	20.159	4.4012	1446	4228	40.5	53518	25.4	0.327
11	21.100	4.2070	1355	10452	100.0	210634	100.0	0.394
12	21.541	4.1219	1295	7415	70.9	146166	69.4	0.406
13	21.889	4.0572	1087	2186	20.9	11366	5.4	0.176
14	22.400	3.9657	1140	1283	12.3	2467	1.2	0.293
15	23.062	3.8533	1020	1270	12.2	5330	2.5	0.362
16	23.442	3.7917	1006	1246	11.9	1931	0.9	0.137
17	24.519	3.6275	1288	2707	25.9	22010	10.4	0.264
18	25.280	3.5201	653	4471	42.8	75930	36.0	0.338
19	26.720	3.3336	643	2902	27.8	46118	21.9	0.347
20	27.900	3.1952	666	1340	12.8	9936	4.7	0.251
21	28.940	3.0827	583	1052	10.1	9037	4.3	0.328
22	31.320	2.8537	496	2791	26.7	57305	27.2	0.424
23	32.461	2.7559	470	1238	11.8	16028	7.6	0.355
24	33.960	2.6376	437	574	5.5	4037	1.9	0.501
25	36.400	2.4662	472	979	9.4	14516	6.9	0.487
26	37.559	2.3927	482	567	5.4	1597	0.8	0.319
27	38.361	2.3445	523	689	6.6	2336	1.1	0.239
28	39.320	2.2895	486	606	5.8	2337	1.1	0.331

	Peak	Intensity
1	414.7	90.854
2	453.27	85.62
3	495.71	78.464
4	534.28	62.842
5	557.43	57.845
6	582.5	67.354
7	634.58	96.203
8	686.66	88.051
9	711.73	85.878
10	732.95	64.339
11	792.74	90.363
12	813.96	76.341
13	833.25	51.962
14	871.82	79.549
15	893.04	77.899
16	941.26	94.002
17	960.55	96.776
18	1014.56	80.614
19	1033.85	83.646
20	1101.35	80.142
21	1159.22	61.513
22	1174.65	87.51
23	1199.72	90.553
24	1228.66	50.082
25	1261.45	83.356
26	1282.66	89.554
27	1301.95	85.98
28	1334.74	92.283
29	1352.1	95.635
30	1390.68	57.492
31	1433.11	89.271
32	1454.33	83.925
33	1462.04	82.472
34	1469.76	80.175
35	1485.19	77.87
36	1504.48	55.288
37	1510.26	52.283
38	1531.48	63.805

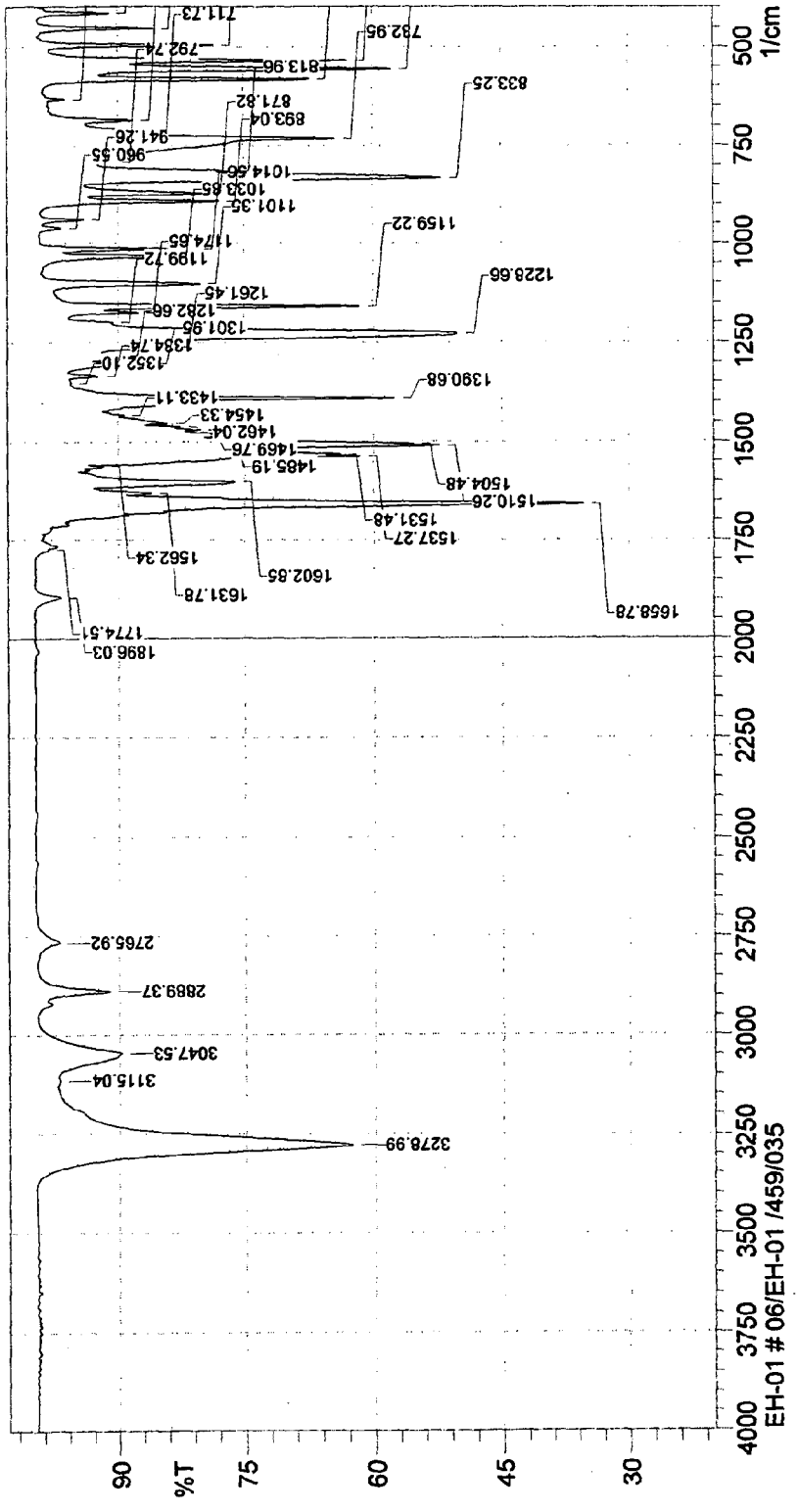


FIG. 3

39	1537.27	61.487
40	1562.34	91.705
41	1602.85	76.106
42	1631.78	85.921
43	1658.78	35.364
44	1774.51	98.374
45	1896.03	96.883
46	2765.92	97.191
47	2889.37	91.081
48	3047.53	89.7
49	3115.04	97.095
50	3278.99	62.632

FIG. 4

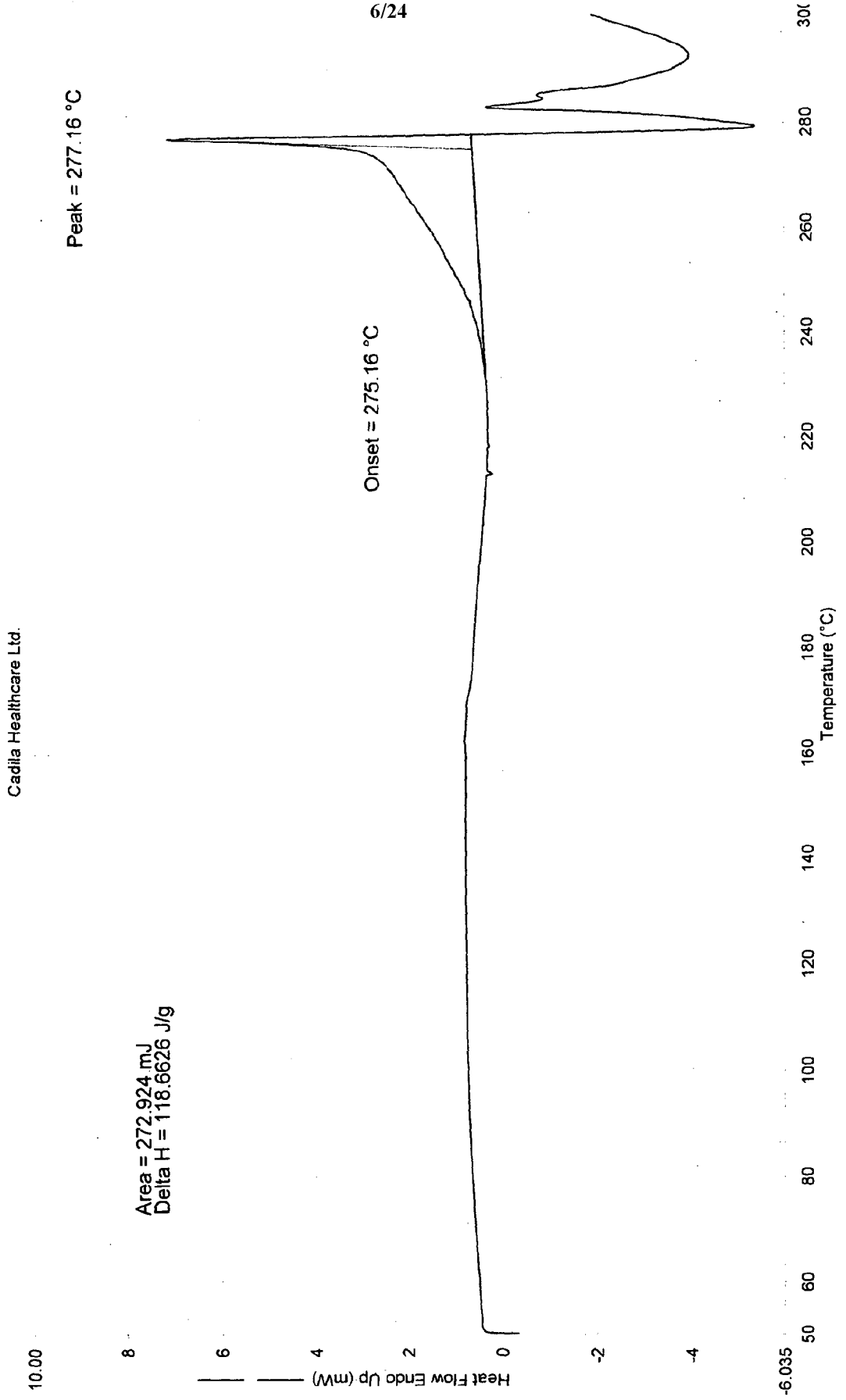
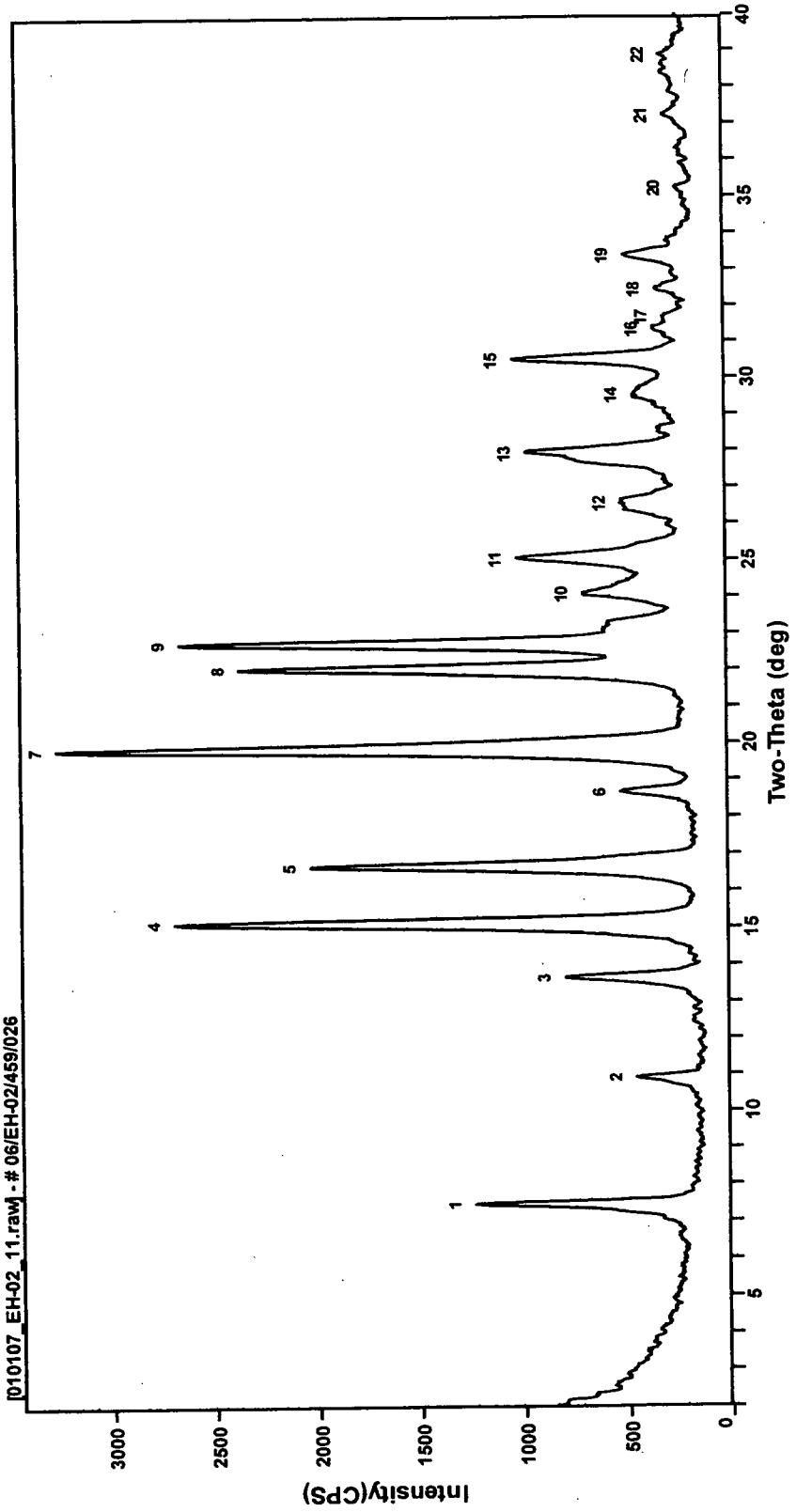

Peak = 277.16 °C
Onset = 275.16 °C
Area = 272.924 mJ
Delta H = 118.6626 J/g
Cadila Healthcare Ltd.
Heat Flow Endo Up (mW)
Temperature (°C)
10.00
8
6
4
2
0
-2
-4
-6.035
50
60
80
100
120
140
160
180
200
220
240
260
280

FIG. 5


[010107_EH-02_11.raw] - # 06/EH-02/459/026
Intensity(CPS)
Two-Theta (deg)
0
500
1000
1500
2000
2500
3000
5
10
15
20
25
30
35
40
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

[010107_EH-02_11.raw] - # 06/EH-02/459/026 | Peak Search Report

SCAN: 2.0/40.0/0.02/0.4(sec), Cu(40kV,40mA), I(cps)=3272, 01/01/07 11:01

PEAK: 23-pts/Parabolic Filter, Threshold=3.0, Cutoff=0.1%, BG=3/1.0, Peak-Top=Summit

NOTE: Intensity = CPS, 2T(0)=0.0(deg), Wavelength to Compute d-Spacing = 1.54056Å (Cu/K-alpha1)

#	2-Theta	d(Å)	BG	Height	Height%	Area	Area%	FWHM
1	7.461	11.8388	200	1230	37.6	13506	23.9	0.223
2	10.919	8.0965	133	449	13.7	5156	9.1	0.277
3	13.660	6.4769	156	790	24.1	9801	17.3	0.263
4	15.140	5.8472	171	2700	82.5	42745	75.5	0.287
5	16.661	5.3167	170	2030	62.0	31842	56.2	0.291
6	18.661	4.7511	189	516	15.8	4621	8.2	0.240
7	19.840	4.4714	210	3272	100.0	56618	100.0	0.314
8	22.039	4.0298	223	2375	72.6	37301	65.9	0.295
9	22.739	3.9073	295	2668	81.5	42833	75.7	0.307
10	24.099	3.6899	364	692	21.1	6315	11.2	0.327
11	25.060	3.5505	369	1009	30.8	12109	21.4	0.322
12	26.560	3.3532	262	507	15.5	6884	12.2	0.478
13	27.940	3.1907	266	962	29.4	17441	30.8	0.426
14	29.539	3.0215	298	445	13.6	3610	6.4	0.417
15	30.500	2.9285	289	1023	31.3	10927	19.3	0.253
16	31.361	2.8500	238	345	10.5	2445	4.3	0.388
17	31.699	2.8204	225	297	9.1	2429	4.3	0.574
18	32.460	2.7560	220	332	10.1	1423	2.5	0.216
19	33.399	2.6806	205	483	14.8	6690	11.8	0.409
20	35.240	2.5447	159	227	6.9	1292	2.3	0.323
21	37.239	2.4126	198	286	8.7	1493	2.6	0.288
22	38.897	2.3134	212	298	9.1	3054	5.4	0.604

	Peak	Intensity
1	408.91	82.002
2	449.41	74.414
3	493.78	95.355
4	536.21	62.987
5	553.57	40.795
6	586.36	78.735
7	634.58	97.913
8	721.38	88.5
9	754.17	83.094
10	775.38	84.841
11	835.18	40.419
12	848.68	59.485
13	941.26	97.634
14	989.48	93.016
15	1014.56	84.438
16	1120.64	90.858
17	1165	61.718
18	1193.94	77.902
19	1244.09	37.623
20	1280.73	91.465
21	1292.31	90.836
22	1342.46	95.099
23	1382.96	80.727
24	1425.4	83.352
25	1469.76	95.876
26	1514.12	31.112
27	1573.91	90.575
28	1602.85	56.363
29	1658.78	93.699
30	1776.44	98.175
31	1896.03	94.65
32	2040.69	92.722
33	2198.85	98.814
34	2289.5	98.796
35	2370.51	97.697
36	2461.17	97.287
37	2505.53	97.688
38	2594.26	79.913

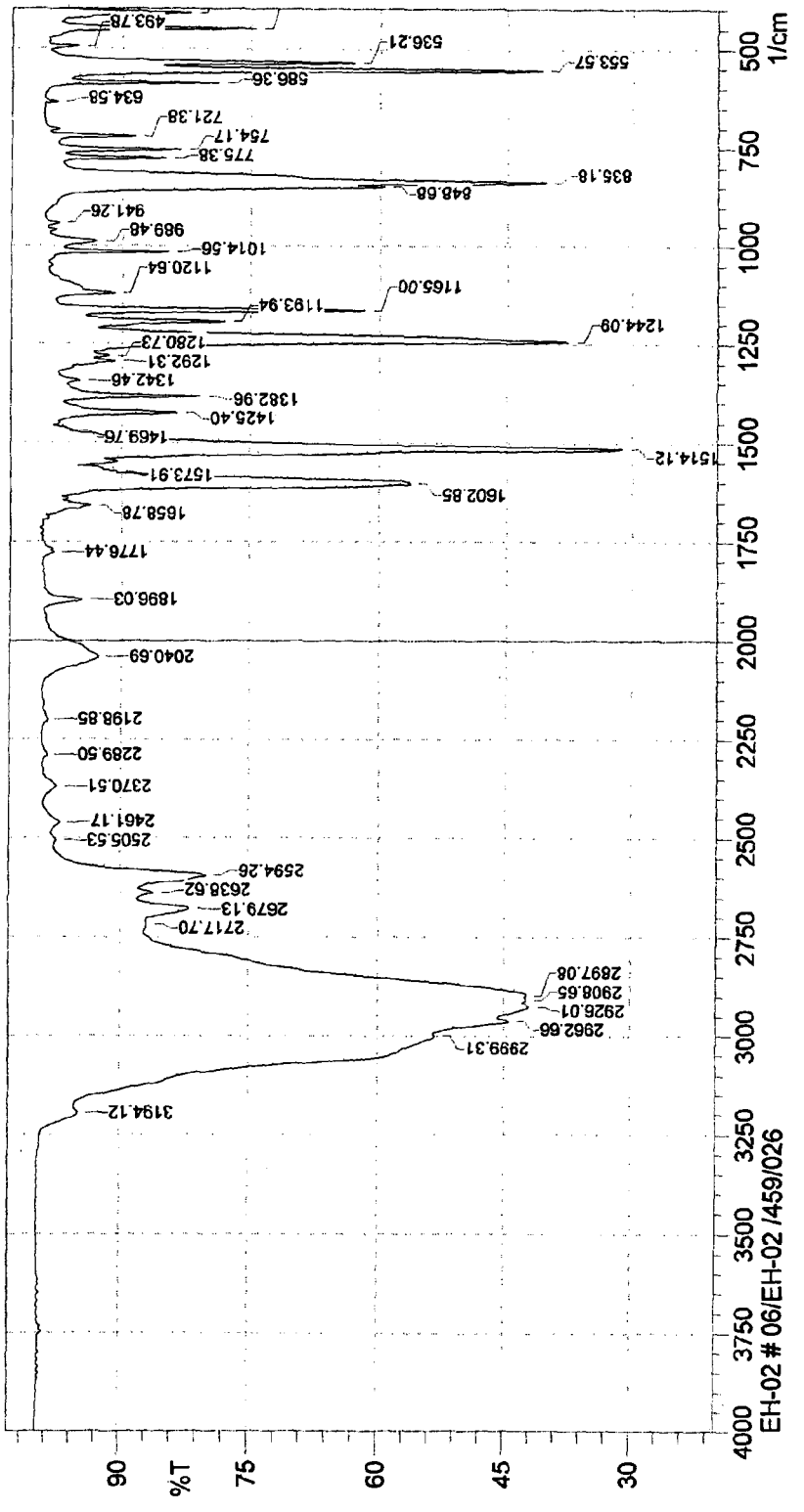


FIG. 6

39	2638.62	86.158
40	2679.13	81.782
41	2717.7	86.832
42	2897.08	42.429
43	2908.65	42.335
44	2926.01	42.005
45	2962.66	44.439
46	2999.31	53.339
47	3194.12	94.955

FIG. 7

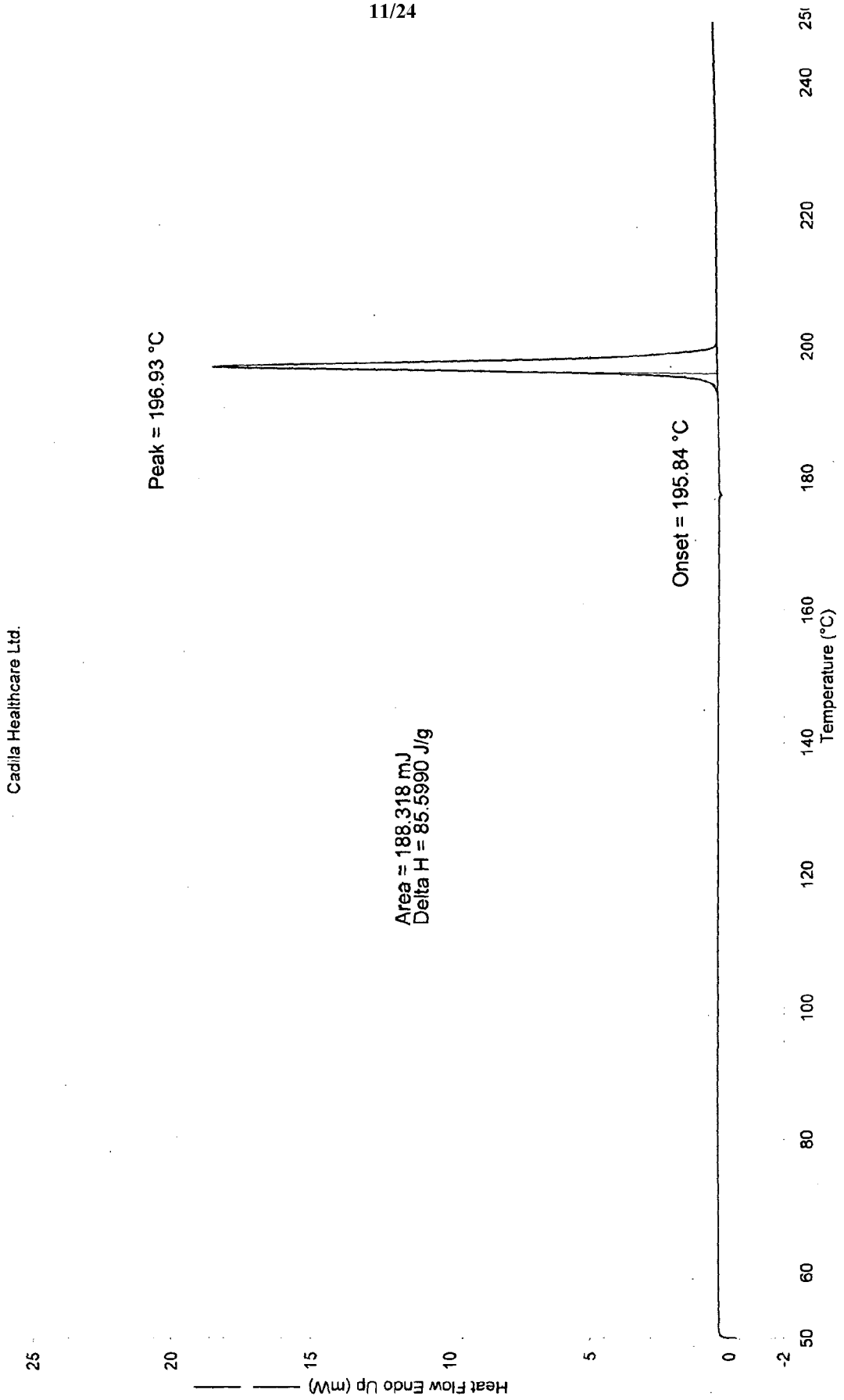
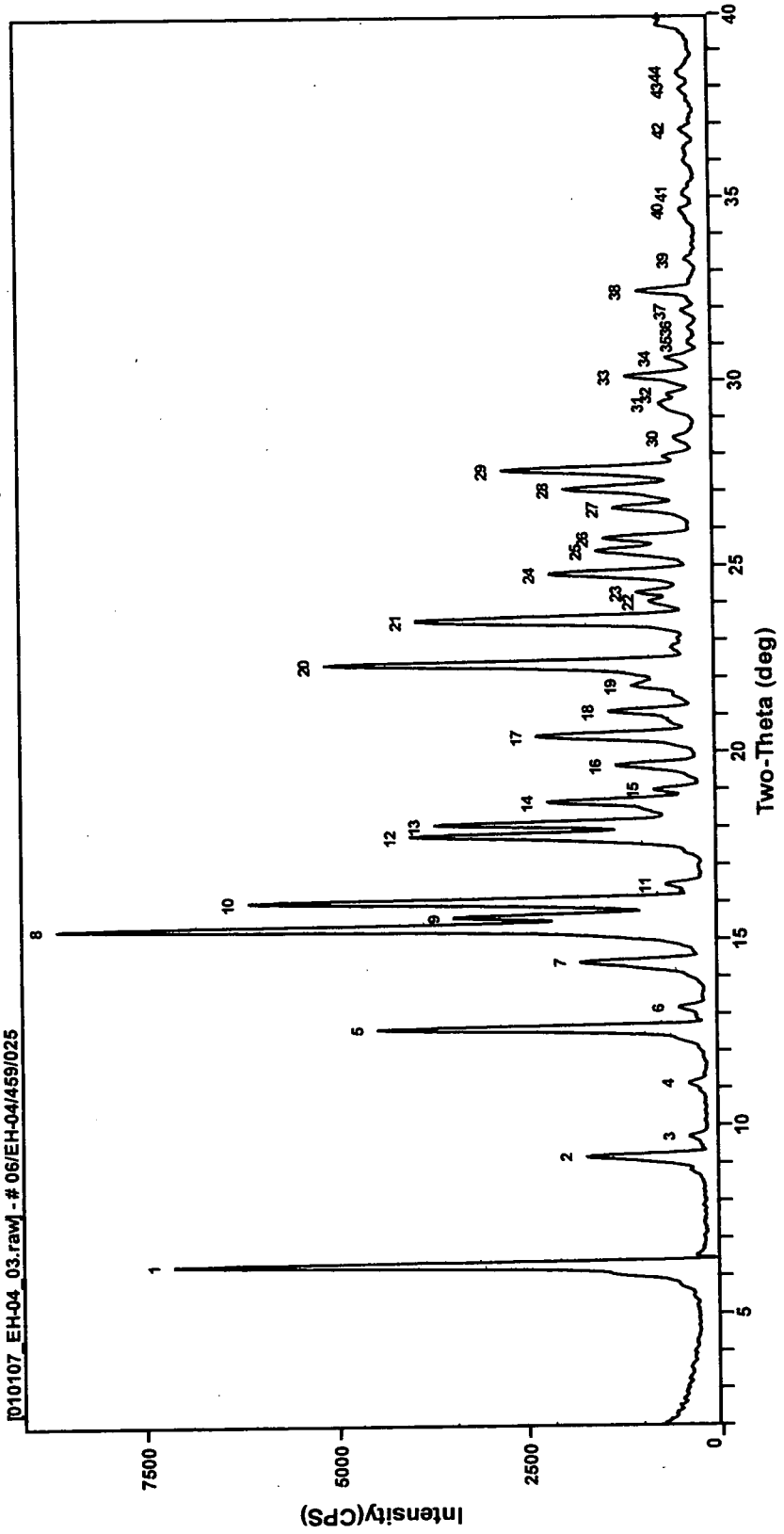

Cadila Healthcare Ltd.
Peak = 196.93 °C
Onset = 195.84 °C
Area = 188.318 mJ
Delta H = 85.5990 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
25
20
15
10
5
0
-2
50
60
80
100
120
140
160
180
200
220
240
25

FIG. 8


D10107_EH-04_03.raw] - # 06/EH-04/459/025
Intensity(CPS)
Two-Theta (deg)
0
2500
5000
7500
5
10
15
20
25
30
35
40

[010107_EH-04_03.raw] - # 06/EH-04/459/025 **Peak Search Report**

SCAN: 2.0/40.0/0.02/0.4(sec), Cu(40kV,40mA), I(cps)=8644, 01/01/07 11:51

PEAK: 21-pts/Parabolic Filter, Threshold=3.0, Cutoff=0.1%, BG=3/1.0, Peak-Top=Summit

NOTE: Intensity = CPS, 2T(0)=0.0(deg), Wavelength to Compute d-Spacing = 1.54056Å (Cu/K-alpha1)

#	2-Theta	d(Å)	BG	Height	Height%	Area	Area%	FWHM
1	6.302	14.0144	273	7148	82.7	74175	68.2	0.183
2	9.179	9.6262	158	1697	19.6	21120	19.4	0.233
3	9.700	9.1109	197	360	4.2	676	0.6	0.071
4	11.120	7.9503	147	367	4.2	3151	2.9	0.243
5	12.619	7.0088	157	4457	51.6	47875	44.0	0.189
6	13.162	6.7208	255	485	5.6	867	0.8	0.064
7	14.399	6.1465	298	1759	20.3	19249	17.7	0.224
8	15.321	5.7785	454	8644	100.0	108829	100.0	0.226
9	15.601	5.6752	296	3436	39.8	49302	45.3	0.267
10	16.039	5.5214	205	6145	71.1	67165	61.7	0.192
11	16.478	5.3751	206	644	7.5	5703	5.2	0.221
12	17.780	4.9845	205	4006	46.3	57248	52.6	0.256
13	18.080	4.9023	299	3681	42.6	45069	41.4	0.227
14	18.680	4.7464	247	2178	25.2	31219	28.7	0.275
15	18.998	4.6675	247	787	9.1	4695	4.3	0.148
16	19.641	4.5161	261	1275	14.8	11682	10.7	0.196
17	20.440	4.3413	311	2314	26.8	25451	23.4	0.216
18	21.100	4.2071	372	1359	15.7	11699	10.7	0.202
19	21.780	4.0772	423	1059	12.3	15557	14.3	0.416
20	22.380	3.9692	478	5120	59.2	57938	53.2	0.212
21	23.559	3.7732	499	3906	45.2	40166	36.9	0.200
22	24.039	3.6989	442	821	9.5	6605	6.1	0.296
23	24.280	3.6628	478	981	11.3	6759	6.2	0.228
24	24.781	3.5898	457	2121	24.5	18907	17.4	0.193
25	25.400	3.5037	403	1501	17.4	17313	15.9	0.268
26	25.740	3.4581	366	1408	16.3	13415	12.3	0.219
27	26.541	3.3556	553	1278	14.8	5298	4.9	0.124
28	27.060	3.2925	344	1924	22.3	25559	23.5	0.275
29	27.580	3.2315	297	2740	31.7	36837	33.8	0.256
30	28.440	3.1357	276	485	5.6	2396	2.2	0.195
31	29.379	3.0376	279	678	7.8	9488	8.7	0.404
32	29.619	3.0136	294	566	6.5	8981	8.3	0.561
33	30.120	2.9646	313	1107	12.8	9317	8.6	0.199
34	30.619	2.9173	280	579	6.7	2935	2.7	0.167
35	31.024	2.8802	222	292	3.4	1265	1.2	0.307
36	31.459	2.8413	213	295	3.4	1258	1.2	0.261
37	31.920	2.8014	212	373	4.3	2143	2.0	0.226
38	32.460	2.7560	206	947	11.0	8743	8.0	0.201
39	33.303	2.6881	201	323	3.7	1530	1.4	0.213
40	34.640	2.5874	201	384	4.4	5687	5.2	0.528
41	35.119	2.5532	203	330	3.8	2910	2.7	0.390
42	36.840	2.4378	210	362	4.2	2091	1.9	0.234
43	37.920	2.3708	208	363	4.2	4159	3.8	0.456
44	38.360	2.3446	213	393	4.5	6131	5.6	0.579

	Peak	Intensity
1	443.63	101.286
2	443.63	101.286
3	478.35	104.418
4	518.85	88.192
5	547.78	81.393
6	584.43	84.18
7	621.08	95.31
8	650.01	88.487
9	732.95	86.711
10	788.89	89.448
11	829.39	86.367
12	867.97	95.143
13	937.4	87.055
14	972.12	96.882
15	1006.84	93.718
16	1060.85	95.374
17	1097.5	90.314
18	1126.43	89.203
19	1155.36	90.185
20	1172.72	87.768
21	1220.94	88.242
22	1278.81	91.747
23	1292.31	93.249
24	1328.95	89.034
25	1396.46	97.661
26	1417.68	98.757
27	1456.26	95.118
28	1502.55	88.326
29	1600.92	91.368
30	1653	104.582
31	1676.14	106.423
32	1695.43	108.315
33	1780.3	106.561
34	1896.03	103.659
35	2816.07	96.893
36	2989.66	101.137
37	3055.24	103.282

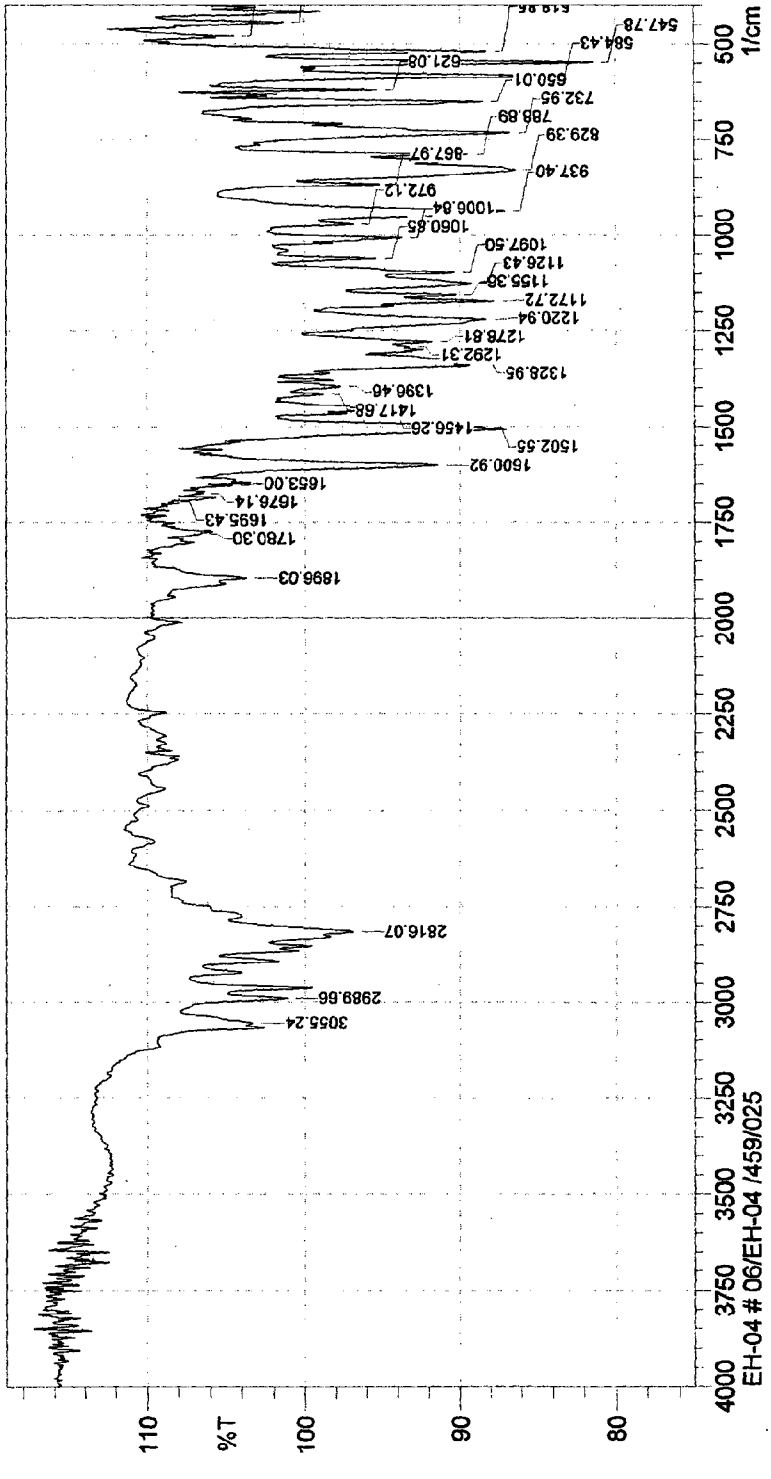


FIG. 9

FIG. 10

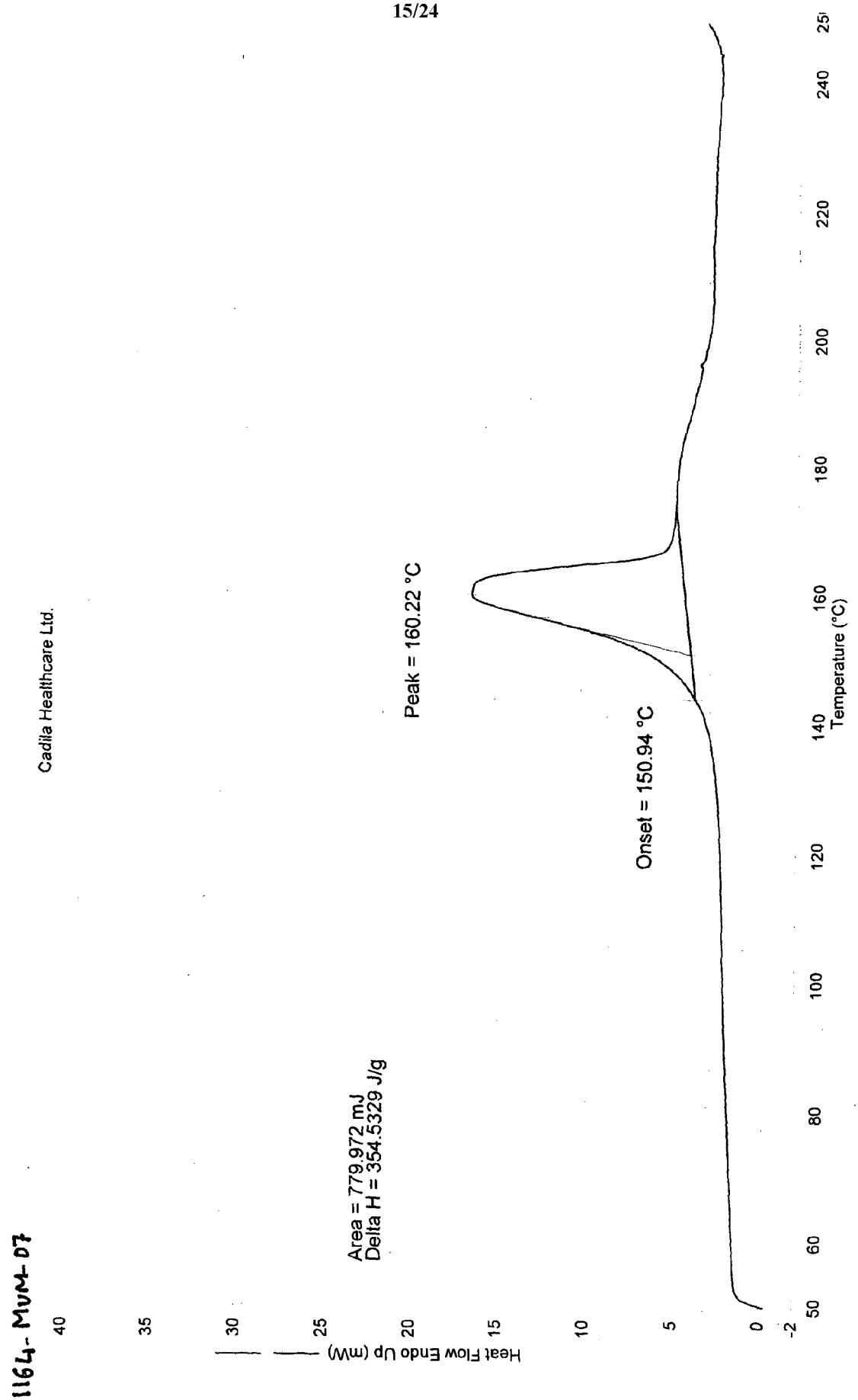
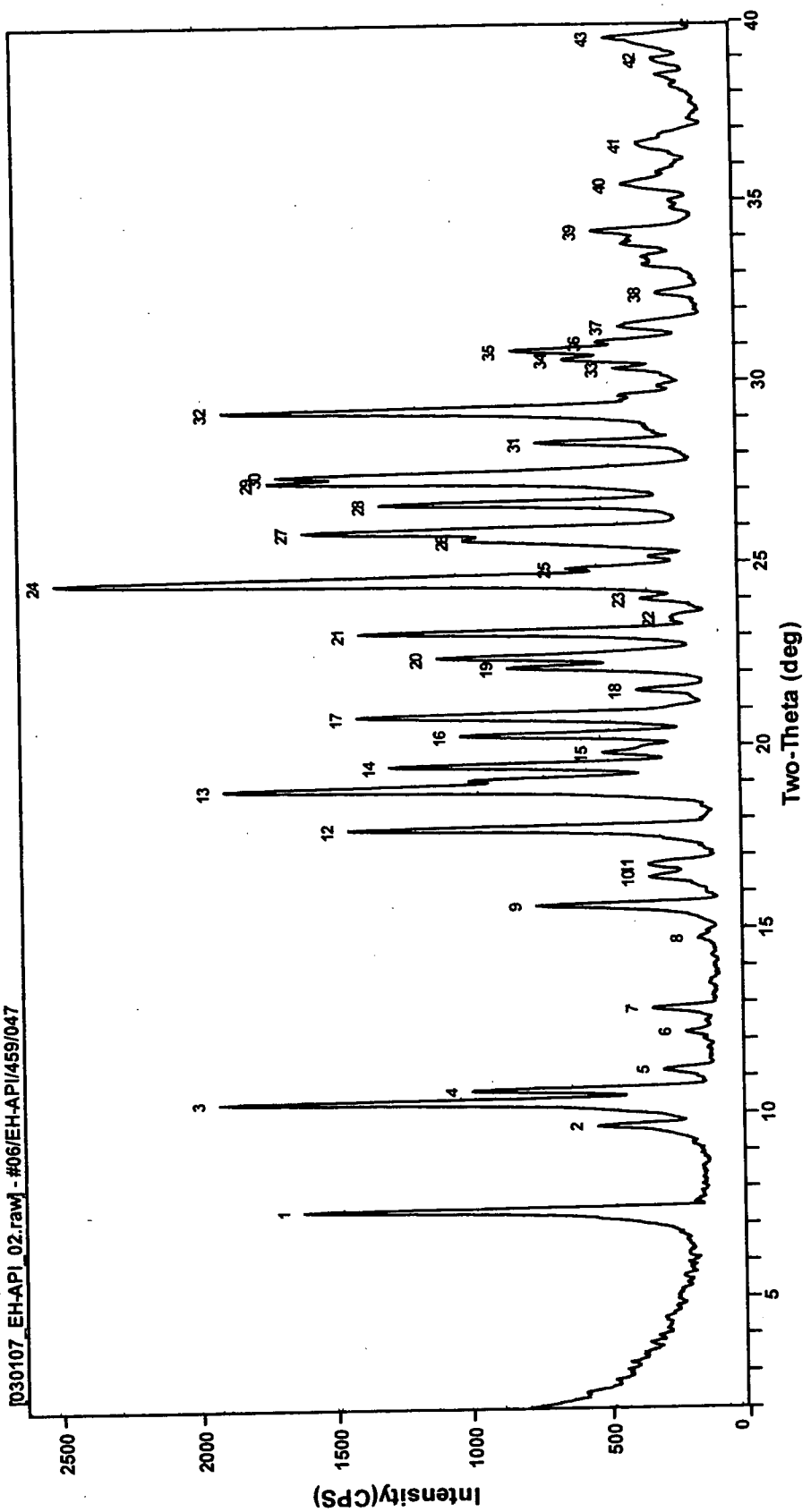

1164- MuM- 07
Cadila Healthcare Ltd.
Peak = 160.22 °C
Area = 779.972 mJ
Delta H = 354.5329 J/g
Onset = 150.94 °C
Heat Flow Endo Up (mW)
Temperature (°C)
40
35
30
25
20
15
10
5
0
-2
50
60
80
100
120
140
160
180
200
220
240

FIG. 11


[030107_EH-API_02.raw] - #06/EH-API/459/047
Intensity(CPS)
Two-Theta (deg)

[030107_EH-API_02.raw] - #06/EH-API/459/047 **Peak Search Report**

SCAN: 2.0/40.0/0.02/0.4(sec), Cu(40kV,40mA), I(cps)=2506, 01/03/07 17:10

PEAK: 19-pts/Parabolic Filter, Threshold=3.0, Cutoff=0.1%, BG=3/1.0, Peak-Top=Summit

NOTE: Intensity = CPS, 2T(0)=0.0(deg), Wavelength to Compute d-Spacing = 1.54056Å (Cu/K-alpha1)

#	2-Theta	d(Å)	BG	Height	Height%	Area	Area%	FWHM
1	7.380	11.9694	163	1624	64.8	17852	45.5	0.208
2	9.661	9.1473	230	533	21.3	2679	6.8	0.150
3	10.340	8.5482	162	1932	77.1	24049	61.3	0.231
4	10.641	8.3071	120	988	39.4	11458	29.2	0.224
5	11.179	7.9083	144	292	11.7	1054	2.7	0.121
6	12.199	7.2492	116	210	8.4	1370	3.5	0.248
7	12.840	6.8887	107	330	13.2	2930	7.5	0.223
8	14.723	6.0116	102	163	6.5	824	2.1	0.230
9	15.640	5.6612	108	745	29.7	7062	18.0	0.188
10	16.400	5.4006	110	337	13.4	4467	11.4	0.335
11	16.740	5.2916	112	338	13.5	4507	11.5	0.339
12	17.759	4.9903	117	1439	57.4	15483	39.5	0.199
13	18.859	4.7015	118	1901	75.9	32832	83.8	0.313
14	19.479	4.5533	231	1281	51.1	12002	30.6	0.194
15	19.820	4.4758	321	499	19.9	1328	3.4	0.127
16	20.301	4.3707	272	1015	40.5	6514	16.6	0.149
17	20.840	4.2589	239	1402	55.9	12757	32.5	0.186
18	21.521	4.1257	151	374	14.9	1852	4.7	0.141
19	22.140	4.0117	168	838	33.4	10139	25.9	0.257
20	22.420	3.9622	187	1097	43.8	12181	31.1	0.228
21	23.101	3.8470	182	1389	55.4	13376	34.1	0.188
22	23.461	3.7887	159	248	9.9	1351	3.4	0.258
23	24.000	3.7049	174	355	14.2	2198	5.6	0.206
24	24.520	3.6275	195	2506	100.0	39201	100.0	0.288
25	24.839	3.5816	225	621	24.8	13000	33.2	0.558
26	25.621	3.4740	239	994	39.7	19554	49.9	0.440
27	25.879	3.4399	238	1597	63.7	24020	61.3	0.300
28	26.621	3.3458	293	1306	52.1	9700	24.7	0.163
29	27.260	3.2688	206	1723	68.8	32773	83.6	0.367
30	27.420	3.2500	242	1691	67.5	29831	76.1	0.329
31	28.300	3.1509	257	725	28.9	3969	10.1	0.144
32	29.219	3.0539	259	1891	75.5	23690	60.4	0.247
33	30.341	2.9435	233	441	17.6	2833	7.2	0.232
34	30.600	2.9191	236	624	24.9	10143	25.9	0.444
35	30.860	2.8951	188	812	32.4	16051	40.9	0.437
36	31.081	2.8751	181	503	20.1	12215	31.2	0.645
37	31.521	2.8359	205	422	16.8	2904	7.4	0.228
38	32.421	2.7592	142	283	11.3	1526	3.9	0.184
39	34.161	2.6226	200	512	20.4	5866	15.0	0.320
40	35.441	2.5307	174	401	16.0	5661	14.4	0.424
41	36.561	2.4557	160	346	13.8	4414	11.3	0.403
42	38.920	2.3121	154	284	11.3	3508	8.9	0.459
43	39.540	2.2773	166	456	18.2	6034	15.4	0.354

	Peak	Intensity
1	406.98	75.946
2	464.84	83.157
3	489.92	83.74
4	505.35	84.64
5	547.78	57.015
6	574.79	54.326
7	617.22	77.431
8	651.94	77.106
9	667.37	78.678
10	721.38	85.602
11	781.17	75.822
12	792.74	80.765
13	831.32	59.196
14	839.03	57.451
15	860.25	65.365
16	869.9	77.895
17	902.69	70.8
18	931.62	71.556
19	954.76	84.174
20	995.27	67.044
21	1014.56	79.971
22	1028.06	79.096
23	1045.42	85.448
24	1062.78	81.989
25	1087.85	67.479
26	1120.64	50.697
27	1151.5	76.398
28	1163.08	64.122
29	1186.22	70.808
30	1224.8	51.712
31	1232.51	52.209
32	1261.45	61.47
33	1282.66	72.299
34	1296.16	84.132
35	1313.52	78.714
36	1346.31	75.373
37	1369.46	75.731
38	1382.96	78.5

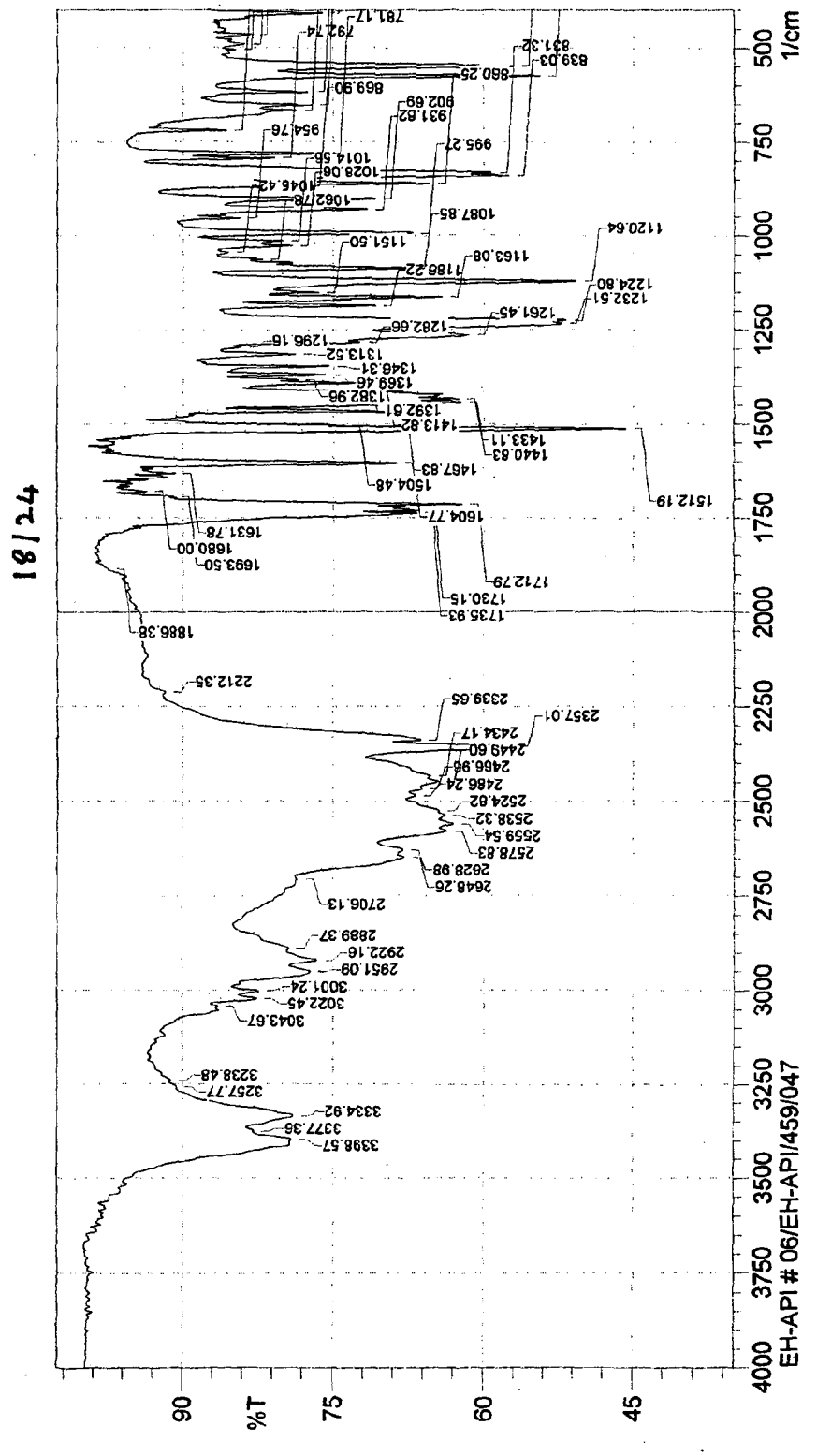


FIG. 12

39	1392.61	72.971
40	1413.82	67.96
41	1433.11	62.437
42	1440.83	62.212
43	1467.83	69.244
44	1504.48	73.845
45	1512.19	45.684
46	1604.77	68.617
47	1631.78	90.698
48	1680	93.618
49	1693.5	90.894
50	1712.79	62.055
51	1730.15	66.366
52	1735.93	66.608
53	1886.38	97.514
54	2212.35	91.777
55	2339.65	66.294
56	2357.01	57.129
57	2434.17	65.308
58	2449.6	64.48
59	2466.96	66.115
60	2486.24	66.784
61	2524.82	64.436
62	2538.32	63.869
63	2559.54	62.979
64	2578.83	63.648
65	2628.98	68.07
66	2648.26	67.902
67	2706.13	78.514
68	2889.37	79.403
69	2922.16	76.565
70	2951.09	77.232
71	3001.24	82.298
72	3022.45	82.552
73	3043.67	86.523
74	3238.48	91.157
75	3257.77	90.604
76	3334.92	78.906
77	3377.36	82.83
78	3398.57	79.13

FIG. 13

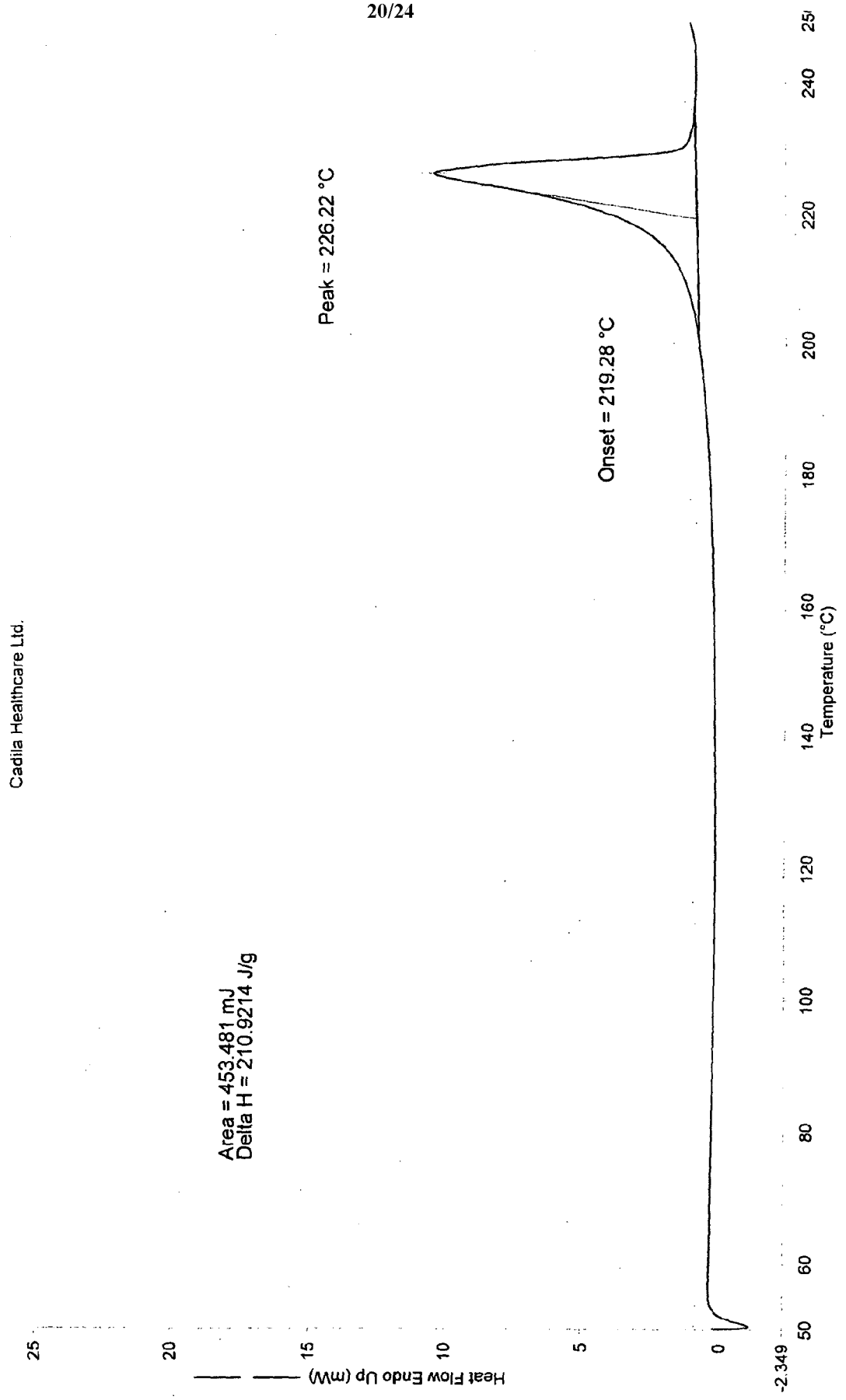
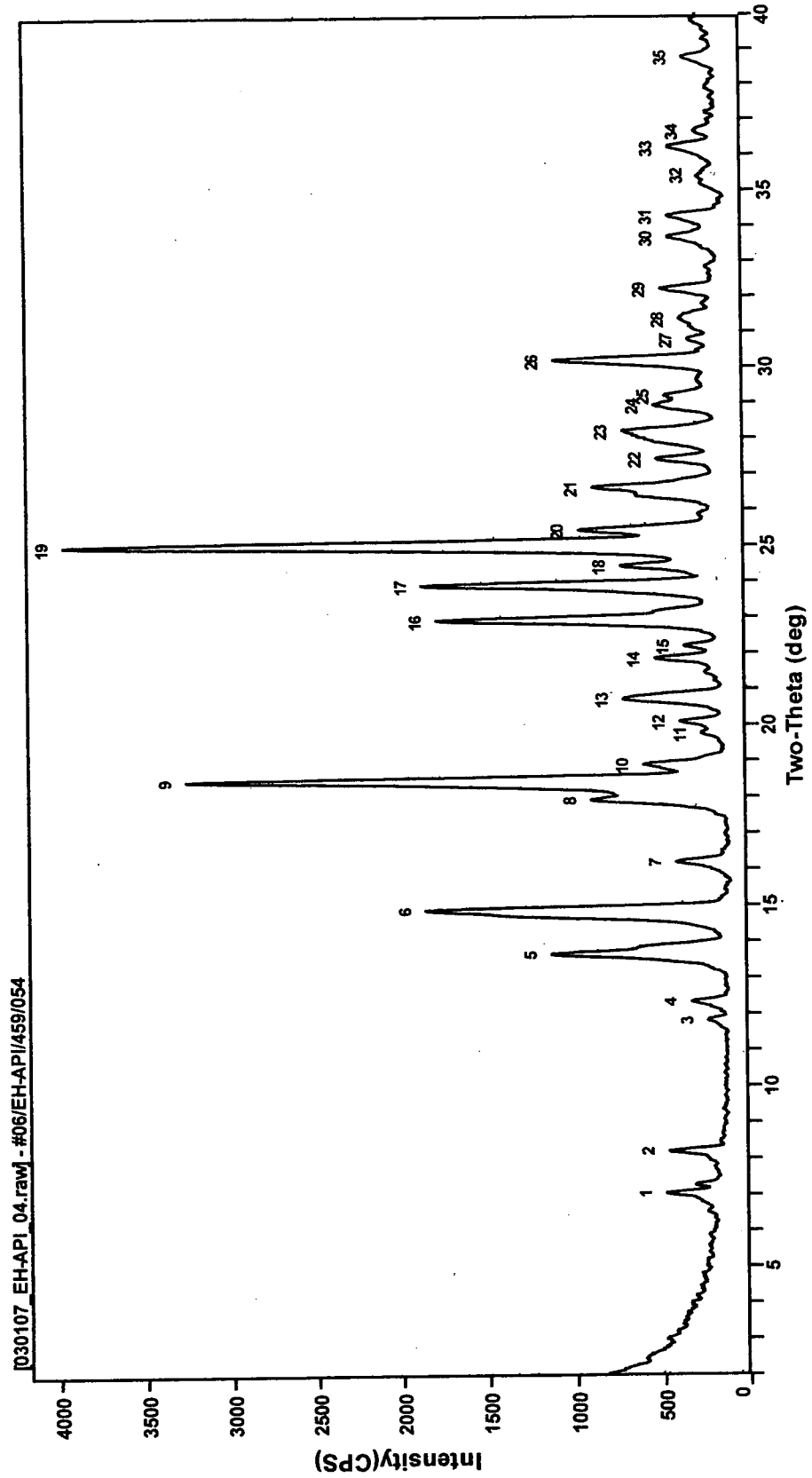

Cadila Healthcare Ltd.
Peak = 226.22 °C
Onset = 219.28 °C
Area = 453.481 mJ
Delta H = 210.9214 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
25
20
15
10
5
0
-2.349
50
60
80
100
120
140
160
180
200
220
240

FIG. 14


[030107_EH-API_04.raw] - #06/EH-API/459/054
Intensity(CPS)
Two-Theta (deg)
0
500
1000
1500
2000
2500
3000
3500
4000
5
10
15
20
25
30
35
40
1
2
3
4
5
6
7
8
9
10
11
12
13
14
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18
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21
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24
25
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31
32
33
34
35

[030107_EH-API_04.raw] - #06/EH-API/459/054 **Peak Search Report**

SCAN: 2.0/40.0/0.02/0.4(sec), Cu(40kV,40mA), I(cps)=3968, 01/03/07 17:45

PEAK: 23-pts/Parabolic Filter, Threshold=3.0, Cutoff=0.1%, BG=3/1.0, Peak-Top=Summit

NOTE: Intensity = CPS, 2T(0)=0.0(deg), Wavelength to Compute d-Spacing = 1.54056Å (Cu/K-alpha1)

#	2-Theta	d(Å)	BG	Height	Height%	Area	Area%	FWHM
1	7.041	12.5440	178	474	11.9	5088	7.1	0.292
2	8.219	10.7488	152	458	11.5	3739	5.2	0.208
3	11.821	7.4800	117	228	5.7	1705	2.4	0.261
4	12.341	7.1665	116	322	8.1	2582	3.6	0.213
5	13.660	6.4770	146	1124	28.3	17319	24.3	0.301
6	14.899	5.9411	129	1852	46.7	29994	42.0	0.296
7	16.200	5.4668	102	404	10.2	4363	6.1	0.246
8	17.920	4.9457	111	891	22.5	16951	23.8	0.369
9	18.480	4.7972	140	3266	82.3	71366	100.0	0.388
10	18.900	4.6915	135	590	14.9	7020	9.8	0.262
11	19.762	4.4888	143	255	6.4	2540	3.6	0.386
12	20.099	4.4142	140	378	9.5	4624	6.5	0.330
13	20.740	4.2792	152	704	17.7	8542	12.0	0.263
14	21.860	4.0625	167	519	13.1	5999	8.4	0.290
15	22.201	4.0009	177	349	8.8	2092	2.9	0.207
16	22.940	3.8736	219	1778	44.8	21676	30.4	0.236
17	23.919	3.7172	298	1865	47.0	19492	27.3	0.211
18	24.440	3.6391	419	713	18.0	1713	2.4	0.099
19	25.040	3.5532	268	3968	100.0	55949	78.4	0.257
20	25.440	3.4983	213	951	24.0	15062	21.1	0.347
21	26.620	3.3458	204	870	21.9	12995	18.2	0.332
22	27.419	3.2501	235	502	12.7	2619	3.7	0.167
23	28.200	3.1619	198	696	17.5	11391	16.0	0.389
24	28.919	3.0848	208	514	13.0	6910	9.7	0.384
25	29.180	3.0578	220	451	11.4	6902	9.7	0.508
26	30.180	2.9588	245	1087	27.4	10979	15.4	0.222
27	30.780	2.9025	230	316	8.0	1474	2.1	0.291
28	31.361	2.8500	223	363	9.1	2738	3.8	0.332
29	32.200	2.7776	193	469	11.8	3525	4.9	0.217
30	33.661	2.6603	146	425	10.7	7313	10.2	0.446
31	34.280	2.6137	135	427	10.8	6049	8.5	0.352
32	35.436	2.5311	161	243	6.1	2280	3.2	0.473
33	36.201	2.4793	177	419	10.6	5110	7.2	0.359
34	36.660	2.4493	166	269	6.8	2380	3.3	0.393
35	38.779	2.3202	170	332	8.4	2416	3.4	0.254

	Peak	Intensity
1	439.77	82.938
2	484.13	95.358
3	540.07	84.201
4	547.78	74.716
5	565.14	86.958
6	576.72	66.693
7	613.36	90.192
8	653.87	86.375
9	721.38	94.84
10	785.03	85.327
11	794.67	88.791
12	808.17	89.903
13	829.39	70.384
14	852.54	79.018
15	860.25	73.96
16	887.26	94.586
17	902.69	94.481
18	920.05	77.49
19	947.05	89.164
20	968.27	92.275
21	1018.41	88.548
22	1028.06	90.811
23	1055.06	84.424
24	1078.21	90.062
25	1109.07	87.991
26	1138	67.359
27	1166.93	76.149
28	1188.15	71.321
29	1230.58	59.372
30	1259.52	78.721
31	1276.88	84.427
32	1317.38	66.812
33	1352.1	72.735
34	1381.03	79.001
35	1433.11	73.438
36	1454.33	74.788
37	1477.47	87.832
38	1514.12	55.053

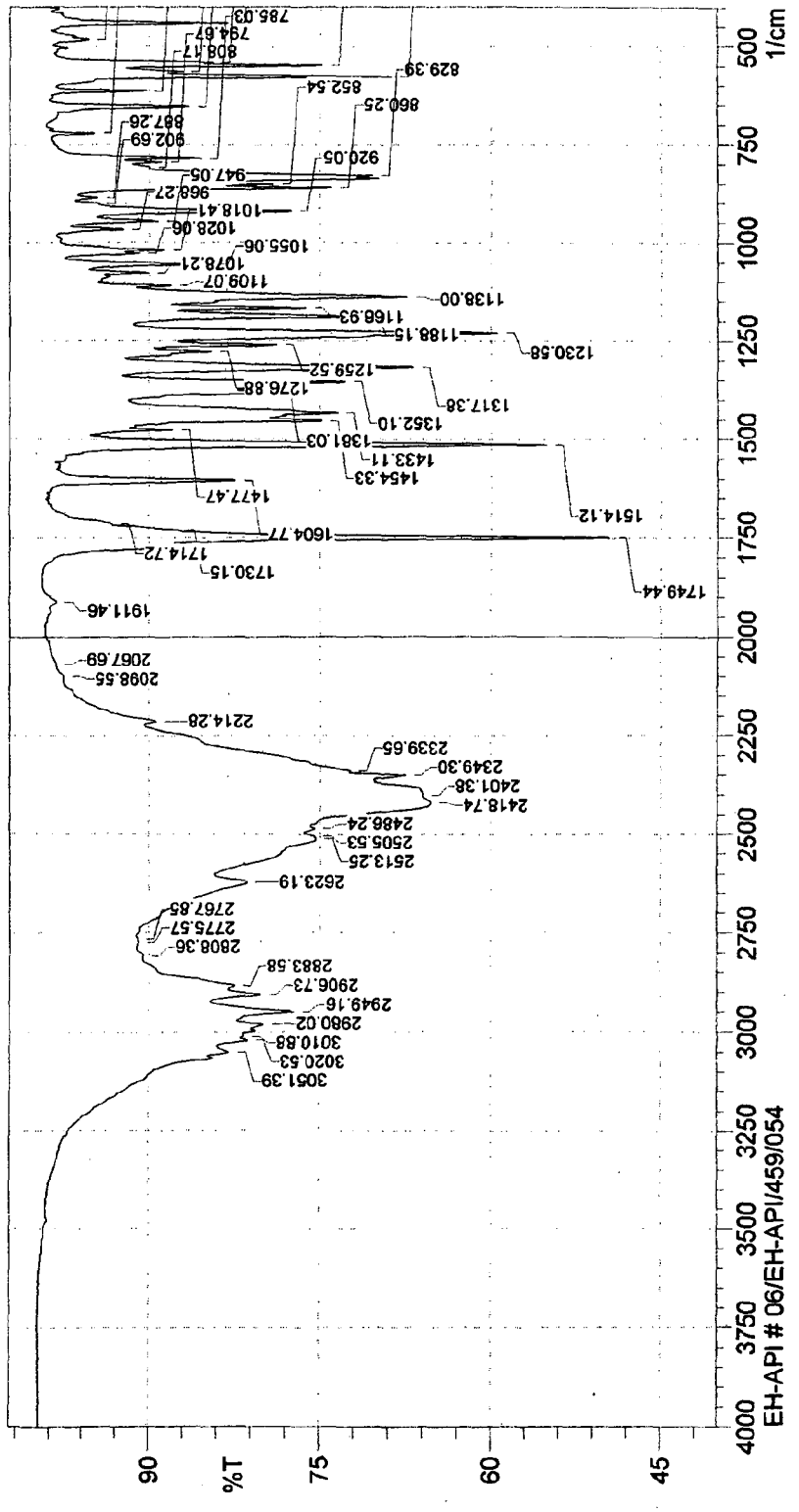

FIG. 15

39	1604.77	82.328
40	1714.72	93.251
41	1730.15	87.202
42	1749.44	49.493
43	1911.46	98.308
44	2067.69	98.342
45	2098.55	97.633
46	2214.28	89.341
47	2339.65	72.297
48	2349.3	67.529
49	2401.38	65.963
50	2418.74	65.295
51	2486.24	75.367
52	2505.53	75.405
53	2513.25	75.277
54	2623.19	81.338
55	2767.85	90.946
56	2775.57	90.909
57	2808.36	90.437
58	2883.58	82.397
59	2906.73	80.134
60	2949.16	77.234
61	2980.02	79.865
62	3010.88	81.606
63	3020.53	81.279
64	3051.39	82.856