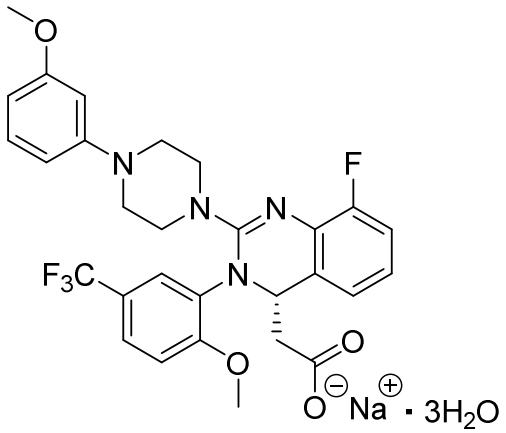
Claims

1. A method of producing a crystalline form of sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate of formula (I)



(**I**)

the method comprising the steps:

Step 1) providing a solution of 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetic acid in a mixture of a (C_1-C_6) alkyl acetate and a (C_1-C_6) dialkyl ether, wherein the molar ratio of (C_1-C_6) alkyl acetate : (C_1-C_6) dialkyl ether is from 1:1 to 1:3 in a concentration range of from 0.3 M to 0.7 M and wherein the temperature of the solution is preferably in the range of from 30 °C to 60 °C;

Step 2) adding 1.0 to 2.0 mole equivalents of an aqueous sodium hydroxide solution based on the 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetic acid content to the solution resulting from step 1 to provide a mixture;

Step 3) stirring the mixture resulting from step 2 for at least 30 minutes at a temperature in the range of from 30 °C to 60 °C to obtain a suspension containing a solid compound;

Step 4) separating the solid compound from the suspension resulting from step 3; and

Step 5) drying the solid compound resulting from step 4 at a temperature in the range of from 30 °C to 60 °C for at least one hour to obtain crystalline sodium 2-[(4S)-

8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4H-quinazolin-4-yl]acetate trihydrate.

2. The method according to claim 1, wherein the concentration of sodium hydroxide in the aqueous sodium hydroxide solution of step 2 is in the range of from 5 M to 30 M and more preferably in the range of from 10 M to 30 M.

3. The method according to claim 1 or 2, wherein 1.1 to 1.5 mole equivalents of sodium hydroxide based on the 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetic acid content are added in step 2 as an aqueous solution at a concentration of sodium hydroxide in the range of from 10 M to 30 M.

4. The method according to any one of claims 1 to 3, wherein step 3 further comprises:
cooling down the stirred suspension to room temperature at a cooling rate of 60 K per hour or below,
filtering the cooled suspension to provide a solid compound, and
optionally washing the solid compound with the (C_1-C_6) dialkyl ether, which is the (C_1-C_6) dialkyl ether used in step 1.

5. The method according to any one of claims 1 to 4, wherein the (C_1-C_6) alkyl acetate is methyl acetate, propyl acetate, isopropyl acetate or butyl acetate, or a mixture thereof and the (C_1-C_6) dialkyl ether is diisopropyl ether, methoxypentane, or methyl tert-butyl ether, or a mixture thereof, preferably wherein the (C_1-C_6) alkyl acetate is isopropyl acetate and the (C_1-C_6) dialkyl ether is diisopropyl ether, and more preferably, wherein the (C_1-C_6) alkyl acetate is isopropyl acetate and the (C_1-C_6) dialkyl ether is diisopropyl ether and the molar ratio of isopropyl acetate : dialkyl ether is 1:2.

6. The method according to any one of claims 1 to 5, wherein in step 1 the concentration of the solution of 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetic acid is between 0.3 M to 0.6 M.

7. The method according to any one of claims 1 to 6, wherein in step 5, drying the solid compound is performed under reduced pressure below 10 hPa, preferably at around 2 to 3 hPa at 50 °C for 15 hours.

8. The method according to any one of claims 1 to 7, wherein step 2 further comprises:

inoculating the solution with seed crystals of sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate in an amount of from 0.5 to 1 wt% based on the total weight of 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetic acid provided in step 1.

9. The method according to any one of claims 1 to 8 further comprising the additional subsequent step:

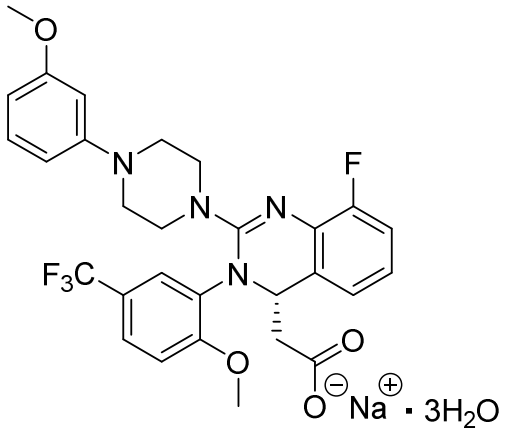
Step 6) micronizing or nanomiling the crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate resulting from step 5 to obtain a pharmaceutical composition comprising the micronized crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate,

wherein the particle size is in a range of 0.3 to 1000 µm and the particle size distribution is defined by d(0.1) from 1 to 100 µm, d(0.5) from 30 to 250 µm and d(0.9) from 100 to 800 µm.

10. The method according to any one of claims 1 to 9 further comprising the additional subsequent step:

Step 7) adding at least one pharmaceutically acceptable carrier, excipient and/or diluent to the crystalline sodium 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4H-quinazolin-4-yl]acetate trihydrate.

11. A crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate of formula (I)



(I)

having a hexagonal crystal system, a space group of R3, and a unit cell dimension of a = 28.22 Å, b = 28.22 Å, c = 9.97 Å, α = 90 ± 3°, β = 90 ± 3°, and γ = 120 ± 3° which is obtainable by the method as defined in any one of claims 1 to 10.

12. The crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate according to claim 11 which is essentially free from ethanol.

13. A crystalline sodium 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4H-quinazolin-4-yl]acetate trihydrate having a hexagonal crystal system, a space group of R3, and a unit cell dimension of a = 28.22 Å, b = 28.22 Å, c = 9.97 Å, α = 90 ± 3°, β = 90 ± 3°, and γ = 120 ± 3°.

14. The crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate according to any one of claims 11 to 13, wherein the X-ray diffraction pattern of said crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate comprises 2-theta angle values of 6.2, 9.5, 12.4, 15.6, 18.0, 19.0, 21.0, 22.5 and 26.8 degrees, and said 2-theta angle values have a normal deviation of ± 0.1°.

15. A pharmaceutical composition comprising the crystalline sodium 2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetate trihydrate as defined in any one of claims 11 to 14.

16. The pharmaceutical composition according to claim 15 which is a dry powder.

17. The pharmaceutical composition according to claim 15 or 16, which is essentially free from ethanol.

18. The pharmaceutical composition according to any one of claims 15 to 17 that is suitable for intravenous administration.

19. The pharmaceutical composition according to any one of claims 15 to 17 that is suitable for oral administration.

20. The pharmaceutical composition according to any one of claims 15 to 19 for use in a method of treatment and/or prevention of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.

21. Use of a pharmaceutical composition as defined in any one of claims 15 to 19 for producing a medicament for the treatment and/or prevention of diseases, in particular of virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group.

22. A method for treating or preventing virus infections, preferably human cytomegalovirus (HCMV) infections or infections with another member of the herpes viridae group, in humans and animals comprising the step of administering the pharmaceutical composition as defined in any one of claims 15 to 19 to a human or an animal who or which requires such a treatment.