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(71) Applicant *(for all designated States except US)*: **NATCO PHARMA LIMITED** [IN/IN]; Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033, Andhra Pradesh (IN).

(72) Inventors; and

(71) Applicants : **KOMPELLA, Amala** [IN/IN]; Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033, Andhra Pradesh (IN). **ADIBHATLA, Kali satya bhujanga rao** [IN/IN]; Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033 Andhra Pradesh (IN). **BALINA, Veera swamy** [IN/IN]; Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033, Andhra Pradesh (IN). **KASA, Srinivasu** [IN/IN]; Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033 Andhra Pradesh (IN). **NANNAPANENI, Venkaiah chowdary** [IN/IN]; Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033 Andhra Pradesh (IN).

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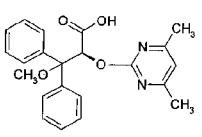
(54) **Title**: A PROCESS FOR THE PREPARATION OF HIGHLY PURE AMBRISENTAN



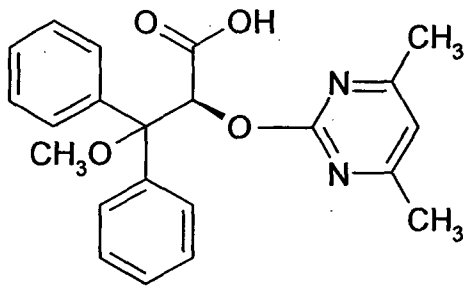
(I)

(57) **Abstract**: The present invention relates to an improved and novel process for the preparation of highly pure (>99.8 %) (+)-2(S)-(4,6-dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid (Ambrisentan) of formula (I).

A PROCESS FOR THE PREPARATION OF HIGHLY PURE AMBRISENTAN

Field of the invention:

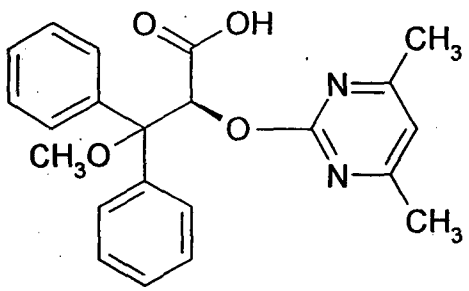
The present invention relates to an improved and novel process for the preparation of highly pure (>99.8%) (+)-2(S)-(4,6-Dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid (Ambrisentan) of formula-I



Formula-I

Back ground of the invention

Ambrisentan which is (+)-2(S)-(4,6-Dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid having the formula – I is approved under the trademark "Letairis" by the US Food and Drug Administration for the treatment of Pulmonary artery hypertension(PAH).

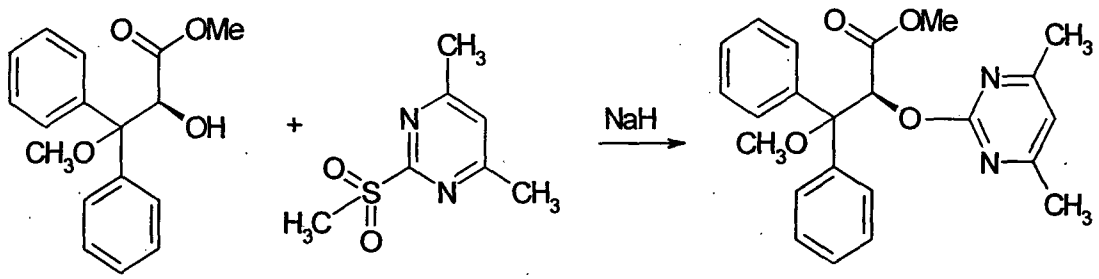


Formula-I

The preparation of (+)-2(S)-(4,6-Dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid(Ambrisentan) having the formula – I is described in WO 9611914; US 5932730(1996, 1998 both to BASF) and J. Med. Chem., 1996, vol.39, No.11, p.no. 2123-2128

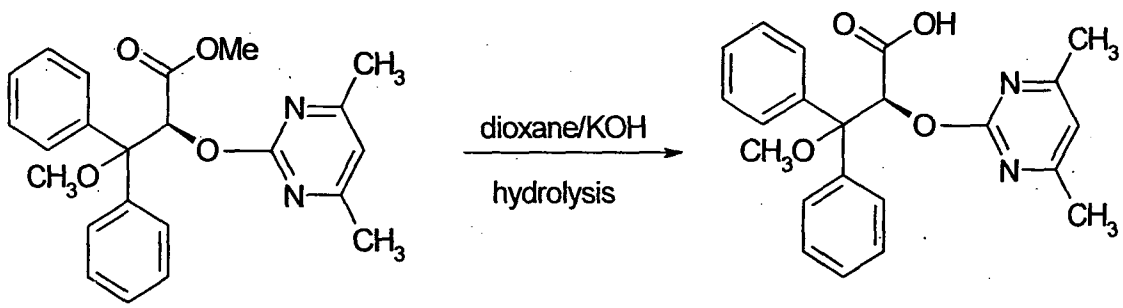
In WO 9611914 and in its equivalent US 5932730 the following route is described (Scheme-1) for related molecules. The route shown below is adapted for ambrisentan for our study.

Step-I



(II) (III) (IV)

Step-2



(IV) (I)

In this process methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate (II) is dissolved in DMF and sodium hydride is added. The mixture is stirred for a hour and then 4,6-dimethyl-2-(methylsulfonyl)pyrimidine is added. After stirring at room temperature for 24hours cautious hydrolysis is carried out with water , the pH is adjusted to 5 with acetic acid. , and the solvent is removed under high vacuum. The residue is taken up in ethyl

acetate, washed with water and the solvent is distilled out. The residue is mixed with ether and the resulting precipitate is filtered off.

In step-2 the step-1 product is hydrolyzed in 1N KOH solution in dioxane medium at reflux temperature. After reaction completion the reaction mass is washed with ethyl acetate to remove unreacted ester. The pH of the aqueous layer is adjusted with concd. HCl pH 1-2 and extracted with ethyl acetate. After water washing, ethyl acetate is distilled off and the product was liberated by the addition of ether/hexane mixture.

The above process adds two more steps to the Route of synthesis viz., esterification and hydrolysis

1. racemic 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid resolution followed by esterification
2. Condensation of the ester with 4,6- dimethyl-2-(methylsulfonyl)pyrimidine to yield Ambrisentan ester followed by hydrolysis to give Ambrisentan
3. When this process is repeated in our laboratory the overall realized yield of final product is less than 15%
4. The purity of the final product obtained is only 95%

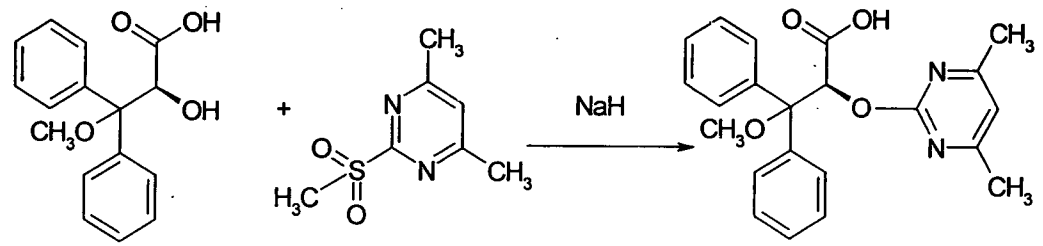
In J. Med. Chem., 1996, vol.39, No.11, p.no. 2123-2128 same chemical route is described using potassium carbonate base in place of sodium hydride at 90°C for step-1.

The overall realized yield of final product is less than 10% with a purity of about 92%

Further the preparation of (+)-2(S)-(4,6-Dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid(Ambrisentan) having the formula – I is described in WO 01/05771(2001 to BASF)

In WO 9611914 the following route is described (Scheme-2) for molecules structurally related to ambrisentan .

Scheme -2 :



S-2-hydroxy-3-methoxy 3,3-diphenyl propionic acid (V)

4,6-dimethyl-2-(methylsulfonyl) pyrimidine (III)

(+)2(S)-(4,6-dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenyl propionic acid (I)

In this process S- 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid(V) is dissolved in DMF is added dropwise to a suspension of sodium hydride in DMF. The mixture is stirred for an hour and then 4,6-dimethyl-2-methylsulfonylpyrimidine in DMF is added. After stirring at room temperature for 24hours it is poured into ice-water , the pH was adjusted to 1 with 2N HCl , and extracted with diethyl ether. The ether phase is extracted with 1N KOH, and the alkaline aqueous phase is readjusted to pH 1 with 2N HCl and extracted with ether. The solvent is stripped off in vacuum. The residue is stirred in diethyl ether overnight, filtered and dried. The solid obtained in this way is chromatographed on silica gel , allowing isolation of the desired product.

In this process mole ratio of S- 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid , 4,6-dimethyl-2-methylsulfonylpyrimidine and sodium hydride is 1:1.3:3.0 .

By following this method in our laboratory, our observations are :

- the reaction is not going to completion.
- Chemical purity of only 95% is realized
- chiral purity of the product is less than 95%
- column chromatography is necessary to isolate the pure product

There is therefore an unfulfilled need to provide an industrially feasible process for the preparation Ambrisentan devoid of above shortcomings.

The objective of this invention is to prepare highly pure Ambrisentan through acid addition salts (1:1)of Ambrisentan. When the base is liberated from the acid addition salts, Ambrisentan of higher purity results.

It is surprisingly found by the inventors that when the less pure Ambrisentan is reacted with

S(-)4-nitro phenyl ethylamine or S(-)-phenyl ethyl amine it selectively forms the corresponding acid addition salt, leaving behind the other related substances and impurities which are otherwise difficult to remove by the conventional methods. The S(-)4-nitrophenyl ethyl amine or S(-)-phenyl ethyl amine salt of Ambrisentan is further converted to highly pure Ambrisentan which in turn is converted into other pharmaceutically acceptable salts with higher purity.

Summary of the invention

The main object of the present invention is to provide an improved process for the preparation of highly pure (>99.8%) Ambrisentan

Another object of the invention is to provide a process for preparation of salts of Ambrisentan with S(-)4-nitro phenyl ethyl amine or S(-)-phenyl ethyl amine in high purity(>99.8%).

Accordingly in the present invention highly pure Ambrisentan is prepared by

i. Preparing Ambrisentan by the condensation of S(+)2-Hydroxy-3-methoxy-3,3-diphenylpropionic acid with 2-(methylsulfonyl)-4,6-dimethylpyrimidine in presence of sodium hydride base in polar aprotic solvents like DMF or THF

ii. Treating Ambrisentan with S(-)4-nitro phenyl ethylamine or S(-)-phenyl ethyl amine yielding the corresponding addition salt of Ambrisentan

iii. Acidifying Ambrisentan S(-)4-nitro phenyl ethylamine or S(-)-phenyl ethyl amine salt and isolating Ambrisentan of purity 99.9%

Detailed description of the invention :

Thus in accordance with the present invention preparation of Ambrisentan comprises of the following steps

i. preparing Ambrisentan by the condensation of S(+)2-Hydroxy-3-methoxy-3,3-diphenylpropionic acid with 2-(methylsulfonyl)-4,6-dimethylpyrimidine in presence of sodium hydride base in DMF/THF medium in 1:1.4:4.3 mole ratio

ii. Treating Ambrisentan with S(-)4-nitro phenyl ethylamine or S(-)-phenyl ethyl amine yielding corresponding addition salts of Ambrisentan

iii. Acidifying Ambrisentan S(-)4-nitrophenylethylamine or S(-)-phenyl ethyl amine salt and isolating Ambrisentan of purity 99.85%

In a typical embodiment, the present invention provides the following process for the preparation of Ambrisentan

1. S(+) 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (HIP-III) is dissolved in DMF/THF under nitrogen atmosphere at 20-25°C
2. Sodium hydride is added slowly to the reaction mass during 1hour at 25-30°C
3. The mixture is stirred for a hour and then 4,6-dimethyl-2-(methylsulfonyl)pyrimidine in DMF/THF is added drop wise
4. The reaction mass is maintained at 25-30°C for 16-17hours
5. After maintenance it is quenched with methanol and poured into ice-water .
6. aqueous layer pH is adjusted with 1N hydrochloride solution to 2-3 during 30-45 minutes
7. Reaction mass is extracted with Ethyl acetate

8. Ethyl acetate layer is extracted with diluted sodium hydroxide solution
9. Sodium hydroxide layer is acidified with diluted hydrochloric acid
10. reaction mass is maintained under stirring for 2hours at RT
11. The product is Filtered and dried to yield Ambrisentan

Further reacting the resultant base of Ambrisentan with S-(-)4-nitro phenylethylamine or S(-)-phenyl ethyl amine as follows :

i. Ambrisentan is dissolved in acetone and S-(-)4-nitro phenylethylamine/ S-(-)-phenyl ethyl amine is added directly or as a solution in acetone
ii. reaction mass temperature is raised to reflux
iii. reaction mass is maintained at reflux temperature for 1hours
iv. reaction mass is brought to room temperature and maintained at the same temperature for
16 -18 hours
iv. The product after filtration and drying at 60-70 °C afforded pure Ambrisentan as corresponding acid addition salt of S-(-)4-nitro phenyl ethylamine or S(-)- phenyl ethylamine

The prepared Ambrisentan S-(-)4-nitro phenyl ethyl amine /S(-)-phenyl ethyl amine acid addition salts(1:1) are novel and are identified and characterized by chemical analysis, IR, NMR & Mass spectral. Ambrisentan acid addition salts are further converted to Ambrisentan as follows :

i. Ambrisentan S-(-)4-nitro phenyl ethyl amine or S(-)-phenyl ethyl amine addition salt is acidified with diluted hydrochloric acid
ii. The reaction mass is maintained at room temperature for 2-3hours
iii. The product is filtered and washed with purified water

The solid state properties of Ambrisentan thus prepared are illustrated by the following figures :

Fig- 1 – XRPD spectrum of the Ambrisentan prepared by the method disclosed in example -1

Fig-2 – DSC curve of the Ambrisentan prepared by the method disclosed in example-1

Fig-3 – IR spectrum of the Ambrisentan prepared by the method disclosed in example-1

Fig- 4 – XRPD spectrum of the Ambrisentan prepared by the method disclosed in example -2

Fig-5 – DSC curve of the Ambrisentan prepared by the method disclosed in example-2

Fig- 6 – IR spectrum of the Ambrisentan prepared by the method disclosed in example-2

The required S- 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid and 4,6-dimethyl-2-(methylsulfonyl)pyrimidine can be prepared by the prior art processes

The details of the inventions are given in the Examples which are provided for illustration only and therefore the Examples should not be construed to limit the scope of the invention.

EXAMPLES

Example-1 : Process for the preparation highly pure Ambrisentan of the formula -I

Step-1 : Condensation of S(+) 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid and 4,6-dimethyl-2-(-(methylsulfonyl)pyrimidine in DMF medium

Into a 1L round bottomed flask a mixture of DMF(400ml) and S-2-Hydroxy-3-mehoxy-3,3-diphenyl propionic acid(50g) were charged and stirred for 30 minutes. sodium hydride(18.9g) was added slowly for 1hour and reaction mass was maintained at room temperature for one hours. 2-(methylsulfonyl)-4,6-dimethyl pyrimidine(47.8g) was dissolved in DMF(100ml) and added to the reaction mass at room temperature during 45-60 minutes and reaction mass was maintained overnight under stirring. After reaction completion methanol(50ml)l was added slowly to the reaction mass during 30 minutes. Reaction mass was quenched into DM water (5L) and acidified with diluted hydrochloric acid(600ml). Aqueous layer was extracted with ethyl acetate(2x500ml) and combined ethyl acetate layer was extracted with 1N sodium hydroxide solution. Sodium hydroxide layer was separated and acidified with 1N hydrochloride solution . Reaction mass was maintained under stirring for 2hours . The product of the formula-I was filtered and washed with purified water. It was dried in oven at 60-65°C

Dry weight : 60g

Purity by HPLC : related : 99.5%

Chiral : 99.5%

Step – II : Preparation of Ambrisentan S(-)4-nitro phenyl ethylamine addition salt(1:1) :

Ambrisentan (60g, purity 99.5%) was dissolved in acetone (900ml) and S-(-)4-nitro phenyl ethyl amine(26.2g) was added to the solution over 30 min . Reaction mass temperature was raised to reflux and maintained for about 1-2hrs. Reaction mass was slowly cooled to room temperature and maintained for about 16-18 hr at the same temperature. The precipitated material was filtered and washed with 200mlof acetone. The product was dried at 60-70°C under vacuum till constant weight.

Dry weight : 60g

Melting point : 156-160-deg C

Purity by HPLC : related : 99.95% (Single impurity less than 0.1%)

Chiral : 99.85% (single impurity less than 0.1%)

Step – III : Preparation of highly pure Ambrisentan from Ambrisentan S(-)P-nitro phenyl ethylamine addition salt (1:1):

Ambrisentan .S(-)4-nitro phenyl ethyl amine addition salt(60g) was suspended in DM

water(3L)and stirred for 15minutes. Aqueous 1N hydrochloric acid solution(500) was added over a period of 30 min to a pH of 1-2 and maintained at the same temperature for 2-3hours.The precipitated product was filtered and washed with purified water. The product was dried at temperature of 60-70°C till constant weight.

Dry weight of Ambrisentan : 42g

Purity by HPLC : related : 99.95% (Single impurity less than 0.1%)

Chiral purity : 99.85% (Single impurity less than 0.1%)

Example-2 : Process for the preparation highly pure Ambrisentan of the formula –I

Step-1 : Condensation of S(+) 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid and 4,6-dimethyl-2-(-(methylsulfonyl)pyrimidine in THF medium

Into a 1L round bottomed flask a mixture of THF(1L) and S-2-Hydroxy-3-mehoxy-3,3-diphenyl propionic acid(50g) were charged and stirred for 30 minutes. sodium hydride(18.9g) was added slowly for 1hour and reaction mass was maintained at room temperature for one hours. 2-(methylsulfonyl)-4,6-dimethyl pyrimidine(47.8g) was dissolved in THF(500ml) and added to the reaction mass at room temperature during 45-60 minutes and reaction mass was maintained overnight under stirring. After reaction completion methanol(50ml) was added slowly to the reaction mass during 30 minutes. Reaction mass was quenched into DM water (15L) and acidified with diluted hydrochloric acid(600ml). Reaction mass was maintained under stirring for 3hours at room temperature. Filtered compound was dissolved in Ethyl acetate and ethyl acetate layer was extracted with 1N sodium hydroxide solution(2L) Sodium hydroxide layer was separated and acidified with 1N hydrochloride solution(1.25L) . Reaction mass was maintained under stirring for 2hours . The product of the formula-I was filtered and washed with purified water. It was dried in oven at 60-65°C

Dry weight : 50g

Purity by HPLC : related : 99.4%

Chiral : 99.36%

Step – II : Preparation of Ambrisentan S(-) phenyl ethylamine addition salt(1:1) : Ambrisentan (50g, purity 99.5%) was dissolved in acetone (500ml) and S-(-) phenyl ethyl amine(16.0g) was dissolved in acetone(32ml)added to the solution over 30 min . Reaction mass temperature was raised to reflux and maintained for about 1-2hrs. Reaction mass was slowly cooled to room temperature and maintained for about 16-18 hr at the same temperature. The precipitated material was filtered and washed with 200mlof acetone. The product was dried at 60-70°C under vacuum till constant weight.

Dry weight : 40g

Melting point : 88-90-deg C

Purity by HPLC : related : 99.90%(Single impurity less than 0.1%)

Chiral : 99.82% (Single impurity less than 0.1%)

Step – III : Preparation of highly pure Ambrisentan from Ambrisentan S(-) phenyl ethylamine addition salt(1:1) :

Ambrisentan .S(-) phenyl ethyl amine addition salt(40g) was suspended in DM water(2L)and stirred for 15minutes. Aqueous 1N hydrochloric acid solution(330ml) was added over a period of 30 min to a pH of 1-2 and maintained at the same temperature for 2-3hours.The precipitated product was filtered and washed with purified water. The product was dried at temperature of

60-70°C till constant weight.

Dry weight of Ambrisentan : 30g

Purity by HPLC : related : 99.90% (Single impurity less than 0.1%)

Chiral purity : 99.80% (Single impurity less than 0.1%)

Advantages of the invention

1) Ambrisentan produced in more than 99.8% chemical purity.
2) The chiral purity of Ambrisentan by the process of the present invention is about 99.8%

We Claim:

1. Novel process for the preparation of Ambrisentan comprising

a) Dissolving S(+) 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid in DMF under nitrogen atmosphere at 20-25°C

b) Adding Sodium hydride slowly to the reaction mass during 1hour at 25-30°C

c) stirring reaction mixture for one hour

d) adding 4,6-dimethyl-2-(methylsulfonyl)pyrimidine solution in DMF drop wise

e) Maintaining reaction mass at 25-30°C for 16-17hours

f) quenching reaction mass with methanol and pouring into ice-water .

g) aqueous layer pH adjustment with 1N hydrochloride solution

h) extraction of reaction mass with ethyl acetate

i) extraction of ethyl acetate layer with 1N sodium hydroxide solution

j) Acidification of ethyl acetate layer with 1N hydrochloric acid slution

k) Maintenance of reaction mass under stirring for 2hours

l) Filtering to yield Ambrisentan .

2. Novel process for the preparation of highly pure (>99.8%) Ambrisentan comprising the following steps

I. Dissolving Ambrisentan in acetone and addition of S-(-)4-nitro phenyl ethyl amine directly or as a solution in acetone

II. Raising reaction mass temperature to reflux

III. Maintenance of reaction mass at reflux temperature for 1hour

IV. Cooling reaction mass to room temperature and maintaining at the same temperature for 16 -18 hours

V. Filtering and to yield pure Ambrisentan as an acid addition salt of S-(-)4-nitro phenylethylamine

VI. Acidification of Ambrisentan S-(-)4-nitro phenyl ethyl amine with diluted hydrochloric acid

VII. Maintenance at room temperature for 2-3hours

VIII. Filtering to yield Ambrisentan of high purity(>99.8%)

3. Novel process for the preparation of Ambrisentan comprising

a) Dissolving S(+) 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid in THF under nitrogen atmosphere at 20-25°C

b) Adding Sodium hydride slowly to the reaction mass during 1hour at 25-30°C

c) stirring reaction mixture for one hour

d) adding 4,6-dimethyl-2-(methylsulfonyl)pyrimidine solution in THF drop wise

e) Maintaining reaction mass at 25-30°C for 16-17hours

f) quenching reaction mass with methanol and pouring into ice-water .

g) aqueous layer pH adjustment with 1N hydrochloride solution

h) Maintaining reaction under stirring for 3hours

i) Filtration and dissolution of filtered solid in ethyl acetate

j) extraction of ethyl acetate layer with 1N sodium hydroxide solution

k) Acidification of ethyl acetate layer with 1N hydrochloric acid solution

l) Maintenance of reaction mass under stirring for 2hours

m) Filtering to yield Ambrisentan

4. Novel process for the preparation of highly pure (>99.8) Ambrisentan comprising the following steps

I. Dissolving Ambrisentan in acetone and addition of S-(-) phenyl ethyl amine directly or as a solution in acetone

II. Raising reaction mass temperature to reflux

III. Maintenance of reaction mass at reflux temperature for 1hour

IV. Cooling reaction mass to room temperature and maintaining at the same temperature for 16 -18 hours

V. Filtering and to yield pure Ambrisentan as an acid addition salt of S-(-) phenyl ethylamine

VI. Acidification of Ambrisentan S-(-) phenyl ethyl amine addition salt with diluted hydrochloric acid

VII. Maintenance at room temperature for 2-3hours

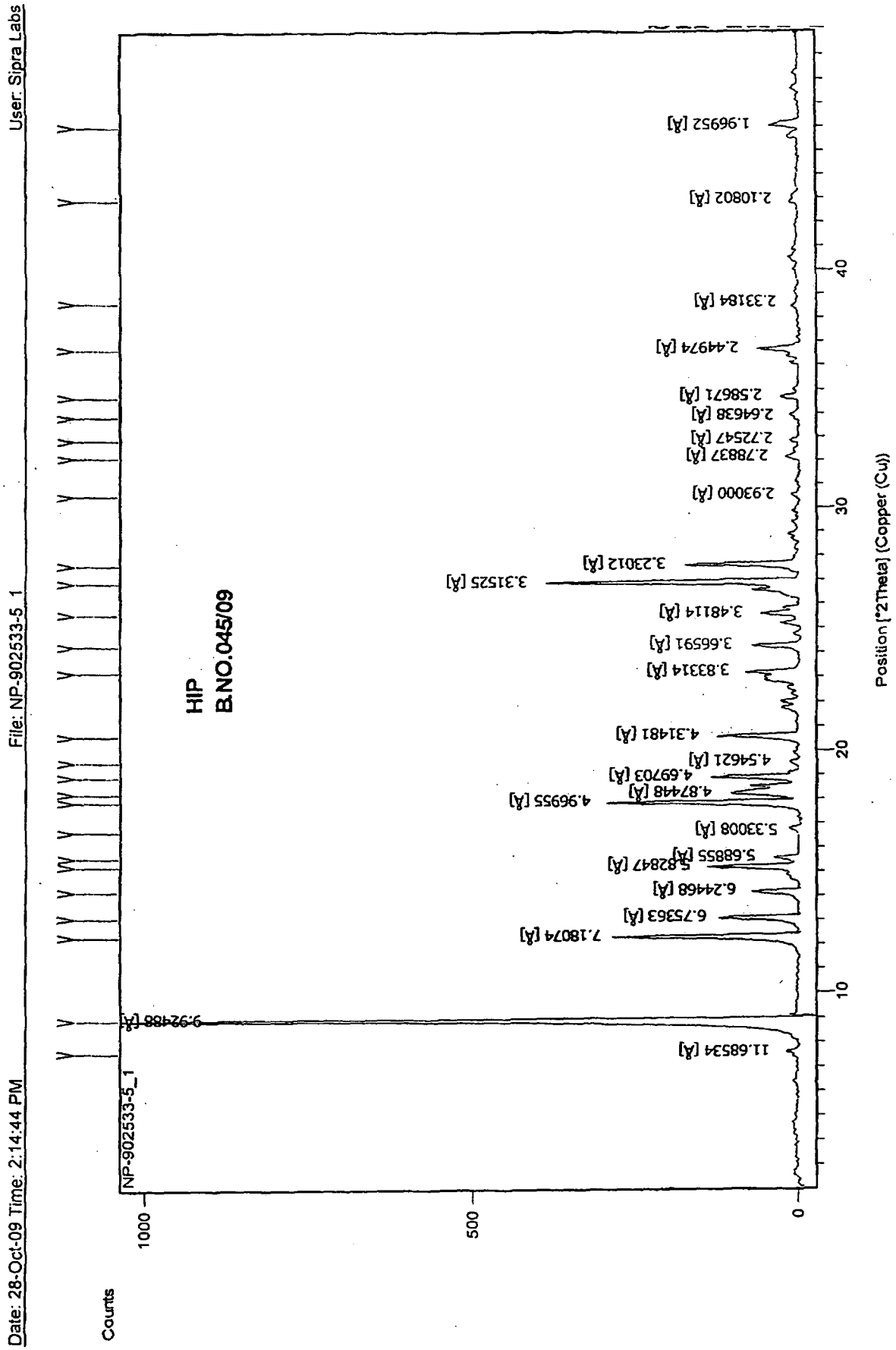
VIII. Filtering to yield Ambrisentan of high purity(>99.8%)

5. A (1:1) addition salt of ambrisentan and S-(-)4-nitro phenyl ethyl amine as a novel pharmaceutically acceptable salt of Ambrisentan

6. A (1:1) addition salt of ambrisentan and S-(-) phenyl ethyl amine as a novel pharmaceutically acceptable salt of Ambrisentan

7. A novel method of preparing highly pure (> 99.8%) Ambrisentan essentially as herein described with reference to example- 1 and example-2

Fig - 1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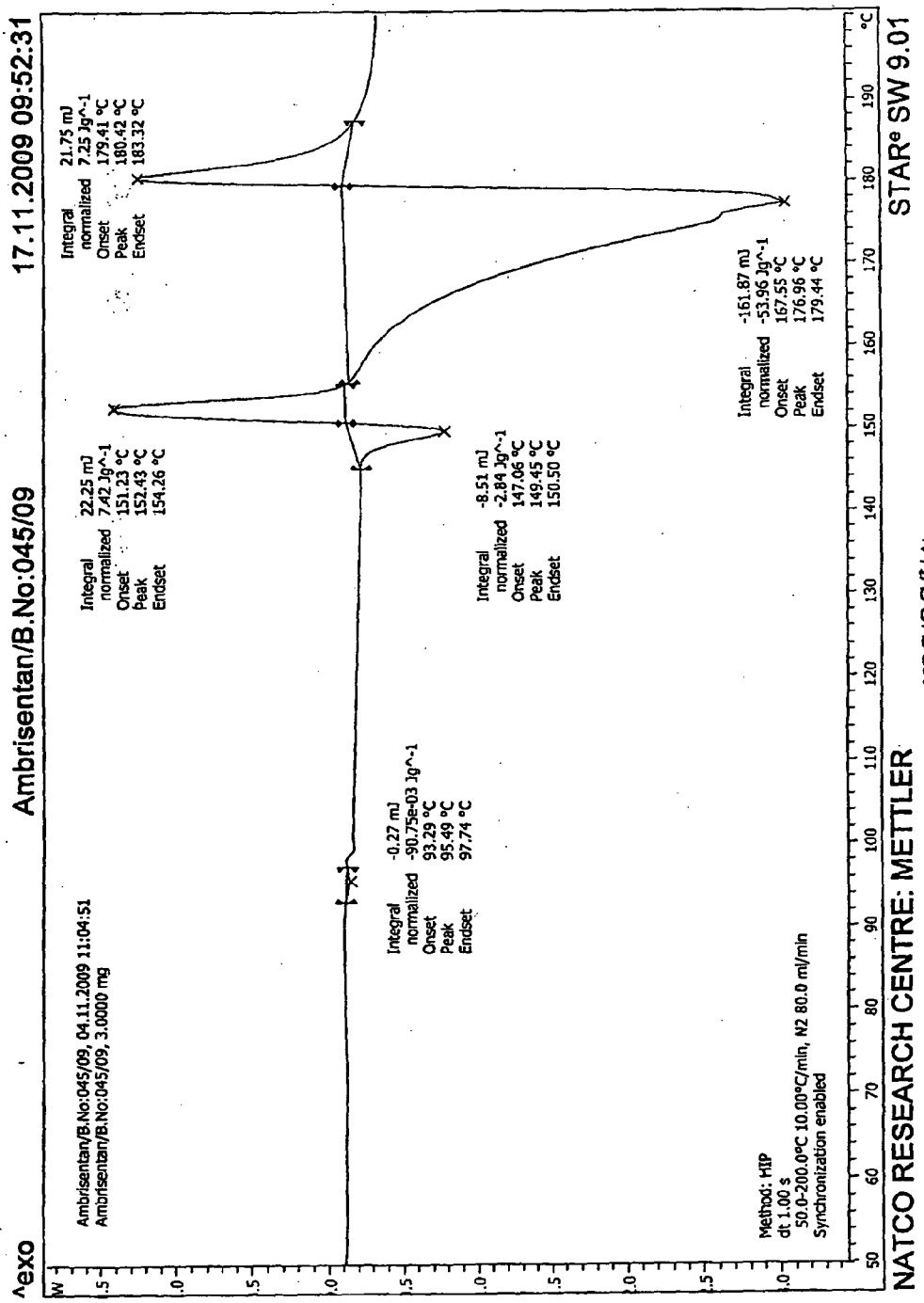
27.6163	173.98	0.1574	3.23012	17.66
30.5104	7.93	0.2362	2.93000	0.81
32.1008	17.98	0.2362	2.78837	1.83
32.8624	11.32	0.2362	2.72547	1.15
33.8738	8.75	0.2362	2.64638	0.89
34.6796	27.13	0.1574	2.58671	2.75
36.6857	61.84	0.1574	2.44974	6.28
38.6120	4.02	0.9446	2.33184	0.41
42.9033	9.44	0.4723	2.10802	0.96
46.0473	43.15	0.2880	1.96952	4.38

Fig-2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17.11.2009 09:52:31
Ambrisentan/B.No:045/09, 04.11.2009 11:04:51
Ambrisentan/B.No:045/09, 3.0000 mg
Integral 22.25 mJ
normalized 7.42 Jg^-1
Onset 151.23 °C
Peak 152.43 °C
Endset 154.26 °C
Integral 21.75 mJ
normalized 7.25 Jg^-1
Onset 179.41 °C
Peak 180.42 °C
Endset 183.32 °C
Integral -0.27 mJ
normalized -90.75e-03 Jg^-1
Onset 93.29 °C
Peak 95.49 °C
Endset 97.74 °C
Integral -8.51 mJ
normalized -2.84 Jg^-1
Onset 147.06 °C
Peak 149.45 °C
Endset 150.50 °C
Integral -161.87 mJ
normalized -53.96 Jg^-1
Onset 167.55 °C
Peak 176.96 °C
Endset 179.44 °C
Method: HIP
dt 1.00 s
50.0-200.0°C 10.00°C/min, N2 80.0 ml/min
Synchronization enabled
mW
°C
NATCO RESEARCH CENTRE: METTLER
STARe SW 9.01
INSTRUMENT No: NRC/QC/I/060
A.R.No DSC/R&D/1604/09

Fig - 3

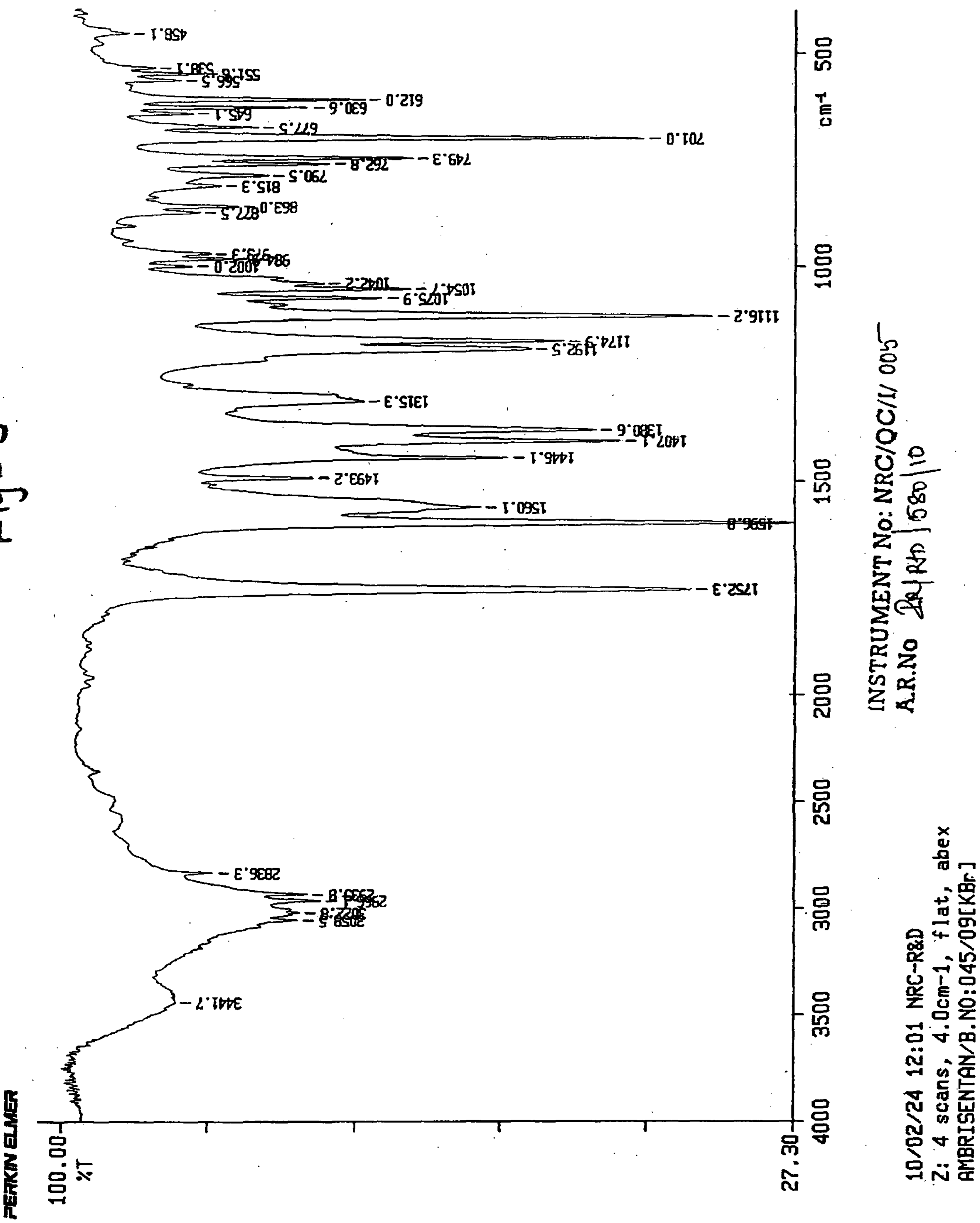
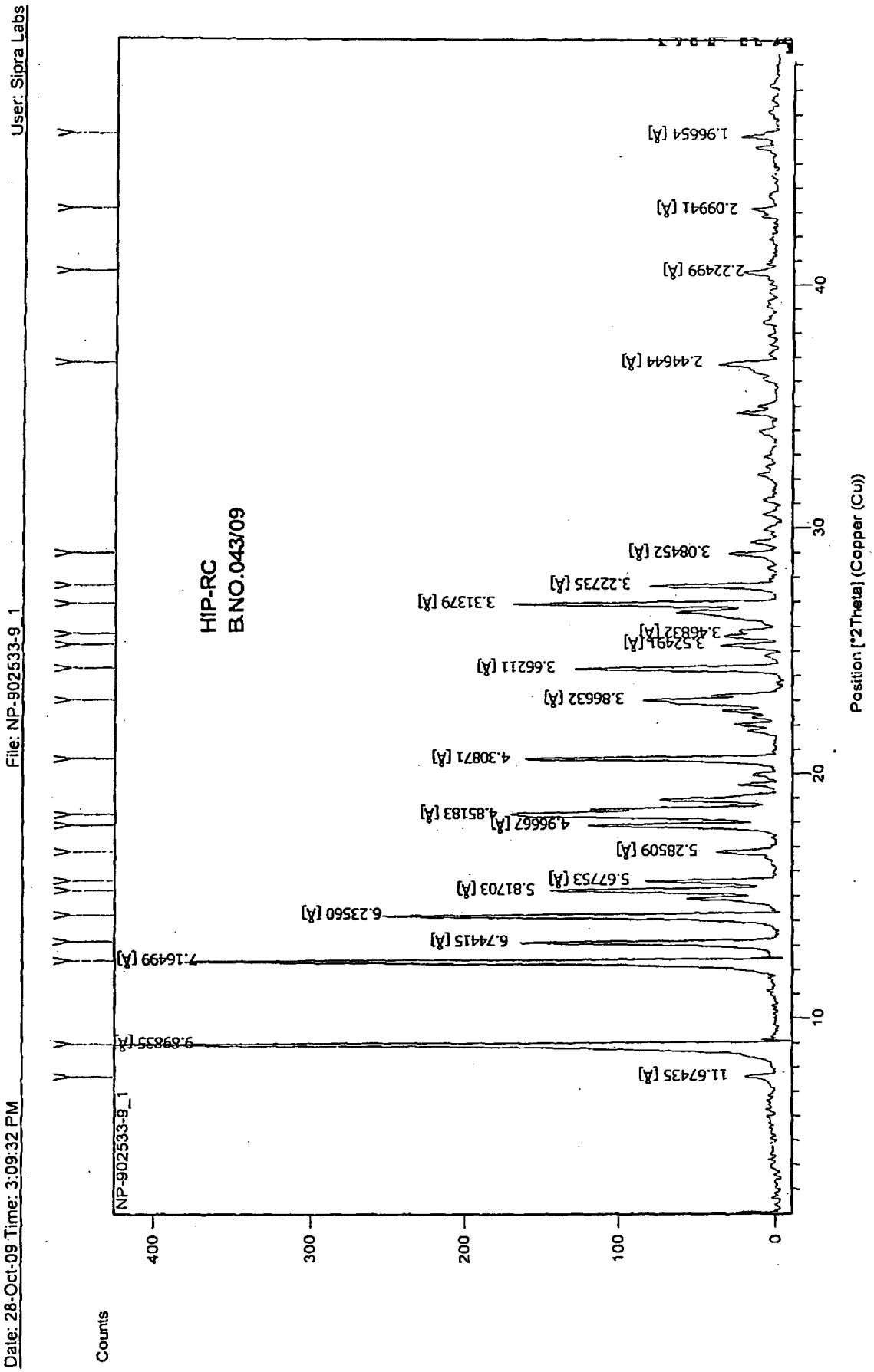

PERKIN ELMER
100.00
%T
27.30
4000
3500
3000
2500
2000
1500
1000
500
cm-1
3441.7
2836.3
1752.3
1596.8
1560.1
1493.2
1445.1
1407.1
1380.6
1315.3
1192.5
1174.9
1116.2
1075.9
1054.7
1042.2
701.0
749.3
762.8
790.5
815.3
612.0
630.6
645.1
677.5
458.1
INSTRUMENT No: NRC/QC/I/ 005
A.R.No
10/02/24 12:01 NRC-R&D
Z: 4 scans, 4.0cm-1, flat, abex
AMBRISENTAN/B.NO:045/09[KBr]

Fig - 4

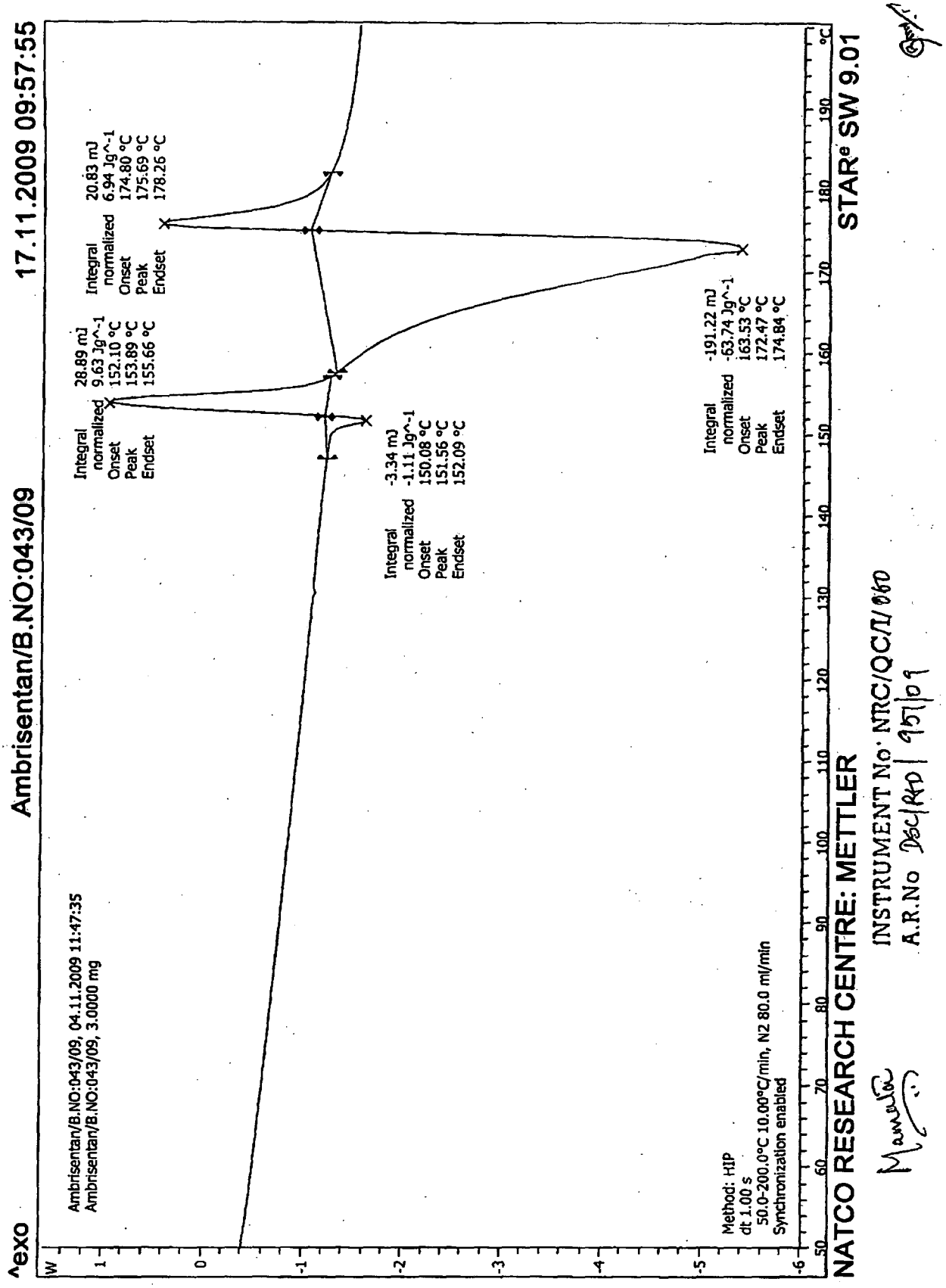

Date: 28-Oct-09 Time: 3:09:32 PM
File: NP-902533-9_1
User: Sipra Labs
HIP-RC
B.NO.043/09
NP-902533-9_1
Counts
Position [°2Theta] (Copper (Cu))
11.67435 [Å]
9.89835 [Å]
7.16499 [Å]
6.74415 [Å]
6.23560 [Å]
5.81703 [Å]
5.67753 [Å]
5.28509 [Å]
4.96667 [Å]
4.85183 [Å]
4.30871 [Å]
3.86632 [Å]
3.66211 [Å]
3.52491 [Å]
3.46832 [Å]
3.31379 [Å]
3.22735 [Å]
3.08452 [Å]
2.44644 [Å]
2.22499 [Å]
2.09941 [Å]
1.96654 [Å]

n Page 2

Peak List:

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.5728	17.03	0.2362	11.67435	4.22
8.9341	403.58	0.1378	9.89835	100.00
12.3537	358.98	0.1378	7.16499	88.95
13.1279	158.62	0.1378	6.74415	39.30
14.2038	242.90	0.1378	6.23560	60.19
15.2317	141.87	0.1574	5.81703	35.15
15.6083	81.10	0.1378	5.67753	20.10
16.7754	38.16	0.1574	5.28509	9.45
17.8594	119.05	0.1378	4.96667	29.50
18.2856	166.33	0.1968	4.85183	41.21
20.6144	158.63	0.1574	4.30871	39.31
23.0035	84.35	0.2362	3.86632	20.90
24.3053	128.27	0.1574	3.66211	31.78
25.2667	33.65	0.1771	3.52491	8.34
25.6859	23.14	0.2362	3.46832	5.73
26.9057	167.22	0.1574	3.31379	41.43
27.6404	79.27	0.1771	3.22735	19.64
28.9476	29.47	0.1574	3.08452	7.30
36.7368	34.92	0.1968	2.44644	8.65
40.5455	7.69	0.9446	2.22499	1.91
43.0881	13.20	0.3936	2.09941	3.27
46.1210	18.93	0.2880	1.96654	4.69

Fig - 5


^exo
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17.11.2009 09:57:55
Ambrisentan/B.NO:043/09, 04.11.2009 11:47:35
Ambrisentan/B.NO:043/09, 3.0000 mg
Integral 28.89 mJ
normalized 9.63 Jg^-1
Onset 152.10 °C
Peak 153.89 °C
Endset 155.66 °C
Integral 20.83 mJ
normalized 6.94 Jg^-1
Onset 174.80 °C
Peak 175.69 °C
Endset 178.26 °C
Integral -3.34 mJ
normalized -1.11 Jg^-1
Onset 150.08 °C
Peak 151.56 °C
Endset 152.09 °C
Integral -191.22 mJ
normalized -63.74 Jg^-1
Onset 163.53 °C
Peak 172.47 °C
Endset 174.84 °C
Method: HIP
dt 1.00 s
50.0-200.0°C 10.00°C/min, N2 80.0 ml/min
Synchronization enabled
STARe SW 9.01
NATCO RESEARCH CENTRE: METTLER
INSTRUMENT No: NRC/QC/I/060
A.R.No Dsc/Rd/ 95/09

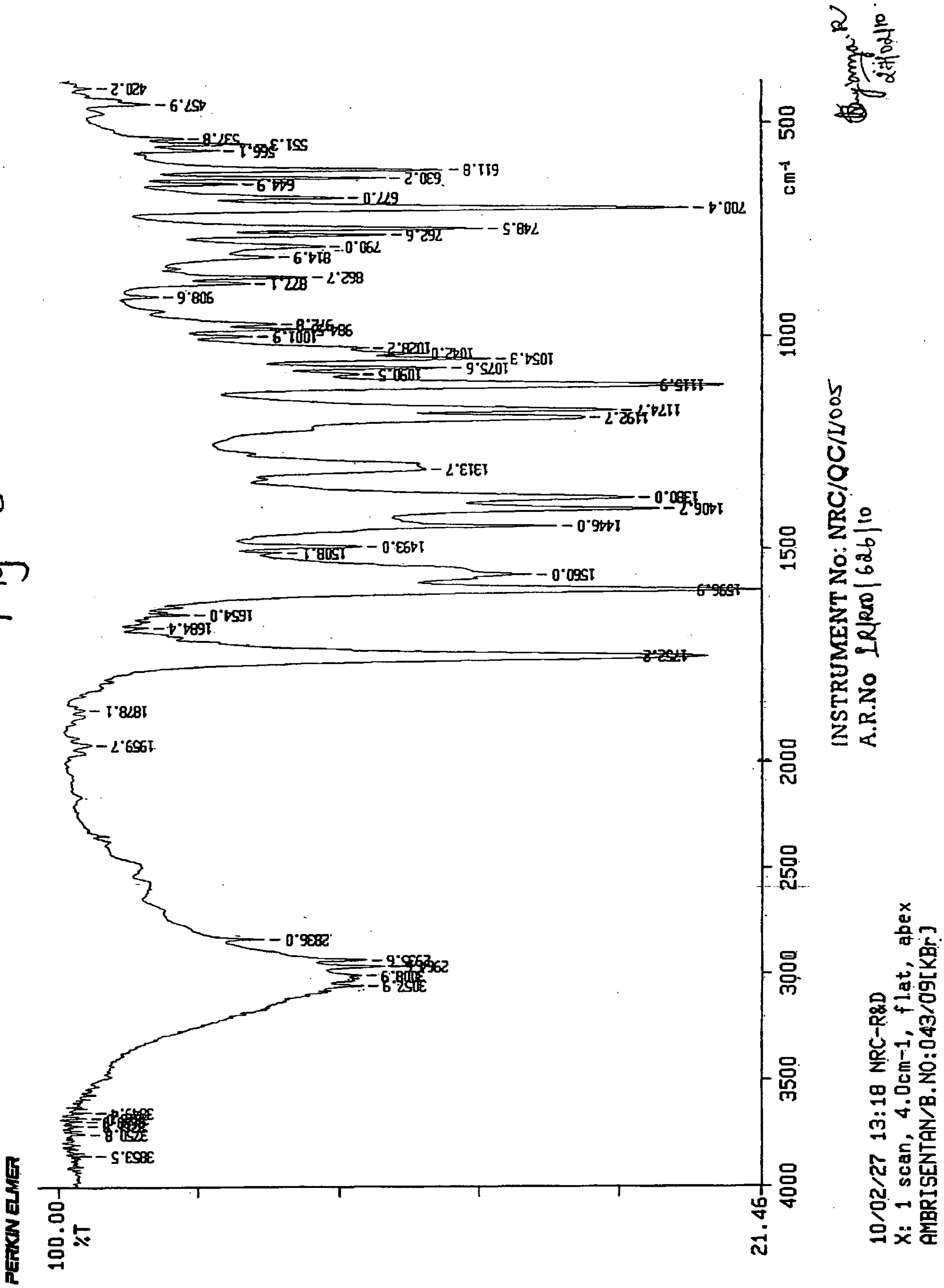
PERKIN ELMER
100.00
%T
21.46
cm-1
INSTRUMENT No: NRC/QC/I/005
10/02/27 13:18 NRC-R&D
X: 1 scan, 4.0cm-1, flat, abex
AMBRISENTAN/B.NO:043/09[KBr]

Fig-6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2010/000153

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/34
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 932 730 A (RIECHERS HARTMUT [DE] ET AL) 3 August 1999 (1999-08-03) examples 3, 4; compounds I-294 -----	1-7
A	DATABASE JOURNAL OF MEDICINAL CHEM [Online] 1 May 1996 (1996-05-01), RIECHERS H ET AL: "DISCOVERY AND OPTIMIZATION OF A NOVEL CLASS OF ORALLY ACTIVE NONPEPTIDIC ENDOTHELIN-A RECEPTOR ANTAGONISTS", XP002023887, retrieved from CHEMICAL PAN - 91407 * abstract; compound 6o -----	1,3,7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2011	01/03/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Miniejew, Catherine

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2010/000153

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

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

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

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

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

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

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

see additional sheet

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

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

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

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 3(completely); 7(partially)

   Preparation processes of Ambrisentan

   ---

2. claims: 2, 4-6(completely); 7(partially)

   Purification processes of Ambrisentan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2010/000153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5932730 A	03-08-1999	AT 277911 T	15-10-2004
		AT 204568 T	15-09-2001
		AU 688611 B2	12-03-1998
		AU 3804595 A	06-05-1996
		BR 9509338 A	04-11-1997
		CA 2201785 A1	25-04-1996
		CN 1160396 A	24-09-1997
		CN 1513844 A	21-07-2004
		CN 1923820 A	07-03-2007
		CZ 9701132 A3	18-03-1998
		DE 19533023 A1	18-04-1996
		DE 59509541 D1	27-09-2001
		DE 59510949 D1	04-11-2004
		DE 122008000049 I1	29-01-2009
		DK 785926 T3	08-10-2001
		WO 9611914 A1	25-04-1996
		EP 1110952 A1	27-06-2001
		EP 0785926 A1	30-07-1997
		ES 2226996 T3	01-04-2005
		ES 2162942 T3	16-01-2002
		FI 971529 A	11-04-1997
		GR 3036931 T3	31-01-2002
		HK 1066541 A1	01-06-2007
		HK 1104293 A1	10-12-2010
		HR 950517 A2	31-10-1997
		HR 20040364 A2	30-06-2005
		HU 77443 A2	28-04-1998
		IL 115560 A	12-02-2003
		JP 3957748 B2	15-08-2007
		JP 10507190 T	14-07-1998
		JP 4512105 B2	28-07-2010
		JP 2007169295 A	05-07-2007
		JP 4512106 B2	28-07-2010
		JP 2007126488 A	24-05-2007
		JP 2007137892 A	07-06-2007
		JP 2007137893 A	07-06-2007
		LU 91487 A9	15-12-2008
		NL 300361 I1	01-12-2008
		NO 971675 A	10-06-1997
		NO 2008015 I1	03-11-2008
		NZ 294849 A	29-04-1999
		PL 319655 A1	18-08-1997
		PT 785926 E	28-02-2002
		RU 2180335 C2	10-03-2002
		SI 9520110 A	31-12-1997
		TW 577880 B	01-03-2004
US 5932730 A		US 5969134 A	19-10-1999
		US 6197958 B1	06-03-2001
		US 2006160808 A1	20-07-2006
