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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF SUBSTANTIALLY PURE TELMISARTAN

(57) **Abstract:** The present invention relates to an improved process for the preparation of substantially pure Telmisartan in polymorphic form A.

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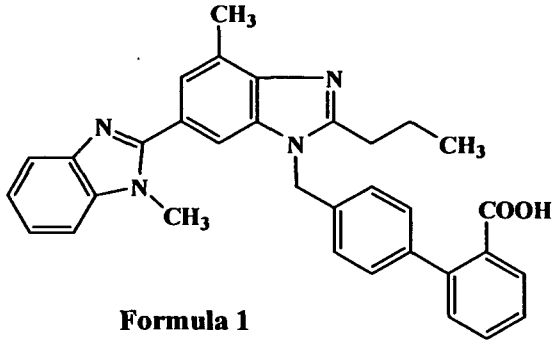
An improved process for the preparation of substantially pure Telmisartan

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of substantially pure Telmisartan in polymorphic form A.

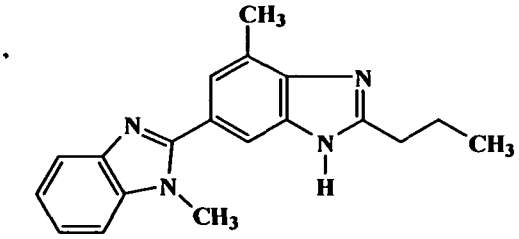
BACKGROUND OF THE INVENTION

Telmisartan is chemically named as 4'-[(1,4'-Dimethyl-2 l-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl][1,1'-biphenyl]-2-carboxylic acid; or 4'-[[4-methyl-6-(1-methyl-2-benzimidazolyO^-propyl-i-benzimidazolyllmethyll^-biphenylcarboxylic acid.



Formula 1

The key raw material used to prepare Telmisartan is Bltyl, chemically named as 1,7'-dimethyl-2'-propyl-2,5'-bi-1H-benzimidazole, also known by other names. i.e 2-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazole; 4-Methyl-6-(1-methyl benzimidazol-2-yl)-2-propylbenzimidazole, and the structure shown as below:



BIM

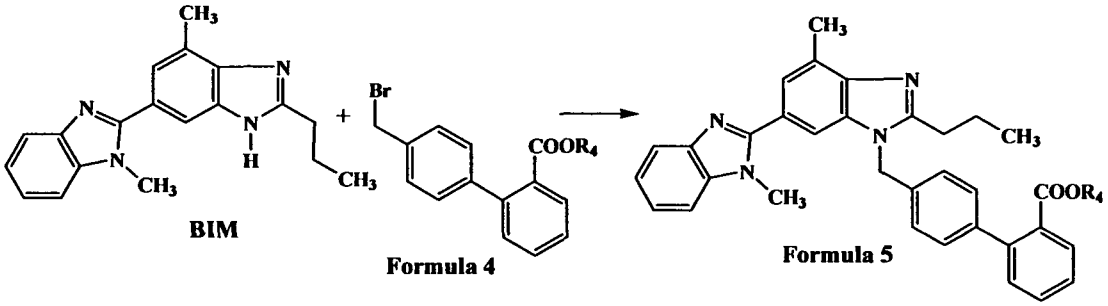
WO2006136916 describes substantially pure micronized particles of Telmisartan or a pharmaceutically acceptable salt, ester or derivative. The "substantially pure" is further defined as *"Telmisartan or pharmaceutically acceptable salt, ester or derivative thereof having a purity of greater than or equal to about 98%, preferably a purity of greater than or equal to about 99% and more preferably a purity of greater than or equal to about 99.5%.*° The substantially pure Telmisartan or a pharmaceutically acceptable salt, ester or derivative has an effective average particle size of less than about 300 microns.

A Journal of www.IP.com (2005), 5(7B), 4 - describes a process for purification of 4'-(2-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl)biphenyl-2-carboxylic acid (Telmisartan). The pure compound was isolated by filtration under reduced pressure.

US20060276525 claims Telmisartan form A having HPLC purity ≥ 99.5 %. It further provides a process for preparing Telmisartan form A by crystallization from a polar organic

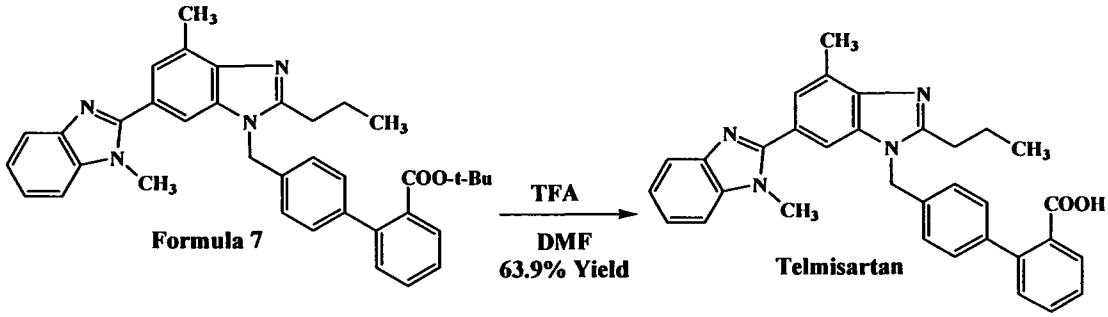
solvent selected from the group consisting of dimethyl sulfoxide, DMF, N.N-dimethyl acetamide, N-methyl 2-pyrrolidone, water and mixtures thereof. The process provides Telmisartan with a limit of DMSO at a level of < 1000 ppm. The process uses high boiling solvent in the last step for getting required purity, and which is also an extra purification step, which limits its commercial application.

US5591762 (column-37,38) described the general process for the preparation of compound of formula-V



wherein bromine in structure IV is leaving group. There are several other leaving groups such as chlorine, iodine, a substituted sulphonyloxy group, e.g. a methane sulphonyloxy, phenylsulphonyloxy or p-toluenesulphonyloxy group are reported.

US5591762 describes preparation of Telmisartan from Telmisartan tert. butyl ester using trifluoroacetic acid in DMF as a solvent in 63.9 % yield. (Example-9) The resulting product had a melting point of 261-263^{0}C.



The process for the preparation of tert. Butyl ester of Telmisartan is not commercially viable and deprotection involving the use of trifluoro acetic acid is not eco-friendly.

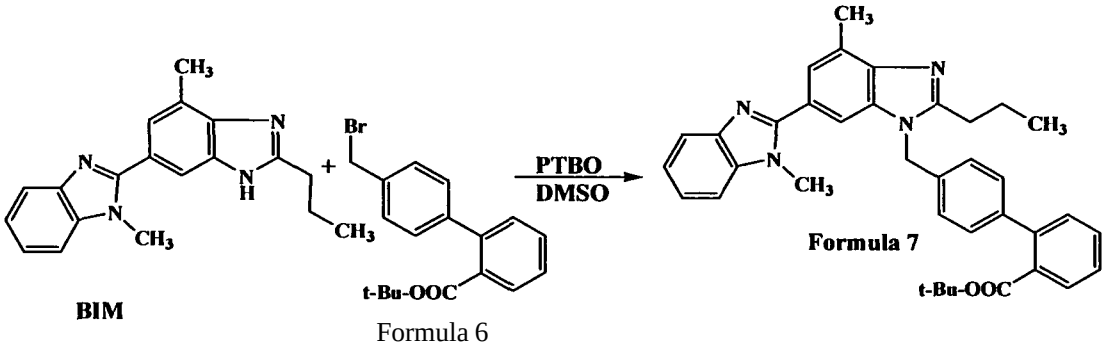
US 6385986 describes polymorphs of 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimid-azol-2-yl) benzimidazol-1-ylmethyl] biphenyl-2-carboxylic acid (Telmisartan) i.e. polymorphic form B, mixtures of the polymorphs. The processes for preparing Telmisartan containing form B and the use for preparing a pharmaceutical composition. US '986 further describes that Telmisartan obtained process of as described in EP502314B1 to give a solid in the form of long needles which is difficult to filter, wash and isolate. It is further characterized that it requires a long time for drying due to the presence of solvent which forms large and hard fragments during the drying process. The fragments on grinding produce a dry powder which exhibits strong tendency to electrostatic charging and is virtually impossible to pour. The polymorphic form B of Telmisartan shows virtually no tendency to electrostatic charging and

easy for suction filtration, centrifuge, washing, drying and is free-flowing even without being ground up.

Therefore, as a consequence of the alleged unsuitability of Telmisartan form A for pharmaceutical use, only a mixture of crystalline Telmisartan form A and form B is claimed in the '986 patent, wherein Telmisartan form A is characterized by having an endothermic maximum at 269±2°C, and Telmisartan form B is characterized by having an endothermic maximum at 183±2°C.

Apparently Telmisartan form A is similar to the original form characterized by its' melting point in the '762 patent. The differences between the DSC value and the measured melting point may be attributed to the different methodologies used-the DSC maxima can be slightly different than the visually observed melting point.

Hence, the prior art teaches a lengthy, complicated and industrially disadvantageous process for obtaining crystalline Telmisartan form A. The need to further reprocess the re-crystallized Telmisartan, as taught in the examples of the '986 patent, shows that the product was not highly-pure and/or that it contained residual solvents, because the solvents used therein have high boiling point. JMC-1993, vol-36, No25 pg-4040-4051 describes preparation of Telmisartan tert. butyl ester using BIM and 2-(4'bromomethyl phenyl) tert. butyl benzoate using pot. Tert butoxide as a base in DMSO as solvent.

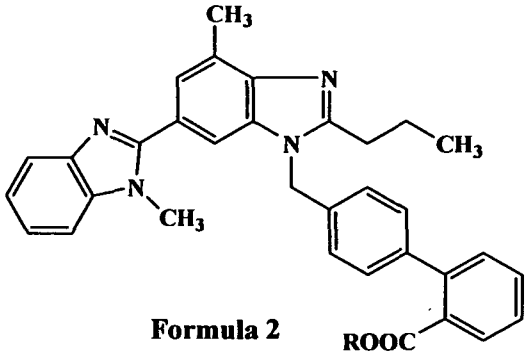


Formula 6

The preparative details for compound of formula-VII on page-4049, coloumn-3, compound 33, paragraph-4; line1-4 reads as follows.

Potassium tert-butoxide was added to the solution of BIM in DMSO at room temperature followed by the addition of the compound of formula VI. Upon stirring for 14 hrs, the mixture was poured into water and extracted with ethyl acetate, the combined extract was dried on $MgSO_4$ and evaporated. Residue was purified by silica gel column chromatography to give compound of formula-VII. The above mentioned process uses chromatographic purification, which is generally cumbersome and time consuming process and also requires solvents in high volume.

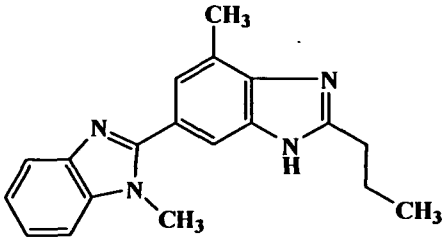
US20060094883 describes a process for the preparing Telmisartan, wherein Telmisartan alkyl ester - a



Formula 2

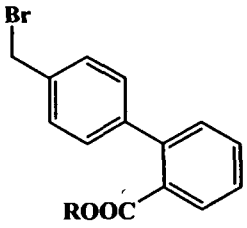
compound of formula-ll is prepared , comprising the steps of :

(a) combining i.y-dimethyl^'-propyl-IH.S'H-p.S [1]] bibenzimidazole (referred to as BIM) of formula III,



Formula 3

with 4'-bromomethyl-biphenyl-2-carboxylic acid alkyl ester (referred to as BMBP alkyl ester) of formula IV_1

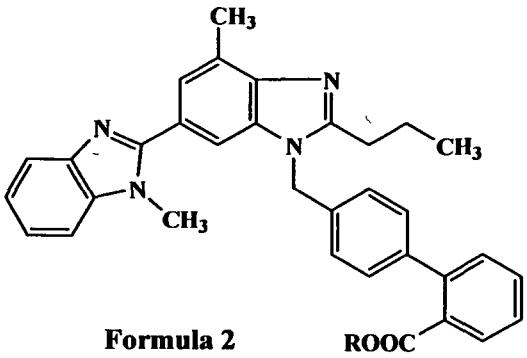


Formula 4

an inorganic base and a low boiling point organic solvent, to obtain a mixture;

(b) heating the mixture obtained in step (a) to a temperature of about 55°C. to about 120^0C ;

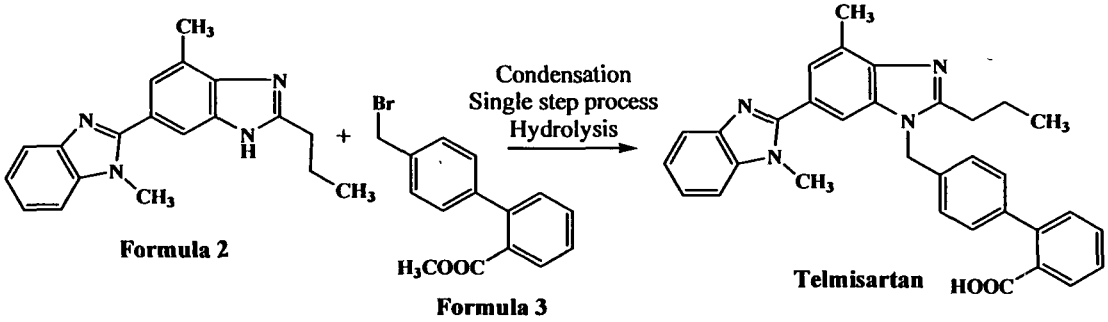
(c) maintaining the mixture obtained in step (b) for about 1 hour to about 8 hours, to obtain Telmisartan alkyl ester of formula II; and



Formula 2

(d) recovering Telmisartan alkyl ester of formula II, wherein, R is a straight or branched chain C_1-C_4 alkyl.

WO2005108375 describes process for the preparation of Telmisartan, characterized in that 1H-Benzimidazole-2-n-propyl-4-methyl-6-(1 '-methyl benzimidazole- 2'yl) of formula (II) and methyl-4- (bromo methyl)biphenyl 2-carboxylate of formula (III) are subjected to **condensation and hydrolysis in a single step**



Formula 2 Formula 3 Telmisartan

WO 2007/010558 describes a method for the preparation of Telmisartan involving Telmisartan dihydrochloride which comprises,

i) condensing 4-Methyl-2-n-propyl-IH- benzimidazole-6-carboxylic acid with N-Methyl-O-phenylene diamine dihydrochloride to yields 4-methyl-6 (1 -methyl benzimidazol-2-yl)-2-n-propyl IH- benzimidazole,

ii) treating 4- methyl-6-(l -methyl benzimidazol-2-yl)-2-n-propyl-IH-benzimidazole with 4*- (bromomethyl)-2-biphenyl-2-carboxylate in presence of a base in an organic solvent and isolating the ester as acid addition salt,

iii) converting ester acid addition salt to Telmisartan dihydrochloride and

iv) converting Telmisartan dihydrochloride to Telmisartan.

CN1344712 describes method comprising reaction of 4-methyl-6-(1-methyl-2(1H)-benzimidazolyl)-1H-benzimidazole with 4'-bromomethyl-biphenyl-2-carboxylic acid alkyl ester [wherein alkyl is methyl or ethyl] in solvent i.e. DMF, DMSO, THF, dioxane, chloroform, dichloroethane, etc. in the presence of base [such as Na alcoholate, triethylamine, tributylamine, tripropylamine, KOH, NaOH, CsOH, $Ba(OH)_2$ etc.] as acid capturer at 20-100^{0}C for 8-10 hrs, and then hydrolyzing with acid (such as H_2SO_4, HCl, HBr, HOAc, etc) at room temp. to reflux temp. or with base in Ci_{-5} alc.-water at 20-160^{0}C for 1-10 hour.

WO 2006/125592 describes a new process for the preparation of saltans 2-butyl-3-[[2"-[1-(triphenylmethyl)-i *H*- tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4] non-1-en-4-one is disclosed, which proceeds via novel intermediate, 4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]phenylboronic acid (Formula (H)) or its analogs. Compound (II) reacts with 5-(2-bromophenyl)-1-(triphenylmethyl)-1H-tetrazole **(III)** in the presence of catalyst, using conditions of Suzuki reaction, to give trityl irbesartan (I), whereas analogs to compound (II) may give candesartan, valsartan, Telmisartan, losartan and olmesartan.

WO 2006/050509 describes the amorphous form of Telmisartan sodium and the preparation thereof. Also provided are the Telmisartan sodium polymorph crystal Forms 0 to **XIII** and XV to XX and preparations thereof. Also provided are pharmaceutical composition of amorphous and polymorphic forms of Telmisartan sodium or mixtures thereof, and methods of treatment of a mammal in need thereof.

WO 2006/044754 describes a process for preparing Telmisartan and intermediates formed in the process.

WO 2004/087676 describes a novel method for the production of Telmisartan by reacting 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazol with a compound of general formula $(IV)_1$ in which Z is a leaving group, wherein the compound 2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1'"-methylbenzimidazol-2'"-yl)benzimidazol-1"-ylmethyl]biphenyl is obtained, and subsequently conducting hydrolysis of the nitrile to acid function.

WO2000/043370 describes polymorphs of 4'-[2-n-propyl-4-methyl-6(1-methyl benzimidazol -2-yl) benzimidazol -1-ylmethyl] biphenyl-2-carboxylic acid (INN: Telmisartan), and in particular the polymorphous form B of formula (I), characterized by an endothermic peak at 183 ± 2°C during thermal analysis by differential scanning calorimetry. The invention also relates to mixtures of said polymorphs, methods for producing Telmisartan containing form B and to the use thereof in the preparation of a medicament.

The prior art processes described above provide Telmisartan with lower purity, hence it is a long felt need of the industry to give a still better process which results in Telmisartan of substantial high purity.

SUMMARY OF THE INVENTION

The object of the invention is to give a process for the preparation Telmisartan of substantial high purity (≥ 99.8 %). Another object of the invention is to give a process for preparing Telmisartan which results in Telmisartan wherein all individual impurities are present below 0.1 %.

Yet another object of the invention is to give a novel process for the preparation of form A of Telmisartan.

Yet another object of the invention to is to give an efficient and rugged process for preparing Telmisartan ethyl ester having purity >99.5 % from about 84-85 % pure Ethyl-4-(bromomethyl) biphenyl-2-carboxylate , thus avoiding purificatory losses.

Yet another object of the invention is to avoid chromatographic purification in all steps of synthesis. Yet another object of the invention is to avoid an extra purification step of Telmisartan and also to avoid high boiling solvent in the last step of getting API.

Yet another object of the invention is to give an improved preparation of preparation of substantially pure 4'methyl biphenyl2-carboxylic acid having HPLC purity >99.9 % without involving additional purification.

Ye another object of present invention is to give a cost effective and industrially scalable process for the preparation of Telmisartan.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1: The X-ray powder diagram of crystalline form of substantially pure Telmisartan ethyl ester

Fig. 2: The Differential Scanning Calorimetry of crystalline form of substantially pure Telmisartan ethyl ester

Fig. 3: The IR-spectroscopic of crystalline form of substantially pure Telmisartan ethyl ester.

Fig. 4: The X-ray powder diagram of crystalline form of substantially pure Telmisartan

Fig. 5: The Differential Scanning Calorimetry of crystalline form of substantially pure Telmisartan

Fig. 6: The IR-spectroscopic of crystalline form of substantially pure Telmisartan

Fig. 7: HPLC chromatographic purity of 4"-Methyl biphenyl-2-carboxylic acid

Fig. 8: HPLC chromatographic purity of Telmisartan ethyl ester

Fig. 9: HPLC chromatographic purity of Telmisartan

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of "substantially pure Telmisartan". The present invention provides Telmisartan in polymorphic form A which is suitable for pharmaceutical use, and process for its preparation.

In accordance with the present invention, Telmisartan is prepared in steps comprising:

[a] converting 2-(4'-methylphenyl) benzonitrile to 2-(4'-methylphenyl)benzoic acid in steps comprising :

(i) reacting 4'-Methyl 2-cyano biphenyl in ethylene glycol, water using a base at elevated temperature for a time sufficient till 2-cyano-4'-methyl biphenyl was ≤ 0.1% diluting with water, adjusting pH to ~2 to 3,

(ii) separating 4'-methyl biphenyl 2-carboxylic acid from reaction mixture followed by washing with water and drying to give substantially pure 4'-methyl biphenyl 2-carboxylic acid [HPLC purity >99.9 %],

[b] converting 2-(4'-methylphenyl)benzoic acid to corresponding ethyl ester,

[c] converting Ethyl - 4'-methyl biphenyl-2-carboxylate to Ethyl - 4-(bromomethyl) biphenyl-2-carboxylate as an oil having purity 84-85 %,

[d] reacting Ethyl - 4-(bromomethyl) biphenyl-2-carboxylate [of purity 84-85 %] with 1,7'-dimethyl-2'-propyl-2,5'-bi-1H-benzimidazole [BIM] using a base in solvent(s) to give Ethyl-4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)- benzimidazol-1-yl]-methyl] biphenyl carboxylate , which is quenched in water followed by extraction using water immiscible organic solvent, followed by layer separation, distillation of organic phase to give residue, dissolving residue in organic solvent at about 65° C , adding an anti-solvent at 55^{0}C , crystallizing at about 10^{0}C followed by filtration and drying to give substantially pure[having purity > 99.5 %]Ethyl-4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)- benzimidazol-1-yl]-methyl] biphenyl carboxylate,

[e] converting Ethyl-4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)- benzimidazol-1-yl]-methyl] biphenyl carboxylate to 4'-[[2-n-propyl-4methyl-6-(1-methylbenzimidazol-2-yl)- benzimidazol-1-yl]-methyl] biphenyl carboxylic acid [Telmisartan], using aqueous acid at about 90-100^{0}C temperature for about 5-10 hours , cooling to 25-30 ^{0}C followed by adding dichloromethane and water, basifying up to pH~10 using aqueous alkali, separating layers , adding fresh dichloromethane and adjusting pH 3.0 to 3.5 using organic acid preferably acetic acid, separating organic phase, followed by charcoal treatment, filtration , concentrating dichloromethane followed by adding acetone and separating Telmisartan , washing and drying to give substantially pure.

The "substantially pure Telmisartan ethyl ester and/or Telmisartan is having HPLC purity ≥ 99.5%. The substantially pure is meant by HPLC purity having ≥ 99.8 % and having all individual impurities below 0.1 %.

"Substantially pure 4'methyl biphenyl 2-carboxylic acid", means 4'methyl biphenyl 2-carboxylic acid having HPLC purity >99.9 % .Further the said compound is obtained without involving any additional purification.

Detailed stepwise process with optional variables and parameters are described as follows:

A step 1 is as described above and step 2 can be carried out as per prior art processes.

The product of step 3, Ethyl - 4-(bromomethyl) biphenyl-2-carboxylate is obtained as an oil which has purity of about 84-85 %. This product is prepared as per known process. There is no need to purify this product as per our process, as the total course of our further processing takes care of contaminating co-produced impurities.

In step-[4], the base used for N-alkylation is selected from hydride bases such as sodium or potassium hydride; C_1-C_4 alkoxides of sodium and potassium; hydroxides of alkali metals, carbonates of alkali metals; the preferred base being potassium *tert.* butoxide.

The solvent used for this step is selected from di alkyl amides such as DMF, DMA, NMP.1,3- dimethyl imidazolidine 2-one, 1,3- dimethyl hexahydropyrimidine 2-one more preferred being DMF.

The solvent used for extracting Telmisartan ethyl ester is selected from water immiscible ester group of solvents such as ethyl, propyl or butyl acetate preferably ethyl acetate; water immiscible ketonic solvent such as MIBK.

The reaction is carried out from 0 to 80^{0}C preferably at 5 to 50^{0}C more preferably at 15-20^{0}C

The anti-solvent which is used with solvent is hexane or heptane , preferably hexane.

The product Telmisartan ethyl ester is preferably crystallized from a [7:3] mixture of Ethyl acetate : Hexane.

The purity of Telmisartan ethyl ester is >99.5 %

In step [5] i.e. converting Telmisartan ethyl ester to Telmisartan:

The acid used is hydrochloric acid or sulfuric acid, preferably hydrochloric acid.

The solvent selected for hydrolysis is water.

The reaction is carried out at 50 to 100^{0}C preferably 80 to 100^{0}C more preferably at 95±2°C.

The reaction is carried out for about 4 to 10 hours preferably for about 8 hours.

The reaction is then cooled to room temperature and dichloromethane is then added.

The reaction mixture is then diluted with water and pH is adjusted to 9 to 10 and the layers are separated. Fresh dichloromethane is added to aqueous layer and pH is adjusted to 3.0 to 3.5 using acetic acid. Layers are separated. The aqueous layer is re extracted with dichloromethane and again layers are separated. The organic layers are combined and washed with water and dried over anhydrous sodium sulfate. Dichloromethane containing compound is charcoal treated and filtered thru hyflo and 80 to 85 % vol of dichloromethane distilled.

The reaction mixture is cooled to 8 to 12°C and stirred at same temperature for 1 hour. Acetone is added and the reaction mixture is stirred for 2 hours at 8 to 12°C. The product is separated by filtration / centrifugation and washed with acetone and dried.

The product Telmisartan has an HPLC purity >99.8 % and does not require any further purification. IR_1 DSC and XRD are consistent with form A of Telmisartan

HPLC chromatogram, DSC graph and IR spectra are attached with this document to support and authenticate our invention.

The present invention is further illustrated by following non-limiting examples,

Example-1 Preparation of 4'-Methyl biphenyl-2-carboxylic acid from 2-Cyano-4'-Methyl biphenyl

250.0 gm of 2-cyano-4'-Methyl biphenyl is mixed with 1250 ml ethylene glycol and added 255 gm of potassium hydroxide along with 12.5 ml of water. The reaction mixture is heated to 155-160^{0}C and stirred for about 12-13 hrs. The reaction mixture was cooled to 80^{0}C, 1L water was added. The reaction mixture was cooled to 20-25 ^{0}C. pH of the reaction mixture is adjusted to ~2 to 3 using cone. HCI. The reaction mixture was stirred for one hour

at 20-25^{u}C and filtered followed washing with water. The product was air dried at temp. 60 - 7O^{0}C. Dry wt. = 265 gm, Purity 99.94% (moisture content <0.25%)

Example-2 Preparation of Ethyl - 4'-methyl biphenyl-2-carboxylate from 4'- methyl biphenyl-2-carboxylic acid

103.96 gm of sulfuric acid was added with stirring into the reaction mixture of 150.0 gm of 4'- methyl biphenyl-2-carboxylic acid and 300 ml of ethyl alcohol at 25 to 30^{0}C. The temperature was maintained at -60 ^{0}C. The reaction mixture was stirred till about 18-20 hours. Ethanol was distilled to give an oily mass and then cooled to 25-30^{0}C. 300 ml of ethyl acetate and 400 ml water were added and stirred for about 15 minutes. The layer was allow to separate and organic layer was washed with 2x400 ml water, and 3 X 500 ml of aq. sodium bicarbonate solution followed by again washing with 2 x 400 ml water and 400 ml sodium chloride brine. The organic layer was dried over anhy. sodium sulphate, filtered and washed with fresh ethyl acetate. Ethyl acetate layer was distilled completely to give an oily mass. 150 ml of Hexane was added to the oily mass and traces of ethyl acetate was removed by distilling hexane under vacuum, to give Ethyl - 4'-methyl biphenyl-2-carboxylate as an oil 157.0 gm, Purity : 99.45 % (By HPLC) .

Example-3 Preparation of Ethyl - 4-(bromomethyl) biphenyl-2-carboxylate from Ethyl-4'-methyl biphenyl-2-carboxylate

150 gm of ethyl - 4'-methyl biphenyl-2-carboxylate was added to 750 ml dichloromethane and stirred at 25-30^{0}C for 10-15 minutes. 98.2 gm of Di bromodimethyl hydantoin [DDH] was added and the reaction mixture was stirred at 25-30^{0}C for 10-15 minutes. 15 gm of AIBN was added in to reaction mixture and heated to 40^{0}C with stirring for about 5 hours. The reaction mixture was cooled to 25-35^{0}C and 300 ml of water was added with stirring for 20-30 min. The layer was allowed to separate and organic layer was washed with 2x 300 ml water and 300 ml of 5% aq. sodium bisulphate solution. The mixture was again washed with 2 X 300 ml water and 300 ml NaCI brine. The organic layer was separated and dried over 50 gm anhydrous sodium sulphate, filtered and washed with fresh DCM, DCM was distilled under vacuum at 30-35^{0}C and 150 ml of Hexane was added. The Hexane was distilled under vacuum at 50-55^{0}CThe reaction mixture was allowed to cooled to 25-35^{0}C. 300 ml of Hexane was added, the reaction mixture was cooled to about 5^{0}C and stirred for 30 minutes. The solid was separated by filtration, washed with 75 ml of chilled hexane. The oily mass and n-Hexane layer transferred to a distillation flask from which hexane was recovered by vac. distillation. 177 gm oily product obtained with 85 .17% purity. (By HPLC).

Example-4 Preparation of Ethyl-4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-**yl)-benzimidazol-1-yl]-methyl] biphenyl carboxylate [Telmisartan ethyl ester]**

90 gm of BIM in 500 ml DMF was added at about 15^{0}C followed by addition of 41.4 gm potassium tertiary butoxide and stirred for about 15-20 minutes at 15-20^{0}C. 138.7 gm of Ethyl-4-(bromomethyl) biphenyl-2-carboxylate in 250 ml DMF was added slowly over 45 to 60 minutes maintaining temperature 15-20^{0}C.The reaction mixture was stirred for about 30 minutes. 1500 ml of Ethyl acetate and 2000 ml water were added to the reaction mixture at 20-30^{0}C and the layer was allowed to separate. Aqueous layer was extracted with 1000 ml of ethyl acetate. The combined organic layer was washed with water [3 X 1000 ml]. The organic layer was dried over anhydrous sodium sulfate and dried ethyl acetate solution was filtered. The ethyl acetate was removed by distillation under vacuum at 50-55^{0}C. 500 ml of fresh ethyl acetate was added to the residue to make **a** solution at 60-65^{0}C. The reaction mixture was cooled to 50-55^{0}C. 200 ml of hexane was added and stirred for 30 minutes. The reaction mixture was cooled to 10^{0}C and further stirred for about 1 hour at 5-10° C.

The material was filtered and washed with a mixture of ethyl acetate and 200 ml hexane (7:3 v/vl) at 8-12^{0}C. The wet cake was dissolved in 600 ml ethyl acetate at 60-65^{0}C and cooled to ~50 ^{0}C. 240 ml of hexane was added and mixture was cooled with stirring to 10^{0}C and then stirred for about one hour. The material was filtered and washed with a mixture of 120 ml Ethyl acetate and hexane (7:3 v/v) at 8-12° C. The material was suction dried and used as such. 108.2 gm of product is obtained with 99.6 % purity (By HPLC).

Example-5 : Preparation of 4'-[[2-n-propyl-4methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl] biphenyl carboxylic acid [Telmisartan]

90 gm of ethyl-4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl] biphenyl carboxylate was stirred with 810 ml aq. HCl [32-35 % wt/ vol] at 95±2°C for about 8-10 hours. The reaction mixture was cooled to 25-30^{0}C. 180 ml of Dichloromethane and 1350 ml of water were added, pH of the reaction mixture was adjusted to -9.0 to 10.0 using 20 % aq. NaOH. The reaction mixture was stirred at 30-35^{0}C for about 30 minutes and the layer was allowed to separate. 1800 ml of MDC was added to aqueous phase at 25-30^{0}C. pH of the solution was adjusted to ~3 to 3.5 with acetic acid. The mixture was stirred for about 20 minutes and the layer was allow to separate. The aqueous layer was extracted with 900 ml DCM and organic layer was separated and washed with 2 X 900 ml water. The organic phase was dried over anhy. Sodium sulfate and charcoalized followed by distillation to remove about 80-85 % of DCM at 40-42^{0}C. The reaction mixture was slowly cooled to 8^{0}C and stirred at 8-12^{0}C for about 1Hr. 2700 ml of acetone (10^{0}C was slowly added and temperature is maintained at 8-12°C.The reaction mixture was stirred for 2 hours with slow RPM. The mixture was filtered at 8-12^{0}C and washed with 2x180 ml of acetone. The product was obtained through suction drying for 30-45 minutes, and under vacuum at 85-90^{0}C. 70.0 gm of Telmisartan is obtained having purity of 99.84%.

We claim,

1. A process of preparing Telmisartan having HPLC purity > 99.8 % comprising steps:
   (a) reacting Ethyl-4-(bromomethyl)-biphenyl-2-carboxylate with 1,7'-dimethyl-2'-propyl-2,5'-bi-1H-benzimidazole in organic solvent using a base to form Telmisartan ethyl ester,
   (b) separating Telmisartan ethyl ester followed by extracting using organic solvent,
   (c) addition of an anti- solvent to give Telmisartan ethyl ester,
   (d) reacting Telmisartan ethyl ester with acid in aqueous medium at acidic pH,
   (e) separating organic layer, extracting aqueous phase with dichloromethane,
   (f) treating with charcoal followed by concentrating reaction mixture,
   (g) adding acetone and separating the product from reaction mixture followed by drying to give Telmisartan.
2. A process of preparing [Telmisartan ethyl ester having HPLC purity > 99.5 % comprising steps:
   (a) reacting Ethyl-4-(bromomethyl) biphenyl-2-carboxylate with 1,7'-dimethyl-2'-propyl-2,5'-bi-1H-benzimidazole in organic solvent using a base to form Telmisartan ethyl ester,
   (b) separating Telmisartan ethyl ester followed by extracting using organic solvent,
   (c) adding an anti solvent to give Telmisartan ethyl ester.
3. The process according to claims 1 or 2 wherein the purity of Ethyl - 4-(brompmethyl) biphenyl-2-carboxylate, used in step (a) is having purity of 80% or more.
4. The process according to claims 1 or 2 wherein the base used in step (a) is selected from hydride bases such as sodium or potassium hydride; hydroxides of alkali metals, carbonates of alkali metals; C_1-C_4 sodium alkoxides, C_1-C_4 potassium alkoxides or like.
5. The process according to claims 1 or 2 wherein the solvent used in step (a) is selected from di alkyl amides such as DMF, DMA, NMP.1,3- dimethyl imidazolidine 2-one , 1,3-dimethyl hexahydropyrimidine 2-one or like.
6. The process according to claims 1 or 2 wherein the organic solvent in step-(b) is selected from water immiscible ester group of solvents or water immiscible ketonic solvent.
7. The process according to claim 6 wherein water immiscible ester group of solvents is selected from ethyl acetate, propyl acetate or butyl acetate.
8 The process according to claims 1 or 2 wherein the anti-solvent in step-(c) is selected from hexane or heptane.
9. Substantially pure Telmisartan having HPLC purity over 99.8 % and all individual impurities below 0.1 %.
10. Substantially pure Telmisartan having HPLC purity over 99.8 % and having all individual impurities below 0.1 % which is further characterized as per figures given for DSC, IR and XRD as form-A of Telmisartan.

* * *

TLM01 / 06 / 07 / 18-B

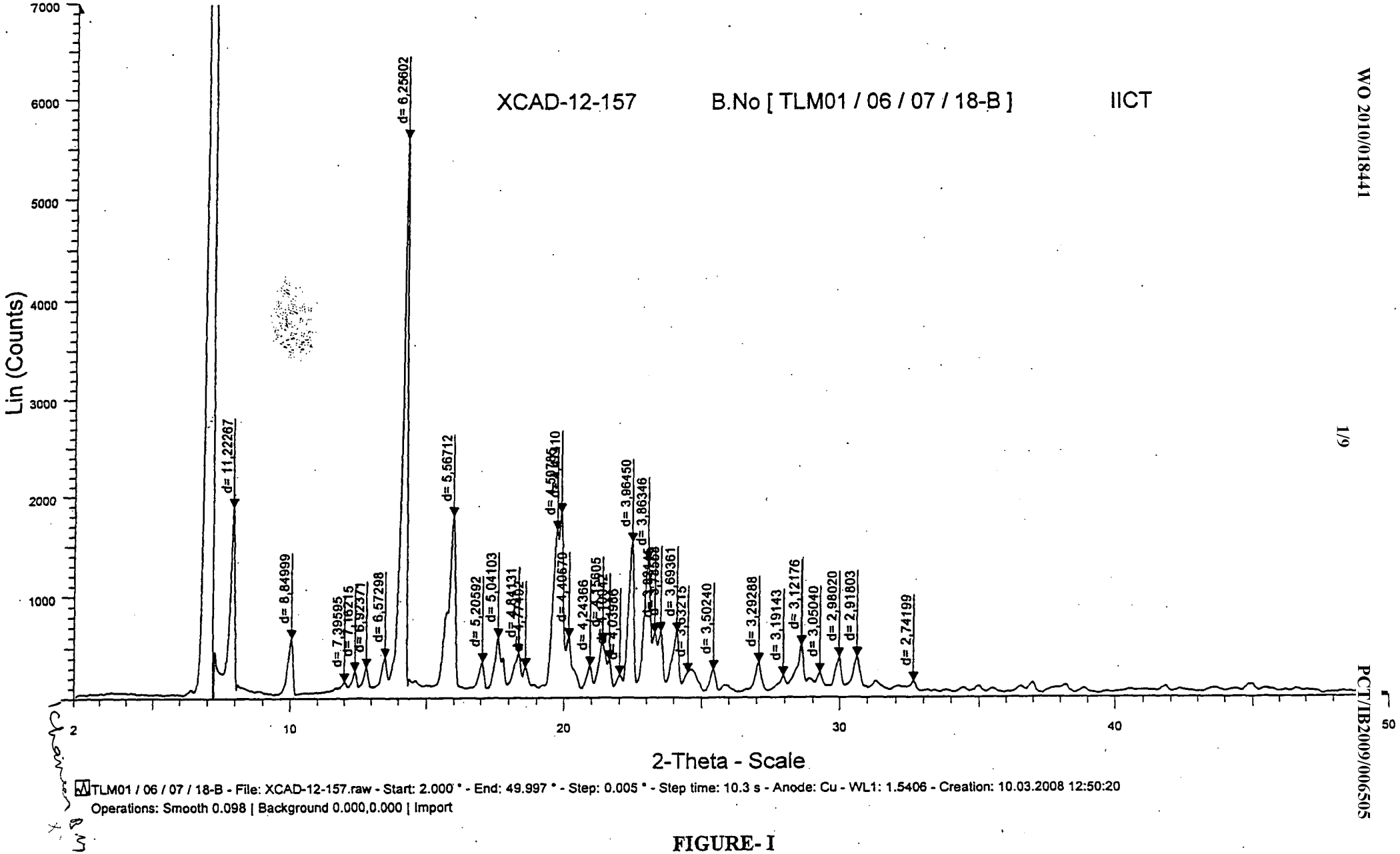


FIGURE- I

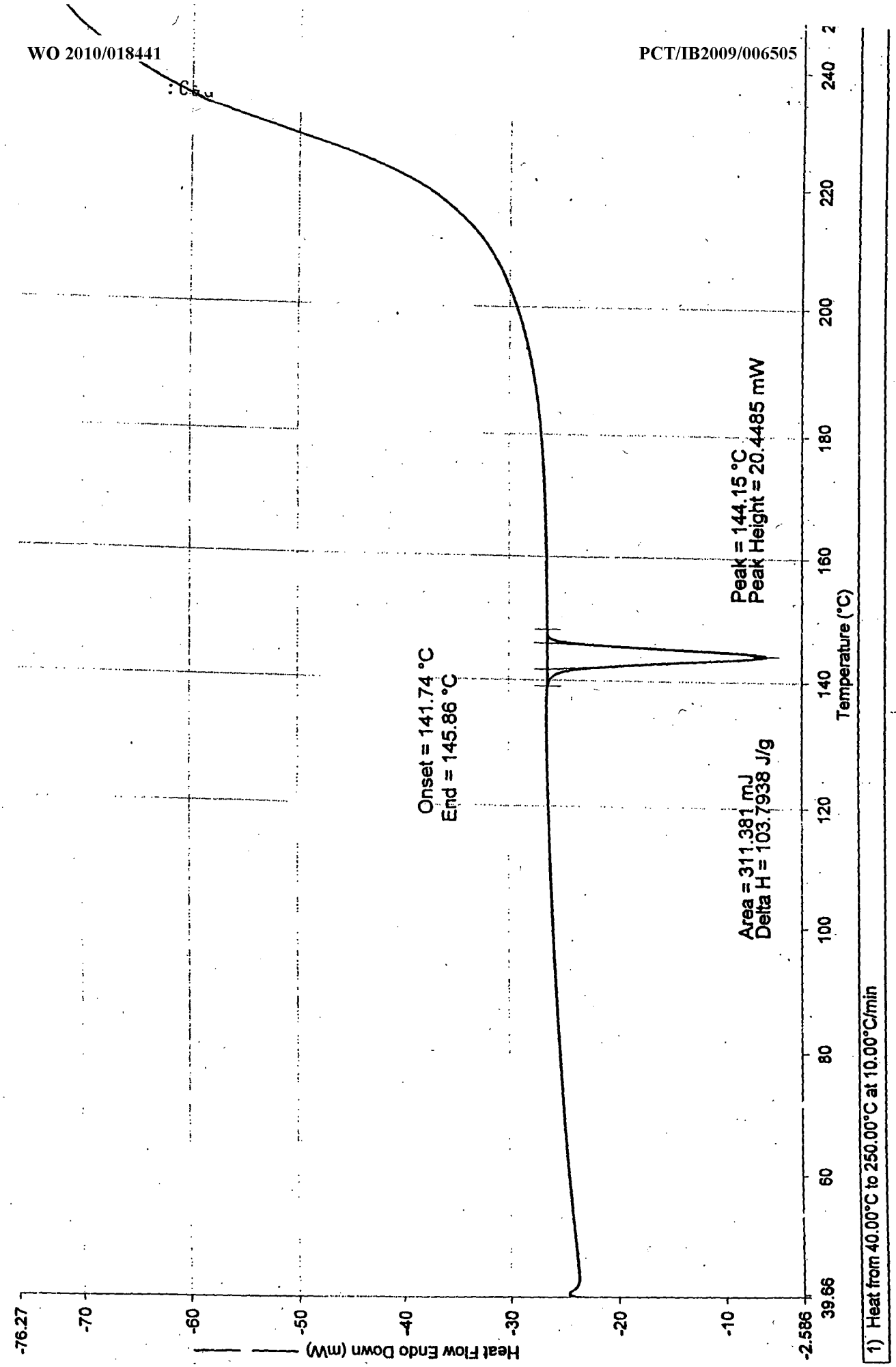

Heat Flow Endo Down (mW)
-76.27
-70
-60
-50
-40
-30
-20
-10
-2.586
Temperature (°C)
39.66
60
80
100
120
140
160
180
200
220
240
Onset = 141.74 °C
End = 145.86 °C
Peak = 144.15 °C
Peak Height = 20.4485 mW
Area = 311.381 mJ
Delta H = 103.7938 J/g
1) Heat from 40.00°C to 250.00°C at 10.00°C/min

FIGURE- II

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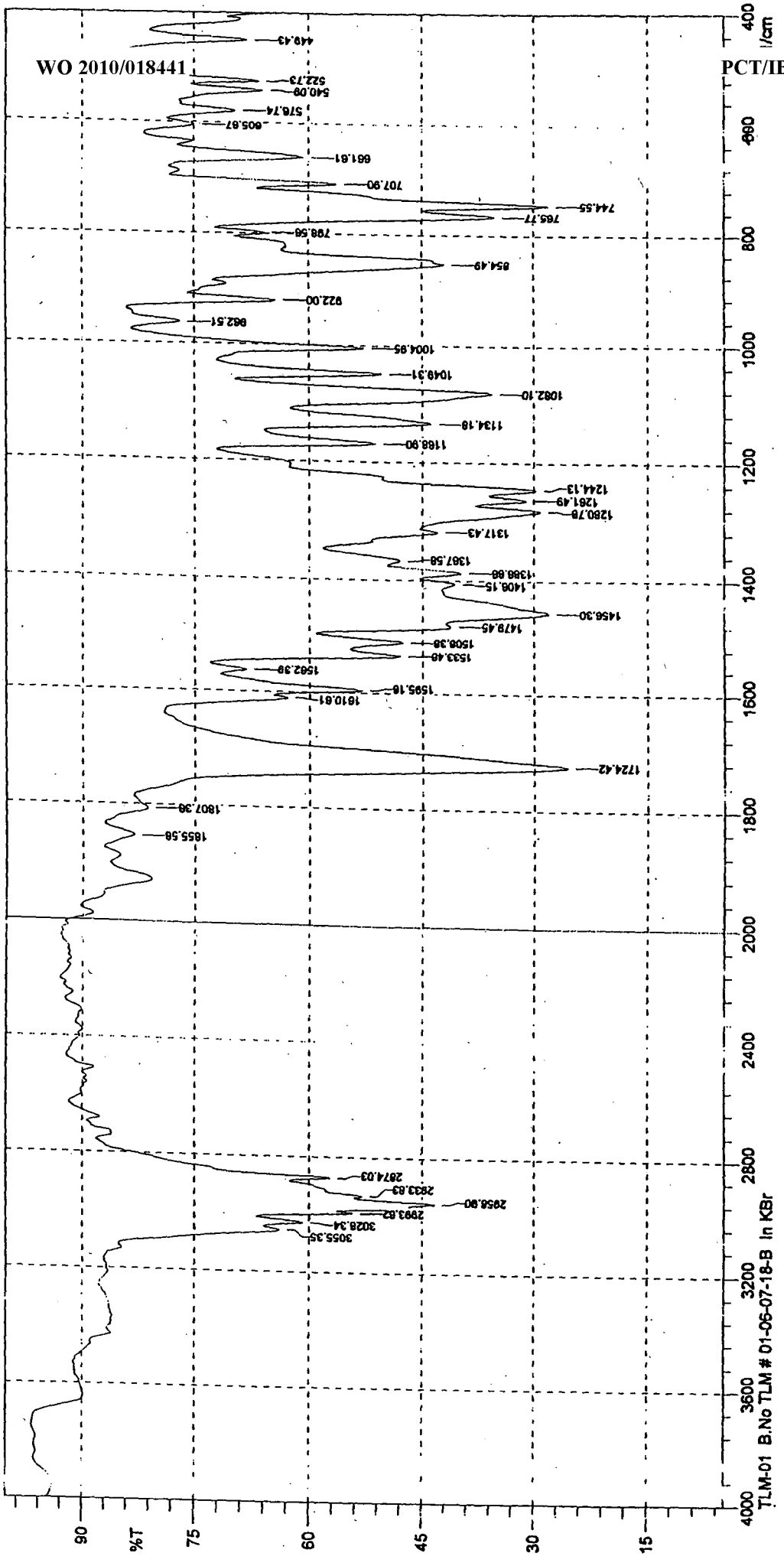
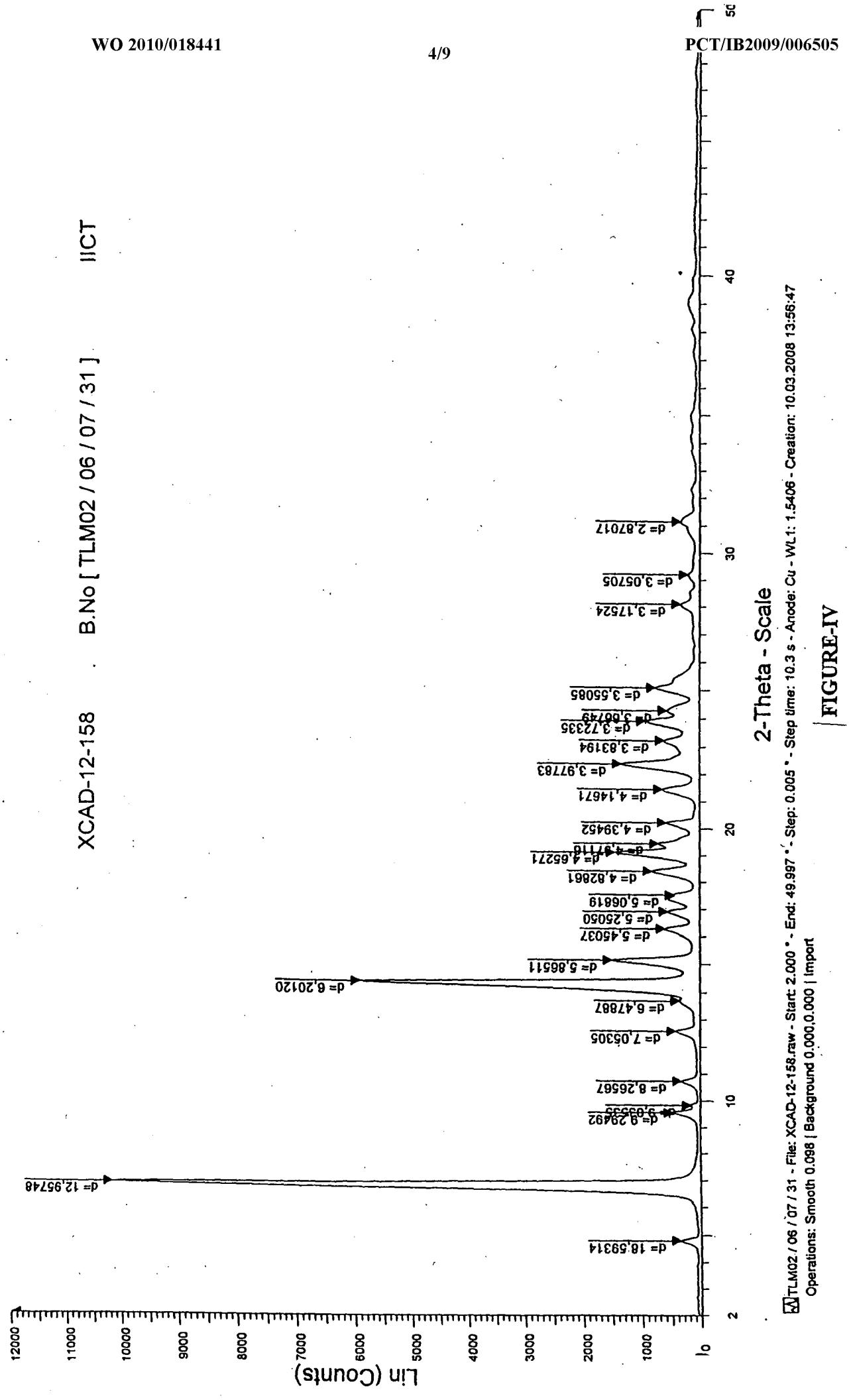


Comment:

TLM-01 B.No TLM # 01-06-07-18-B In KBr

FIGURE- III


TLM02 / 06 / 07 / 31
XCAD-12-158
B.No [TLM02 / 06 / 07 / 31]
IICT
Lin (Counts)
2-Theta - Scale
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d= 18,59314
d= 9,29492
d= 8,26567
d= 7,05305
d= 6,47887
d= 6,20120
d= 5,86511
d= 5,45037
d= 5,25050
d= 5,06819
d= 4,82061
d= 4,65271
d= 4,39452
d= 4,14671
d= 3,97783
d= 3,83194
d= 3,72335
d= 3,65085
d= 3,17524
d= 3,05705
d= 2,87017
TLM02 / 06 / 07 / 31 - File: XCAD-12-158.raw - Start: 2.000 ° - End: 49.997 ° - Step: 0.005 ° - Step time: 10.3 s - Anode: Cu - WL1: 1.5406 - Creation: 10.03.2008 13:56:47
Operations: Smooth 0.098 | Background 0.000,0.000 | Import

FIGURE-IV

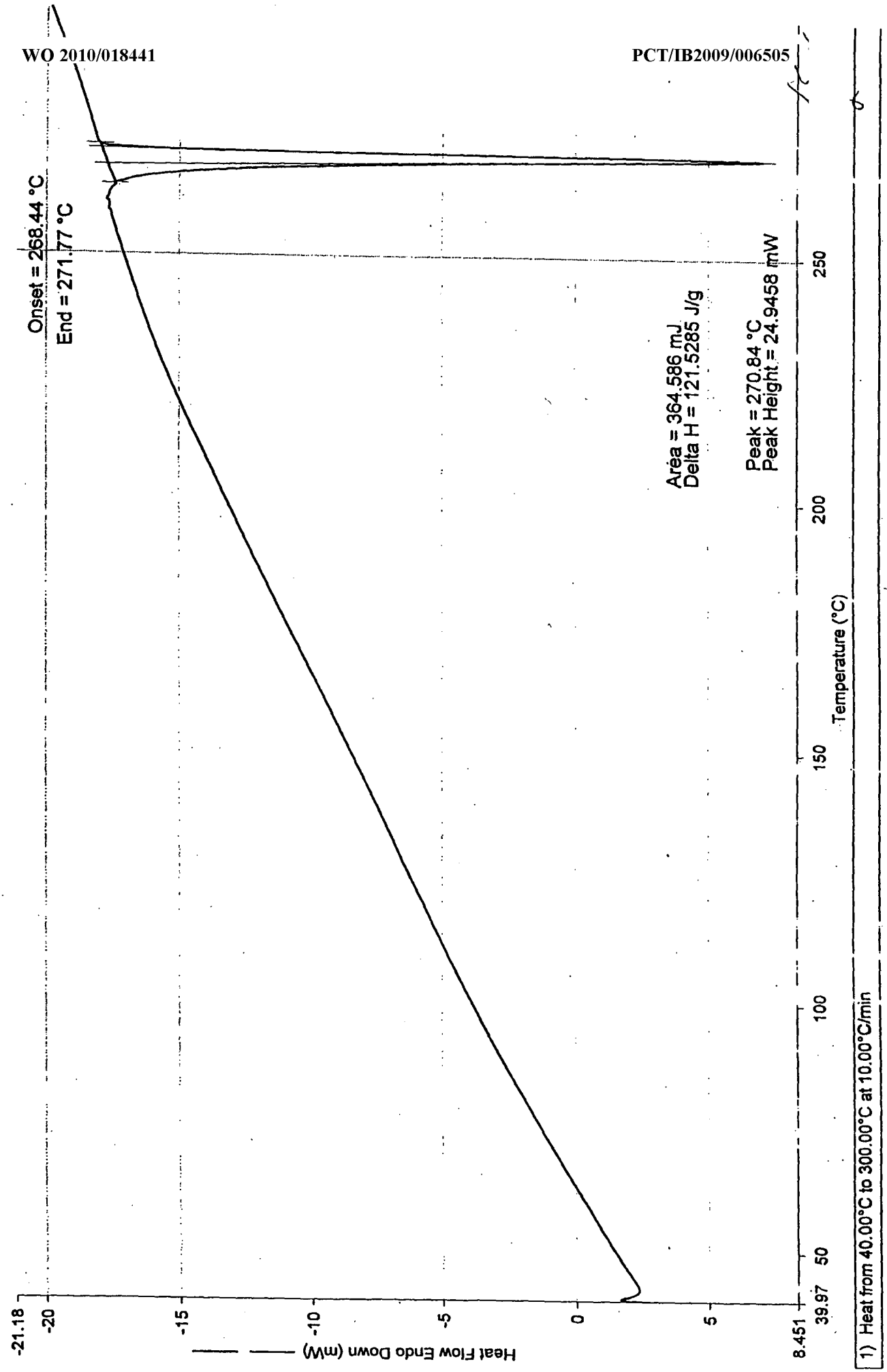
Onset = 268.44 °C
End = 271.77 °C
Area = 364.586 mJ
Delta H = 121.5285 J/g
Peak = 270.84 °C
Peak Height = 24.9458 mW
Heat Flow Endo Down (mW)
Temperature (°C)
-21.18
-20
-15
-10
-5
0
5
8.451
39.97
50
100
150
200
250
1) Heat from 40.00°C to 300.00°C at 10.00°C/min

FIGURE- V

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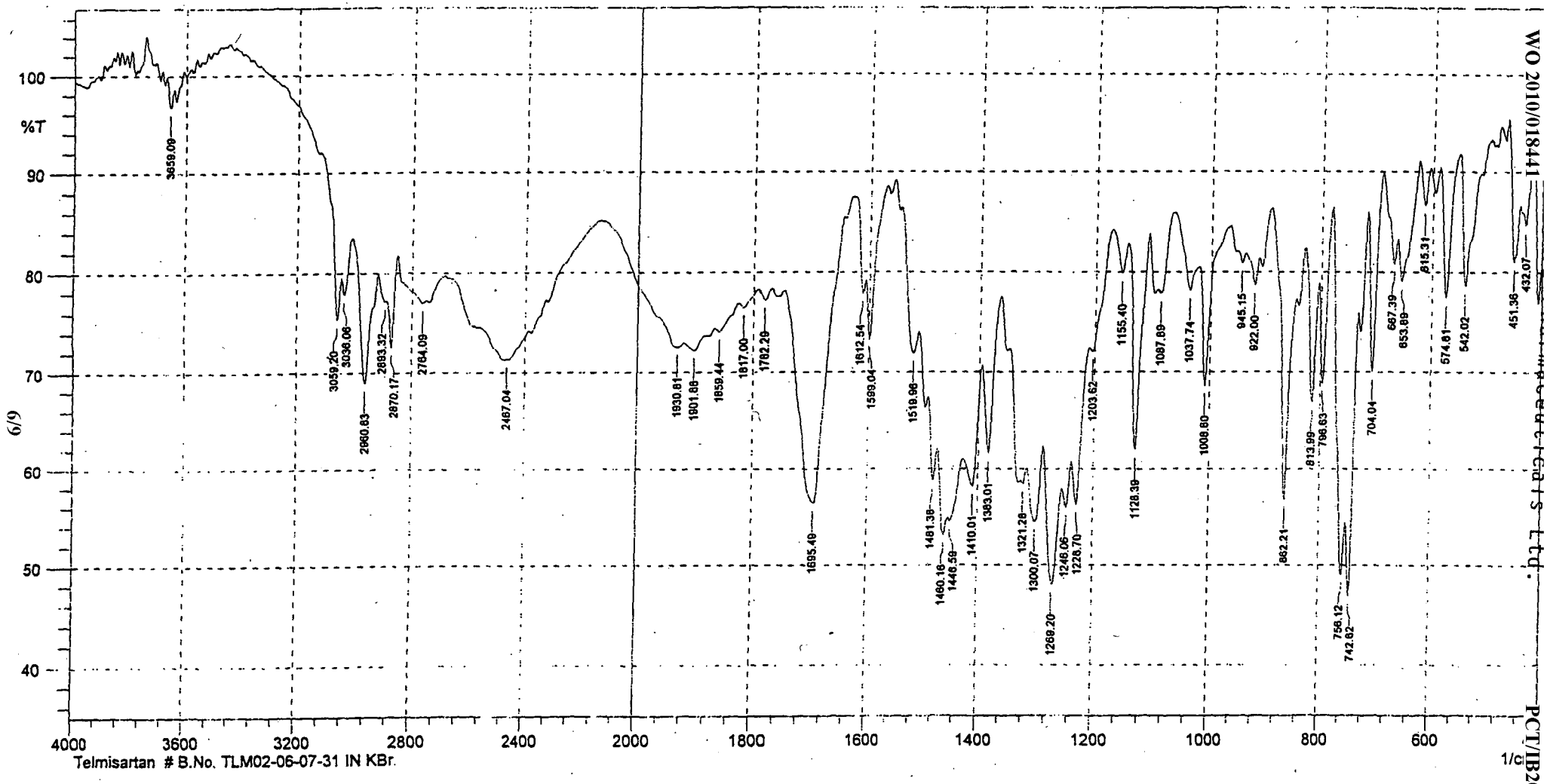
CHEMICAL SBU



Comment:

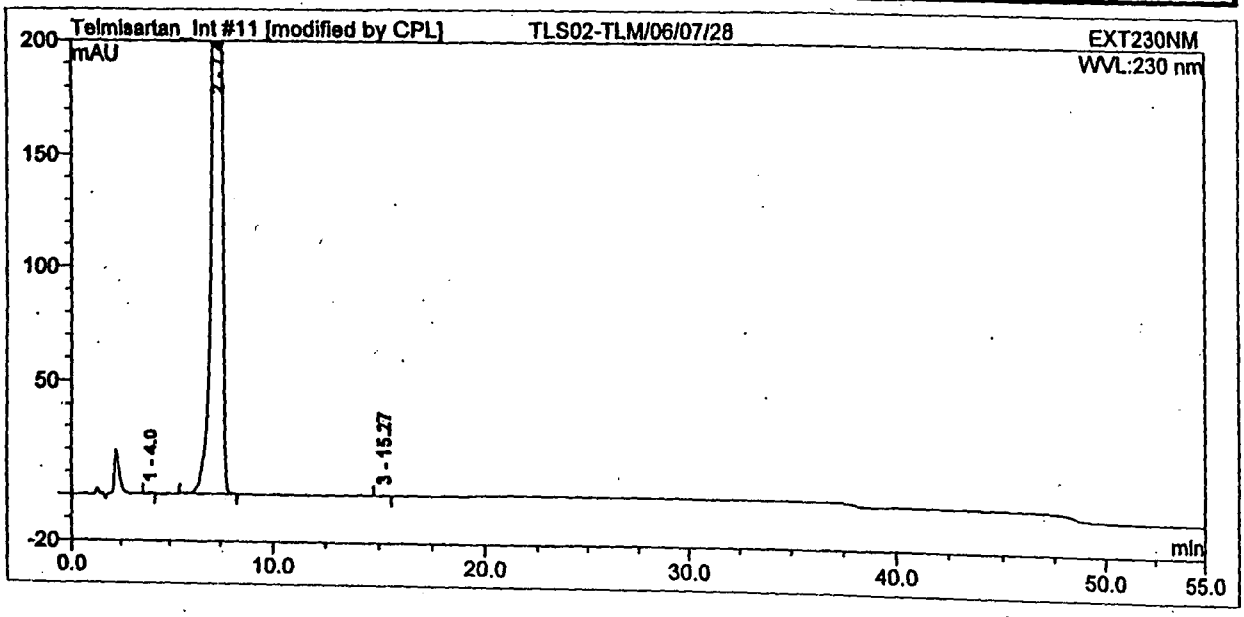
Telmisartan # B.No. TLM02-06-07-31 IN KBr

FIGURE- VI

WO 2010/018441 PCT/IB2009/006505

CADILA PHARMACEUTICALS LTD.

Sample Name:	TLS02-TLM/06/07/28		
Vial Number:	GB7	*Channel:*	EXT230NM
Sample Type:	unknown	*Wavelength:*	230
Control Program:	Telmisartan_TLS-4	*Bandwidth:*	0
Quantif. Method:	TEST	*Run Time (min):*	55.00
Recording Time:	25.12.07 05:17	*Injection Volume:*	10.0

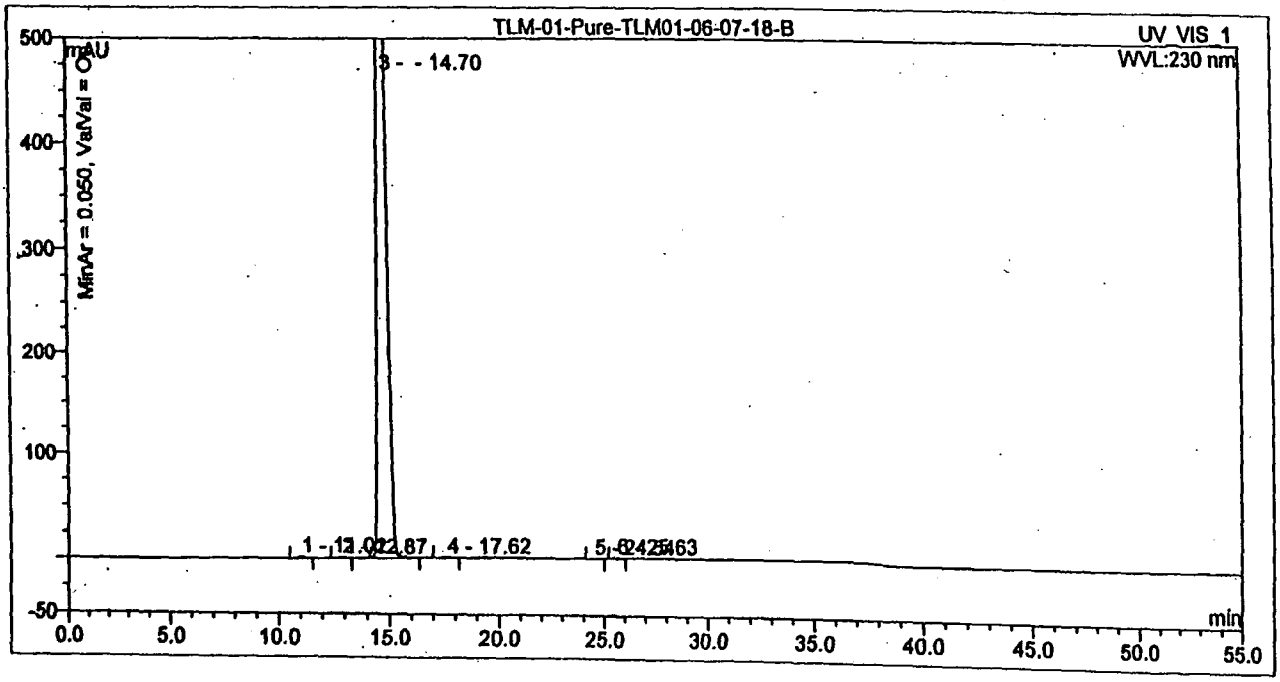


No.	Ret.Time	Peak Name	Height	Area	RRT	Rel.Area
	min		mAU	mAU*min		%
1	4.04	Amide Int	0.576	0.137	n.a.	0.04
2	7.43	TLS-2	917.448	334.826	n.a.	99.94
3	15.27	n.a.	0.193	0.073	n.a.	0.02
Total:						

FIGURE-VII

CADILA PHARMACEUTICALS LTD.

Sample ID	TLM-01-Pure-TLM01-06-07-18-B		
Instrument Name	DIONEX_HPLC-12	**Injection Volume**	10.0
Sequence Name	TELMISARATAN	**Wavelength**	230
Sequence Path	DIONEX_HPLC-12\SEQUENCE\November2007\171107		
Programme Name	Telmisartan	**Vial No.**	RC9
Injection Time	17.11.07 15:23	**Run Time (min)**	55.00
Print Time	24.11.07 11:18	**Method File**	Test

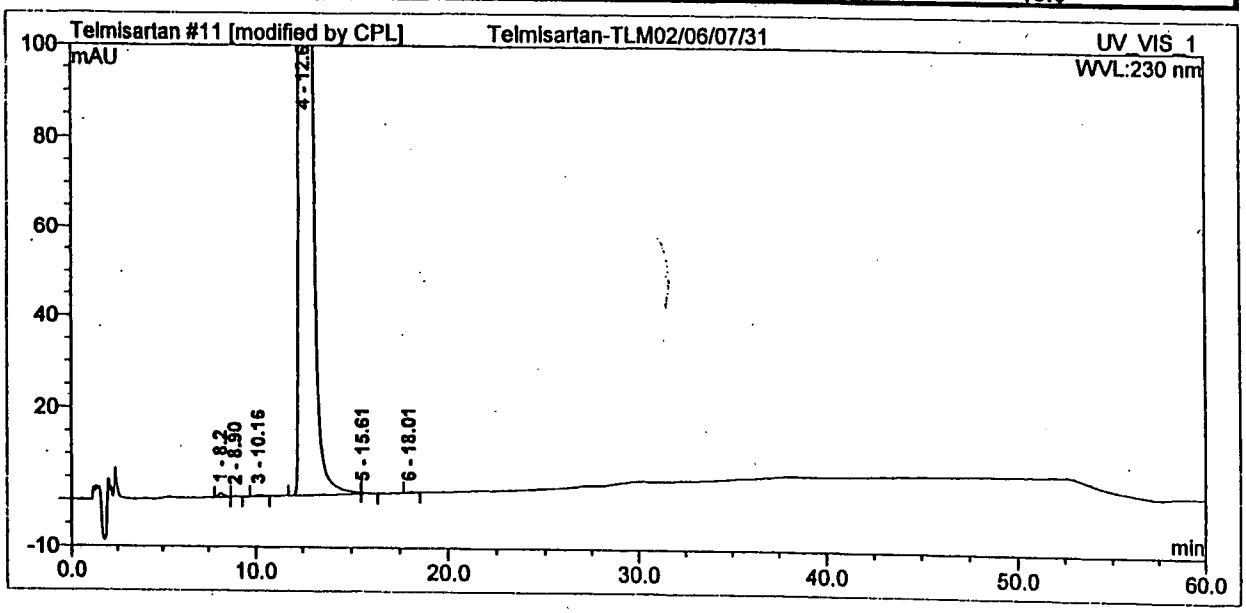


No.	Peak Name	Ret.Time min	Height mAU	Area mAU*min	RRT	Rel.Area %
1	n.a.	11.02	1.568	0.576	n.a.	0.15
2	n.a.	12.87	0.565	0.204	n.a.	0.05
3	TEL-01	14.70	1023.822	381.227	n.a.	99.60
4	n.a.	17.62	0.741	0.373	n.a.	0.10
5	n.a.	24.54	0.201	0.077	n.a.	0.02
6	n.a.	25.63	0.829	0.314	n.a.	0.08
Total:			1027.726	382.770		100.000

FIGURE-VIII

CADILA PHARMACEUTICALS LTD.

Sample Name:	Telmisartan-TLM02/06/07/31		
Vial Number:	GA7	*Channel:*	UV_VIS_1
Sample Type:	unknown	*Wavelength:*	230
Control Program:	Telmisartan_Final	*Bandwidth:*	1
Quantif. Method:	TEST	*Run Time (min):*	60.00
Recording Time:	24.12.07 12:20	*Injection Volume:*	10.0



No.	Ret.Time	Peak Name	Height	Area	RRT	Rel.Area
	min		mAU	mAU*min		%
1	8.15	Imp-B	0.769	0.282	0.65	0.07 x 1.24
2	8.90	n.a.	0.129	0.045	0.71	0.01
3	10.16	n.a.	0.301	0.131	0.81	0.03
4	12.59	Telmisartan	866.212	405.200	1.00	99.84
5	15.61	n.a.	0.255	0.100	1.24	0.02
6	18.01	n.a.	0.175	0.072	1.43	0.02
Total:						

FIGURE-IX