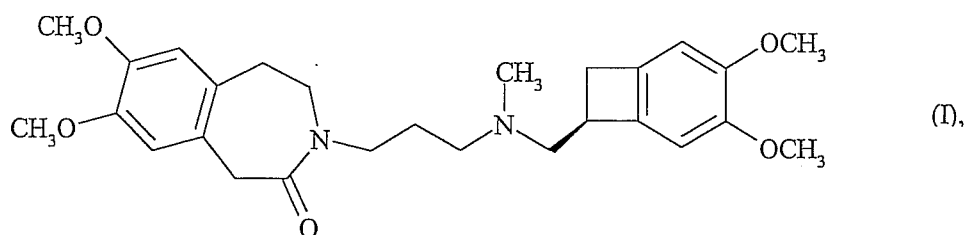


New process for the synthesis of ivabradine and addition salts thereof with a pharmaceutical acceptable acid

The present invention relates to a process for the industrial synthesis of ivabradine of formula (I) :



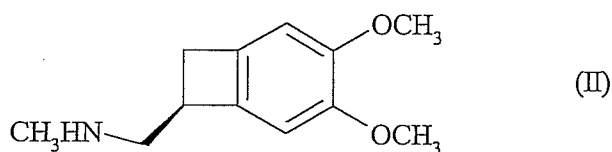
or 3-{3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl](methylamino)]-propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one,

addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Ivabradine, and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also of various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in the treatment of heart failure.

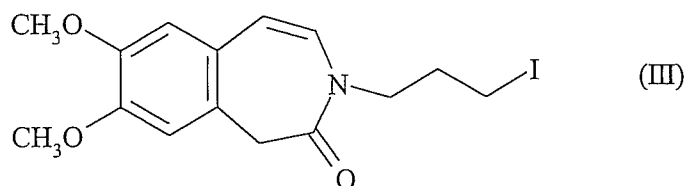
The preparation and therapeutic use of ivabradine and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in the European patent specification EP 0 534 859.

That patent specification describes the synthesis of ivabradine hydrochloride by reacting the compound of formula (II) :

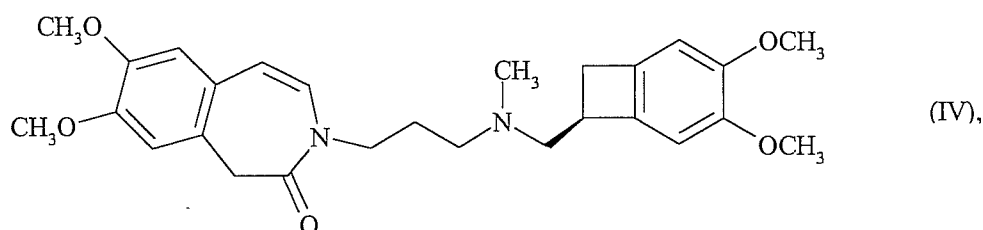


-2-

with the compound of formula (III) :



to yield the compound of formula (IV) :



5 the catalytic hydrogenation of which results in ivabradine, which is then converted into its hydrochloride.

That method has the disadvantage of yielding ivabradine hydrochloride in only a very low yield - less than 17 % over the 3 steps as a whole.

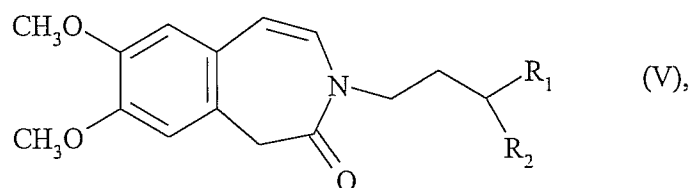
10 In view of the pharmaceutical value of ivabradine and its salts, and more especially its hydrochloride, it has been important to be able to obtain it by an effective industrial synthesis process comprising a minimal number of steps and allowing ivabradine and its salts, and more especially its hydrochloride, to be obtained in a satisfactory yield.

15 The Applicant has now developed a synthesis process allowing ivabradine salts to be obtained in a single step starting from a salt of the compound of formula (II), in a very good yield.

More specifically, the present invention relates to a process for the synthesis of ivabradine of formula (I), addition salts thereof with a pharmaceutically acceptable acid, and hydrates thereof,

-3-

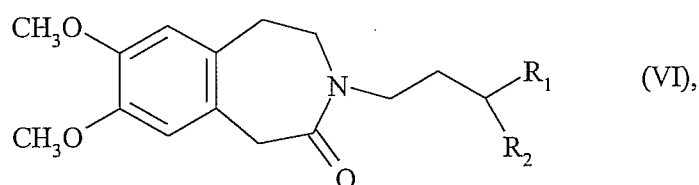
characterised in that the compound of formula (V) :



wherein R_1 and R_2 , which may be the same or different, each represent a linear or branched (C₁-C₈)alkoxy group or form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

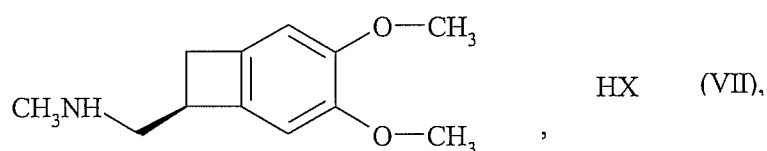
is subjected to a catalytic hydrogenation reaction,

and then the compound of formula (VI) thereby obtained :



wherein R_1 and R_2 are as defined hereinbefore,

is subjected to a reaction with the compound of formula (VII) :



wherein HX represents a pharmaceutically acceptable acid,

in the presence of hydrogen and a catalyst,

to yield directly, after filtering off the catalyst and isolation, the addition salt of ivabradine with the acid HX, which is optionally subjected, when it desired to obtain free ivabradine, to the action of a base.

Among the pharmaceutically acceptable acids, there may be mentioned by way of non-limiting example hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, trifluoroacetic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, tartaric, maleic, nitric, citric, ascorbic, oxalic, methanesulphonic, benzenesulphonic and camphoric acids.

This process makes it possible for addition salts of ivabradine, and especially its hydrochloride, to be obtained directly in a single step starting from the corresponding salt of the amine of formula (II), with excellent purity and in a very good yield.

Among the catalysts which can be used in the hydrogenation reaction of the compound of formula (V), there may be mentioned, without implying any limitation, palladium, platinum, nickel, ruthenium, rhodium, and their compounds, particularly in supported form or in oxide form.

The catalyst for the hydrogenation reaction of the compound of formula (V) is preferably palladium-on-carbon.

The temperature of the hydrogenation reaction of the compound of formula (V) is preferably from 20 to 100°C, more preferably from 40 to 80°C, even more preferably from 45 to 65°C.

The hydrogen pressure during the hydrogenation reaction of the compound of formula (V) is preferably from 1 to 220 bars, more preferably from 1 to 100 bars, even more preferably from 1 to 30 bars.

The hydrogenation reaction of the compound of formula (V) is preferably carried out in a non-acidic solvent.

Among the preferred non-acidic solvents which can be used in the hydrogenation reaction of the compound of formula (V), there may be mentioned, without implying any limitation,

acetates, alcohols, preferably ethanol, methanol or isopropanol, tetrahydrofurane, toluene, dichloromethane and xylene.

Advantageously, the intermediate compound of formula (VI) is not isolated and the crude reaction product is used as such in the reductive amination reaction.

5 Among the catalysts which can be used in the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII), there may be mentioned, without implying any limitation, palladium, platinum, nickel, ruthenium, rhodium, and their compounds, particularly in supported form or in oxide form.

10 The catalyst for the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII) is preferably palladium-on-carbon.

The temperature of the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII) is preferably from 30 to 120°C, more preferably from 40 to 100°C, even more preferably from 60 to 95°C.

15 The hydrogen pressure during the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII) is preferably from 1 to 220 bars, more preferably from 1 to 100 bars, even more preferably from 10 to 60 bars.

20 In the process according to the invention, the compounds of formulae (V) and (VI) that are preferably used are the compounds of formulae (Va) and (VIa), particular cases of the compounds of formulae (V) and (VI) wherein R₁ and R₂ form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring.

25 The compounds of formulae (Va), a particular case of the compounds of formula (V) wherein R₁ and R₂ form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring, and also the compounds of formula (VI), are new products which are useful as synthesis intermediates in the chemical or pharmaceutical industry, especially in the synthesis of ivabradine and addition salts thereof with a

pharmaceutically acceptable acid, and as such they form an integral part of the present invention.

A process which is preferred according to the invention is the process that uses, as synthesis intermediate, the compound of formula (VIIa), a particular case of the compounds of formula (VII) wherein HX represents hydrochloric acid, thereby yielding ivabradine hydrochloride of formula (Ia).

In that case, the process according to the present invention yields ivabradine hydrochloride in a crystalline form - the α form - which is well defined and perfectly reproducible and which especially has valuable characteristics in terms of filtration, drying, stability and ease of formulation.

That α crystalline form is new and constitutes another aspect of the present invention.

The α crystalline form of ivabradine hydrochloride is characterised by the following powder X-ray diffraction diagram measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of ray position (Bragg's angle 2 theta, expressed in degrees), ray height (expressed in counts), ray area (expressed in counts x degrees), ray width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å) :

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	1341	177	0.1338	21.486
2	7.7	1266	146	0.1171	11.440
3	8.1	1325	197	0.1506	10.923
4	10.4	1630	161	0.1004	8.488
5	11.8	753	87	0.1171	7.473
6	12.1	292	29	0.1004	7.301
7	13.2	917	106	0.1171	6.709
8	13.8	875	130	0.1506	6.423
9	15.3	281	37	0.1338	5.790
10	16.2	816	108	0.1338	5.478
11	16.5	2784	459	0.1673	5.381

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
12	17.4	1308	129	0.1004	5.106
13	18.1	455	52	0.1171	4.885
14	19.4	223	37	0.1673	4.569
15	20.2	3282	487	0.1506	4.389
16	20.6	305	45	0.1506	4.310
17	21.3	550	91	0.1673	4.165
18	21.9	1266	230	0.184	4.050
19	22.4	416	41	0.1004	3.972
20	23.0	262	35	0.1338	3.861
21	23.3	184	27	0.1506	3.814
22	24.4	309	51	0.1673	3.651
23	25.0	362	72	0.2007	3.566
24	25.7	1076	142	0.1338	3.459
25	26.5	2925	579	0.2007	3.363
26	26.8	821	135	0.1673	3.325
27	27.8	488	97	0.2007	3.212
28	28.4	620	123	0.2007	3.142
29	29.2	428	56	0.1338	3.057

The invention relates also to pharmaceutical compositions comprising as active ingredient the α crystalline form of ivabradine hydrochloride together with one or more appropriate, inert and non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and drinkable suspensions.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. The dosage varies from 1 to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention.

The X-ray powder diffraction spectrum was measured under the following experimental conditions :

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- PANalytical X'Pert Pro diffractometer, X'Celerator detector,
- voltage 45 kV, intensity 40 mA,
- mounting θ - θ ,
- $K\beta$ (Ni) filter,
- 5 - incident-beam and diffracted-beam Soller slit : 0.04 rad,
- fixed angle of divergence slits : $1/8^\circ$,
- mask : 10 mm,
- antiscatter slit : $1/4^\circ$,
- measurement mode : continuous from 3° to 30° , in increments of 0.017° ,
- 10 - measurement time per step : 19.7 s,
- total time : 4 min 32 s,
- measurement speed : $0.108^\circ/\text{s}$,
- measurement temperature : ambient.

15 **EXAMPLE 1 : Alpha crystalline form of 3-{3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one hydrochloride**

Load 5.5 kg of 3-[2-(1,3-dioxolan-2-yl)ethyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one, 27.5 litres of ethanol and 550 g of palladium-on-carbon into an autoclave.

20 Purge with nitrogen and then with hydrogen, heat to 55°C and then hydrogenate at that temperature under a pressure of 5 bars until the theoretical amount of hydrogen has been absorbed.

Then return to ambient temperature and release the autoclave pressure.

25 Then add 4 kg of (7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]-N-methylmethanamine hydrochloride, 11 litres of ethanol, 5.5 litres of water and 1 kg of palladium-on-carbon.

Purge with nitrogen and then with hydrogen, heat at 85°C and then hydrogenate at that temperature under a pressure of 30 bars until the theoretical amount of hydrogen has been absorbed.

Then return to ambient temperature and purge the autoclave; then filter the reaction mixture, distil off the solvents and then isolate the ivabradine hydrochloride by crystallisation from a toluene/1-methyl-2-pyrrolidinone mixture.

Ivabradine hydrochloride is thereby obtained in a yield of 85 % and with a chemical purity greater than 99 %.

X-ray powder diffraction diagram :

The X-ray powder diffraction profile (diffraction angles) of the α form of ivabradine hydrochloride is given by the significant rays collated in the following table :

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	1341	177	0.1338	21.486
2	7.7	1266	146	0.1171	11.440
3	8.1	1325	197	0.1506	10.923
4	10.4	1630	161	0.1004	8.488
5	11.8	753	87	0.1171	7.473
6	12.1	292	29	0.1004	7.301
7	13.2	917	106	0.1171	6.709
8	13.8	875	130	0.1506	6.423
9	15.3	281	37	0.1338	5.790
10	16.2	816	108	0.1338	5.478
11	16.5	2784	459	0.1673	5.381
12	17.4	1308	129	0.1004	5.106
13	18.1	455	52	0.1171	4.885
14	19.4	223	37	0.1673	4.569
15	20.2	3282	487	0.1506	4.389
16	20.6	305	45	0.1506	4.310
17	21.3	550	91	0.1673	4.165
18	21.9	1266	230	0.184	4.050
19	22.4	416	41	0.1004	3.972
20	23.0	262	35	0.1338	3.861
21	23.3	184	27	0.1506	3.814
22	24.4	309	51	0.1673	3.651
23	25.0	362	72	0.2007	3.566

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
24	25.7	1076	142	0.1338	3.459
25	26.5	2925	579	0.2007	3.363
26	26.8	821	135	0.1673	3.325
27	27.8	488	97	0.2007	3.212
28	28.4	620	123	0.2007	3.142
29	29.2	428	56	0.1338	3.057

EXAMPLE 2 : Pharmaceutical composition

Formula for the preparation of 1000 tablets each containing 5 mg of ivabradine base :

Compound of Example 1 5.39 g

Corn starch..... 20 g

5 Anhydrous colloidal silica..... 0.2 g

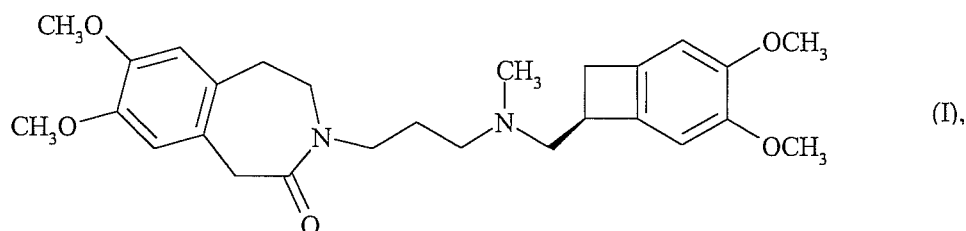
Mannitol 63.91 g

PVP..... 10 g

Magnesium stearate 0.5 g

CLAIMS

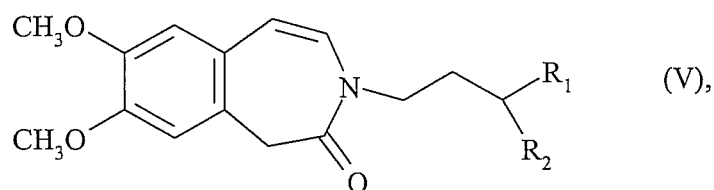
1. Process for the synthesis of ivabradine of formula (I) :



or 3-{3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl](methyl)amino]-
5 propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one,

addition salts thereof with a pharmaceutically acceptable acid, and hydrates thereof,

characterised in that the compound of formula (V) :

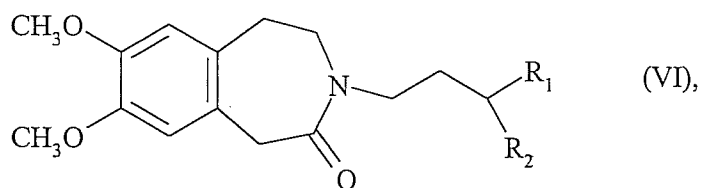


wherein R₁ and R₂, which may be the same or different, each represent a linear or branched
10 (C₁-C₈)alkoxy group or form, together with the carbon atom carrying them, a 1,3-dioxane,
1,3-dioxolane or 1,3-dioxepane ring,

is subjected to a catalytic hydrogenation reaction,

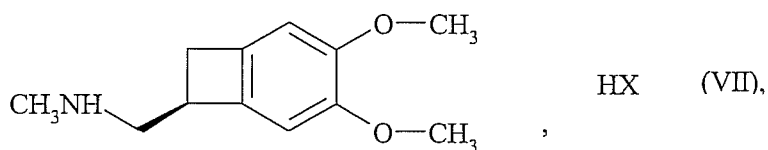
and then the compound of formula (VI) thereby obtained :

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wherein R_1 and R_2 are as defined hereinbefore,

is subjected to a reaction with the compound of formula (VII) :



5 wherein HX represents a pharmaceutically acceptable acid,

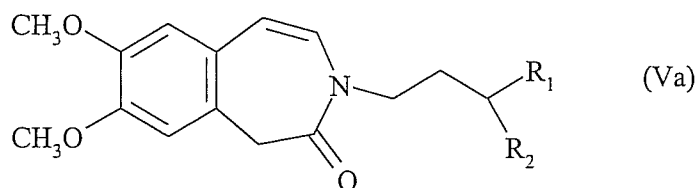
in the presence of hydrogen and a catalyst,

to yield directly, after filtering off the catalyst and isolation, the addition salt of ivabradine with the acid HX, which is optionally subjected, when it desired to obtain free ivabradine, to the action of a base.

- 10 2. Synthesis process according to claim 1, wherein the catalyst for the hydrogenation reaction of the compound of formula (V) is palladium-on-carbon.
3. Synthesis process according to either claim 1 or claim 2, wherein the hydrogen pressure during the hydrogenation reaction of the compound of formula (V) is from 1 to 220 bars.
- 15 4. Synthesis process according to any one of claims 1 to 3, wherein the temperature of the hydrogenation reaction of the compound of formula (V) is from 20 to 100°C.

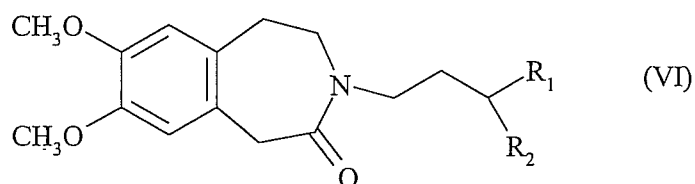
5. Synthesis process according to claim 4, wherein the temperature of the hydrogenation reaction of the compound of formula (V) is from 40 to 80°C.
6. Synthesis process according to any one of claims 1 to 5, wherein the intermediate compound of formula (VI) is not isolated.
- 5 7. Synthesis process according to any one of claims 1 to 6, wherein the catalyst for the reaction between the compound of formula (VI) and the compound of formula (VII) is palladium-on-carbon.
8. Synthesis process according to any one of claims 1 to 7, wherein the hydrogen pressure during the reaction between the compound of formula (VI) and the compound
10 of formula (VII) is from 1 to 220 bars.
9. Synthesis process according to any one of claims 1 to 8, wherein the temperature of the reaction between the compounds of formulae (VI) and (VII) is from 30 to 120°C.
10. Synthesis process according to claim 9, wherein the temperature of the reaction between the compounds of formulae (VI) and (VII) is from 40 to 100°C.
- 15 11. Synthesis process according to any one of claims 1 to 10, which uses compounds of formulae (Va) and (VIa), particular cases of the compounds of formulae (V) and (VI) wherein R₁ and R₂ form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or dioxepane ring.
12. Synthesis process according to any one of claims 1 to 11, which uses the intermediate
20 of formula (VIIa), a particular case of the compounds of formula (VII) wherein HX represents hydrochloric acid, thereby yielding ivabradine hydrochloride.
13. Compound of formula (Va) :

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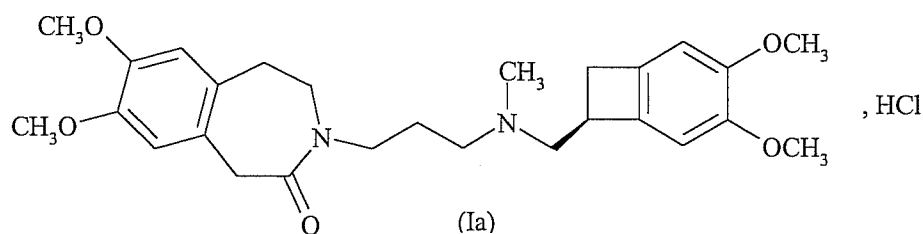
wherein R_1 and R_2 form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or dioxepane ring.

14. Compound of formula (VI) :



wherein R_1 and R_2 , which may be the same or different, each represent a linear or branched (C_1 - C_8)alkoxy group or form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or dioxepane ring.

15. α crystalline form of ivabradine hydrochloride of formula (Ia) :



characterised by the following powder X-ray diffraction diagram measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of ray position (Bragg's angle 2θ , expressed in degrees), ray height (expressed in counts), ray area (expressed in counts x degrees), ray width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

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9	15.3	281	37	0.1338	5.790
10	16.2	816	108	0.1338	5.478
11	16.5	2784	459	0.1673	5.381
12	17.4	1308	129	0.1004	5.106
13	18.1	455	52	0.1171	4.885
14	19.4	223	37	0.1673	4.569
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18	21.9	1266	230	0.184	4.050
19	22.4	416	41	0.1004	3.972
20	23.0	262	35	0.1338	3.861
21	23.3	184	27	0.1506	3.814
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23	25.0	362	72	0.2007	3.566
24	25.7	1076	142	0.1338	3.459
25	26.5	2925	579	0.2007	3.363
26	26.8	821	135	0.1673	3.325
27	27.8	488	97	0.2007	3.212
28	28.4	620	123	0.2007	3.142
29	29.2	428	56	0.1338	3.057

16. Pharmaceutical composition comprising as active ingredient the α crystalline form of ivabradine hydrochloride according to claim 15, in combination with one or more pharmaceutically acceptable, inert and non-toxic carriers.

17. Use of the α crystalline form of ivabradine hydrochloride according to claim 15 in the manufacture of medicaments which are of use as bradycardics.

18. Use of the α crystalline form of ivabradine hydrochloride according to claim 15 in the manufacture of medicaments which are of use in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial

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infarct and associated rhythm disturbances, and also of various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in the treatment of heart failure.