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(54) Title: NOVEL TRIMETAZIDINE SALTS

(57) Abstract: The present invention relates to novel trimetazidine salts, leading to a reduced formation of trimetazidine nitrosamine in presence of nitrites.



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NOVEL TRIMETAZIDINE SALTS

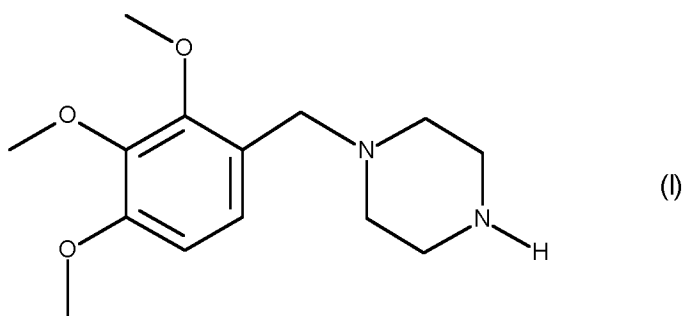
The present invention relates to novel trimetazidine salts, their hydrates, and crystalline forms thereof.

5

Trimetazidine, or 1-(2,3,4-trimethoxybenzyl)piperazine (formula (I)), is a compound which, by maintaining the energy metabolism of a cell exposed to hypoxia or ischaemia, avoids the collapse of the intracellular level of adenosine triphosphate (ATP). It thus ensures functioning of the ion pumps and sodium-potassium transmembrane flows and maintains

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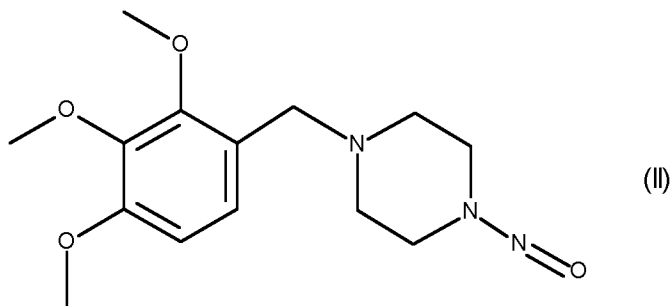
cellular homeostasis.



Trimetazidine dihydrochloride is currently used therapeutically for the prophylactic treatment of angina pectoris crisis, in chorioretinal attacks and for the treatment of vertigo of vascular origin (Ménière's vertigo, tinnitus).

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Trimetazidine nitrosamine of formula (II) is an impurity which may be formed during the process of synthesis of trimetazidine salts or during the formulation process of such salts, in presence of nitrites coming from water and/or excipients.



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The Applicant has now found that the trimetazidine salts of the present invention allow to reduce the formation of trimetazidine nitrosamine in presence of nitrites.

The patent applications CN110105307, CN110183398 and CN110054599 respectively disclose the synthesis of the trimetazidine hemioxalate, oxalate and dioxalate salts, in order to overcome flowability, poor tableting property and hygroscopicity issues of the trimetazidine dihydrochloride salt.

The present invention relates especially to trimetazidine hemimalate, hemiadipate, hemitartrate, hemiphosphate, hemisulfate, hemisuccinate and hemifumarate salts.

The present invention also relates to a process of synthesis of trimetazidine salts, wherein trimetazidine is reacted with an organic acid in a solvent, leading to the corresponding salt having a trimetazidine/organic acid ratio of 2/1, wherein the organic acid is selected from malic acid, adipic acid, tartaric acid, phosphoric acid, sulfuric acid, succinic acid, and fumaric acid.

In an embodiment of the present invention, trimetazidine is reacted with 0.5 eq. malic acid, adipic acid, tartaric acid, phosphoric acid, sulfuric acid, succinic acid or fumaric acid, in a solvent, leading to the corresponding trimetazidine hemimalate, hemiadipate, hemitartrate, hemiphosphate, hemisulfate, hemisuccinate or hemifumarate having a trimetazidine/ malic acid, trimetazidine/ adipic acid, trimetazidine/ tartaric acid, trimetazidine/ phosphoric acid, trimetazidine/ trimetazidine/ sulfuric acid, trimetazidine/ succinic acid or trimetazidine/ fumaric acid molar ratio of 2/1.

Among the solvents there may be mentioned more especially anisole, methyl isobutyl ketone, toluene, n-heptane, acetonitrile, methyl ethyl ketone, ethyl acetate, 1,3-dioxalane, tetrahydrofuran, acetone, methyl tert-butyl ether, water, alcohols such as methanol, ethanol, isopropanol, isobutanol or n-butanol, and mixtures thereof.

The salification reaction is preferably performed at a temperature of 20°C to 70°C.

The trimetazidine salts of the present invention allow to reduce the formation of trimetazidine nitrosamine in presence of nitrites.

According to an embodiment of the present invention, the trimetazidine salts of the present invention form less than 1 ppm of trimetazidine nitrosamine in a solution containing nitrites, after 22h at 40°C.

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The present invention also relates to pharmaceutical compositions comprising a trimetazidine hemimalate, hemiadipate, hemitartrate, hemiphosphate, hemisulfate, hemisuccinate or hemifumarate salt in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

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The useful dosage varies according to the age and weight of the patient, the administration route, the nature and severity of the disorder and any associated treatments, and ranges from 15 mg to 200 mg per day in one or more administrations.

15 Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory administration, and especially tablets or dragées, sublingual tablets, gelatin capsules, capsules, minigranules, suppositories, creams, ointments, dermal gels, injectable or drinkable
20 preparations, aerosols, and eye or nasal drops.

The pharmaceutical compositions may be in the form of immediate release or prolonged release compositions.

According to one aspect of the present invention, the pharmaceutical composition is a tablet for
25 immediate release oral administration.

According to another aspect of the present invention, the pharmaceutical composition is a matrix tablet for prolonged release oral administration.

According to another aspect of the present invention, the pharmaceutical composition is in the form of coated minigranules in capsules, for oral, once-a-day administration.

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In addition to the trimetazidine salt, the tablets according to the invention comprise one or more excipients or carriers, such as diluents, retardants, lubricants, binders, disintegrators, absorbents, plasticizers, colourants and sweeteners.

There may be mentioned as examples of excipients or carriers:

- ♦ *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, glycerol, calcium hydrogen phosphate dihydrate, calcium carbonate, cellulose, cellulose ethers such as hydroxypropylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, methylcellulose or hydroxypropyl methylcellulose,
- ♦ *for the controlled-release agent*: ethylcellulose, ethylcellulose derivatives such as cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate and/or polymethacrylates,
- ♦ *for the lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol, glycerol behenate or sodium benzoate,
- ♦ *for the binders*: aluminium and magnesium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- ♦ *for the plasticizers*: acetyl tributyl citrate, glycerol triacetate, acetyl triethyl citrate, acetyl ethyl citrate, diethyl sebacate, dibutyl sebacate, ethyl phthalate, dibutyl phthalate, polyethylene glycol, glycerol and/or propylene glycol,
- ♦ *for the disintegrants*: agar, alginic acid and its sodium salt, effervescent mixtures.

The percentage of active ingredient of formula (I) in the tablet is preferably between 5% and 50% by weight.

According to one aspect of the present invention, the trimetazidine salt according to the present invention is administered in association with one or more additional active ingredients.

The administration in association may be in the form of a simultaneous or successive co-administration of two or more separate pharmaceutical compositions each containing one of the active ingredients (free association), or in the form of the administration of a fixed-dose combination including two or more active ingredients combined in a single dosage form.

Among the additional active ingredients, there may be mentioned more especially betablockers.

According to one aspect of the present invention, the trimetazidine salt of the present invention is administered in association with a betablocker in the form of a fixed-dose combination.

Among the betablockers, there may be mentioned more especially metoprolol and bisoprolol.

5 According to a preferred aspect of the present invention, the fixed-dose combination of the trimetazidine salt and bisoprolol is a capsule containing 80 mg trimetazidine salt minigranules and 5 or 10 mg bisoprolol hemifumarate pellets.

10 According to another preferred aspect of the present invention, the fixed-dose combination of the trimetazidine salt and metoprolol is a capsule containing 80 mg trimetazidine salt minigranules, and 47.5 or 95 mg metoprolol succinate pellets.

A formulation of bisoprolol hemifumarate pellets is already disclosed in Example 4a of WO2016/071631.

15

ABBREVIATIONS

eq. molar equivalent

NMR Nuclear Magnetic Resonance

20 XRPD X-Ray Powder Diffraction

EXPERIMENTAL PART

25 For the compounds of Examples 1, 3, 4, 5 and 7, the XRPD patterns were recorded from 3.5 °2θ to 35°2θ using an X-ray diffractometer operating in the transmission mode with CuKα radiation ($\lambda = 1.5418\text{\AA}$) at 45kV and 40 mA and with a 0.013 °2θ step size for 10 minutes.

For the compounds of Examples 2 and 6, the XRPD patterns were recorded from 3.5 °2θ to 55°2θ using an X-ray diffractometer operating in the transmission mode with CuKα radiation ($\lambda = 1.5418\text{\AA}$) at 45kV and 40 mA and with a 0.013 °2θ step size for 30 minutes.

30

Only the peaks with a relative intensity higher than 10% have been mentioned in the XRPD tables.

The chemical shifts, in ppm, are given with respect to tetramethylsilane (TMS), using partially deuterated dimethylsulfoxide or partially deuterated methanol as internal standard.

In solution in partially deuterated dimethylsulfoxide, the resonance at 2.5 ppm on the 1D ¹H NMR spectrum is due to partially deuterated dimethylsulfoxide and the resonance at 3.30 ppm is due to the presence of water.

In solution in partially deuterated methanol, the resonance at 3.3 ppm on the 1D ¹H NMR spectrum is due to partially deuterated methanol and the resonance at 4.83 ppm is due to the presence of water.

EXAMPLE 1 : Trimetazidine hemiadipate

1.0 g of trimetazidine and 0.28g (0.5 eq) of adipic acid were placed in 4mL of isopropanol. The mixture was placed under stirring for 22h at ambient temperature. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to a crystalline powder.

¹H NMR: 6.95 ppm, 6.75 ppm, 3.77 ppm, 3.76 ppm, 3.73 ppm, 3.33 ppm, 2.67 ppm, 2.29 ppm, 2.18 ppm, 1.49 ppm.

The corresponding ¹H NMR spectrum is in Figure 1a.

XRPD table:

	Position [°2θ]	Relative Intensity [%]
1	8.64	31
2	12.17	12
3	12.32	20
4	13.74	15
5	14.64	12
6	15.65	11
7	15.95	27
8	16.81	20
9	17.35	12
10	18.15	100
11	19.33	33
12	19.57	28

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	Position [$^{\circ}2\theta$]	Relative Intensity [%]
13	20.54	11
14	21.91	11
15	22.29	12
16	22.99	56
17	23.77	21
18	24.48	19
19	26.15	11
20	27.49	15

The corresponding XRPD pattern is in Figure 1b.

EXAMPLE 2 : Trimetazidine hemisuccinate

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Process A.

5.0 g of trimetazidine and 1.11 g of succinic acid were placed in 75mL of ethanol. The mixture was placed under stirring at 70°C for 2 hours and then stirred for 60h at ambient temperature. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The
10 obtained powder corresponds to a crystalline powder.

^1H NMR: 6.96 ppm, 6.75 ppm, 3.77 ppm, 3.77 ppm, 3.73 ppm, 3.37 ppm, 2.80 ppm, 2.37 ppm, 2.26 ppm.

The corresponding ^1H NMR spectrum is in Figure 2a.

XRPD table:

	Position [$^{\circ}2\theta$]	Relative Intensity [%]
1	15.50	80
2	15.80	100
3	16.29	19
4	19.03	36
5	19.77	25
6	23.20	19
7	24.34	17
8	24.64	17
9	26.74	21

The corresponding XRPD pattern is in Figure 2b.

Process B.

- 5 64kg of trimetazidine, 14kg of succinic acid, 4.9kg of water and 569kg of isopropyl alcohol were placed in a reactor.

The mixture was placed under mechanical stirring at 72°C for 30 minutes. This solution was cooled to 63°C with a rate of 0.3°C/min. After 60 minutes at 63°C and under stirring, the suspension was cooled to 5°C with a rate of 0.25°C/min. The suspension was filtered, and the powder was dried at 40°C overnight. The obtained powder corresponds to a crystalline powder. The yield is about 91%.

The XRPD pattern is the same as with Process A.

EXAMPLE 3: Trimetazidine hemimalate

15

1.0 g of trimetazidine and 0.25 g of malic acid were placed in 4mL of isopropanol. The mixture was stirred for 22h at ambient temperature. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to a crystalline powder.

- 20 ¹H NMR: 6.96 ppm, 6.76 ppm, 3.77 ppm, 3.77 ppm, 3.73 ppm, 3.39 ppm, 2.85 ppm, 2.45 ppm, 2.40 ppm, 2.30 ppm.

The corresponding ¹H NMR spectrum is in Figure 3a.

XRPD table:

	Position [°2θ]	Relative Intensity [%]
1	10.46	31
2	13.97	14
3	15.28	49
4	15.57	100
5	16.07	43
6	16.72	15
7	19.32	34
8	19.54	44
9	23.22	32

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	Position [$^{\circ}2\theta$]	Relative Intensity [%]
10	23.88	24
11	24.28	18
12	24.97	21
13	26.10	25
14	28.74	10

The corresponding XRPD pattern is in Figure 3b.

5 **EXAMPLE 4 : Trimetazidine hemisulfate**

550.0 g of trimetazidine and 211 g of sulfuric acid solution at 96% were placed in 2.2 L of toluene. The mixture was stirred for 24h at 20°C. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to a crystalline powder.

XRPD table:

	Position [$^{\circ}2\theta$]	Relative Intensity [%]
1	3.71	38
2	11.19	42
3	13.46	11
4	15.41	40
5	15.74	24
6	16.29	100
7	17.95	12
8	18.39	31
9	19.00	24
10	20.17	15
11	22.44	18
12	22.82	11
13	24.06	35
14	24.91	10
15	26.33	15
16	26.84	14

The corresponding X-Ray spectrum is in Figure 4.

EXAMPLE 5 : Trimetazidine hemifumarate

5

1.0 g of trimetazidine and 0.23 g of fumaric acid were placed in 4mL of isopropanol. The mixture was stirred for 22h at ambient temperature. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to a crystalline powder.

10 ¹H NMR: 7.01 ppm, 6.76 ppm, 6.66 ppm, 3.87 ppm, 3.84 ppm, 3.82 ppm, 3.56 ppm, 3.12 ppm, 2.66 ppm.

The corresponding ¹H NMR spectrum is in Figure 5a.

XRPD table:

	Position [°2θ]	Relative Intensity [%]
1	10.47	16
2	13.99	13
3	15.29	66
4	15.61	100
5	16.14	21
6	20.75	15
7	21.67	73
8	24.29	78

15

The corresponding XRPD pattern is in Figure 5b.

EXAMPLE 6 : Trimetazidine hemitartrate

20 5.0 g of trimetazidine and 1.42 g of L-tartaric acid were placed in 75mL of anisole. The mixture was placed under stirring at 70°C for 2 hours and then stirred for 60h at ambient temperature. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to a crystalline powder.

¹H NMR: 6.96 ppm, 6.76 ppm, 3.77 ppm, 3.73 ppm, 3.39 ppm, 2.86 ppm, 2.41 ppm.

The corresponding ^1H NMR spectrum is in Figure 6a.

XRPD table:

	Position [$^{\circ}2\theta$]	Relative Intensity [%]
1	10.39	22
2	15.02	58
3	15.43	100
4	16.53	21
5	18.28	16
6	19.58	20
7	20.47	29
8	23.14	29
9	23.43	25
10	24.21	32
11	25.70	23

The corresponding XRPD pattern is in Figure 6b.

5

EXAMPLE 7 : Trimetazidine hemiphosphate

1.0 g of trimetazidine and 0.18 g of phosphoric acid were placed in 4mL of isopropanol. The mixture was stirred for 22h at ambient temperature. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to a crystalline powder.

10

XRPD table:

	Position [$^{\circ}2\theta$]	Relative Intensity [%]
1	3.58	23
2	10.78	29
3	13.65	11
4	14.56	27
5	15.21	18
6	15.87	35
7	16.01	91
8	16.23	49

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	Position [$^{\circ}2\theta$]	Relative Intensity [%]
9	16.37	31
10	16.90	100
11	17.08	22
12	17.54	15
13	23.67	12

The corresponding XRPD pattern is in Figure 7.

EXAMPLE 8: Comparative experiment: trimetazidine nitrosamine formation

5

In order to model the formation of trimetazidine nitrosamine during the formulation process, an aqueous solution of sodium nitrite was added to the trimetazidine salt. The sodium nitrite mimics the presence of nitrites in water and/or excipients during a drug product manufacturing process.

- 10 The trimetazidine salt, in an amount corresponding to 600 mg trimetazidine, was placed in 2 mL volumetric flask. 150 μ L of sodium nitrite aqueous solution at 0.12mg/mL was placed in the 2mL volumetric flask and the volume was adjusted to 2mL with water to obtain a solution at 300 mg/mL in trimetazidine equivalent.

- 15 The solution was stirred at 40°C for 22 hours. The trimetazidine nitrosamine dosage was performed by LC/MS.

Due to the low solubilities of the dioxalate and oxalate trimetazidine salts, the experiments with these two salts were respectively performed at 6 mg/mL and 30 mg/mL instead of 300 mg/mL in trimetazidine equivalent.

20

Results:

Compound	Trimetazidine salt	Trimetazidine nitrosamine content (ppm)
Example 1	Hemiadipate	0.7
Example 2	Hemisuccinate	0.5
Example 3	Hemimalate	0.7
Example 4	Hemisulfate	0.6

Compound	Trimetazidine salt	Trimetazidine nitrosamine content (ppm)
Example 5	Hemifumarate	0.1
Example 6	Hemitartrate	0.6
Example 7	Hemiphosphate	0.6
Comparative Example A	Dihydrochloride	126.0
Comparative Example B	Hemioxalate	1.1
Comparative Example C	Oxalate	104.0
Comparative Example D	Dioxalate	83.1
Comparative Example E	Hydrochloride	22.0
Comparative Example F	Maleate	121.2
Comparative Example G	Fumarate	31.9

The above results show that the trimetazidine salts of the present invention perform better than the trimetazidine salts of the prior art.

5 **EXAMPLE 9 : Immediate release formulation - corresponding to a formulation containing 20 mg trimetazidine dihydrochloride**

Trimetazidine salt 18.6 to 20.1 mg (see the table below)

Maize starch 26 mg

10 Mannitol 34 mg

Polyvidone 4 mg

Magnesium stearate 1 mg

Talc 5 mg

15 **Equivalence table**

Compound	Trimetazidine salt	M (g/mol)	Amount of trimetazidine salt in the IR tablet formulation (mg)
Example 1	Hemiadipate	339.40	20.0
Example 2	Hemisuccinate	325.38	19.2
Example 3	Hemimalate	333.38	19.7
Example 4	Hemisulfate	315.37	18.6
Example 5	Hemifumarate	324.37	19.1

Compound	Trimetazidine salt	M (g/mol)	Amount of trimetazidine salt in the IR tablet formulation (mg)
Example 6	Hemitartrate	341.38	20.1
Example 7	Hemiphosphate	315.33	18.6

EXAMPLE 10 : MR matrix tablet - corresponding to the matrix MR tablet containing 35 mg trimetazidine dihydrochloride

5	Trimetazidine salt.....	32.5 to 35.2 mg (see the table below)
	Hydroxypropyl methylcellulose.....	74.0 mg
	Povidone	8.7 mg
	Calcium hydrogen phosphate dihydrate	80.9 mg
	Magnesium stearate	1.0 mg
10	Anhydrous colloidal silica	0.4 mg

Equivalence table

Compound	Trimetazidine salt	M (g/mol)	Amount of trimetazidine salt in the MR matrix tablet formulation (mg)
Example 1	Hemiadipate	339.40	35.0
Example 2	Hemisuccinate	325.38	33.6
Example 3	Hemimalate	333.38	34.4
Example 4	Hemisulfate	315.37	32.5
Example 5	Hemifumarate	324.37	33.5
Example 6	Hemitartrate	341.38	35.2
Example 7	Hemiphosphate	315.33	32.5

15 **EXAMPLE 11 : OD formulation - corresponding to the OD formulation containing 80 mg trimetazidine dihydrochloride**

	Trimetazidine salt.....	74.4 to 80.5 mg (see the table below)
	Neutral sucrose/maize starch minigranules	36.67 mg
20	Hydroxypropyl methylcellulose.....	6.40 mg

Acetyl tributyl citrate.....	1.20 mg
Ethylcellulose.....	8.00 mg
Talc.....	12.00 mg
Magnesium stearate.....	0.43 mg

5

Equivalence table

Compound	Trimetazidine salt	M (g/mol)	Amount of trimetazidine salt in the OD formulation (mg)
Example 1	Hemiadipate	339.40	80.0
Example 2	Hemisuccinate	325.38	76.7
Example 3	Hemimalate	333.38	78.6
Example 4	Hemisulfate	315.37	74.4
Example 5	Hemifumarate	324.37	76.5
Example 6	Hemitartrate	341.38	80.5
Example 7	Hemiphosphate	315.33	74.4

EXAMPLE 12: OD formulation- combination with bisoprolol hemifumarate

- 10 The trimetazidine salt minigranules obtained in Example 11 and bisoprolol hemifumarate pellets containing 5 mg bisoprolol hemifumarate are mixed together and encapsulated.

EXAMPLE 13: OD formulation- combination with metoprolol succinate

- 15 The trimetazidine salt minigranules obtained in Example 11 and metoprolol succinate pellets containing either 47.5 mg, or 95 mg metoprolol succinate are mixed together and encapsulated.

CLAIMS

1- A trimetazidine salt which is selected from trimetazidine hemimalate, trimetazidine hemiadipate, trimetazidine hemitartrate, trimetazidine hemiphosphate, trimetazidine hemisulfate, trimetazidine hemisuccinate and trimetazidine hemifumarate, their hydrates, and crystalline forms thereof.

2- A process of synthesis of a trimetazidine salt according to Claim 1, wherein trimetazidine is reacted with an organic acid selected from malic acid, adipic acid, tartaric acid, phosphoric acid, sulfuric acid, succinic acid, and fumaric acid in a solvent, leading to the corresponding salt having a trimetazidine/organic acid ratio of 2/1.

3- A process according to Claim 2, wherein trimetazidine is reacted with 0.5 eq. malic acid, adipic acid, tartaric acid, phosphoric acid, sulfuric acid, succinic acid or fumaric acid, in a solvent, leading to the corresponding trimetazidine hemimalate, hemiadipate, hemitartrate, hemiphosphate, hemisulfate, hemisuccinate or hemifumarate having a trimetazidine/ malic acid, trimetazidine/ adipic acid, trimetazidine/ tartaric acid, trimetazidine/ phosphoric acid, trimetazidine/ trimetazidine/ sulfuric acid, trimetazidine/ succinic acid or trimetazidine/ fumaric acid molar ratio of 2/1.

4- A process according to anyone of Claims 2-3, wherein the solvent is selected from anisole, methyl isobutyl ketone, toluene, n-heptane, acetonitrile, methyl ethyl ketone, ethyl acetate, 1,3-dioxalane, tetrahydrofuran, acetone, methyl tert-butyl ether, water, methanol, ethanol, isopropanol, isobutanol, n-butanol, and mixtures thereof.

5-A pharmaceutical composition comprising a trimetazidine salt according to Claim 1, in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

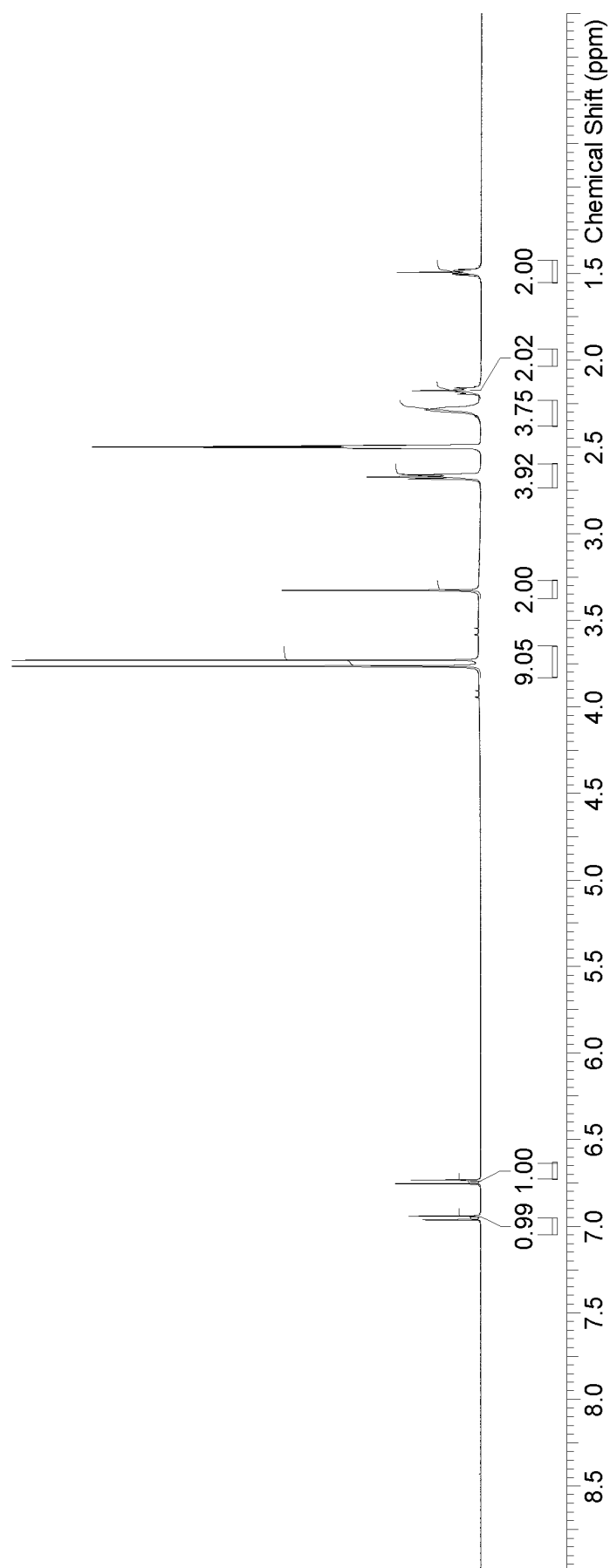
6-A pharmaceutical composition according to Claim 5, which is in the form of an immediate-release oral tablet, in the form of a prolonged release oral matrix tablet or in the form of coated minigranules in capsules, for oral, once-a-day administration.

7-A pharmaceutical composition according to any one of Claims 5 or 6, further comprising a betablocker.

8-A pharmaceutical composition according to Claim 7, wherein the betablocker is metoprolol
5 or bisoprolol.

9- A trimetazidine salt according to Claim 1 or a pharmaceutical composition according to any one of Claims 5 to 8, for use in the prophylactic treatment of angina pectoris, in the course of chorioretinal disorders or for the treatment of vertigo of vascular origin.

FIGURES

Figure 1a – ^1H NMR spectrum of the trimetazidine hemiadipate salt obtained in Example 1

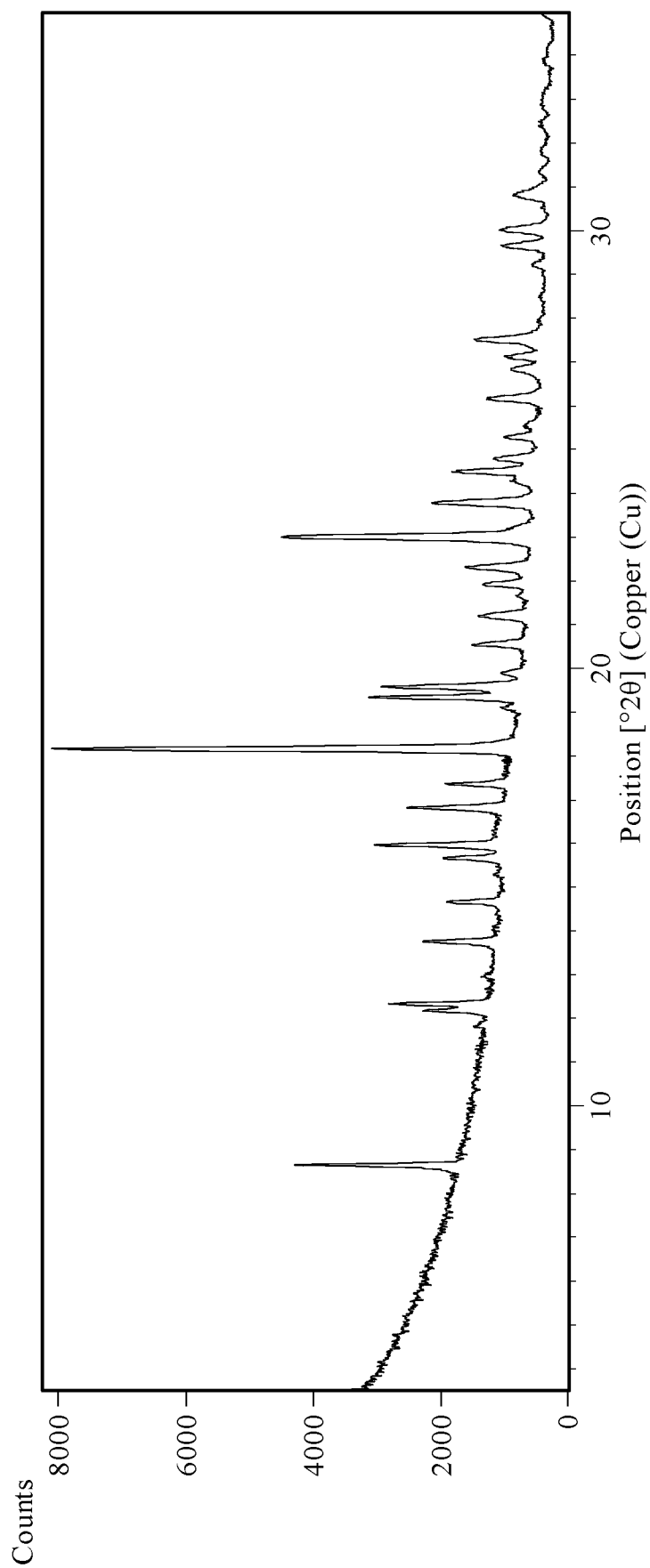


Figure 1b – XRPD pattern of the trimetazidine hemiadipate salt obtained in Example 1

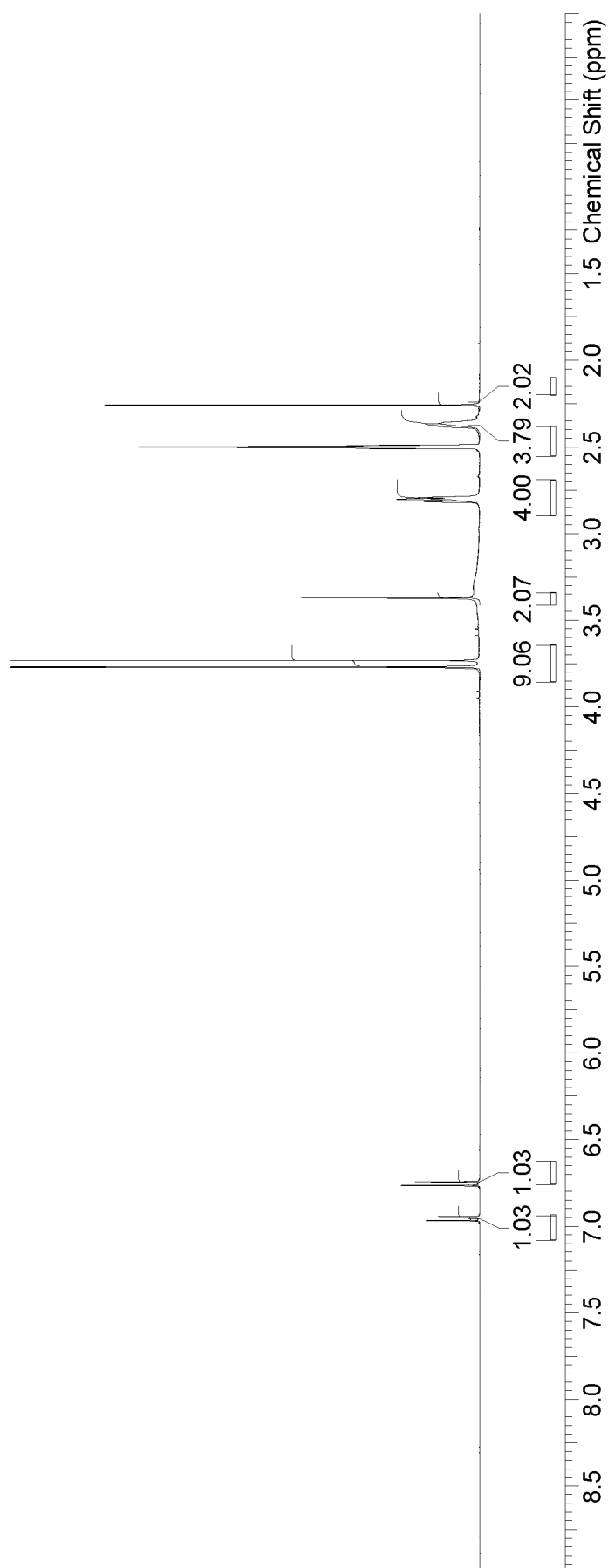


Figure 2a – ^1H NMR spectrum of the trimetazidine hemisuccinate salt obtained in Example 2

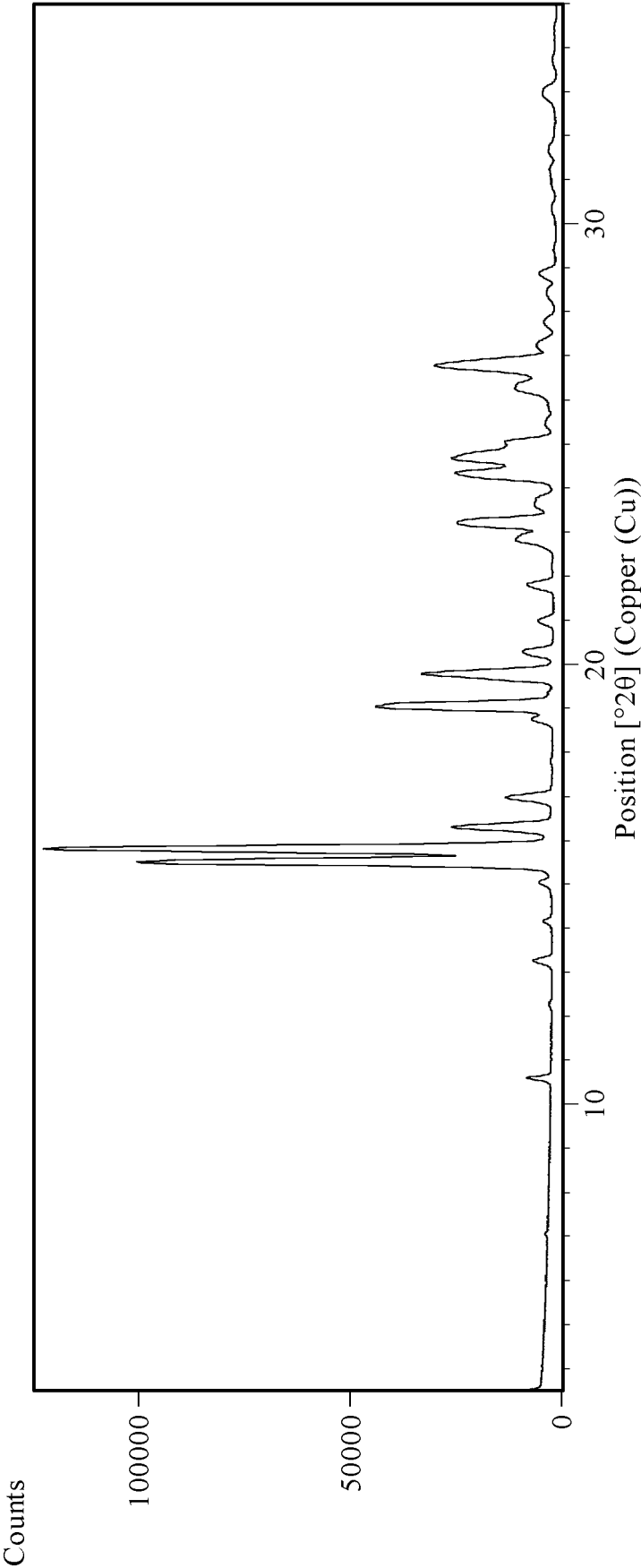


Figure 2b – XRPD pattern of the trimetazidine hemisuccinate salt obtained in Example 2

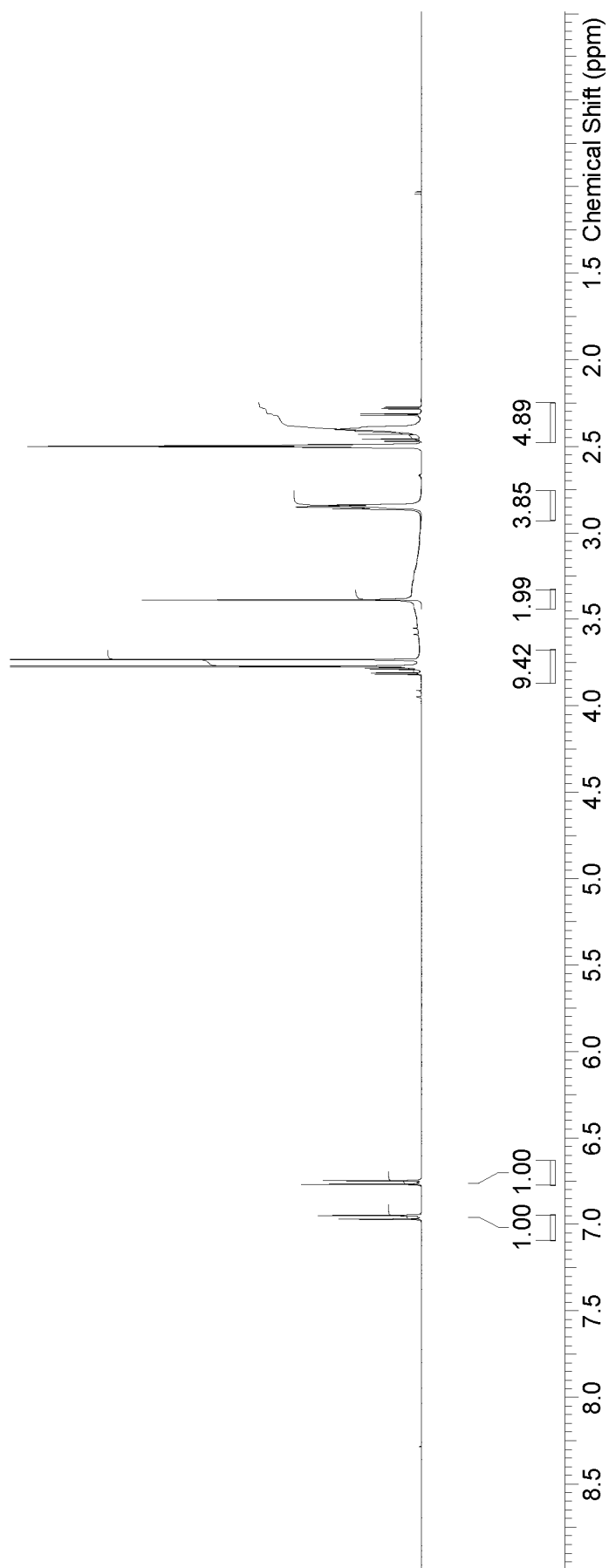


Figure 3a – ^1H NMR spectrum of the trimetazidine hemimalate salt obtained in Example 3

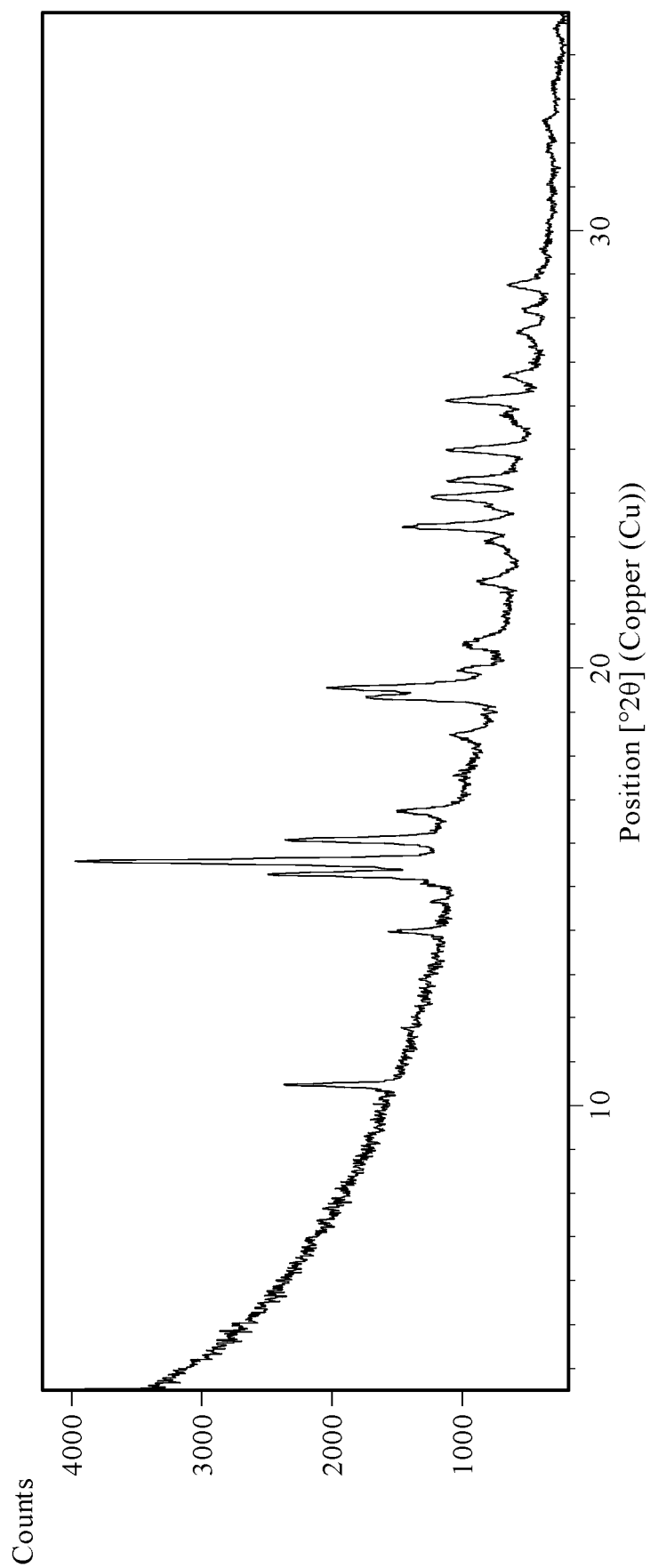


Figure 3b – XRPD pattern of the trimetazidine hemimalate salt obtained in Example 3

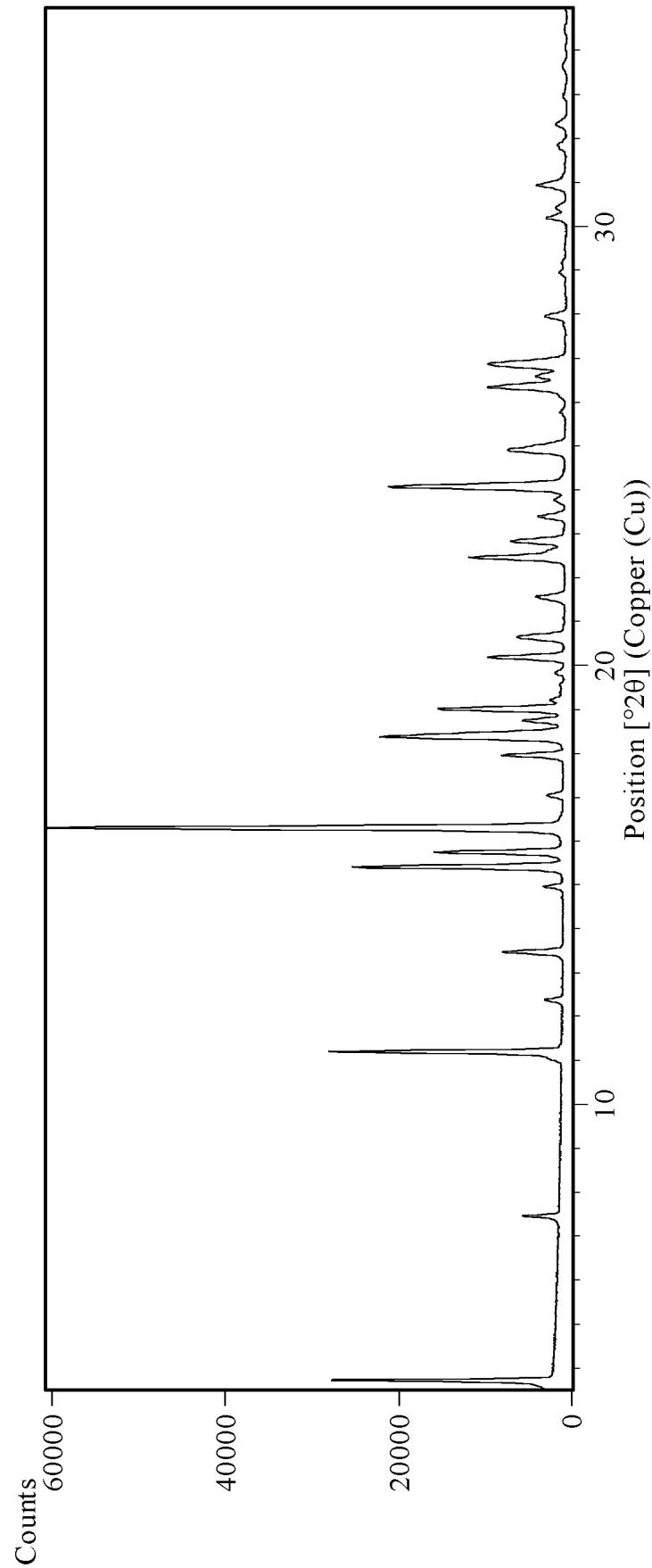


Figure 4 – XRPD pattern of the trimetazidine hemisulfate salt obtained in Example 4

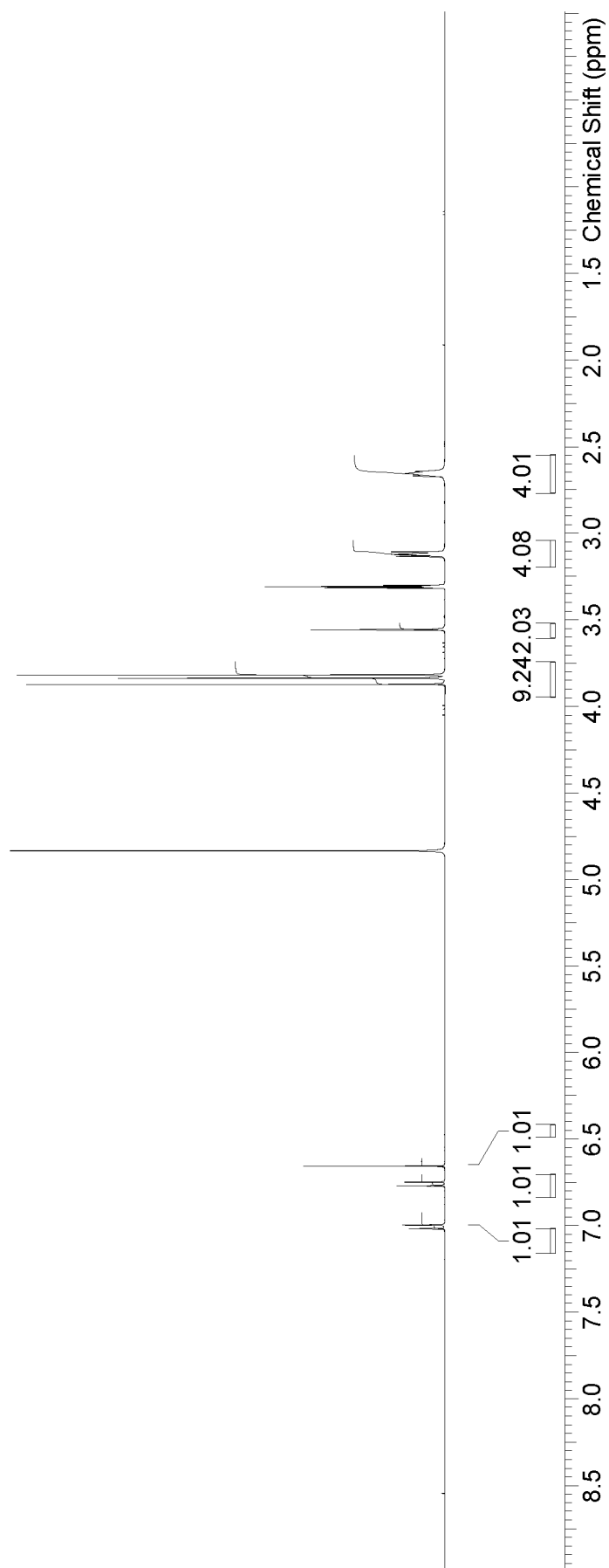


Figure 5a – ^1H NMR spectrum of the trimetazidine hemifumarate salt obtained in Example 5

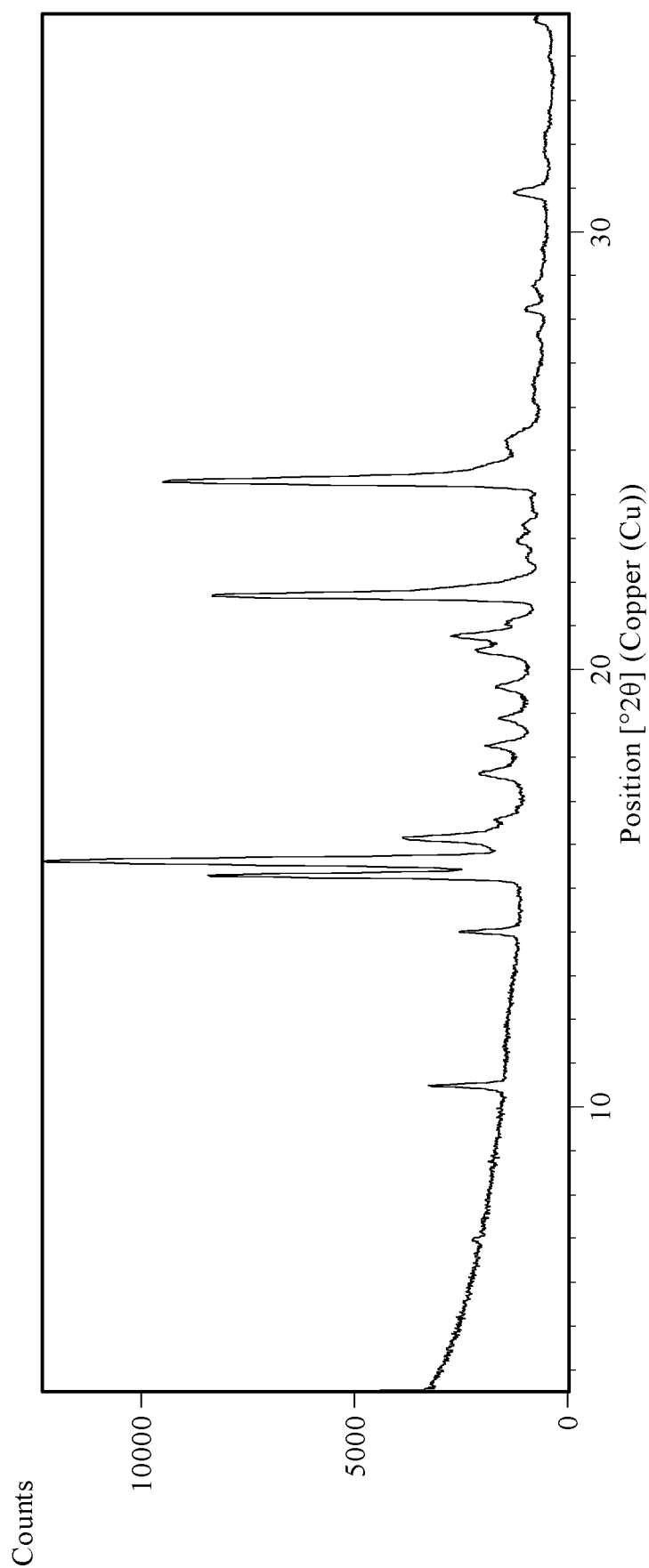


Figure 5b – XRPD pattern of the trimetazidine hemifumarate salt obtained in Example 5

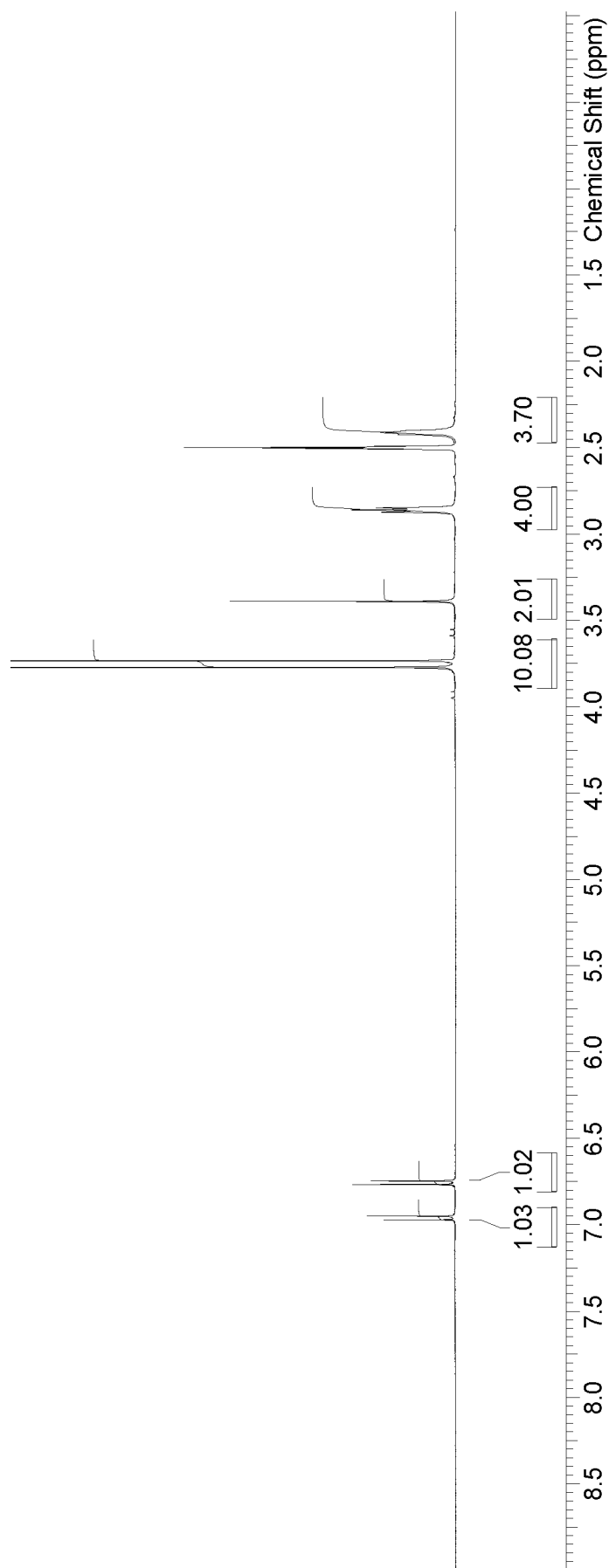


Figure 6a – ^1H NMR spectrum of the trimetazidine hemitartrate salt obtained in Example 6

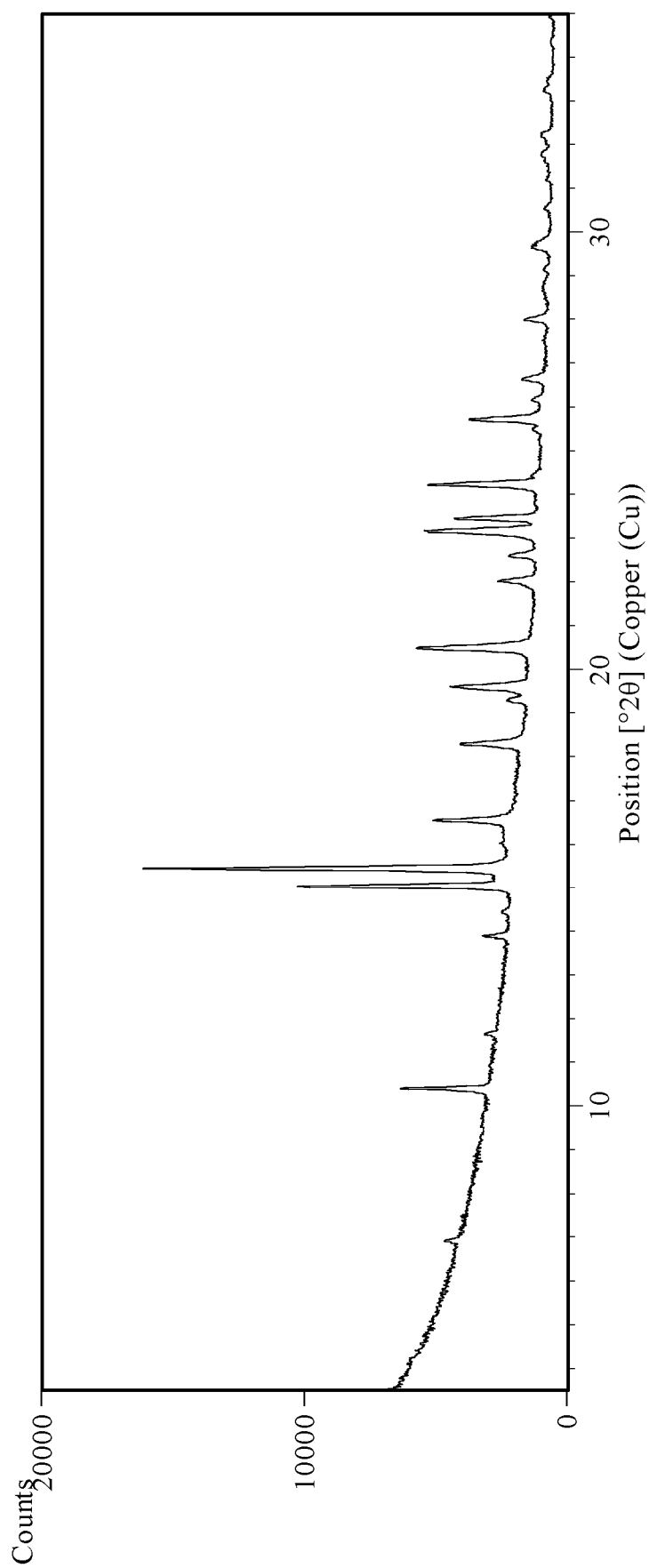


Figure 6b – XRPD pattern of the trimetazidine hemitartrate salt obtained in Example 6

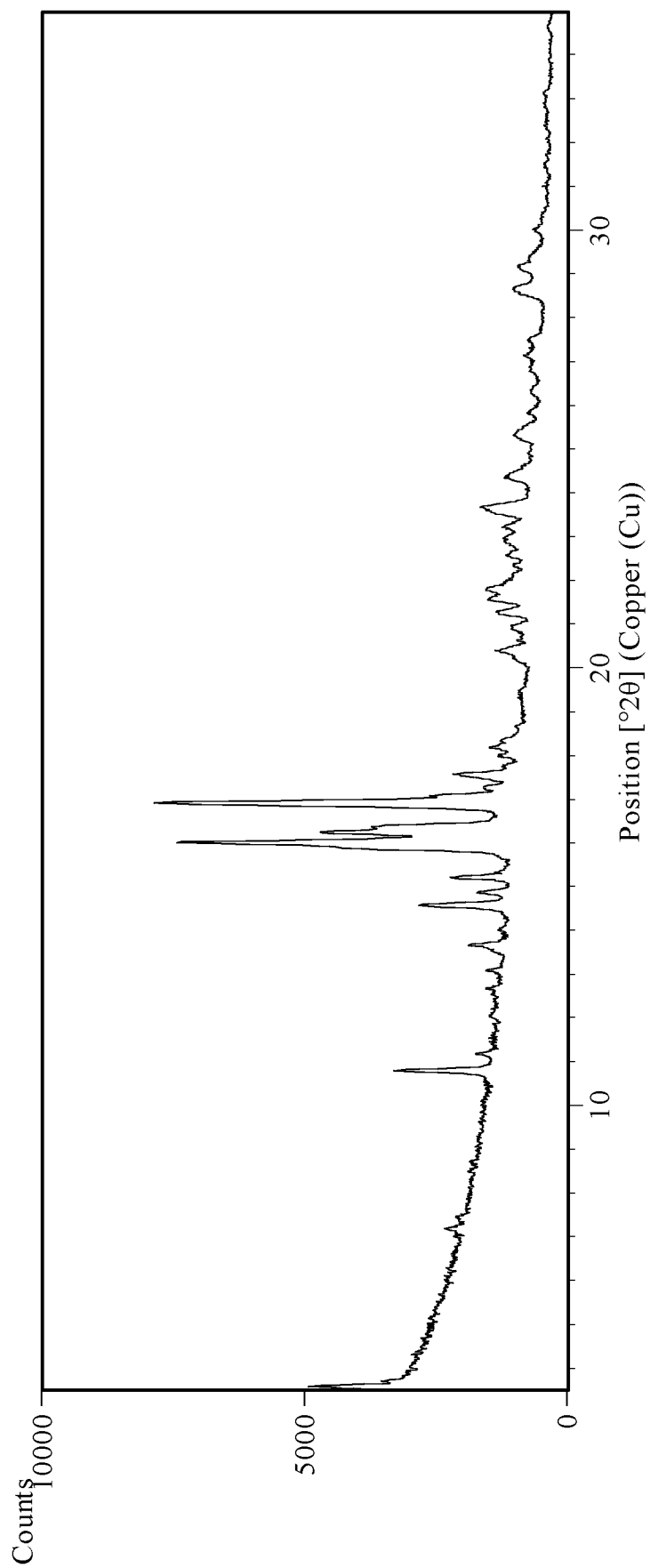


Figure 7 – XRPD pattern of the trimetazidine hemiphosphate salt obtained in Example 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/079054

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D295/096 A61P9/00 A61P9/10 A61K31/495 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 practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 110 105 307 A (UNIV SOUTH CENTRAL NATIONALITI) 9 August 2019 (2019-08-09) cited in the application claims; examples -----	1-9
A	CN 110 054 599 A (UNIV SOUTH CENTRAL NATIONALITI) 26 July 2019 (2019-07-26) cited in the application claims; examples -----	1-9
A	CN 110 183 398 A (UNIV SOUTH CENTRAL NATIONALITI) 30 August 2019 (2019-08-30) cited in the application claims; examples -----	1-9
A	WO 2014/180240 A1 (CHANGZHOU HI TECH DISTR MULTIPLE DIMENSION INDUSTRY TECHNOLOGY INST CO) 13 November 2014 (2014-11-13) claim 3 -----	1-9
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Date of the actual completion of the international search 1 December 2022		Date of mailing of the international search report 14/12/2022
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2022/079054

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			WO 2014180240 A1	13-11-2014
