

- 58 -

Claims:

1. A salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane wherein said salt is the fumarate, maleate, chloride, phosphate, succinate or malonate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane.
2. The salt according to claim 1, wherein the salt is the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form.
3. The salt according to claim 2, wherein the salt is characterized by an XRPD pattern substantially the same as the XRPD pattern shown in Figure 1.
4. The salt according to claim 1, wherein the salt is the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form, wherein the mean particle size of the crystals is at least 15 μm .
5. The salt according to any one of claims 2 to 4, wherein the salt is the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form, and wherein the salt is in substantially pure form.
6. The salt according to any one of claims 2 to 4, wherein the salt is the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form, and wherein the salt has a purity greater than 90 weight %.
7. A pharmaceutical composition, which comprises a salt as defined in any one of claims 1 to 6 as active ingredient and at least one pharmaceutically acceptable carrier.
8. A pharmaceutical composition, which comprises a salt as defined in any one of claims 1 to 6 in combination with one or more further therapeutic agent as active ingredients and at least one pharmaceutically acceptable carrier.
9. A pharmaceutical composition comprising mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane according to any one of claims 2 to 6 as active ingredient and at least one pharmaceutically acceptable carrier, wherein the composition is in the form of a tablet.

10. A pharmaceutical composition in the form of a tablet comprising

(a) mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane according to any one of claims 2 to 6 as active ingredient;

(b) a filler;

(c) a disintegrant;

(d) a lubricant; and

(e) a gliding agent;

wherein the only lubricant present is a lubricant selected from sodium stearyl fumarate, sodium lauryl sulfate, glyceryl behenates, hydrogenated vegetable oils, wax cetyl esters and talc.

11. A pharmaceutical composition in the form of a tablet comprising

(a) up to 10% by weight mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane according to any one of claims 2 to 6 as active ingredient;

(b) from 1 to 20% by weight maize starch; from 15 to 35% by weight microcrystalline cellulose; and from 40 to 75% by weight sprayed lactose;

(c) from 0.5 to 5% by weight sodium carboxymethylcellulose XL;

(d) from 0.5 to 3% by weight sodium stearyl fumarate; and

(e) from 0.1 to 1% by weight Aerosil.

12. A pharmaceutical composition in the form of a tablet comprising from 1 to 10% by weight mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane according to any one of claims 2 to 6 as active ingredient and at least one pharmaceutically acceptable carrier;

wherein the composition comprises an active ingredient layer comprising the mono-fumarate and an auxiliary layer being devoid of the mono-fumarate;

wherein the weight ratio of the active ingredient layer to the auxiliary layer is from 10 : 90 to 90 : 10.

13. A pharmaceutical composition in the form of a tablet comprising from 1 to 10% by weight mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane according to any one of claims 2 to 6 as active;

wherein the composition comprises an active ingredient layer comprising the mono-fumarate and an auxiliary layer being devoid of the mono-fumarate;

- 60 -

wherein the weight ratio of the active ingredient layer to the auxiliary layer is from 10 : 90 to 90 : 10;

wherein the active ingredient layer comprises

(1a) from 10 to 25% by weight of the active ingredient layer the mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

(1b) from 15 to 25% by weight of the active ingredient layer microcrystalline cellulose; and from 40 to 70% by weight of the active ingredient layer sprayed lactose;

(1c) from 1 to 5% by weight of the active ingredient layer sodium carboxymethylcellulose XL;

(1d) from 1 to 5% by weight of the active ingredient layer sodium stearyl fumarate; and

(1e) from 0.1 to 1% by weight of the active ingredient layer Aerosil; and

wherein the auxiliary layer comprises

(2a) from 10 to 35% by weight of the auxiliary layer microcrystalline cellulose; and from 50 to 75% by weight of the auxiliary layer sprayed lactose;

(2b) from 1 to 3% by weight of the auxiliary layer sodium carboxymethylcellulose XL;

(2c) from 1 to 5% by weight of the auxiliary layer sodium stearyl fumarate; and

(2d) from 0.1 to 1% by weight of the auxiliary layer Aerosil.

14. A method for the prevention, treatment and / or delay of progression of a disease or condition, in which nAChR $\alpha 7$ activation plays a role or is implicated, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a salt as defined in any one of claims 1 to 6.

15. A method for the prevention, treatment and / or delay of progression of of psychiatric or neurodegenerative disorders in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a salt as defined in any one of claims 1 to 6.

16. A composition comprising at least 90 weight % of salt according to any one of claims 1 to 4, based on the weight of the composition.

17. A method of preparing a mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form comprising the steps of
(a) preparing a solution of a mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in a solvent mixture of a primary alcohol, a secondary

- 61 -

alcohol and water, wherein the primary alcohol : secondary alcohol volume ratio is from 9 : 1 to 1 : 1; and wherein the primary alcohol : water volume ratio is from 17 : 1 to 7 : 1;

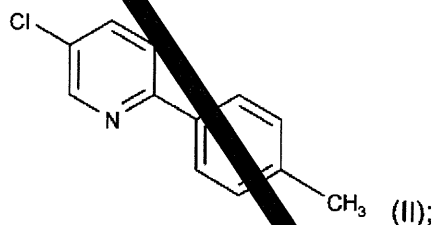
(b) heating the solution of step (a) to elevated temperature;

(c) adding the solution of step (b) gradually to an ether antisolvent at a temperature ranging from ambient temperature to 55°C until a primary alcohol : ether antisolvent volume ratio from 5 : 1 to 1 : 1 is reached; wherein after an amount of the solution of step (b) from 10% to 40% of the total amount is added, the resulting solution is seeded with seed crystals of a mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form, wherein the seed crystals are suspended in a secondary alcohol;

(d) cooling the seeded solution of step (c) gradually to a temperature below ambient; and

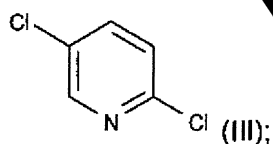
(e) isolate the solids by filtration to obtain the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form.

18. A process for the production of a compound of formula II or a salt thereof

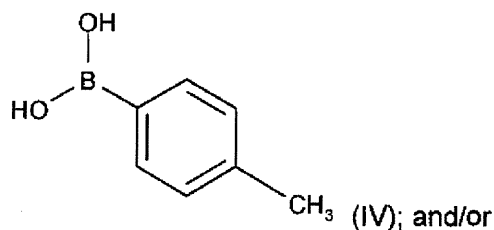


comprising

a) reacting a compound of formula III

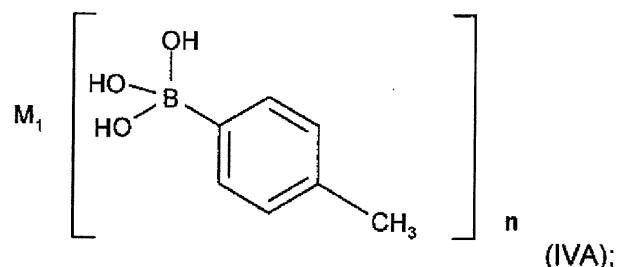


with a compound of formula IV



with a compound of formula IVA

- 62 -

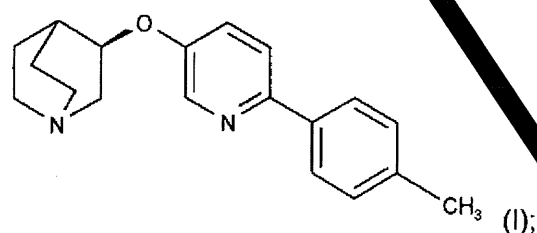


wherein M_1 is alkali and n is 1 or M_1 is earth alkali and n is 2;
 in the presence of a palladium catalyst; a base selected from a carbonate base, a phosphate base, a hydroxide base and an alcoholate base; water and an inert solvent;
 to form the compound of formula II; and
 b) optionally converting the compound of formula II to a salt thereof.

19. The process according to claim 18, wherein the reaction is carried out at a pH from 10.5 to 13.

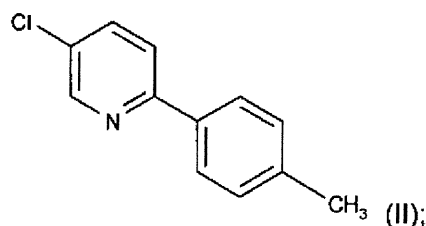
20. The process according to claim 18 or 19,
 wherein the inert solvent is a partly water soluble solvent;
 wherein cysteine is added to the biphasic reaction mixture after formation of the compound of formula II; the phases are separated; and the compound of formula II is isolated from the non-aqueous phase.

21. A process for the production of a compound of formula



or a salt thereof comprising

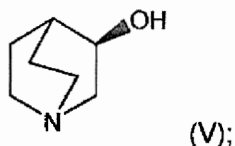
c) reacting a compound of formula II



or a salt thereof;

- 63 -

with a compound of formula V



or a salt thereof;

at elevated temperature in the presence of a base and an inert dipolar aprotic solvent;

wherein the base is $M_2OC(R)_3$, wherein M_2 is sodium or potassium and each R

independently is C_{1-6} alkyl or two R together with the carbon atom they are bound to form C_{4-6} cycloalkyl, or the base is a hydroxide base;

to form the compound of formula I; and

d) optionally converting the compound of formula I to a salt thereof.

22. The process according to claim 21, wherein the base is gradually added to the reaction mixture.

23. The process according to claim 21 or 22, wherein the base is sodium *tert*-butanolate or potassium *tert*-butanolate.

24. The process according to any one of claims 21 to 23, wherein the inert dipolar aprotic solvent is dimethylsulfoxide.

25. The process according to claim 24, wherein the reaction mixture further comprises toluene.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane wherein said salt is the fumarate, maleate, chloride, phosphate, succinate or malonate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane.
2. A salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane, wherein the salt is the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form.
3. The salt according to claim 2, wherein the mono-fumarate salt is characterized by an XRPD pattern including the following peaks:

No.	2 theta (deg°)	Intensity		No.	2 theta (deg°)	Intensity
1	17.4	75.2		13	29.3	18.5
2	15.2	49.8		14	20.9	16.7
3	3.8	46.3		15	26.5	15.8
4	20.1	45.2		16	21.8	15.7
5	19.8	35.7		17	30.8	9.1
6	13.7	33.8		18	27.5	8.4
7	22.8	31.2		19	7.6	8.3
8	19.2	25.9		20	25.1	8
9	26.7	24		21	23.2	7.6
10	18.5	22.5		22	36.4	7.6
11	25.9	22.2		23	23.9	7.4
12	11.3	21.5		24	38.9	6.5

4. The salt according to claim 2, wherein the mean particle size of the mono-fumarate salt crystals is at least 15 μm .

5. The salt according to any one of claims 2 to 4, wherein the mono-fumarate salt is in substantially pure form.
6. The salt according to any one of claims 2 to 4, wherein the mono-fumarate salt has a purity greater than 90 weight %.
7. A pharmaceutical composition comprising a salt as defined in any one of claims 1 to 6 as active ingredient and at least one pharmaceutically acceptable carrier.
8. The pharmaceutical composition according to claim 7, further comprising one or more further therapeutic agent as active ingredients.
9. A pharmaceutical composition comprising mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane according to any one of claims 2 to 6 as active ingredient, and at least one pharmaceutically acceptable carrier, wherein the composition is in the form of a tablet.
10. The pharmaceutical composition according to claim 9, further comprising:
 - (a) a filler;
 - (b) a disintegrant;
 - (c) a lubricant; and
 - (d) a gliding agent;wherein the only lubricant present is a lubricant selected from sodium stearyl fumarate, sodium lauryl sulfate, glyceryl behenates, hydrogenated vegetable oils, wax cetyl esters and talc.
11. The pharmaceutical composition according to claim 9, comprising:
 - (a) up to 10% by weight mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane as active ingredient;
 - (b) from 1 to 20% by weight maize starch; from 15 to 35% by weight microcrystalline cellulose; and from 40 to 75% by weight sprayed lactose;

- (c) from 0.5 to 5% by weight sodium carboxymethylcellulose XL;
- (d) from 0.5 to 3% by weight sodium stearyl fumarate; and
- (e) from 0.1 to 1% by weight Aerosil.

12. The pharmaceutical composition according to claim 9, comprising from 1 to 10% by weight mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane as active ingredient;

wherein the composition comprises an active ingredient layer comprising the mono-fumarate and an auxiliary layer being devoid of the mono-fumarate; and

wherein the weight ratio of the active ingredient layer to the auxiliary layer is from 10 : 90 to 90 : 10.

13. The pharmaceutical composition according to claim 12, wherein the active ingredient layer comprises

(1a) from 11 to 25% by weight of the active ingredient layer the mono-fumarate of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

(1b) from 15 to 35% by weight of the active ingredient layer microcrystalline cellulose; and from 40 to 70% by weight of the active ingredient layer sprayed lactose;

(1c) from 1 to 5% by weight of the active ingredient layer sodium carboxymethylcellulose XL;

(1d) from 1 to 5% by weight of the active ingredient layer sodium stearyl fumarate; and

(1e) from 0.1 to 1% by weight of the active ingredient layer Aerosil; and wherein the auxiliary layer comprises

(2a) from 10 to 35% by weight of the auxiliary layer microcrystalline cellulose; and from 50 to 75% by weight of the auxiliary layer sprayed lactose;

(2b) from 1 to 3% by weight of the auxiliary layer sodium carboxymethylcellulose XL;

(2c) from 1 to 5% by weight of the auxiliary layer sodium stearyl fumarate; and

(2d) from 0.1 to 1% by weight of the auxiliary layer Aerosil.

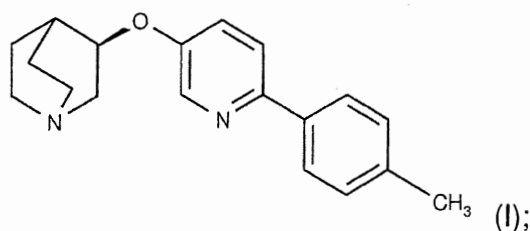
14. Use of a salt as defined in any one of claims 1 to 6 in the manufacture of a medicament for the prevention, treatment, or delay of progression of a disease or condition, in which nAChR $\alpha 7$ activation plays a role or is implicated.
15. Use of a salt as defined in any one of claims 1 to 6 in the manufacture of a medicament for the prevention, treatment, or delay of progression of psychiatric or neurodegenerative disorders in a subject in need of such treatment.
16. A composition comprising:
 - at least 90 weight % of active ingredient, wherein the active ingredient is a salt according to any one of claims 1 to 4, and
 - 10 weight % or less of inactive ingredient, wherein the inactive ingredient is at least one of: water, a glycol, an oil, an alcohol, a filler, a granulating agent, a lubricant, a binder, a disintegrant, or a gliding agent,
 - wherein the weight % is based on the weight of the composition.
17. A method of preparing a mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form comprising the steps of
 - (a) preparing a solution of a mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in a solvent mixture of a primary alcohol, a secondary alcohol and water, wherein the primary alcohol : secondary alcohol volume ratio is from 9 : 1 to 1 : 1, and wherein the primary alcohol : water volume ratio is from 17 : 1 to 7 : 1;
 - (b) heating the solution of step (a) to elevated temperature;
 - (c) adding the solution of step (b) gradually to an ether antisolvent at a temperature ranging from ambient temperature to 55°C until a primary alcohol : ether antisolvent volume ratio from 5 : 1 to 1 : 1 is reached; wherein after an amount of the solution of step (b) from 10% to 40% of the total amount is added, the resulting solution is seeded with seed crystals of a mono-fumarate salt of (R)-

3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form, wherein the seed crystals are suspended in a secondary alcohol;

(d) cooling the seeded solution of step (c) gradually to a temperature below ambient; and

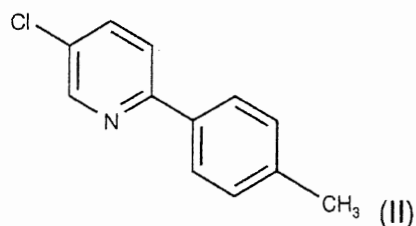
(e) isolate the solids by filtration to obtain the mono-fumarate salt of (R)-3-(6-(4-methylphenyl)-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane in crystalline form.

18. A process for the production of a fumarate salt of a compound of formula I



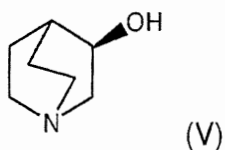
comprising

reacting a compound of formula II



or a salt thereof,

with a compound of formula V



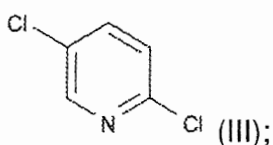
or a salt thereof,

at elevated temperature in the presence of a base and an inert dipolar aprotic solvent, to form the compound of formula I;

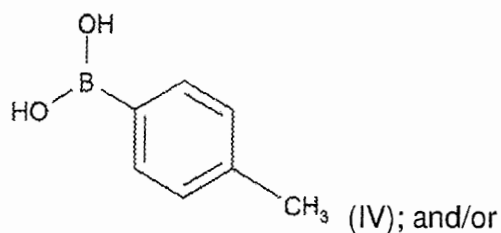
wherein the base is $(M_2)OC(R)_3$, wherein M_2 is sodium or potassium and each R independently is C_{1-6} alkyl or two R together with the carbon atom they are bound to form C_{4-6} cycloalkyl, or the base is a hydroxide base; and

converting the compound of formula I to a salt thereof.

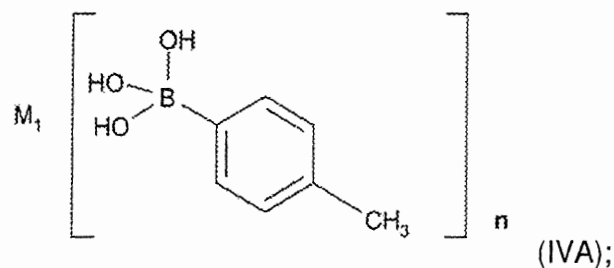
19. The process according to claim 18, wherein the base is gradually added to the reaction mixture.
20. The process according to claim 18 or 19, wherein the base is sodium *tert*-butanolate or potassium *tert*-butanolate.
21. The process according to any one of claims 18 to 19, wherein the inert dipolar aprotic solvent is dimethylsulfoxide.
22. The process according to claim 18, wherein the reaction mixture further comprises toluene.
23. The process according to any of claims 18-22, wherein prior to reacting the compound of formula II with the compound of formula V, the compound of formula II or the salt thereof is produced according to a process comprising:
reacting a compound of formula III



with a compound of formula IV



with a compound of formula IVA



wherein M_1 is alkali and n is 1 or M_1 is earth alkali and n is 2;
in the presence of a palladium catalyst; a base selected from a carbonate base, a phosphate base, a hydroxide base and an alcoholate base; water and an inert solvent;
to form the compound of formula II; and
converting the compound of formula II to a salt thereof.

24. The process according to claim 23, wherein the reaction between the compound of formula III and the compound of formula IV and/or formula IVA is carried out at a pH from 10.5 to 13.

25. The process according to claim 23 or 24,
wherein the inert solvent is a partly water soluble solvent;
wherein cysteine is added to the biphasic reaction mixture after formation of the compound of formula II; the phases are separated; and the compound of formula II is isolated from the non-aqueous phase.