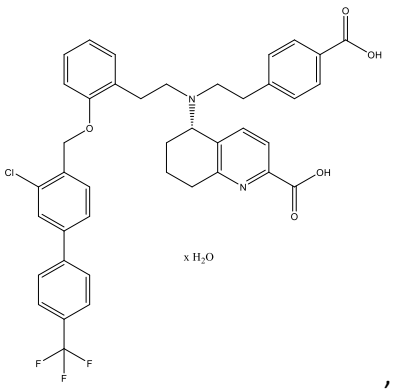
Patent claims:

1. A crystalline monohydrate form of Compound 1:

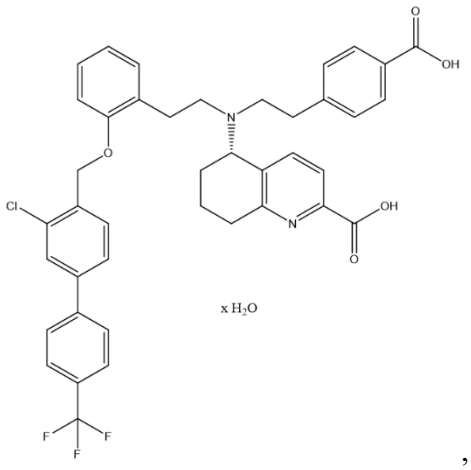


,

comprising X-ray powder diffraction reflections at 12.8 ± 0.2 °2θ, 29.2 ± 0.2 °2θ, and at least one additional reflection at 6.9 ± 0.2 °2θ, 7.2 ± 0.2 °2θ, or 7.3 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

2. The crystalline monohydrate form of claim 1, comprising at least one additional reflection at 15.2 ± 0.2 °2θ or 23.0 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

3. A crystalline monohydrate form of Compound 1:

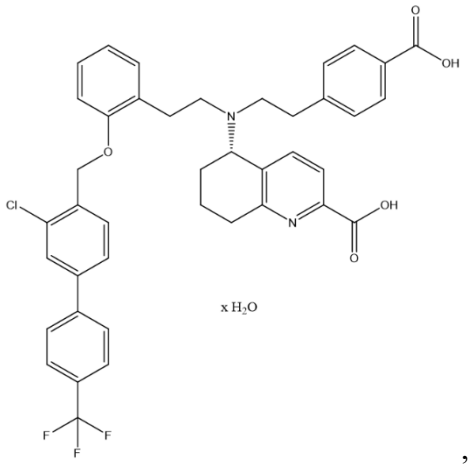


,

comprising X-ray powder diffraction reflections at 12.8 ± 0.2 °2θ, 16.0 ± 0.2 °2θ, and 25.8 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

4. The crystalline monohydrate form of claim 3, comprising at least one additional reflection at 6.9 ± 0.2 °2θ, 7.2 ± 0.2 °2θ, 7.3 ± 0.2 °2θ, or 15.2 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

5. A crystalline monohydrate form of Compound 1:

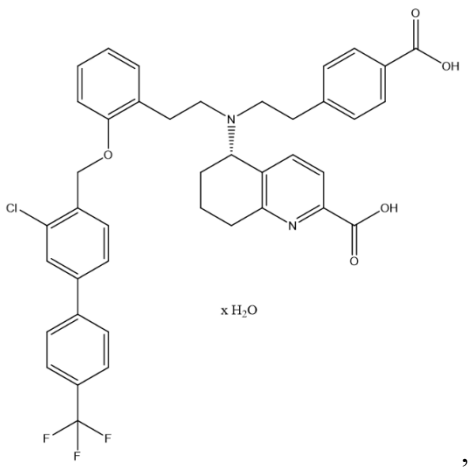


,

comprising X-ray powder diffraction reflections at 12.8 ± 0.2 °2θ, 20.5 ± 0.2 °2θ, and 25.8 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

6. The crystalline monohydrate form of claim 5, comprising at least one additional reflection at 6.9 ± 0.2 °2θ, 7.2 ± 0.2 °2θ, 7.3 ± 0.2 °2θ, 15.2 ± 0.2 °2θ, or 25.1 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

7. A crystalline monohydrate form of Compound 1:



,

comprising at least three X-ray powder reflections selected from 5.7 ± 0.2 °2θ, 6.9 ± 0.2 °2θ, 7.2 ± 0.2 °2θ, 7.3 ± 0.2 °2θ, 9.9 ± 0.2 °2θ, 10.4 ± 0.2 °2θ, 10.6 ± 0.2 °2θ, 11.1 ± 0.2 °2θ, 11.5 ± 0.2 °2θ, 12.0 ± 0.2 °2θ, 12.3 ± 0.2 °2θ, 12.4 ± 0.2 °2θ, 12.8 ± 0.2 °2θ, 13.7 ± 0.2 °2θ, 14.1 ± 0.2 °2θ, 14.3 ± 0.2 °2θ, 15.2 ± 0.2 °2θ, 15.6 ± 0.2 °2θ, 16.0 ± 0.2 °2θ, 16.9 ± 0.2 °2θ, 17.2 ± 0.2 °2θ, 17.5 ± 0.2 °2θ, 17.7 ± 0.2 °2θ, 18.0 ± 0.2 °2θ, 18.4 ± 0.2 °2θ, 18.8 ± 0.2 °2θ, 19.2 ± 0.2 °2θ, 19.9 ± 0.2 °2θ, 20.2 ± 0.2 °2θ, 20.5 ± 0.2 °2θ, 20.7 ± 0.2 °2θ, 21.3 ± 0.2 °2θ, 21.9 ± 0.2 °2θ, 22.2 ± 0.2 °2θ, 22.5 ± 0.2 °2θ, 23.0 ± 0.2 °2θ, 23.4 ± 0.2 °2θ, 23.7 ± 0.2 °2θ, 24.1 ± 0.2 °2θ, 25.1 ± 0.2 °2θ, 25.8 ± 0.2 °2θ, 26.0 ± 0.2 °2θ, 26.4 ± 0.2 °2θ, 28.9 ± 0.2 °2θ, 29.2 ± 0.2 °2θ, 29.4 ± 0.2 °2θ, 30.6 ± 0.2 °2θ, 31.1 ± 0.2 °2θ, 32.2 ± 0.2 °2θ, and 35.3 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

8. The crystalline monohydrate form of claim 1, not having a reflection at 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, or 9.3 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

9. The crystalline monohydrate form of claim 3, not having a reflection at 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, or 9.3 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

10. The crystalline monohydrate form of claim 5, not having a reflection at 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, or 9.3 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

11. The crystalline monohydrate form of claim 7, not having a reflection at 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, or 9.3 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

12. The crystalline monohydrate form of claim 1, not having a reflection at one of 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 7.6 ± 0.2 °2θ, 7.9 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 14.8 ± 0.2 °2θ, 30.0 ± 0.2 °2θ, or 31.6 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

13. The crystalline monohydrate form of claim 3, not having a reflection at one of 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 7.6 ± 0.2 °2θ, 7.9 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 14.8 ± 0.2 °2θ, 30.0 ± 0.2 °2θ, or 31.6 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

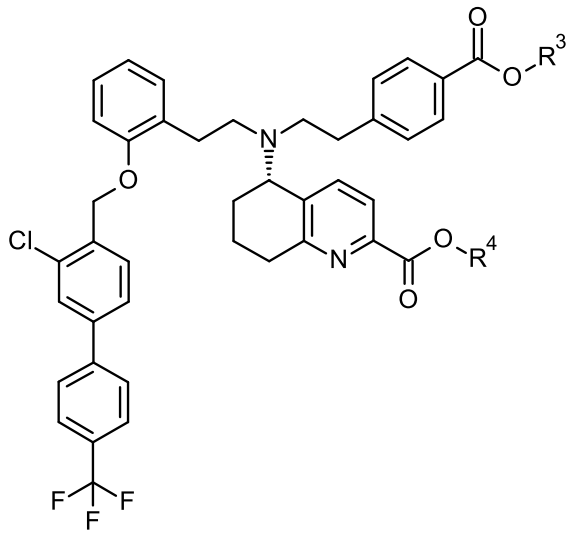
14. The crystalline monohydrate form of claim 5, not having a reflection at one of 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 7.6 ± 0.2 °2θ, 7.9 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 14.8 ± 0.2 °2θ, 30.0 ± 0.2 °2θ, or 31.6 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

15. The crystalline monohydrate form of claim 7, not having a reflection at one of 3.1 ± 0.2 °2θ, 6.1 ± 0.2 °2θ, 7.6 ± 0.2 °2θ, 7.9 ± 0.2 °2θ, 8.5 ± 0.2 °2θ, 9.3 ± 0.2 °2θ, 14.8 ± 0.2 °2θ, 30.0 ± 0.2 °2θ, or 31.6 ± 0.2 °2θ, using Cu K alpha radiation when measured at 25 °C.

16. The crystalline monohydrate form of claim 1, having an X-ray powder diffractogram as shown in Figure 6.

17. The crystalline monohydrate form of claim 1, having a Raman spectrum with at least the following band maxima: 3073, 2950, 2937, 1685, 1616, 1527, 1293, 1278, and 1259 cm-1.

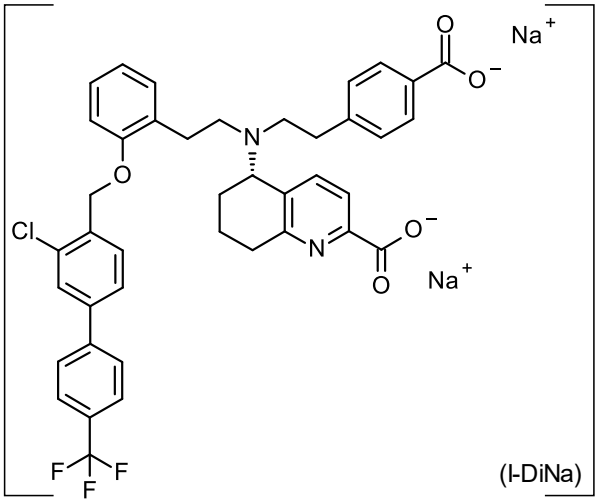
18. Process for preparing the compound of the formula (I), characterized in that in a first step [A] the compound of the formula (XII-1):



(XII-1),

wherein R^3 and R^4 are independently C_1-C_4-alkyl,

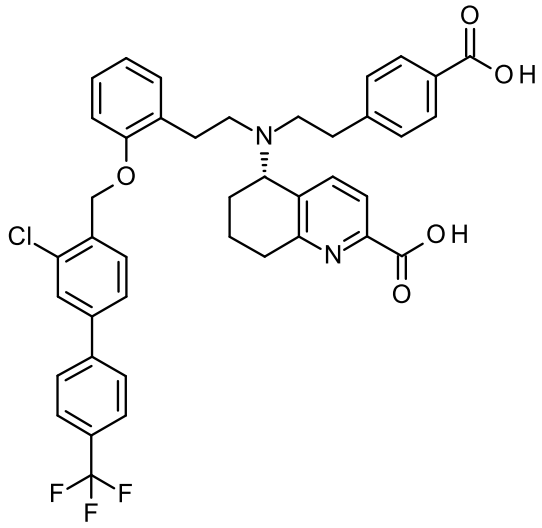
solubilized in a suitable solvent is reacted with a sodium hydroxide solution to yield the disodium salt (I-DiNa):



(I-DiNa),

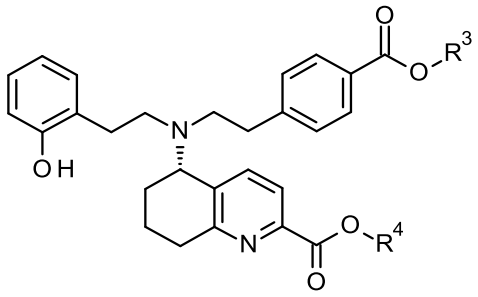
which is after extractive purification but without further isolation reacted in a second step [B]

by adding the reaction solution portionwise to a mixture of a mineral acid in a suitable solvent until a pH value of 3.8 to 4.2 is reached, wherein the pH value of the initially charged mineral acid mixture has a value of less than 3.8 and comprises at maximum two acid equivalents related to the disodium salt to finally yield compound of the formula (I):



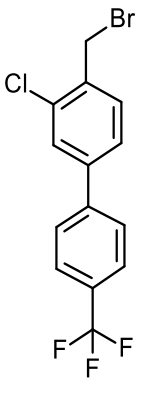
(I).

19. Process for preparing the compound of the formula I according to claim 18, characterized in that in a first step [C] the compound of the formula (X-1),



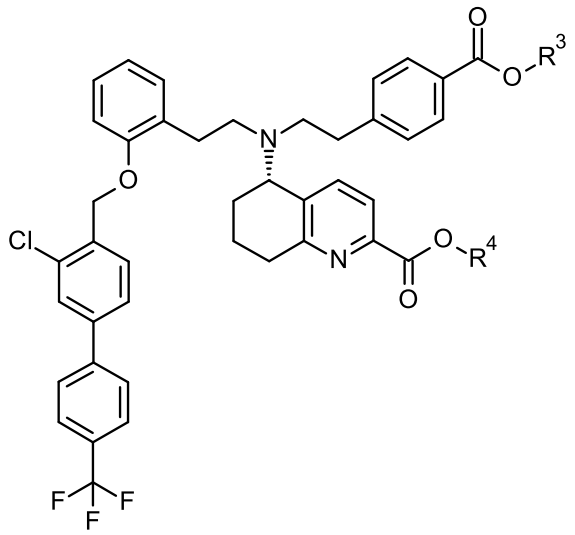
(X-1),

wherein R^3 and R^4 are independently C_1-C_4-alkyl,
is reacted in the presence of a base, selected from the group consisting of alkalicarbonate, alkalihydroxide or tetraalkylammoniumcarbonate with a compound of formula (XI),



(XI),

to provide compound of formula (XII-1),

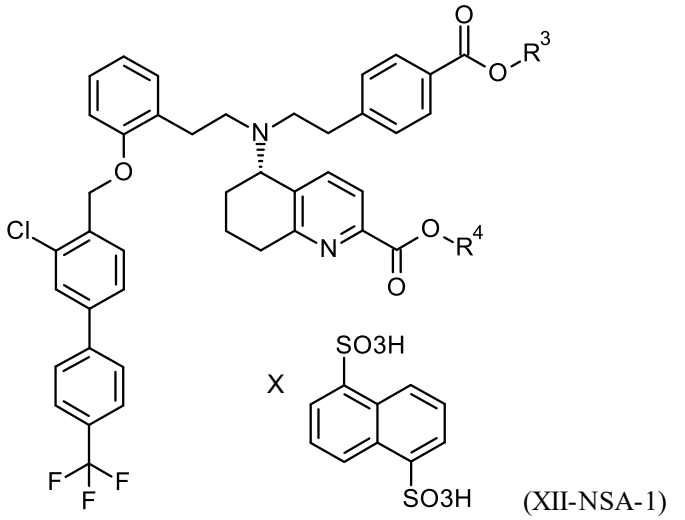


(XII-1),

wherein R^3 and R^4 are independently C_1-C_4-alkyl,

further characterized in that compound of formula (XII-1) is reacted further without purification in the sequential steps [A] and [B] according to claim 18.

20. Process for preparing the compound of the formula I according to claim 18, characterized in that in a first step [D] the NSA salt of formula (XII-NSA-1):



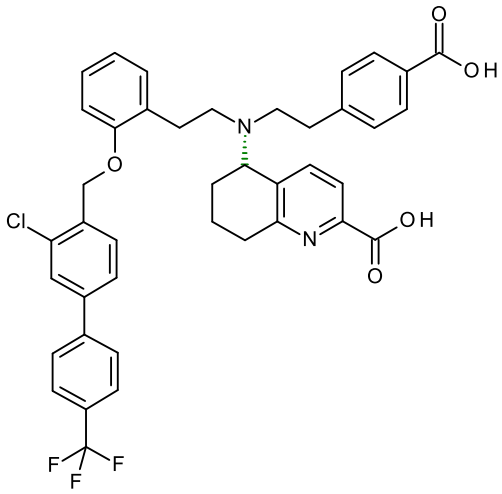
(XII-NSA-1),

wherein R^3 and R^4 are independently C_1-C_4-alkyl,

is treated with a suitable ether and stirred with water and aqueous ammonia at temperatures of 10°C to 25°C , whereby finally a pH-value of 7.8 to 8.2 is reached, afterwards the reaction mixture is treated with an organic solvent not miscible with water, the phases are separated and finally organic phase is concentrated to yield butylester of formula (XII-1), which is reacted further without purification in the sequential steps [A] and [B] according to claim 18.

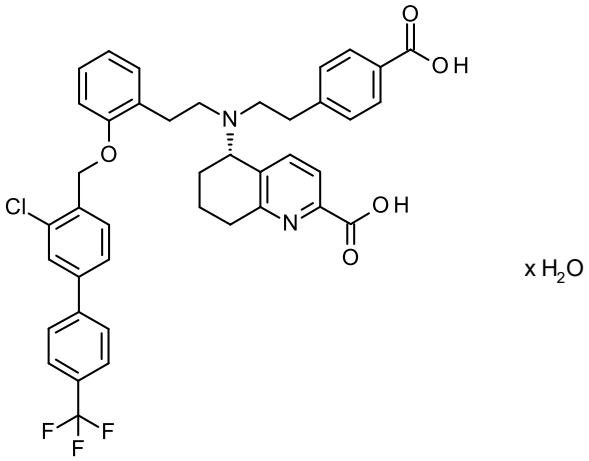
21. Process for preparing (5S)-{[2-(4-Carboxyphenyl)ethyl][2-(2-{[3-chloro-4'-(trifluoromethyl)

biphenyl-4-yl]methoxy}phenyl)ethyl]amino}-5,6,7,8-tetrahydroquinoline-2-carboxylic acid (I) in crystalline form, characterized in that the compound of the formula (I):



(I),

is crystallized from a mixture of polar solvents wherein the polar solvent is selected from methanol, acetone, and, water, wherein at least a mixture of methanol and water is necessary at a temperature of from 20°C to 100°C and the compound (I-M-I):



(I-M-I),

is isolated, optionally after cooling,

characterized in that the x-ray diffractogram (at 25°C and with Cu-K alpha 1 as radiation source) of the compound of formula (I-M-I) displays at least the following reflections: 12.8 ± 0.2 °2θ and 29.2 ± 0.2 °2θ

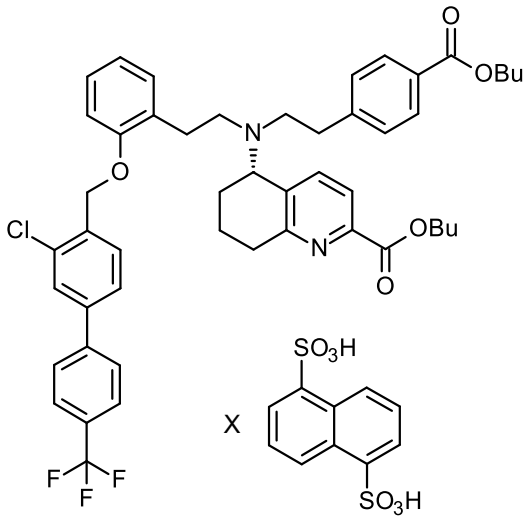
.

22. Process for preparing (5S)-{[2-(4-Carboxyphenyl)ethyl][2-(2-{[3-chloro-4'-(trifluoromethyl) biphenyl-4-yl]methoxy}phenyl)ethyl]amino}-5,6,7,8-tetrahydroquinoline-2-carboxylic acid (I) in crystalline form according to claim 21, characterized in that the acid of formula I is firstly dissolved in a 1:1 mixture of methanol and acetone, preferably in a 4 fold amount of each solvent (8 fold amount in relation to the 1:1 mixture) in g in relation to amount of solid compound of formula I in g, at a temperature of 50°C and cooled to room temperature, preferably 20°C, the solution is clarified by filtration, heated

again to 50 °C and water in a 1.8 fold amount in g in relation to amount of solid compound of formula I in g is added dropwise over a period of time.

23. Process for preparing (5S)-{[2-(4-Carboxyphenyl)ethyl][2-(2-{[3-chloro-4'-(trifluoromethyl) biphenyl-4-yl]methoxy}phenyl)ethyl]amino}-5,6,7,8-tetrahydroquinoline-2-carboxylic acid (I) in crystalline modification monohydrate I (I-M-I) according to claim 21 or claim 22, characterized in that the acid of formula I is prepared by one process according to any one of claims 18 to 20.

24. A compound of formula (XIII):



(XIII).

25. A pharmaceutical composition comprising the crystalline monohydrate form of Compound 1 of any one of claims 1-17 and one or more pharmaceutically acceptable excipients.

26. Use of a crystalline monohydrate form of Compound 1 of any one of claims 1-17 in the manufacture of a medicament for the treatment and/or prophylaxis of a cardiopulmonary disease or disorder.

27. Use of the pharmaceutical composition of claim 25 in the manufacture of a medicament for the treatment and/or prophylaxis of a cardiopulmonary disease or disorder.

28. Use of the crystalline monohydrate form of Compound 1 of any one of claims 1-17 in the manufacture of a pharmaceutical composition of claim 25 for the treatment and/or prophylaxis of a cardiopulmonary disease or disorder.

29. Use of the crystalline monohydrate form of Compound 1 of any one of claims 1-17 for the manufacture of a stable inhalative dosage form for use in a dry powder inhaler.

30. The use of any one of claims 26-28, wherein the cardiopulmonary disease or disorder is selected from the group consisting of pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH), and pulmonary hypertension (PH) associated with chronic lung disease (PH group 3).

31. The use of claim 30, wherein the pulmonary hypertension (PH) associated with chronic lung disease (PH group 3) is pulmonary hypertension in chronic obstructive pulmonary disease (PH-COPD) or pulmonary hypertension with idiopathic interstitial pneumonia (PH-IIP).