

Process for manufacturing 5-(2-{[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one.

The present invention relates to an improved process for the manufacture of 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one and pharmaceutically acceptable salts thereof.

5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one (compound (I)) as well as a process for its manufacture are described in WO 2006122788 A1.

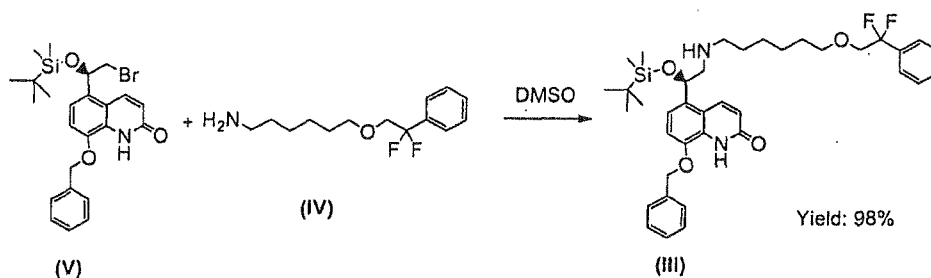
Napadisylate salt of 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl] amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one as well as a process for its manufacture are described in WO 2008095720 A1.

The inventors have now unexpectedly found that it is possible to (a) increase the yield of compound (I) and its salts, (b) minimise the amount of impurities in the final product and/or (c) decrease the reaction time, by modifying the synthetic processes described in WO 2006122788 A1 and WO 2008095720 A1.

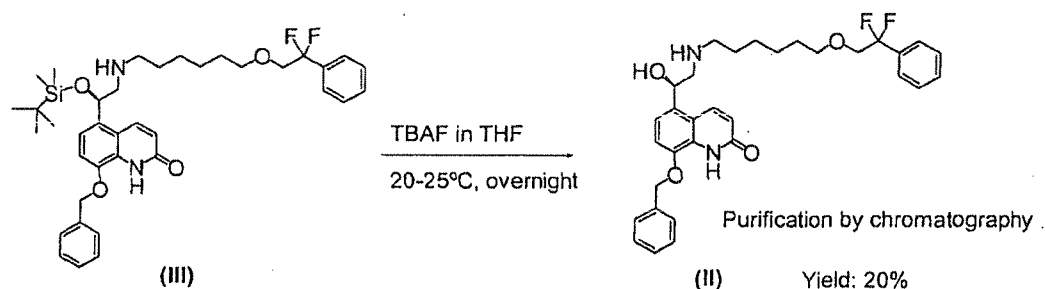
These objectives can be achieved by selecting specific solvents and/or modifying or even removing some purification steps, thus reducing the reaction time while increasing the overall yield of the final product. Moreover, the process of the present invention is more suitable for large scale manufacture.

WO 2006122788 A1 describes a three step process for the preparation of 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl] amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one

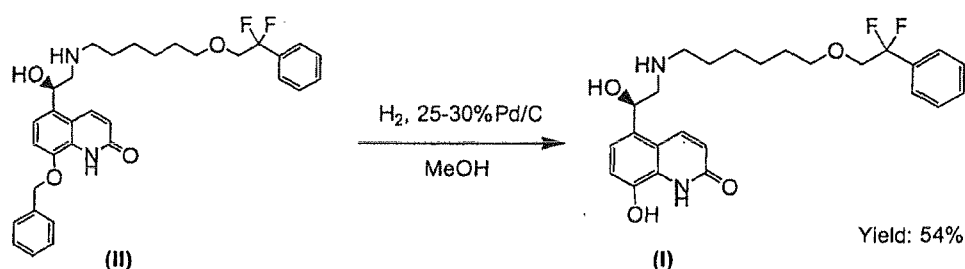
Step a)



Step b)

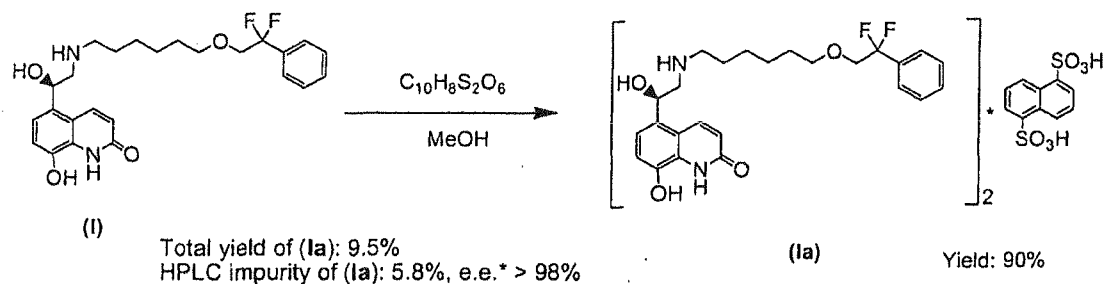


5 Step c)



WO 2008095720 A1 discloses a method for preparing the napadisylate salt compound of formula (Ia):

10 Step d)



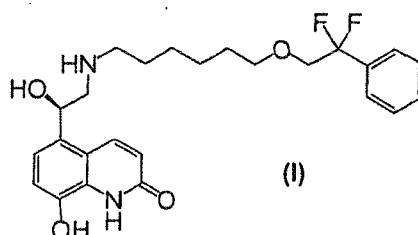
* e.e.: enantiomeric excess

As a consequence, in order to prepare a napadisylate salt compound of formula (Ia) from intermediates (V) and (IV), according to the techniques disclosed in the prior art, four reaction steps must be carried out, wherein each intermediate, once obtained, was isolated and purified before being used as a starting material in the following step. The purification steps in the prior art techniques were carried out using conventional purification methods already known in the art such as, for example, solvent extraction or chromatography techniques. The

overall yield for preparing the napadisylate compound (Ia) was calculated to be about 9.5% while the level of impurities determined by HPLC analysis was about 5-6%.

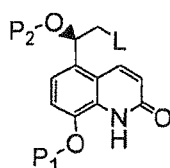
It has been surprisingly found that the process for preparing 5-(2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one and its salts can be significantly improved by modifying the reaction conditions, particularly by modifying or even removing purification processes in some steps thus simplifying the numerous reaction steps while increasing the overall yield of the reactions. Moreover, it has been found that by proper selection of solvents, the required product can be obtained with a higher yield and in a more pure form compared with the earlier process.

Accordingly, the present invention provides a process for preparing a 5-(2-{{6-(2,2-difluoro-2-phenylethoxy) hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one compound of formula (I), or a pharmaceutically acceptable salt thereof,



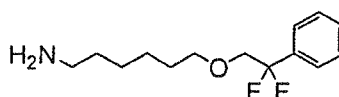
which process comprises:

- a) reacting, in a xylene solvent, a compound of formula (V)



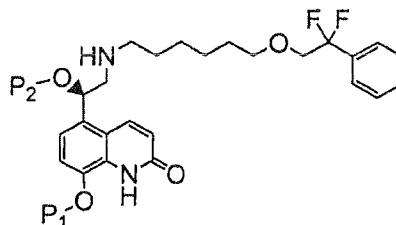
wherein P_1 and P_2 represent hydroxy protecting groups and L is a leaving group, with 6-(2,2-difluoro-2-phenylethoxy)hexan-1-amine of formula (IV),

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(IV)

to give a compound of formula (III)



(III)

- b) effecting a P_1 deprotection step and a P_2 deprotection step, to remove the protecting groups P_1 and P_2 and give a compound of formula (I).

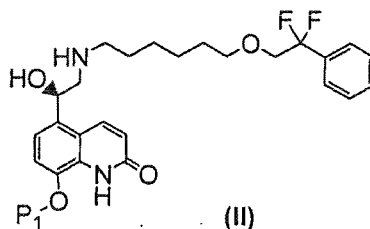
Typically,

- (i) the P_2 deprotection step is carried out at a temperature ranging from 30-60 °C for up to 8 hours, and/or
- (ii) the P_1 deprotection step is carried out in the presence of a solvent which is acetic acid or a mixture of acetic acid with an alcohol or with an ester.

Step (a) is conducted in a xylene solvent. In contrast, the corresponding reaction step disclosed in WO 2006/122788 is effected in DMSO. It is a surprising finding of the present invention that the use specifically of a xylene solvent enables a significant improvement in the purity of the compound of the formula (III).

In a preferred embodiment, step (b) above comprises:

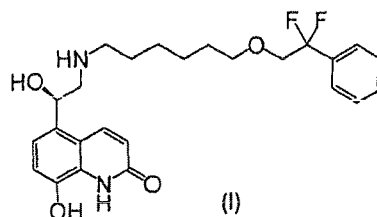
- effecting said P_2 deprotection step on the compound of formula (III) to yield a compound of formula (II),



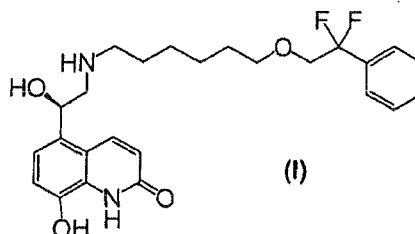
(II)

wherein P_1 is as defined above; and

- effecting said P₁ deprotection step on the compound of formula (II) to give a compound of formula (I),



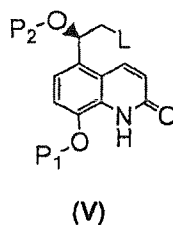
- 5 Thus, in this embodiment, the present invention provides a process for preparing a 5-(2-[[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one compound of formula (I), or a pharmaceutically acceptable salt thereof,



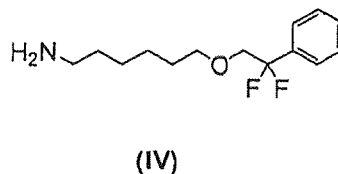
which process comprises:

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- a) reacting, in a xylene solvent, a compound of formula (V)

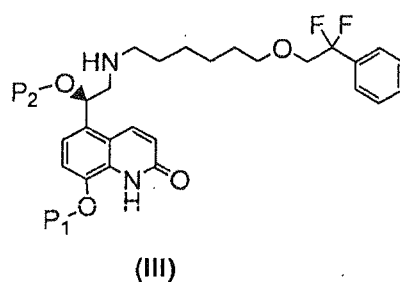


- 15 wherein P₁ and P₂ represent hydroxy protecting groups and L is a leaving group, with 6-(2,2-difluoro-2-phenylethoxy)hexan-1-amine of formula (IV),

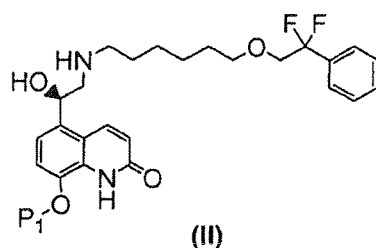


- 20 to give a compound of formula (III)

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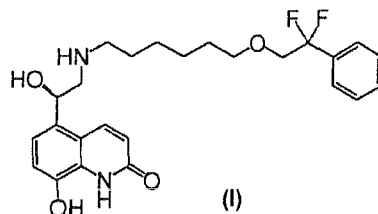
b) deprotecting the compound of formula (III) to yield a compound of formula (II),



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wherein P₁ is as defined above; and

c) deprotecting the compound of formula (II) to give a compound of formula (I).

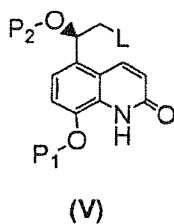


Typically, in this embodiment:

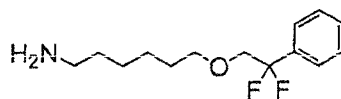
- 10 (i) step b) is carried out at a temperature ranging from 30-60 °C for up to 8 hours, and/or
- (ii) step c) is carried out in the presence of a solvent which is acetic acid or a mixture of acetic acid with an alcohol or with an ester.

In a further embodiment, the process of the present invention comprises:

- 15 a) reacting, in a xylene solvent, a compound of formula (V)



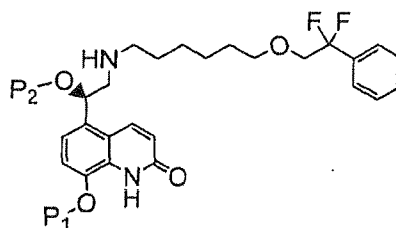
wherein P_1 and P_2 represent hydroxy protecting groups and L is a leaving group, with 6-(2,2-difluoro-2-phenylethoxy)hexan-1-amine of formula (IV),



(IV)

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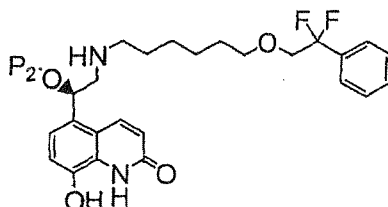
to give a compound of formula (III)



(III)

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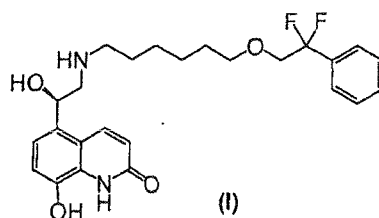
- b) deprotecting the compound of formula (III) to yield a compound of formula (II'),



(II')

wherein P_2 is as defined above; and

- c) deprotecting the compound of formula (II') to give a compound of formula (I).



(I)

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Typically, in this embodiment:

- (i) step b) is carried out in the presence of a solvent which is acetic acid or a mixture of acetic acid with an alcohol or with an ester; and/or
- (ii) step c) is carried out at a temperature ranging from 30-60 °C for up to 8 hours.

P₁ and P₂ are hydroxy protecting groups. P₁ and P₂ may be the same or different. Preferably, they are different. A skilled chemist can easily select suitable hydroxy protecting groups for the P₁ and P₂ positions. For example, appropriate protecting groups are discussed in T. W.

- 5 Greene and G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

Examples of suitable hydroxy protecting groups include alkyl groups, such as methyl, ethyl, and *tert*-butyl; acyl groups, for example alkanoyl groups, such as acetyl; arylmethyl groups, 10 such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), and diphenylmethyl (benzhydryl, DPM); silyl groups, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS); and the like.

Typically P₁ is a benzyl group. In this embodiment, the P₁ deprotection step is typically 15 effected by hydrogenation, preferably in the presence of a catalyst such as, palladium (II) hydroxide (Pd(OH)₂) or palladium (0) (Pd(0)). Preferably, the catalyst is palladium (0) on charcoal.

Typically, in this embodiment, the hydrogenation reaction of the P₁ deprotection step is 20 carried out in the presence of catalyst in an amount less than 10%, preferably less than 5% most preferably about 4% by weight with respect of the amount of the reactant used. The use of catalyst in these amounts typically enables a reduction in the level of impurities generated. In particular, it can reduce the formation of the defluoro impurity, i.e. 5-(2-{[6-(2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one. It can also 25 reduce the formation of dihydroquinoline impurities.

Typically, P₂ is a *tert*-butyldimethylsilyl moiety. In this embodiment, the P₂ deprotection step is typically effected by reaction with tetra-*n*-butyl ammonium fluoride, trihydrate (TBAF) preferably in a solvent such as tetrahydrofuran (THF), or with hydrogen chloride in a solvent 30 selected from ethers, esters and alcohols. Preferably, in this embodiment, the P₂ deprotection step is carried out with hydrogen chloride in a solvent selected from diethyl ether, *tert*-butylmethylether (TBME), ethanol and isopropylacetate.

Alternatively, in this embodiment, the P₂ deprotection step is preferably carried out with 35 TBAF in tetrahydrofuran (THF) or 2-methyltetrahydrofuran, preferably in THF.

Alternatively, in this embodiment the P₂ deprotection step is preferably carried out with naphthalene-1,5-disulfonic acid in tetrahydrofuran (THF).

- 5 L is a leaving group. A skilled chemist would easily be able to select appropriate leaving groups for the L position. Examples of suitable leaving groups include halogen atoms, mesylate groups (-O-S(O)₂-CH₃) and triflate (-OS(O)₂-CF₃) groups.

Preferably, L is halogen atom. More preferably, L is a bromine atom.

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Typically, the solvent used in step (a) is substantially free of DMSO. More preferably, it is substantially free of DMSO and dioxane.

15

Use of the xylene solvent detailed above in step (a) enables an overall improvement in purity and/or yield, as compared with analogous processes in which step (a) is conducted in solvents such as DMSO.

20

In another embodiment of the present invention, the P₂ deprotection step is carried out at a temperature ranging from 40-50 °C for a time period not exceeding 6 hours, preferably not longer than 4 hours, more preferably not longer than 2 hours, most preferably up to one hour. The reduction in the reaction time for the P₂ deprotection step enables a surprising decrease in the formation of undesired by-products.

25

In a still another embodiment, the hydrogenation of the P₂ deprotection step is optionally carried out in the presence of tetrabutylammonium fluoride in an amount of about 0.3-0.9 g of TBAF per gram of reactant. Typically, the reactant is the compound of formula (II).

30

In another embodiment of the present invention, the compound obtained from the P₂ deprotection step is purified by crystallization. Typically, crystallization is effected with 1,5-naphthalenedisulphonic acid in alcohol, preferably ethanol. Purification of the compound obtained from the P₂ deprotection step by crystallization, rather than by chromatography, enables an improvement in purity and/or yield. Preferably, in this embodiment, the P₂ deprotection step is effected before the P₁ deprotection step, and the compound obtained from the P₂ deprotection step is therefore a compound of formula (II).

In a preferred embodiment of the invention, the P₁ deprotection step is carried out in the presence of a solvent which is acetic acid or a mixture of acetic acid with an alcohol or with an ester. Preferably, in this embodiment, the solvent is acetic acid alone or a mixture of acetic acid/methanol (1:1), more preferably acetic acid/methanol (1:1).

Typically, said solvent contains less than 5% (v/v), preferably less than 3%, more preferably less than 1%, of any liquid other than acetic acid, an alcohol and an ester, preferably of any liquid other than acetic acid and methanol.

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In a preferred embodiment of the invention, a pharmaceutically acceptable salt of a compound of formula (I) is prepared. Preferably said salt is a napadisylate salt or a mesylate salt.

The napadisylate salts are typically those described in WO 2008/095720. Preferably the napadisylate salt is a heminapadisylate salt or a mononapadisylate salt. A mononapadisylate salt typically contains between about 0.8 and 1.2 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base, more typically about 1.0 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base. A heminapadisylate salt typically contains between about 0.35 and 0.65 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base, more typically about 0.5 molar equivalents of naphthalene-1,5-disulfonic acid per molar equivalent of the free base.

The present invention is also directed to 5-(2-{{[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, obtainable by the process of the invention. Preferably, the present invention is directed to a napadisylate salt or mesylate salt of 5-(2-{{[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one obtainable by the process of the invention. More preferably, the salt is the napadisylate salt.

The above molar ratios can be determined by standard techniques, for example ¹H NMR, elemental analysis and HPLC methods.

When a napadisylate salt of a compound of formula (I) is prepared, typically, following step (b), naphthalene-1,5-disulfonic acid is added without isolating the 5-[2-{{[6-(2,2-difluoro-2-

phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one of formula (I). Preparing the final product in a one-pot reaction in this way without isolating the free base can improve purity and/or yield. Further, such a one-pot reaction is also advantageous because it enables greater process efficacy.

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In a preferred embodiment of the invention, step (b) and, if required, the subsequent salification step are each conducted without purifying the intermediate obtained from the previous reaction step.

10 The compounds of formula (V) can be obtained by known methods, or by analogy with known methods. For example, the compound in which P₁ is benzyl and P₂ is TBS can be obtained by the synthetic methods described in US2004059116 (Example 9C), WO2004/011416 (Example 2) and WO2004/016578 (Example 1ii).

15 6-(2,2-Difluoro-2-phenylethoxy)hexan-1-amine (IV) is obtained by synthetic method described in WO 2006122788 A1 (Intermediate 9).

The reagents and solvents used in the present invention are commercially available, for example from Aldrich Chemical Company, Inc. or Fluka Chemie GmbH.

20

The preferred conditions for the process of step (a) are the following:

To a solution of 10.30-11.30 g (40-44 mmol) of 6-(2,2-Difluoro-2-phenylethoxy)hexan-1-amine (IV) in 15-25 ml of a xylene solvent, is added 19.9 g (40 mmol) of (R)-8-(Benzyloxy) -
25 5-(2-bromo-1-(tert-butyldimethylsilyloxy)ethyl)quinolin-2(1H)-one (V) and 9-12 g of sodium bicarbonate or 15-20 g of potassium carbonate. The reaction mixture is heated to reflux during 4-6 h. After cooling down to room temperature, the precipitated inorganic salts are filtered and washed with 80-120 ml of xylene. The solvent is removed thus obtaining an oily residue which is used in the next step without further purification

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The preferred conditions for the P₂ deprotection step are the following:

The oily residue obtained from the previous step is dissolved in 300-350 ml of THF. Then 20-25 g of TBAF is added to the reaction medium. The reaction mixture is stirred during 1-2

hour at 40-50°C. After cooling down to room temperature, the solvent is removed under vacuum. A total 250-300 ml of water/organic solvent (1:1) is added to the residue. The organic layer is separated and the aqueous layer is extracted twice with the organic solvent (2 x 20-30 ml). The organic layers are combined and concentrated under vacuum to remove the solvent. The preferred organic solvents used in the extraction work-up are toluene, dichloromethane, isopropyl acetate or Methyl-Isobutyl-Ketone (MIK), more preferably toluene, isopropyl acetate or dichloromethane, being most preferably isopropyl acetate or dichloromethane. In an alternative process, the residue obtained, once the reaction solvent (THF) has been removed, may be used directly in the next crystallization purification without aqueous extraction work-up

The residue is purified by crystallization with 8-9 g of 1,5-naftalenedisulphonic acid tetrahydrate in 300-400 ml of ethanol. The product obtained is filtered and washed with 50-70 ml of ethanol. The wet cake obtained is treated with in 250-260 ml of methanol/dichloromethane (1:2), methanol/isopropyl acetate (1:2) or methanol/toluene (1:2). To this suspension is added a solution of 3.5-4 g of NaOH in 170-190 ml of water. The reaction mixture is stirred at 20-30 °C during 40-50 minutes. The organic phase is separated and the solvent is removed under vacuum.

The preferred conditions for the process of the P₁ deprotection step are the following

Intermediate (II) is dissolved in a total volume of 160-170 ml of acetic acid/alcohol (1:1), preferably acetic acid/methanol. 1-1.5 g of 10% Pd/C, 50% water is added to the solution. Then, about 5-15 g of TBAF is optionally added to the solution. After several purges of nitrogen, the reaction mixture is hydrogenated at a temperature of 20-30 °C at less than 4 bars, preferably at 1-2 bars, during 6-8 h. The catalyst is then filtered and washed with 190-200 ml of methanol. About 200-250 ml of acetic acid is added to the filtrate and a solution of 6-6.5 g of 1,5-naphtalenedisulfonic acid tetrahydrate in 50-70 ml of methanol/acetic acid (1:1) is added to this filtrate. The mixture is heated to reflux for 30 minutes. After cooling down to room temperature, the product is filtered and washed with 25-30 ml of methanol. The product obtained may optionally be purified by slurry with methanol in hot conditions such as at a boiling temperature of methanol. The final product (Ia) is dried under vacuum at 50 °C.

The method of synthesis described in the present invention will be further illustrated by the following examples. The examples are given by the way of illustration only and are not to be construed as limiting.

- 5 The structures of the prepared compounds were confirmed by ¹H-NMR and MS. NMR were recorded using a Varian Gemini-200 NMR spectrometer operating at frequency of 200 or 300 MHz. Tetramethyl silane was used as a reference and samples were solved in deuterated dimethylsulphoxide (DMSO-d₆) or deuterated chloroform (CDCl₃).
- 10 Their purity was determined by HPLC, in Alliance 2795 Waters instrument equipped with diode array detector (DAD) and ZMD or ZQ mass detector (electrospray ionization). HPLC method used a Symmetry C18 column (3.5 μm, 21x100 mm) and mobile phase was composed by two phases: Phase A: Buffered (Formic acid/ammonia) aqueous solution at pH: 3. Phase B: 50:50 mixture acetonitrile/methanol with ammonium formate. Gradient was from 0% to
- 15 95% of phase B in 10 minutes.

Preparative HPLC-MS experiments were performed on a Gilson instrument equipped with a binary pump (Gilson piston pump 321); a vacuum degasser (Gilson 864); an injector-fraction collector (Gilson liquid handler 215); two injection modules, analytical and preparative

20 (Gilson 819); a valve (Gilson Valvemate 7000); a 1/1000 splitter (Acurate by LC Packings); a make-up pump (Gilson 307); a diode array detector (Gilson 170) and a MS detector (a Thermoquest Finnigan aQa, a quadrupole mass spectrometer with ES and APCI ionisation modes). The HPLC-MS instrument was controlled by an IBM PC.

Experimental section**Comparative Example I (according to WO 2006122788 and WO 2008095720):****5 Intermediate III. 8-(benzyloxy)-5-((1*R*)-1-{{*tert*-butyl(dimethyl)silyl}oxy}-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}ethyl)quinolin-2(1*H*)-one**

To a solution of (8-(benzyloxy)-5-((1*R*)-2-bromo-1-{{*tert*-butyl(dimethyl)silyl}oxy}ethyl)quinolin-2(1*H*)-one (V) (4.80 g, 9.83 mmol) and 6-(2,2-Difluoro-2-phenylethoxy)hexylamine (IV) (3.04 g, 11.8 mmol) in dimethylsulfoxide (13.5 mL) was
10 added sodium bicarbonate (2.49g, 29.4 mmol) and sodium iodide (2.22 g, 14.8 mmol). The mixture was heated at 140°C for 2 hours. After cooling, the reaction was diluted with water (40 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic extracts were washed with water (2 x 10 mL) and brine (20 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. The title compound was obtained (6.40 g, 98%) as oil.

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Intermediate (II). 8-(benzyloxy)-5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)quinolin-2(1*H*)-one

To a solution of Intermediate (III) (6.4 g, 9.63 mmol) in tetrahydrofuran (60 mL) was added TBAF (5.02 g, 19.26 mmol). The mixture was stirred at room temperature overnight. The
20 solvent was removed under reduced pressure. Purification by column chromatography using methylene chloride/methanol (from 95:5 to 85:15) as eluent gave 8-(benzyloxy)-5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxy ethyl)quinolin-2(1*H*)-one (II) (1.1 g, 20%) as oil.

25 5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one (I)

To Intermediate (II) (1.10 g, 2.0 mmol) in methanol (50 mL) was added 20% palladium on charcoal (300 mg). The mixture was hydrogenated at 2 bars for 3 hours. The catalyst was filtered through Celite and the solvent concentrated. The resulting oil was purified by column
30 chromatography with silica gel eluting with methylene chloride/methanol (95:5) to give the title compound (0.50 g, 54%) as oil.

5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one napadisylate salt (Ia)

5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one (6.63 g; 14,4 mmol) was dissolved in 134 ml of methanol to form a 1,075 M solution which is heated to approximately 50°C. Then, 7.74 mmol of naphthalene-1,5-disulfonic acid, tetrahydrate were added to the heated solution. The mixture was then stirred for 30 minutes at reflux temperature and then cooled down to 20/25°C and stirred at this temperature for 1 additional hour. The precipitate formed was isolated by filtration, washed with methanol and dried in vacuum at 50°C. (15.67 g, 90%)

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Example II (according to the present invention)

Intermediate III. 8-(benzyloxy)-5-((1*R*)-1-{{*tert*-butyl(dimethyl)silyl}oxy}-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}ethyl)quinolin-2(1*H*)-one

15 To a solution of [6-(2,2-Difluoro-2-phenylethoxy)hexyl]amine (IV) (11.0 g, 42.8 mmol) in xylene (20 mL) were added (8-(benzyloxy)-5-((1*R*)-2-bromo-1-{{*tert*-butyl(dimethyl)silyl}oxy} ethyl)quinolin-2(1*H*)-one (V) (19.9 g, 40.7 mmol) and sodium bicarbonate (10.4 g, 123 mmol). The mixture was heated at reflux for 6 hours. After cooling down to room temperature, additional xylene (176 ml) was added to the reaction mixture and the precipitated inorganic salts were filtrated and washed with xylene (100 ml). The obtained filtrate was concentrated under vacuum to remove the solvent, thus yielding an oily residue (Intermediate (III)) which was used in the next step without purification.

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Intermediate (II). 8-(benzyloxy)-5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)quinolin-2(1*H*)-one

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Intermediate (III) was dissolved in tetrahydrofuran (330 mL). Then TBAF (23.3 g, 73 mmol) was added to this solution. The mixture was stirred at 45°C during 1 hour. After cooling down to room temperature, the solvent was removed under vacuum and the resulting residue was optionally extracted with 266 ml of a mixture water/dichloromethane (1:1). The organic layers were recovered and then removed under vacuum. Then 352 ml of ethanol 96% was added and the mixture was heated to 50-60°C. At this temperature, a solution of 8.5 g of 1,5-naphthalenedisulphonic acid tetrahydrate in 35 ml of ethanol 96% is added during 1 hour. The system of addition was washed with 29 ml of ethanol 96% which is added to the reaction mixture. The reaction mixture is stirred at reflux during 30 minutes and then cooled down to

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room temperature. The product is filtered and washed with 60 ml of ethanol. The wet cake product is treated with 252 ml of methanol/dichloromethane (1:2). Then a solution of 3.6 g of NaOH in 116 ml of water is added and the reaction mixture is stirred at 20-25 °C during 45 minutes. The aqueous layer is separated and extracted with dichloromethane (3 x 42 ml). The organic phases are recovered and stirred together with a solution of 4.2 g of NaCl in 168 ml of water. The organic phase is separated and the solvent is removed under vacuum, thus yielding 8-(benzyloxy)-5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)quinolin-2(1*H*)-one (**II**) (16.8 g, 75%) as oil.

10 **5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one napadisylate salt (**Ia**)**

To a solution of Intermediate (**II**) (16.8 g, 30.5 mmol) in a mixture of methanol (69 mL) and acetic acid (77 ml) was added a suspension of 10% palladium on charcoal, 50% water, (1.33 g) in a mixture of methanol (15 ml) and acetic acid (7 ml). The mixture was hydrogenated at 1-2 bars for 8 hours. The catalyst was filtered through Celite and washed with methanol (193 ml). Acetic acid (220 ml) was added to this filtrate. Then a solution of 1,5-naphthalenedisulphonic acid, tetrahydrate (6.33 g) in a mixture of methanol (54 ml) and acetic acid (27 ml) was added slowly to the filtrate. The reaction mixture is heated at reflux during 30 minutes, and then cooled down to room temperature. The precipitated was filtered and washed with methanol (27 ml). The wet crude product is dissolved in methanol (800 ml) and heated to reflux during 30 min. The product is filtered and washed with additional methanol (34 ml). The solid thus obtained is dried under vacuum at 50°C, thus yielding 5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one napadisylate salt (14.9 g, 81 %).

25 The overall yield of 5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)hexyl}amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one napadisylate salt (**Ia**) is Calculated to be about 60,7 % (75% x 81%) and the purity thereof is HPLC imp = 1.5%, e.e. > 98%.

Table 1: comparative results

Reaction step	Comparative Example	Example of the invention
Step (a)	Product obtained included 39% of impurities	Product obtained included 7% of impurities
Step (b)*	Yield: 20%	Yield: 75 %
Step (c)**	Yield: 54%	Yield: 81%
Step (d)	Yield: 90%	
Total Yield	9.5%	60.75%
Impurities of final product (Ia)	5.8%	1.5%

* P₂ deprotection step** P₁ deprotection step

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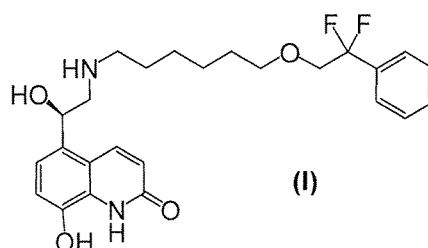
As it can be observed from Table 1, use of a xylene solvent in step (a) significantly reduced the amount of impurities in the intermediate of formula (III). Further, the overall yield of 5-((1*R*)-2-{{6-(2,2-difluoro-2-phenylethoxy)-hexyl}amino}-1-hydroxyethyl)-8-

hydroxyquinolin-2(1*H*)-one napadisylate salt has drastically increased while the impurity has decreased at a lower level when compared with the comparative example. This is achieved by modifying some purification techniques, thus simplifying the reaction steps and reducing the quantity of different reagents.

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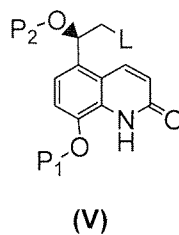
CLAIMS

1. A process for preparing a 5-(2-{[6-(2,2-difluoro-2-phenylethoxy) hexyl]amino}-
1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one compound of formula (I), or a
5 pharmaceutically acceptable salt thereof,

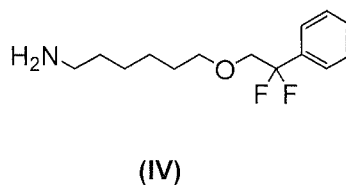


which process comprises:

- a) reacting, in a xylene solvent, a compound of formula (V)

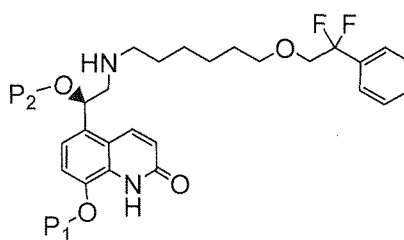


- 10 wherein P₁ and P₂ represent hydroxy protecting groups and L is a leaving group,
with 6-(2,2-difluoro-2-phenylethoxy)hexan-1-amine of formula (IV),



to give a compound of formula (III)

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(III)

b) effecting a P₁ deprotection step and a P₂ deprotection step, to remove the protecting groups P₁ and P₂ and give a compound of formula (I).

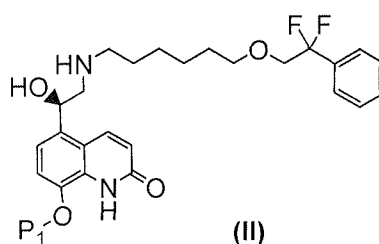
5 2. A process according to claim 1, wherein:

- (i) the P₂ deprotection step is carried out at a temperature ranging from 30-60 °C for up to 8 hours, and/or
- (ii) the P₁ deprotection step is carried out in the presence of a solvent which is acetic acid or a mixture of acetic acid with an alcohol or with an ester.

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3. A process according to claim 1 or 2, wherein step (b) comprises:

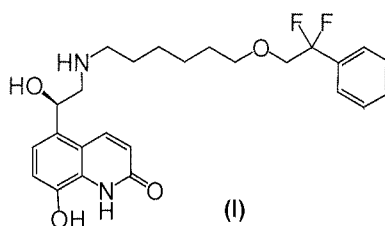
- effecting said P₂ deprotection step on the compound of formula (III) to yield a compound of formula (II),



(II)

15 wherein P₁ is as defined above; and

- effecting said P₁ deprotection step on the compound of formula (II) to give a compound of formula (I),



4. A process according to any one of the preceding claims, wherein (a) P₁ is a benzyl group and the P₁ deprotection step is effected by hydrogenation, and/or (b) P₂ is a *tert*-butyldimethylsilyl group and the P₂ deprotection step is effected by reaction with tetra-*n*-butyl ammonium fluoride trihydrate or with hydrogen chloride, and/or (c) L is bromine.
5. A process according to any one of the preceding claims, wherein (a) the P₂ deprotection step is carried out with tetra-*n*-butyl ammonium fluoride trihydrate in tetrahydrofuran, and/or (b) the P₂ deprotection step is carried out at a temperature of from 40-50 °C for a time period not exceeding 6 hours.
6. A process according to claim 5(b), wherein the time period is not longer than 4 hours.
7. A process according to any one of the preceding claims, for preparing the heminapadisylate or mesylate salt of the compound of formula (I).
8. A process according to claim 7, for preparing the heminapadisylate salt of the compound of formula (I), wherein, following step (b), naphthalene-1,5-disulfonic acid is

added without isolating the 5-[2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl]-8-hydroxyquinolin-2(1*H*)-one of formula (I).

9. A process according to claim 3, wherein the intermediate of formula (II)
5 obtained from the P₂ deprotection step is purified by crystallization with 1,5-naphthalenedisulphonic acid tetrahydrate in ethanol.
10. A process according to any one of the preceding claims, wherein P₁ is benzyl
and the P₁ deprotection step is effected by hydrogenation in the presence of palladium
10 on charcoal catalyst in an amount less than 10% (w/w) with respect of the amount of the compound of formula (II).
11. A process according to claim 10, wherein the amount of the catalyst used is less
than 5%.
- 15 12. A process according to any one of the preceding claims, wherein, when the P₁
deprotection step is carried out in the presence of a solvent which is acetic acid or a
mixture of acetic acid with an alcohol or with an ester, preferably, the solvent is acetic
acid or a mixture of methanol/acetic acid (1:1).
- 20 13. A process according to claim 12, wherein the solvent is methanol/acetic acid
(1:1).
14. A process according to any one of the preceding claims, wherein

- (i) the P_2 deprotection step is carried out at a temperature ranging from 30-60 °C for up to 8 hours, and
- (ii) the P_1 deprotection step is carried out in the presence of a solvent which is acetic acid or a mixture of acetic acid with an alcohol or with an ester.