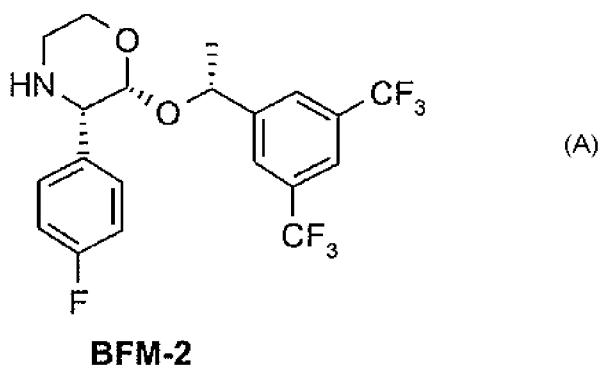




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(54) **Title:** NOVEL INTERMEDIATES FOR THE PREPARATION OF HIGHLY PURE APREPITANT OR FOSAPREPITANT



(57) **Abstract:** The invention provides a salt, preferably in crystalline form, of (2R,3S)-2-[(R)-1-(3,5-Bis- trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) with a O,O'-substituted tartaric acid derivative. Furthermore, a composition comprising said salt is provided. In another embodiment, a process for the preparation of said salt or said composition is provided. In a further embodiment, a process for the preparation of aprepitant or fosaprepitant is provided. One embodiment refers to the use of a salt or a composition according to the invention for the preparation of aprepitant or fosaprepitant. A further embodiment refers to aprepitant or fosaprepitant obtained or obtainable according to the process according to the invention. A further embodiment refers to a composition comprising aprepitant or fosaprepitant obtained or obtainable according to the process of the invention, preferably for use as a medicament (Formula (A)).

Novel intermediates for the preparation of highly pure aprepitant or fosaprepitant

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The invention provides a salt, preferably in crystalline form, of (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) with a O,O'-substituted chiral tartaric acid derivative. Furthermore, a composition comprising said salt is provided. In another aspect, a process for the preparation of said salt or said composition is provided. In a further embodiment, a process for the preparation of aprepitant or fosaprepitant is provided. One embodiment refers to the use of a salt or a composition according to the invention for the preparation of aprepitant or fosaprepitant. A further embodiment refers to aprepitant or fosaprepitant obtained or obtainable according to the process according to the invention. A further embodiment refers to a composition comprising aprepitant or fosaprepitant obtained or obtainable according to the process of the invention, preferably for use as a medicament.

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Background prior art

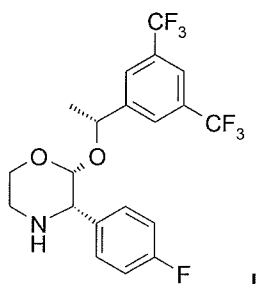
Aprepitant (Formula IX below) has been firstly disclosed in EP 0734381 B1 and is currently being marketed as a treatment for chemotherapy-induced nausea and vomiting under the trade name Emend®. In EP 0734381 B1 a synthetic route for this compound and a series of other morpholine derivatives is described. However, the disclosed processes for these compounds suffer from low product purity.

In EP 0748320 B1 the structure of fosaprepitant is disclosed. US 5,719,147 discloses morpholine and thiomorpholine tachykinin receptor antagonists. In WO 99065900 A1 an improved process for the introduction of the 1,2,4-triazolin-5-on-yl-methyl side chain by using 3-chloromethyl-1,2,4-triazolin-5-one as alkylating agent is described. In WO 2003089429 A1 the prior art process for the introduction of the side chain is improved by conducting step 2 of the introduction of the side chain at a temperature ranging from 140°C to 150°C.

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A stereoselective synthesis for the key intermediate of Formula I, in the following also referred to as BFM2, is disclosed in WO2001096319 A1:

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The process makes use of a chiral auxiliary attached to the nitrogen of the morpholine ring. A major drawback of this route is that the chiral auxiliary is destroyed during removal thus making the process expensive.

Another synthesis of key intermediate of Formula I is described in WO 2001096320 A1. This route makes use of an intramolecular rearrangement to correctly set the hard to make acetal center. The stereochemistry of the exocyclic methyl group is established by a prior art process, giving an unfavorable mixture of isomers at this center.

US 5668280 A and US 6130331 A disclose approaches for the synthesis of key intermediate of Formula I based on crystallization induced diastereomeric transformations. In both patents a selective reduction of a lactone using an expensive metal hydride is required.

In WO2007044829 A2 a mixture of 4 of 8 possible stereoisomers is prepared in an unselective manner. The desired isomer is isolated by several purification steps from this mixture of isomers, resulting in a low overall yield.

In WO 2001094322 A1, WO 2001094323 A1, and WO 2001094324 A1 an efficient process for the synthesis of the key intermediate of Formula I by making use of a crystallization induced diastereomeric transformation is described. In this process the isolation of only three intermediates en route to aprepitant is required, making this process interesting from an economical point of view. Pye et al. (*Chem. Eur. J.* 2002, 8, No. 6, pages 1372-1376) describe a crystallization-induced asymmetric transformation that can be used for preparing morpholine derivatives. Zhao et al. (*J. Org. Chem.* 2002, 67, 6743-6747) describe an asymmetric synthesis of aprepitant by using an enantiopure oxazinone, obtained by a crystallization-induced dynamic resolution process, as starting material.

Furthermore, WO 2009106486 (A1) discloses a process for preparation of aprepitant of Formula I. However, the procedure disclosed in WO 2009106486 (A1) results in a number of (diastereomeric) impurities as depicted in Figure 1. If the key intermediate of Formula I is then converted into aprepitant, then corresponding diastereomeric impurities will also be present in the final product.

Gangula et al. (*Synthetic Communications*[®], 40: 2254-2268, 2010) disclose the crystallization of diastereomer of the key intermediate of formula I with tartaric acid for removing contamination with another diastereomer.

Although some efficient processes for the synthesis of aprepitant and fosaprepitant are available, it is an object of the present invention to provide an enhanced process that overcomes at least one of the problems of the prior art processes.

Summary of the invention

Surprisingly, it was found that a highly pure salt of BFM2 with Di-p-toluoyl-D-tartaric acid (D-DTTA) which is substantially free from other stereoisomers can be prepared. It is contemplated that it is also possible to prepare highly pure salts of BFM2 when using any other chiral tartaric acid derivative that is O,O'-substituted as described below.

As a result, aprepitant or fosaprepitant which is prepared from the highly pure salt of BFM2 with the tartaric acid derivative, which salt is an intermediate during the preparation of aprepitant or fosaprepitant, is also free from other stereoisomers.

Thus, one embodiment provides a salt, preferably in crystalline form, of (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) with a O,O'-substituted chiral tartaric acid derivative as described herein. Furthermore, a composition comprising said salt is provided.

In another embodiment, a process for the preparation of said salt or said composition is provided, comprising the steps of:

- a) providing a composition comprising (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2), and

- b) bringing into contact the composition of step (a) and a O,O'-substituted chiral tartaric acid derivative, preferably the tartaric acid derivative is Di-p-toluoyl-D-tartaric acid (D-DTTA).

5 In a further embodiment, a process for the preparation of aprepitant or fosaprepitant is provided comprising the steps of:

- a) providing a salt according to the invention or a composition according to the invention, and
- b) carrying out an alkylation reaction to give aprepitant or fosaprepitant directly or *via* e.g. protected intermediates and optionally, conversion of aprepitant to fosaprepitant by phosphorylation or a phosphorylation - deprotection sequence.

One embodiment refers to the use of a salt or a composition according to the invention for the preparation of aprepitant or fosaprepitant. A further embodiment refers to aprepitant or fosaprepitant obtained or obtainable according to the process according to the invention. A further embodiment refers to a composition comprising aprepitant or fosaprepitant obtained or obtainable according to the process of the invention, preferably for use as a medicament.

Short description of the Figures

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Figure 1 shows (diastereomeric) impurities of Formula II-VIII that are formed when preparing BFM2. Impurity of Formula II is BFM1 intermediate which gets generated during preparation of BFM2. Impurity of Formula III is carried over from the first step of synthesis (see Figure 2 below) as mentioned in WO 2009106486. Impurity of Formula IV is formed from impurity of Formula III during the preparation of BFM2. Impurities of Formula V, VI, and VII are corresponding impurities of Formula II, III and IV formed if the chiral alcohol (R-Bis trifluoromethylphenyl ethanol) which is used in second step (see Figure 2 below) is contaminated with the S-isomer. Impurity of Formula VIII is corresponding impurity of BFM2 if chiral alcohol (R-Bis trifluoromethylphenyl ethanol) which is used in second step is contaminated with the S-isomer.

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Figure 2 shows a reaction scheme for preparing aprepitant (Formula IX) or fosaprepitant (Formula XV) by using a novel key intermediate (BFM2·D-DTTA, Formula I) according to the invention.

35

Detailed description

The synthesis of aprepitant as described herein involves the key intermediate (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) (Formula I). This intermediate is associated with other diastereomeric impurities such as (2R,3R)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (Formula II in Figure 1), (2S,3R)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (Formula III in Figure 1) and (2S,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (Formula IV in Figure 1).

These impurities are difficult to remove by conventional crystallization methods and if BFM2 containing these impurities is converted into aprepitant or fosaprepitant, the API will contain said impurities. When BFM2 is converted into its Di-*p*-toluoyl-D-tartaric acid salt, all these impurities are depleted to below 0.1 % and BFM2 of very high purity is obtained. BFM2 obtained from BFM2 Di-*p*-toluoyl-D-tartaric acid salt allows preparing highly pure aprepitant or fosaprepitant.

To confirm this result, the crystallization according to the invention was carried out with relatively high amounts of all three impurities (Formula II, III and IV). As can be derived from the experimental data provided below, it was possible to prepare a highly pure D-DTTA salt of BFM2 with isomeric impurities well below 0.1%.

In addition to the above impurities, impurities V, VI, VII and VIII as shown in Figure 1 are also possible in the route of synthesis. These impurities can also be removed by this method.

Thus, one embodiment of the invention refers to a salt, preferably in crystalline form, of (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) with a O,O'-substituted chiral tartaric acid derivative. The salt may be present as a hydrate or in amorphous form.

Additionally preferred, the salt is in crystalline form, further preferred the salt may have the crystal structure that is obtained when crystallizing the salt from a mixture of water and 2-propanol.

The term "O,O'-substituted chiral tartaric acid derivative" as used herein refers to a stereoisomer of a tartaric acid derivative. Preferably, the stereoisomer is a derivative of the D-form of the tartaric acid. Additionally preferred, the substituents comprise a phenyl group which is optionally substituted. Preferably, the tartaric acid derivative is selected from the group consisting of di-O,O'-toluoyl tartaric acid, di-O,O'-benzoyl tartaric acid, di-O,O'-anisoyl tartaric acid, O,O'-dibenzoyl tartaric acid mono(dimethylamide), and Di-p-toluoyl-D-tartaric acid (D-DTTA). Further preferred, the aforementioned tartaric acid derivatives are in the D-form. Further preferred, the tartaric acid derivative is Di-p-toluoyl-D-tartaric acid (D-DTTA).

- 10 Additionally preferred, the salt described herein comprises (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) and the O,O'-substituted chiral tartaric acid derivative in a molar ratio of between 1:1.3 and 1.3:1, preferably in a 1:1 ratio.
- 15 Additionally preferred, the salt of the invention has an enantiomeric purity of at least 99.0% (which e.g. means that all diastereomeric impurities are at most 1.0%), further preferred of at least 99.4%, further preferred of at least 99.6%, further preferred of at least 99.8%, further preferred of at least 99.9%, preferably of more than 99.9%, as determined by chiral HPLC, and/or a purity of at least 99.0%, further preferred of at least 99.4%, further preferred of at least 99.6%, further preferred of at least 99.8%, further preferred of at least 99.9%, preferably of more than 99.9%, as determined by HPLC/chiral HPLC. The methods for determining enantiomeric purity and purity are described below. In another embodiment, purity of the salt may be determined by ¹H-NMR (nuclear magnetic resonance) spectroscopy, wherein purity may refer to the amount of all enantiomers of said salt without distinguishing between stereoisomers.

Another embodiment refers to a composition comprising a salt of BFM2 as described herein.

- In a preferred embodiment, the enantiomeric purity and/or purity of said salt in the composition is at least 99.8%, further preferred at least 99.9%, even further preferred more than 99.9% as determined by chiral HPLC. The methods for determining enantiomeric purity and purity are described below. In one embodiment, the composition may thus comprise a salt of BFM2 as described herein, having an enantiomeric purity as described above, and additionally comprises other components, preferably components, such as pharmaceutical excipients or other pharmaceutically active compounds, that do not represent by-products from the process of preparing said salt, particularly preferred, the composition comprises by-products that result

from the process as described in Figures 1 and 2 in amounts of less than 0.2%, further preferred less than 0.1% as measured by HPLC/chiral HPLC.

In one embodiment, the composition comprises a salt of BFM2 as described herein in an amount of at least 99.0%, further preferred of at least 99.4%, further preferred of at least 99.6%, further preferred of at least 99.8%, further preferred of at least 99.9%, preferably of more than 99.9%, as determined by chiral HPLC/HPLC.

The invention also refers to a process for the preparation of a BMF2 salt as described herein or a composition comprising a BMF2 salt as described herein comprising the steps of:

- a) providing a composition comprising (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethyl-phenyl)ethoxy]-3-(4-fluoro-phenyl)morpholine (BFM2), and
- b) bringing into contact the composition of step (a) and a O,O'-substituted tartaric acid derivative as described herein, preferably the tartaric acid derivative is selected from the group consisting of di-O,O'-toluoyl tartaric acid, di-O,O'-benzoyl tartaric acid, di-O,O'-anisoyl tartaric acid, O,O'-dibenzoyl tartaric acid mono(dimethylamide), and Di-p-toluoyl-D-tartaric acid (D-DTTA), further preferred the tartaric acid derivative is Di-p-toluoyl-D-tartaric acid (D-DTTA).

Preferably, step (b) of the above process comprises contacting.

Additionally preferred, step (b) of the above process comprises crystalizing and isolating the desired salt or composition from an organic solvent or organic solvent mixture.

Additionally preferred, step (b) in the above process, comprises:

- b1) dissolving the composition of step (a) in an organic solvent or mixture of organic solvents, preferably the organic solvent is or comprises a polar solvent such as an alcohol, preferably 2-propanol, and/or
- b2) adding the tartaric acid derivative as described herein to the solution of step (b1), and/or
- b3) adding water to the reaction mixture of step (b2) and obtaining said salt or composition.

Suitable organic solvents are polar solvents, preferably alcohols, such as ethanol, *n*-butanol, *sec*-butanol, *tert*-butanol, methanol, 2-propanol, or toluene, tetrahydrofuran, acetonitrile, DMF,

DMSO, dioxane, DME, diglyme, nitromethane, methyl *tert*-butyl ether, CH₂Cl₂, or NMP or mixtures thereof, with toluene and ethanol, 2-propanol, *n*-butanol, *sec*-butanol, or *tert*-butanol, 2-propanol being particularly preferred.

- 5 Additionally preferred, process step (b1) comprises increasing the temperature of the obtained solution from preferably about room temperature (between 18°C and 24°C), preferably under stirring, to a temperature of between 40°C and 70°C, preferably between 45°C and 65°C, most preferably between 50°C and 55°C.
- 10 Additionally preferred, the reaction mixture obtained in step (b2) is kept at said increased temperature for a period of time of between 10 and 60 minutes, preferably, between 15 and 30 minutes, most preferably about 20 minutes.

- 15 Additionally preferred, in process step (b3), water is preferably slowly added, preferably, the water is added over a period of time of between 20 minutes and 2 hours. Water may e.g. be added in an amount of 20% to 40% by volume based on the total volume of solvents that are already present in the mixture.

- 20 Additionally preferred, process step (b3) includes cooling the reaction mixture obtained after addition of water to a temperature of between 20°C and 35°C, further preferred to a temperature of between 25°C and 30°C, further preferred, the cooled reaction temperature is kept at said temperature under stirring for at least 1 hour, preferably between 2 and 10 hours, further preferred between 4 and 8 hours.

- 25 Additionally preferred, process step (b3) comprises to further reduce the temperature in a second cooling step to below 20°C, further preferred to a temperature of below 10°C; Additionally preferred, the cooled reaction temperature is kept at said temperature for at least 1 hour, preferably between 2 and 10 hours, further preferred between 4 and 8 hours.

- 30 Additionally preferred, the salt in step (b3) is obtained by filtration, optionally followed by washing the product, preferably with a mixture of 2-propanol and water, e.g. a 1:1 mixture of 2-propanol and water.

- 35 Additionally preferred, the composition provided in step (a) comprises at least 85% by weight based on the total weight of the composition, further preferred at least 90% by weight, and even

further preferred at least 95% by weight, further preferred at least 97% by weight of BFM2. Additionally preferred to each of the aforementioned minimum amounts of BFM2, the composition provided in step (a) comprises at most 99% by weight based on the total weight of the composition, further preferred at most 98% by weight of BFM2.

5

In another embodiment, the composition provided in step (a) comprises (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethyl-phenyl)ethoxy]-3-(4-fluoro-phenyl)morpholine (BFM2) with a purity and/or enantiomeric purity of at least 85%, further preferred of at least 90%, further preferred of at least 95%, and even further preferred of at least 97% of as determined by chiral HPLC/HPLC.

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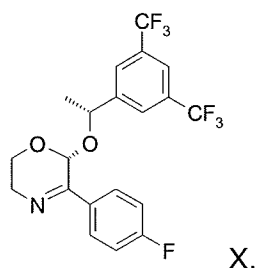
Additionally preferred to each of the aforementioned minimum purity levels of BFM2, said BFM2 has a maximum purity and/or enantiomeric purity of at most 99%, further preferred of at most 98%.

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In another embodiment, the composition provided in step (a) comprises BFM2 having an enantiomeric purity of at least 70%, further preferred of at least 80%, even further preferred of at least 90%, preferably as determined by chiral HPLC.

Additionally preferred, the composition provided in step (a) is prepared from aprimin having the Formula X:

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X.

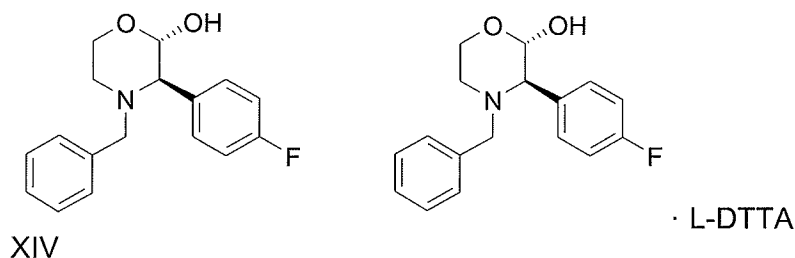
Additionally preferred, the composition provided in step (a) is prepared from aprimin of Formula X by reducing aprimin with H₂ or an H₂ equivalent in the presence of a catalyst and by removing the catalyst by filtration, preferably, aprimin is reduced in the presence of methanol/H₂/Pd/C.

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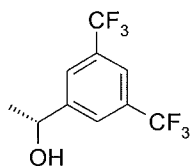
Additionally preferred, the composition provided in step (a) is not isolated after the reduction step but is directly used for step (b2).

Additionally preferred, the preparation of aprimin comprises the steps of:

- a1) a three component coupling of N-benzyl amino ethanol, 4-fluorophenylboronic acid and glyoxal in the presence of a chiral acid, preferably Di-p-toluoyl-L-tartaric acid (L-DTTA), preferably by using toluene and 2-propanol as solvent system, and followed by crystallization and isolation of an addition salt of the compound of Formula XIV with the chiral acid, preferably as Di-p-toluoyl-L-tartaric acid salt (L-DTTA) according to Formula XII:

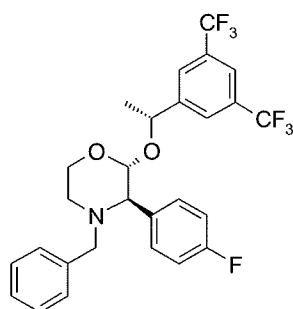


- a2) portioning the salt of the compound of Formula XIV and the chiral acid, preferably the compound of Formula XII, between an alkaline aqueous layer and a water-immiscible organic phase; activation of the hemi-acetal functionality by transforming the OH-group into an activated derivative; reaction of the resulting activated acetal with an alcohol of Formula XIII



XIII.

and removal of impurities by extraction to get a solution of a compound according to Formula XI:



XI;

a3) removal of the *N*-protecting group to give (2R,3R)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM1);

5 a4) oxidation of the amine of (2R,3R)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM1) to the corresponding cyclic imine aprimin and isolation of aprimin.

10 Additionally preferred, the oxidation in step (a4) is carried out in the presence of an oxidizing agent and a base, preferably in the presence of dimethylformamide (DMF), K₂CO₃, *N*-chlorosuccinimide (NCS) and 1,8-diazabicyclo[5.4.0]undec-7-en (DBU);

15 The above process for preparing aprimin is described in detail in WO2009/106486 A1. In step a1), a three component coupling of an amino alcohol, of 4-fluorophenylboronic acid or a C₁₋₆ alkyl or cyclic ester thereof, and of glyoxal is carried out. The obtained morpholine derivative can be crystalized as addition salt with a chiral acid as described in WO2009/106486 A1, such as Di-*p*-toluoyl-L-tartaric acid salt (L-DTTA). The product of Formula XII can then be isolated. Optionally, the undesired isomers in the mother liquor are racemized by treatment with acid or base, optionally at higher temperature, and the racemic morpholine derivative is resubjected to
20 a crystallization with a chiral acid. Optionally, the racemization of the undesired isomers and the crystallization of the desired isomer as a chiral acid addition salt is performed in a one pot fashion;

25 Instead of *N*-benzyl amino ethanol and 4-fluorophenylboronic acid, other agents can be used as described in WO2009/106486 A1.

30 The amino alcohol, glyoxal, and the phenylboronic acid are dissolved in an organic solvent in the presence or absence of water or in a mixture of organic solvents with or without water. The order of addition is not critical. The reagents can be added in any order. In all cases, compound of Formula XIV in the form of its free base is formed.

Suitable organic solvents are e.g. alcohols, such as ethanol, *n*-butanol, *sec*-butanol, *tert*-butanol, methanol, 2-propanol, or toluene, tetrahydrofuran, acetonitrile, DMF, DMSO, dioxane, DME, diglyme, nitromethane, methyl *tert*-butyl ether, CH₂Cl₂, or NMP or mixtures thereof, with

toluene and ethanol, 2-propanol, *n*-butanol, *sec*-butanol, or *tert*-butanol, 2-butanol being particularly preferred.

Further process details for preparing apremim are described in WO2009/106486 A1.

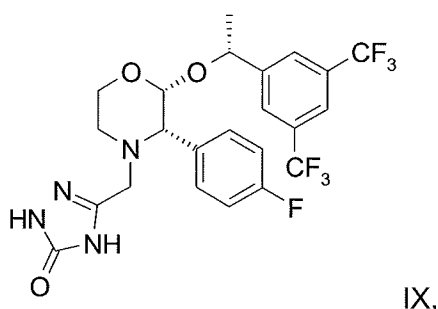
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A further embodiment refers to a process for the preparation of aprepitant or fosaprepitant comprising the steps of providing a BMF2 salt as described herein or a composition comprising a BMF2 salt as described herein and converting BMF2 contained in said salt or composition into aprepitant or fosaprepitant. Additionally preferred, the step of providing a BMF2 salt or
10 composition containing a BMF2 salt comprises crystallizing and isolating said BMF2 salt as described herein from an organic solvent/organic solvent mixture.

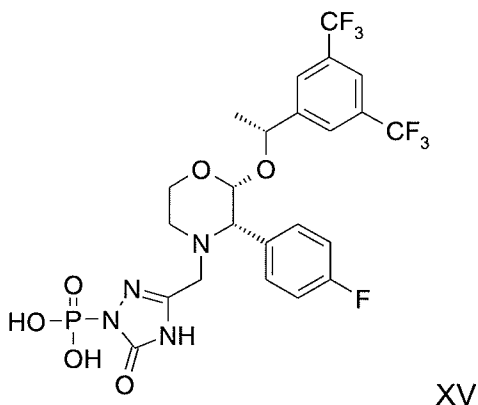
Particularly preferred, the process additionally comprises the steps of:

- 15 a) providing a BMF2 salt as described herein or a composition comprising a BMF2 salt as described herein, and
b) carrying out an alkylation reaction to give aprepitant of Formula IX:

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25 or fosaprepitant according to Formula XV:



directly or *via* e.g. protected intermediates and optionally, conversion of aprepitant to fosaprepitant by phosphorylation or a phosphorylation - deprotection sequence.

Additionally preferred, said alkylation is carried out by using an amidrazone, preferably N'-[1-Amino-2-chloro-eth-(Z)-ylidene]-hydrazinecarboxylic acid methyl ester.

5 Additionally preferred, the alkylation in step (b) comprises:

- b1) reacting (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethyl-phenyl)ethoxy]-3-(4-fluoro-phenyl)morpholine (BFM2) in the presence of toluene, water, NaHCO₃ and DMF;
- b2) reacting the reaction mixture of step (b1) with amidrazone, preferably N'-[1-Amino-2-chloro-eth-(Z)-ylidene]-hydrazinecarboxylic acid methyl ester, in the presence of
10 diisopropyl ethyl amine, and
- b3) adding the methanol and water to the reaction mixture of step (b2).

A further embodiment refers to the use of a BMF2 salt as described herein, preferably a salt of BMF2 with Di-p-toluoyl-D-tartaric acid (D-DTTA), or a composition comprising said salt for the
15 preparation of aprepitant of Formula IX or fosaprepitant according to Formula XIV.

A further embodiment refers to aprepitant or fosaprepitant obtained or obtainable according to the process as described herein. A further embodiment refers to aprepitant or fosaprepitant having impurities of less than 0.2%, preferably, less than 0.1% as determined by chiral
20 HPLC/HPLC.

A further embodiment refers to a composition comprising aprepitant or fosaprepitant obtained or obtainable according to the process as described herein, preferably for use as a medicament. For example, the compositions as described herein can be used for prevention of
25 acute and delayed chemotherapy-induced nausea and vomiting (CINV) and for prevention of postoperative nausea and vomiting. Preferably, compositions comprising aprepitant or fosaprepitant contain pharmaceutical excipients.

A further embodiment is a process of purifying BMF2 by converting it to a salt with a chiral
30 tartaric acid derivative as described herein.

Methods

Method for determining enantiomeric purity by HPLC

Chromatographic conditions:

35 Column: Chiracel ODH, 250 mm x 4.6 mm, 5 µm or equivalent column

Mobile Phase: n- heptane: ethanol: dried methanol; 100: 1: 1 v/v

Diluent: n- heptane: ethanol: dried methanol; 80: 10: 10 v/v

Flow rate: 0.8 ml/minute

Injection volume: 10 μ l

5 Detection : 210 nm

Sample temp. : 25°C

Column oven temp : 25°C

Run time: 30 minutes

System: Isocratic

10 Test concentration: 2000 µg/ ml of BFM2 · D-DTTA

Method for determining purity by HPLC

Chromatographic conditions:

15 Column: Waters, X-bridge C18, 250 x 4.6 mm x 5 μ or equivalent column

Buffer: Weigh 1.74 g of dipotassium hydrogen orthophosphate anhydrous in 1000ml of water, dissolve and adjust the pH to 8.0 ± 0.05 by adding dilute ortho phosphoric acid using pH meter.

Filter through 0.45 µm filter and degass.

Mobile Phase A : Buffer : Acetonitrile : Methanol; 80 : 15 : 5

20 Mobile Phase B : Buffer : Acetonitrile : Methanol; 25 : 70 : 5

Flow rate: 1.5 ml/minute

Injection volume: 10 μ l

Detection: 210 nm

Sample temp.: 5°C

25 Oven temp: 25°C

Run time: 35 minutes

System: gradient

Gradient program: Time (min.) % mobile phase

0 45

[illegible]

20 90

30 90

32 45

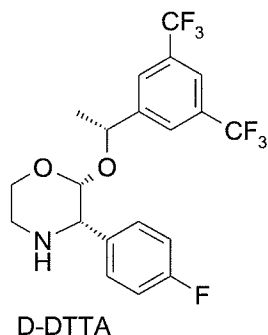
35 45

35 Test concentration: 2000 µg/ml of BFM2-D-DTTA

Examples

The following examples describe the present invention in detail, but they are not to be construed to be in any way limiting for the present invention.

Procedure for Synthesis of BFM2·(D)-DTTA



Example 1: (Input BFM2 containing 1.0 % of impurity of Formula II and 9% of impurity of Formula III)

In a 10 liter glass reaction vessel equipped with a condenser, stirrer and thermometer, a solution of 6.5 liter 2-propanol and 0.438 kg of BFM2 (compound of Formula I obtained as per Example 7 of WO 2009/106486 A1) were taken. The resultant solution was heated to 50°C to 55°C under stirring and 0.386 kg of Di-*p*-toluoyl-D-tartaric acid was added to it. The reaction mixture was maintained at 50°C to 55°C for about 20 minutes. To the resultant reaction mixture was then added 2.1 liter of water in about 30 minutes. The reaction mixture was then slowly cooled to about 25°C to 30°C and maintained with stirring for about 6 to 7 hrs. The slurry was further cooled to about 10°C and maintained for about 6 hr. The resulting crystals were collected by filtration, washed with 0.4 liter of a mixture of 2-propanol and water (1:1), and dried at 55°C and 20mbar to give 0.661kg (80 %) of the title compound as white crystals (HPLC purity >99.9 %, impurities of Formula II and III are below limit of detection).

Example 2: (Input BFM2 containing 6.0% of impurity of Formula II and 9% of impurity Formula III)

In a 250ml glass reaction vessel equipped with a condenser, stirrer and thermometer a solution of 165 ml. 2-propanol and 11 g of BFM2 (compound of Formula III spiked with 6.0 % impurity of Formula II) were taken. The resultant solution was heated to 50°C to 55°C under stirring and 9.65 g of Di-*p*-toluoyl-D-tartaric acid was added to it. The reaction mixture was maintained at 50°C to 55°C for about 20 minutes. To the resultant reaction mixture was then added 55 ml of

water in about 30 minutes. The reaction mixture was then slowly cooled to about 25°C to 30°C and maintained with stirring for about 6 to 7 hrs. The resulting crystals were collected by filtration, washed with 10 ml of a mixture of 2-propanol and water (1:1), and dried at 55°C and 20mbar to give 11.4 g (55%) of the title compound as white crystals (HPLC purity >99.9 %, 5 impurities of Formula II and III are below limit of detection).

Example 3: (Input BFM2 containing 1.0 % of impurity of Formula II and 2.0% of impurity Formula IV)

10 In a 250ml glass reaction vessel equipped with a condenser, stirrer and thermometer a solution of 82.5 ml 2-propanol and 5.5 g of BFM2 (compound of Formula III spiked with 2.0 % impurity of Formula IV). The resultant solution was heated to 50°C to 55°C under stirring and 4.8 g of Di-*p*-toluoyl-D-tartaric acid was added to it. The reaction mixture was maintained at 50°C to 55°C for about 20 minutes. To the resultant reaction mixture was then added 27.5 ml of water in about 30 minutes. The reaction mixture was then slowly cooled to about 25°C to 30°C and 15 maintained with stirring for about 6 to 7 hrs. The resulting crystals were collected by filtration, washed with 6 ml of a mixture of 2-propanol and water (1:1), and dried at 55°C and 20mbar to give 5.6 g (68 %) of the title compound as white crystals (HPLC purity >99.9 %, impurities of Formula II and IV are below limit of detection).

20 **Example 4:** (Input BFM2 containing 1.0 % of impurity of Formula II and 2.0% of impurity of Formula V)

In a 250ml glass reaction vessel equipped with a condenser, stirrer and thermometer a solution of 75 ml 2-propanol and 5.0 g of BFM2 (compound of Formula III spiked with 2.0 % impurity of Formula V). The resultant solution was heated to 50°C to 55°C under stirring and 4.35 g of Di-*p*-toluoyl-D-tartaric acid was added to it. The reaction mixture was maintained at 50°C to 55°C 25 for about 20 minutes. To the resultant reaction mixture was then added 25 ml of water in about 30 minutes. The reaction mixture was then slowly cooled to about 25°C to 30°C and maintained with stirring for about 6 to 7 hrs. The resulting crystals were collected by filtration, washed with 5.5 ml of a mixture of 2-propanol and water (1:1), and dried at 55°C and 20mbar to give 5.76 g 30 (70 %) of the title compound as white crystals (HPLC purity >99.8 %, impurity of Formula II is below limit of detection and impurity of Formula V is 0.11%).

Example 5: (Input BFM2 containing 1.0 % of impurity of Formula II, 2.0 % of impurity of Formula VI and 2.0 % of impurity VIII)

In a 100ml glass reaction vessel equipped with a condenser, stirrer and thermometer a solution of 30 ml 2-propanol and 2.0 g of BFM2 (compound of Formula III spiked with 3.0 % impurity of Formula VI). The resultant solution was heated to 50°C to 55°C under stirring and 1.7 g of Di-*p*-toluoyl-D-tartaric acid was added to it. The reaction mixture was maintained at 50°C to 55°C for about 20 minutes. To the resultant reaction mixture was then added 10 ml of water in about 30 minutes. The reaction mixture was then slowly cooled to about 25°C to 30°C and maintained with stirring for about 6 to 7 hrs. The resulting crystals were collected by filtration, washed with 2 ml of a mixture of 2-propanol and water (1:1), and dried at 55°C and 20mbar to give 2.5 g (65 %) of the title compound as white crystals (HPLC purity >99.9 %, impurities of Formula II and VI are below limit of detection and impurity of Formula VIII is 0.12 %)

Cited literature

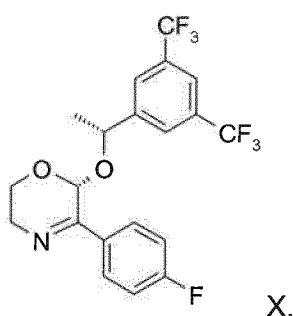
EP 0734381; EP 0748320; WO 99065900; WO 2003089429; WO2001096319; WO 2001096320; US 5668280; US 6130331; WO2007044829; US 5,719,147, WO 2001094322; WO 2001094323; WO 2001094324; WO 2009106486; US 2007265442; Gangula et al. (*Synthetic Communications*[®], 40: 2254-2268, 2010); Pye et al. (*Chem. Eur. J.* 2002, 8, No. 6, pages 1372-1376); and Zhao et al. (*J. Org. Chem.* 2002, 67, 6743-6747).

Claims

1. Salt, preferably in crystalline form, of (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) with a O,O'-substituted
5 chiral tartaric acid derivative.
2. The salt of claim 1, wherein the tartaric acid derivative is selected from the group consisting of di-O,O'-toluoyl tartaric acid, di-O,O'-benzoyl tartaric acid, di-O,O'-anisoyl tartaric
10 acid, O,O'-dibenzoyl tartaric acid mono(dimethylamide), and Di-p-toluoyl-D-tartaric acid (D-DTTA), preferably, the tartaric acid derivative is Di-p-toluoyl-D-tartaric acid (D-DTTA).
3. The salt of claim 1 or 2, having an enantiomeric purity of at least 99.0%, further preferred
15 of at least 99.8%, as determined by chiral HPLC, and/or a purity of at least 99.0%, further preferred of at least 99.8%, as determined by HPLC.
4. Composition comprising a salt according to any of claims 1-3.
5. Process for the preparation of a salt according to any of claims 1-3 or a composition
20 according to claim 4 comprising the steps of:
 - a) providing a composition comprising (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluoro-phenyl)morpholine (BFM2), and
 - b) bringing into contact the composition of step (a) and a O,O'-substituted chiral
25 tartaric acid derivative, preferably the tartaric acid derivative is selected from the group consisting of di-O,O'-toluoyl tartaric acid, di-O,O'-benzoyl tartaric acid, di-O,O'-anisoyl tartaric acid, O,O'-dibenzoyl tartaric acid mono(dimethylamide), and Di-p-toluoyl-D-tartaric acid (D-DTTA), further preferred the tartaric acid derivative is Di-p-toluoyl-D-tartaric acid (D-DTTA).
- 30 6. The process of claim 5, wherein step (b), comprises:
 - b1) dissolving the composition of step (a) in an organic solvent or mixture of organic solvents, preferably the organic solvent is or comprises a polar solvent such as an alcohol, preferably 2-propanol,
 - b2) adding the chiral tartaric acid derivative to the solution of step (b1), and
35 b3) adding water to the reaction mixture of step (b2) and obtaining said salt.

7. The process of claim 5 or 6, wherein the composition provided in step (a) comprises at least 85% by weight based on the total weight of the composition, further preferred at least 90% by weight, and even further preferred at least 95% by weight, of (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethyl-phenyl)ethoxy]-3-(4-fluoro-phenyl)morpholine (BFM2).

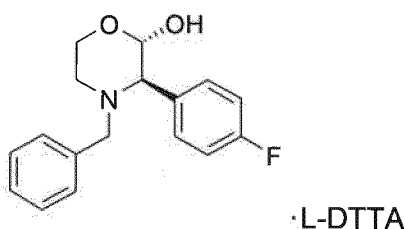
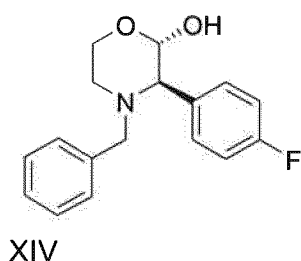
8. The process of any of claims 5-7, wherein the composition provided in step (a) is prepared from aprimin having the Formula X:



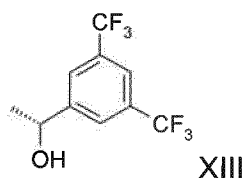
9. The process of any of claims 5-8, wherein the composition provided in step (a) is prepared from aprimin of Formula X by reducing aprimin with H_2 or an H_2 equivalent in the presence of a catalyst and by removing the catalyst by filtration, preferably, aprimin is reduced in the presence of methanol/ H_2 /Pd/C.

10. The process of claim 8 or 9, wherein the preparation of aprimin comprises the steps of:

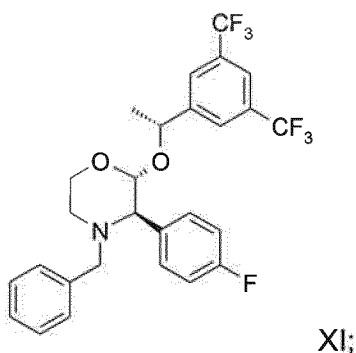
- a1) a three component coupling of N-benzyl amino ethanol, 4-fluorophenylboronic acid and glyoxal in the presence of a chiral acid, preferably Di-p-toluoyl-L-tartaric acid (L-DTTA), preferably by using toluene and 2-propanol as solvent system, and followed by crystallization and isolation of an addition salt of the compound of Formula XIV with the chiral acid, preferably as Di-p-toluoyl-L-tartaric acid salt (L-DTTA) according to Formula XII:



- a2) portioning the salt of the compound of Formula XIV and the chiral acid, preferably the compound of Formula XII, between an alkaline aqueous layer and a water-immiscible organic phase; activation of the hemi-acetal functionality by transforming the OH-group into an activated derivative; reaction of the resulting activated acetal with an alcohol of Formula XIII



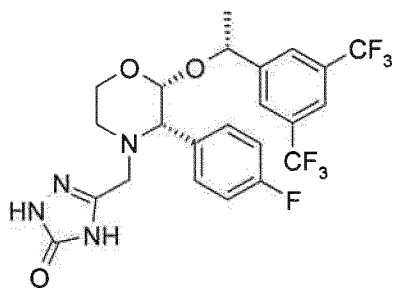
and removal of impurities by extraction to get a solution of a compound according to Formula XI:



- a3) removal of the *N*-protecting group to give (2R,3R)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM1);
- a4) oxidation of the amine of (2R,3R)-2-[(R)-1-(3,5-Bis-trifluoromethylphenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM1) to the corresponding cyclic imine aprimin and isolation of aprimin.

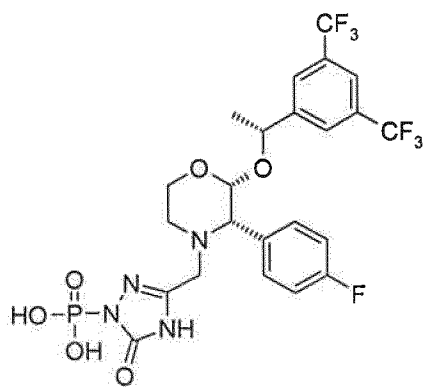
11. Process for the preparation of aprepitant or fosaprepitant comprising the steps of:

- a) providing a salt according to any of claims 1-3 or a composition according to claim 4, and
- b) converting (2R,3S)-2-[(R)-1-(3,5-Bis-trifluoromethyl-phenyl)ethoxy]-3-(4-fluorophenyl)morpholine (BFM2) contained in the salt or composition into aprepitant of Formula IX:



IX,

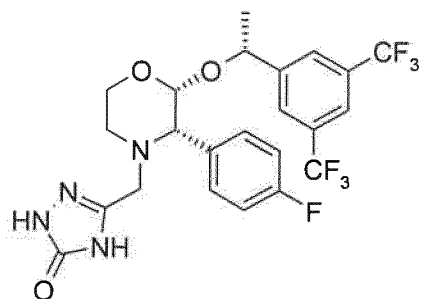
or fosaprepitant according to Formula XV



XV,

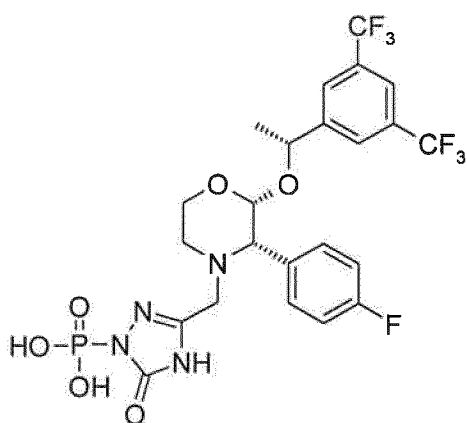
12. The process of claim 11, wherein step (b) comprises carrying out an alkylation reaction, wherein the alkylation reaction can be carried out directly or *via* protected intermediates and optionally, conversion of aprepitant to fosaprepitant by phosphorylation or a phosphorylation - deprotection sequence, and wherein preferably said alkylation is carried out by using an amidrazone, preferably N'-[1-Amino-2-chloro-eth-(Z)-ylidene]-hydrazinecarboxylic acid methyl ester.

13. Use of a salt according to any of claims 1-3 or a composition according to claim 4 for the preparation of aprepitant of Formula IX:



IX,

or fosaprepitant according to Formula XV:



XV.

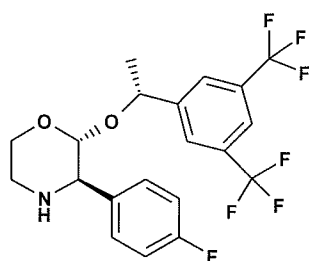
14. Aprepitant or fosaprepitant obtained or obtainable according to the process of claims 11 or 12.

15. Composition comprising aprepitant or fosaprepitant obtained or obtainable according to the process of claims 11 or 12, preferably for use as a medicament.

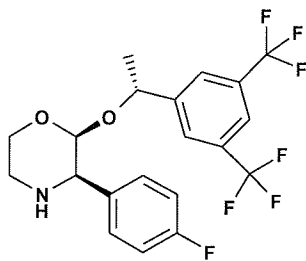
1 / 2

Figure 1:

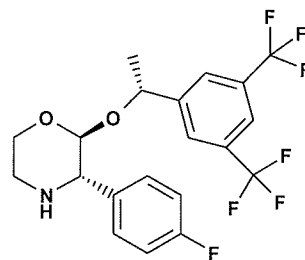
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**II**

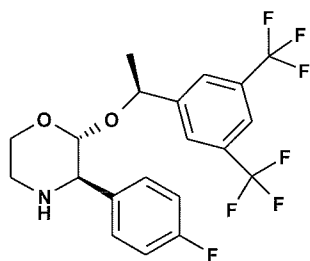
(2R,3R)-2-[(R)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine (BFM1)

**III**

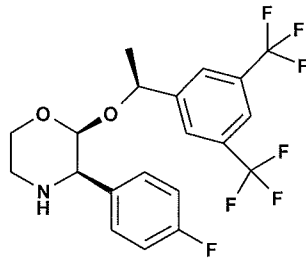
(2S,3R)-2-[(R)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine

**IV**

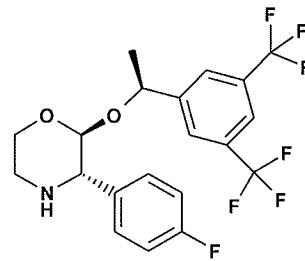
(2S,3S)-2-[(R)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine

**V**

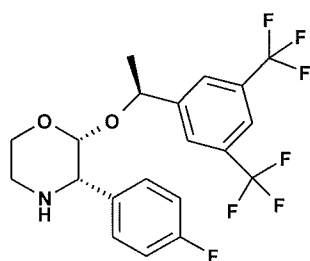
(2R,3R)-2-[(S)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine

**VI**

(2S,3R)-2-[(S)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine

**VII**

(2S,3S)-2-[(S)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine

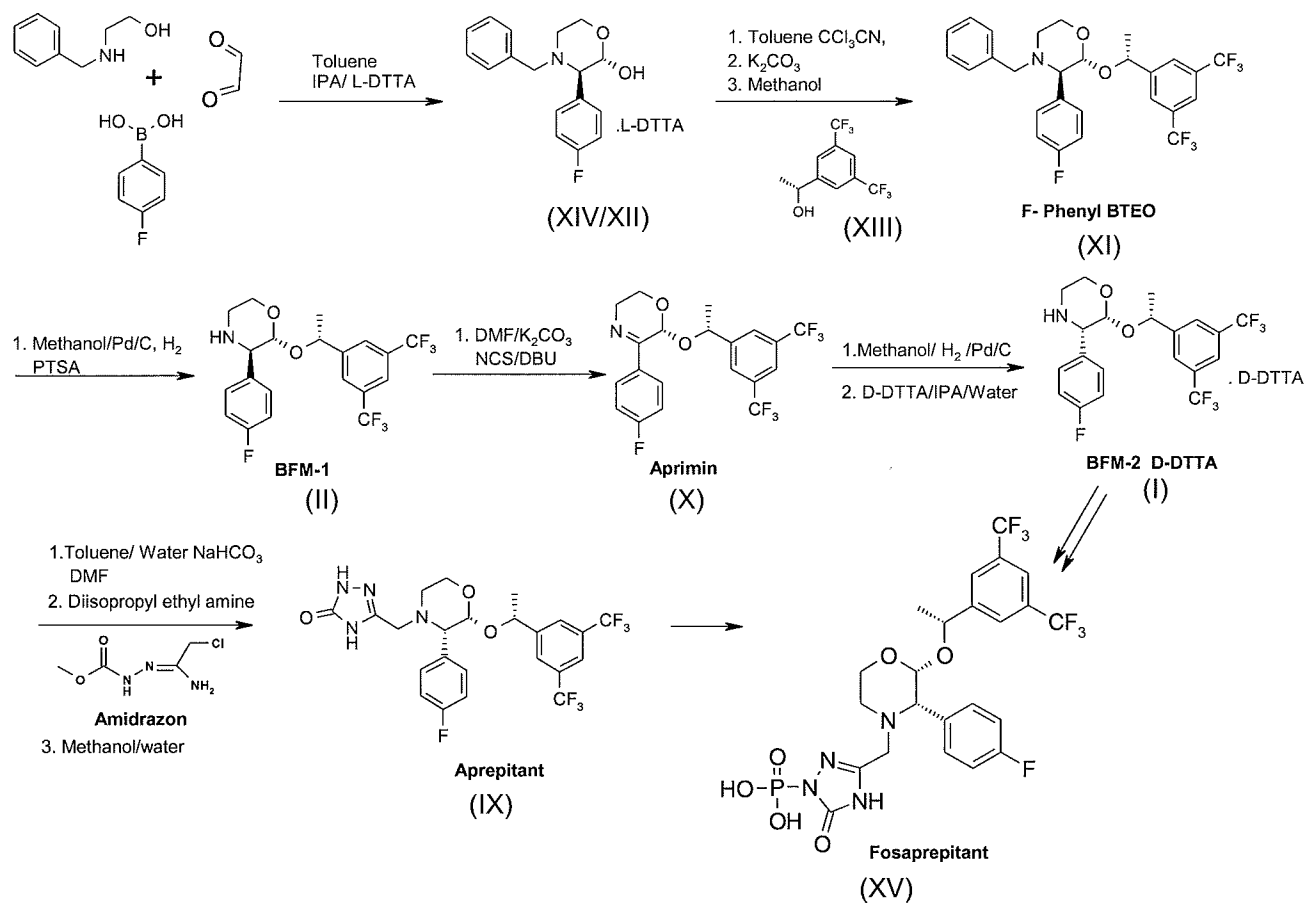
**VIII**

(2R,3S)-2-[(S)-1-(3,5-Bis-trifluoro methyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine

2 / 2

Figure 2:

5



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/057716

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D265/32 C07D413/06 C07F9/6558
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/106486 A1 (SANDOZ AG [CH]; ALBERT MARTIN [AT]; DE SOUZA DOMINIC [AT]; KNEPPER KER) 3 September 2009 (2009-09-03)	14, 15
Y	*Scheme 1*; page 5, lines 7-8 page 5, lines 26-38	1-15
Y	----- SRINIVAS GANGULA ET AL: "Synthesis of All Enantiomerically Pure Diastereomers of Aprepitant", SYNTHETIC COMMUNICATIONS, vol. 40, no. 15, 12 July 2010 (2010-07-12) , pages 2254-2268, XP55029061, ISSN: 0039-7911, DOI: 10.1080/00397910903221084 *Scheme 1*; page 2255 - page 2256 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 June 2012

Date of mailing of the international search report

20/06/2012

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Authorized officer

Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/057716

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CN 101959870 A	26-01-2011
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		US 2011009629 A1	13-01-2011
		WO 2009106486 A1	03-09-2009
