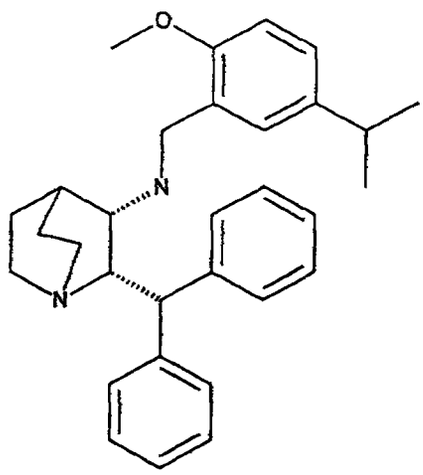
POLYMORPHS OF CRYSTALLINE (2-BENZHYDRYL-1-AZABICYCLO[2,2,2]OCT-3-YL)-(5-ISO-PROPYL-2-METHOXYBENZYL)-AMMONIUMCHLORIDE AS NK-1 RECEPTOR ANTAGONISTS

This invention is directed to certain polymorphs and forms of crystalline (2-Benshydryl-1-azo-bicyclo 2,2,2 oct-3yl)-(5-isopropyl-2-methoxybenzyl)-amine dihydrochloride (hereafter the dihydrochloride salt) and their pharmaceutical compositions. The dihydrochloride salt is a CNS active NK-1 receptor antagonist and this invention is directed to methods of treating conditions effected or facilitated by a decrease in substance P mediated neuro-transmission. This invention is also directed to a substance P antagonist which is evaluated for acute and delayed anti-emetic efficacy in a mammal including humans receiving chemotherapy. Treating is defined here as preventing and treating.



. 2HCl

United States Patent Number 5,393,762 and United States Serial Number 08/816,016 both incorporated by reference, describe pharmaceutical compositions and treatment of emesis using NK-1 receptor antagonists. The crystalline anhydrous dihydrochloride is hygroscopic at humidities of about 52 % or greater and forms dihydrates. The dihydrates do not readily dehydrate when exposed to low relative humidity of about 33% or less.

Summary of the Invention

The present invention relates to the anhydrous dihydrochloride of (2-Benzhydryl-1-azo-bicyclo 2,2,2oct-3-yl)-(5-isoproyl-2-methoxybenzyl)-amine, the dihydrochloride dihydrate and its two polymorphs.

In one embodiment of the invention, the anhydrous dihydrochloride is a crystalline hygroscopic single form. The morphology of the anhydrous dihydrochloride is rods with particle size of about 5 to 30μm yielding birefringence. A differential scanning calorimetry

(DSC) thermogram gave a sharp endotherm with an onset at 224°C, Tmax at 236°C and a △Hf of 32.8 cal/gram.

In two other embodiments, the dihydrochloride dihydrate is in Form I or Form II. Form I is characterized by the X-ray diffraction pattern below:

Dihydrochloride Dihydrate Form I

Peak No.	1	2	3	4	5	6	7	8
d space	17.2	9.5	8.4	6.9	4.9	4.4	3.9	3.5

Form I of the dihydrochloride dihydrate is a nonhydroscopic single form and discloses a Differential Scanning Calorimetry thermogram with onsets at about 150°C and 230°C. Form I has a solubility of about 110 to 120 milligrams per milliliter. The crystalline habit of Form I is flakes with a size range of about 30μm to 60μm.

Form II is characterized by the X-ray diffraction pattern below:

Dihydrochloride Dihydrate Form II

Peak No.	1	2	3	4	5	6	7	8	9
d space	11.3	8.8	7.5	6.4	4.9	4.5	3.8	3.7	3.0

Form II is a lower energy, more stable form than Form I. Form II has a solubility of about 390-400 milligrams per milliliter. Form II's crystalline habit is flakes of about 15 to 25 μm.

The method of making the polymorphic Form I of the dihydrochloride dihydrate comprises stirring at ambient temperature the anhydrous dihydrochloride in an organic solvent containing about 0.5 to 2.5% water for about 15 to 25 hours to effect crystallization. The organic solvents are selected from ethyl or isopropyl alcohol, ethyl acetate, acetonitrile, tetrahydrofuran and acetone all containing about 0.5% to 2.5% water.

The method of making the polymorphic Form II of the dihydrochloride dihydrate comprises stirring Form I or the anhydrous dihydrochloride at ambient temperature in an organic solvent containing about 3 to 5% water for about 15 to 25 hours to effect crystallization. The solvents are chosen from ethyl acetate with about 5% water, tetrahydrofuran with about 5% water, acetone with about 5% water and acetonitrile with about 5% water.

Another aspect of the invention relates to a pharmaceutical composition having pharmaceutical activity which comprises at least one of polymorphic Forms I and II of the dihydrochloride dihydrate and the anhydrous dihydrochloride in the treatment of emesis. A

method of treating emesis comprises administering to a subject in need of treatment, an antiemetic effective amount of Form I or II or the anhydrous dichloride.

Detailed Description of the Invention

Polymorphic Form I of the dihydrochloride dihydrate may be formed by stirring the anhydrous form of the compound in an appropriate organic solvent containing 0.5% to 2.5% water for a suitable time to effect the crystallization. Appropriate solvents may include the following: ethyl or isopropyl alcohol, ethyl acetate, acetonitrile, tetrahydrofuran, and acetone, all containing between 0.5% to 2.5.% water.

Polymorphic Form II may be formed by stirring either Form I or the anhydrous form of the dihydrochloride in an appropriate organic solvent containing 3% to 5% water for a suitable time to effect the crystallization. Appropriate solvents may include the following; Ethyl acetate containing 3.5% water, tetrahydrofuran (THF) containing 5% water, acetone containing 5% water and water.

The "wet" THF bridge resulted in complete conversion to Form II. When Form I is slurried in THF with less than 2% H_2O there is no conversion to Form II. When Form I is slurried in THF with about 3% to 5% H_2O, the conversion is to Form II. When Form I is slurried in THF with >5% H_2O, solubility increases dramatically due to the high aqueous solubility.

Table I below shows an ambient polymorph screen with wet solvents:

Table I

Polymorph Isolated	Starting Form	Solvent	Isolation Temperature	Isolation Method
Form I	Form I	IPO/5% H_2O	ambient	Slurry
Form II	Form I	Ethyl Acetate/3.5% H_2O	ambient	Slurry
Form I	Form I	Acetonitrile/5% H_2O	ambient	Slurry
Form II	Form I	Tetrahydrofuran/5%H_2O	ambient	Slurry
Form II	Form I	Acetone/ 5% H_2O	ambient	Slurry
Form II	Form I	H_2O	ambient	solutions seeded with Form II

Table II below gives a polymorph characterization of Form I and Form II:

Table II

Assay	Form I	Form II
Combination Analysis	dihydrochloride, dihydrate	dihydrochloride, dihydrate
Karl Fisher	7.08%	7.10%
Powder X-ray	Form I	Form II
Fusion Microscopy	Slow water loss (50°C-75°C)	Sharp water loss ~100°C
VTI (% H_2O absorbed)	0.8% wt.	0.4% wt.
Aqueous Intrinsic Solubility	>648 mg/ml.	<329 mg.ml
Aqueous Equilibrium	>1155 mg/ml.	395 mg/ml.
Crystal Habit	flake, ~ 30 x 60 µm	flake, ~15 x 25 µm
TGA/DTA	Water loss 30°C-110°C, two events prior to degradation @194°C	Water loss 30°C-100°C with apparent degradation @ 178°C
Differential Scanning Calorimetry (DSC)	Event @ ~ 175°C then degradation @ ~230°C. Water loss is undetected,	Hydrates Off @ ~ 130°C and ~155°C, possible re-cryst @ ~170°C, possible anhydrous melt @ 240°C, then degradation

EXAMPLE 1

Preparation of crystalline anhydrous dihydrochloride

A mixture of Benshydryl-1-azo-bicyclo 2,2,2 oct-3yl)-(5-isopropyl-2-methoxybenzyl)-amine dihydrochloride dihydrate (10.0g) in ethylacetate (100ml) was heated at reflux in a Dean and Start apparatus for 23 hours. The reaction was cooled to room temperature and stirred for 1 hour. The solid was removed by filtration, washed with ethylacetate (20 ml) and dried in vacuo at 55°C with a nitrogen bleed for 24 hours to give the anhydrate as a white solid.

EXAMPLE 2

Preparation of the crystalline dihydrate Form I

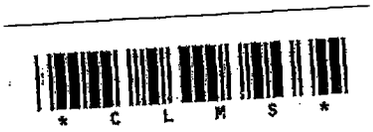
A 53.2 Kg portion of the 1-R-(-)-camphorsulfonate salt is dissolved in a mixture of 266 L of water and 266 L of methylene chloride. The pH is adjusted to a range of 10-14 with 5.08 L of 50% sodium hydroxide. The product rich methylene chloride layer is separated and back washed with 53.2 L of water. The methylene chloride is concentrated atmospherically and is displaced by tetrahydrofran (668.4L). A 13.9 L portion of 12 N hydrochloric acid is added to

the tetrahydrofuran and the mixture is heated to reflux for 3 hours. The resulting slurry is cooled to 25°C to 30°C, granulated for 1 hour and the Form 1 crystal is collected by filtration.

EXAMPLE 3

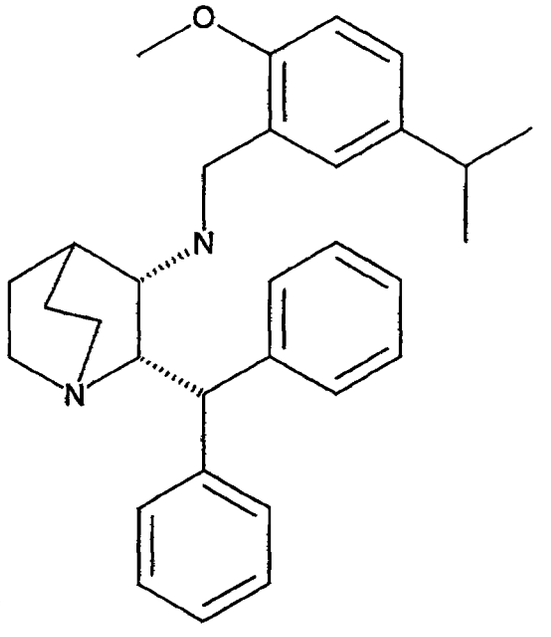
Preparation of the crystalline dihydrate Form II

A 25 Kg portion of Form I dihydrate is slurried in THF/3%-5% water (3001 L THF+ 101 L water) at reflux (-64°C) for 48 hours. The slurry is cooled to 25°C to 30°C, granulated for 1 hour and the Form II collected by filtration.



WE CLAIM

1. The crystalline forms of (2-Benzhydryl-1-azo-bicyclo[2.2.2]oct-3-yl)-(5-isopropyl-2-methoxy-benzyl)-amine dihydrochloride having the formula



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wherein said crystalline form is selected from the group consisting of

a) a hygroscopic dihydrochloride anhydrous form;

b) a nonhygroscopic dihydrochloride dihydrate, Form I polymorph exhibiting the x-ray powder diffraction pattern.

Peak No.	1	2	3	4	5	6	7	8
d space	17.2	9.5	8.4	6.9	4.9	4.4	3.9	3.5

and

c) a nonhygroscopic dihydrochloride dihydrate, Form II polymorph exhibiting the x-ray powder diffraction pattern

Peak No.	1	2	3	4	5	6	7	8	9
d space	11.3	8.8	7.5	6.4	4.9	4.5	3.8	3.7	3.0

2. The anhydrous dihydrochloride according to claim 1 wherein the anhydrous dihydrochloride crystalline habits are rods.

3. The anhydrous dihydrochloride according to Claim 2 wherein said rods have a particle size of about 5 to 30 μm.

4. The anhydrous dihydrochloride according to Claim 1 wherein a differential scanning calorimetry thermogram gave a sharp endothern with an onset at about 224°C, temperature maximum at about 236°C and a ΔHf of about 32.8 cal/gram.

5. The nonhygroscopic dihydrochloride dihydrate polymorph according to Claim 1 wherein Form I's crystalline habit are flakes.

6. The dihydrochloride dihydrate polymorph according to Claim 5 wherein Form I's crystalline flake size is about 30 μm to 60 μm.

7. The dihydrochloride dihydrate polymorph according to Claim 1, wherein Form I's solubility is about 640 - 1160 mg/ml.

8. The dihydrochloride dihydrate polymorph according to Claim 1 wherein Form I has a differential scanning calorimetry thermogram with onsets at about 175°C and 230°C.

9. The dihydrochloride dihydrate polymorph according to Claim 1, wherein Form II has a solubility of about 390 to 400 mg/ml.

10. The dihydrochloride dihydrate polymorph according to Claim 1 wherein Form II's crystalline habit are flakes.

11. The Form II polymorph according to Claim 10 wherein the crystalline flakes have a size range of about 15 to 25 μm.

12. The dihydrochloride dihydrate polymorph according to Claim 1 wherein Form II has a solubility of about 390 to 400 mg/ml.

13. A pharmaceutical composition having substance P antagonist activity comprising at least one of the polymorphic Forms I or II according to Claim 1, in an amount effective in the treatment of emesis and a pharmaceutically acceptable carrier.

14. A method of treating emesis which comprises administering to a subject in need of treatment an antiemetic effective amount of the polymorphic Form I of the compound according to Claim 1.

15. A method of treating emesis which comprises administering to a subject in need of treatment an antiemetic effective amount of the polymorphic Form II of the compound according to Claim 13.

16. A pharmaceutical composition having substance P antagonist activity comprising the anhydrous dihydrochloride according to Claim 1, in an amount effective in the treatment of emesis, and a pharmaceutically acceptable carrier.

17. A method of treating emesis which comprise administering to a subject in need of treatment an antiemetic effective amount of the anhydrous dihydrochloride of the compound according to Claim 16.

18. A method of making crystalline dihydrochloride dihydrate polymorphic Form I of the anhydrous dihydrochloride of (2-Benzhydryl-1-azo-bicyclo 2,2,2 Oct-3-yl)-(5-isopropyl-2-methoxybenzyl)-amine comprising stirring at ambient temperature the anhydrous dihydrochloride in an organic solvent containing about 0.5 to 2.5% water for about 15 25 hours to effect crystallization.

19. A method of Claim 18 wherein the organic solvents are selected from ethyl alcohol, isopropyl alcohol, ethyl acetate, acetonitrile, tetrahydrofuran and acetone.

20. A method of making crystalline dihydrochloride dihydrate polymorphic Form II of the anhydrous dihydrochloride of (2-Benzhydryl-1-azo-bicyclo 2,2,2Oct-3-yl)-(5-isopropyl-2-methoxybenzyl)-amine comprising stirring at ambient temperature Form I of the dihydrochloride dihydrate or the anhydrous dichloride in an organic solvent containing about 3 to 5% water for about 15 to 25 hours to effect crystallization.

21. The method of Claim 20 wherein the organic solvents are chosen from ethyl acetate with about 3.5% water, tetrahydrofuran with about 5% water, acetone with about 5% water and acetonitrile with about 5% water.