

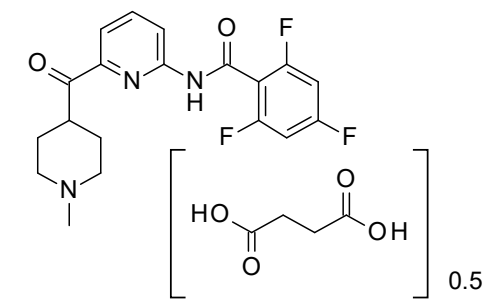
minimizing the number of synthetic steps needed, reducing the inputs required and/or the by-products produced, or any useful combination of such improvements, to achieve important real-world outcomes including decreased costs, providing less resource intensive processes, and facilitating efficient production. Improved methods of making lasmiditan are needed which may achieve one or more of these aims, particularly for large-scale synthesis.

Further, migraine is one of the most common presenting symptoms in emergency rooms. Current methods for headache relief in the emergency room setting, when using lasmiditan for patients who have difficulty administering a tablet due to nausea and/or vomiting, may need to rely on the preparation of a diluted formulation of about 1 mg/ml lasmiditan delivered intravenously over an extended period of time, for example from about 20-60 minutes. Lasmiditan has been delivered intravenously in clinical studies in doses from about 1- 60 mg delivered in 60 ml infusions over 20 minutes (See US Patent Application Publication No. 2010/0256187). The safe and effective treatment of migraine with lasmiditan for patients unable to administer tablets would be enabled by the availability of a high concentration parenteral dosage form. The present disclosure also addresses this need.

Summary

The ~~embodiment examples~~ of the present ~~invention disclosure~~ provide processes for the preparation of lasmiditan hemisuccinate, 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate salt, and/or compositions thereof, and/or particularly useful intermediates for use in these processes. The ~~embodiment examples~~ of the present ~~invention disclosure~~ further provide for the preparation of lasmiditan acetate, 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide acetate salt, and/or compositions thereof, and/or uses of lasmiditan acetate, and formulations thereof, in subcutaneous drug delivery.

In one aspect of the present disclosure, there is provided a process for preparing a compound of the formula:



comprising the steps of:

- 5 i.) Treatment of piperidine-4-carboxylic acid under reductive amination conditions comprising formaldehyde and formic acid in water with subsequent treatment with aqueous HCl followed by water distillation and acetonitrile addition, with repeated dilution/distillation until the water content is not more than 0.2% by Karl-Fischer analysis, to obtain solid 1-methylpiperidine-4-carboxylic acid hydrochloride;
- 10 ii.) Treatment of 1-methylpiperidine-4-carboxylic acid hydrochloride with a chlorinating agent such as thionyl chloride in chlorobenzene to obtain 1-methylpiperidine-4-carboxylic acid chloride;
- 15 iii.) Treatment of 1-methylpiperidine-4-carboxylic acid chloride with N,N-diethylamine in chlorobenzene containing triethylamine with subsequent base wash and subsequent treatment with aqueous HCl in isopropanol to obtain solid N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride;

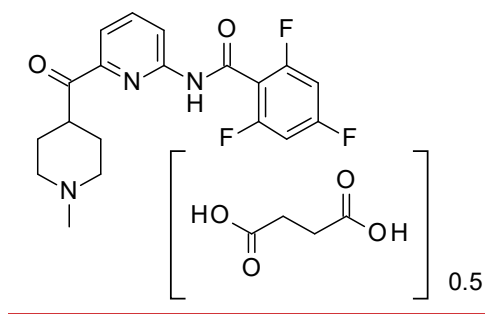
- iv.) Treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride with a mineral base such as aqueous NaOH in a non-polar solvent such as methyl-tert-butyl ether with subsequent water wash, phase separation, and distillation of the organic solvent until the water content is not more than 0.1 weight t% by Karl Fischer analysis to obtain N,N-diethyl-1-methyl-piperidine-4-carboxamide;
- 5
- v.) Subsequent treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide with (6-bromo-2-pyridyl)lithium in a non-polar organic solvent such as methyl-tert-butyl ether with subsequent extraction of the resulting mixture with water and a suitable organic solvent such as *n*-butanol, phase separation, and repeated distillation of the organic solvent until the water content is not more than 0.2 weight % by Karl-Fischer analysis, to obtain (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone;
- 10
- 15
- vi.) Treatment of (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone with aqueous HBr and subsequent extraction with *n*-butanol followed by repeated distillation of the organic solvent until the water content is not more than 0.3% by Karl-Fischer analysis, to obtain solid (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone hydrobromide;
- 20
- vii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone hydrobromide with a solution of NH₃ in ethylene glycol in the presence of Cu₂O catalyst at about 80 °C for about 2 hr, with subsequent washes with water, saturated aqueous NaCl, and 20% aqueous NaOH and subsequent extraction with a non-polar aprotic solvent such as methyl-tert-butyl ether, phase separation, and treatment of the organic phase with 5 weight % carbon;
- 25

- viii.) Filtration of the above mixture, dilution with a suitable polar alcoholic solvent such as isopropanol, and repeated distillation of the organic solvent until the water content is not more than 0.2% by Karl-Fischer analysis, with subsequent treatment of the resulting residue with isopropanol, water, and 20 weight % HCl, wherein the water concentration of the resulting slurry is at least 2%, filtration of the resulting slurry, and drying under vacuum at 40 °C for 16-24 hr to obtain solid (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride;
- ix.) Treatment of (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride in chlorobenzene with 6 weight/weight % NaOH in water at about 54 °C for about 30 min, with subsequent phase separation and vacuum distillation of the aqueous solution to obtain (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone;
- x.) Subsequent treatment of (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone with 2,4,6-trifluorobenzoic acid chloride in chlorobenzene at about 100 °C for about 4 hr, with subsequent cooling, charging with acetonitrile and heating the resulting slurry to 80 °C for about 1 hr, and subsequent collection of the resulting solid by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hydrochloride;
- xi.) Treatment of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hydrochloride with saturated aqueous Na₂CO₃ in methyl-tert-butyl ether;

xii.) Treatment of the mixture of step xi above with SiO₂ with subsequent filtration, treatment with carbon, filtration, and evaporation, dilution with ethanol, and distillation until the water content is not more than 1% by Karl-Fischer analysis, to obtain 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide;

xiii.) Treatment of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide in ethanol with a solution of 0.5 equivalents succinic acid in ethanol at about 55 °C for not less than 3 hr at RT, and subsequent collection of the solid by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

In another aspect of the present disclosure, there is provided a process for preparing a compound of the formula:



comprising the steps of:

i.) Treatment of piperidine-4-carboxylic acid under reductive amination conditions comprising formaldehyde and formic acid in water with subsequent treatment with aqueous HCl followed by water distillation and acetonitrile addition, with repeated dilution/distillation until the water content is not more than 0.2% by Karl-Fischer analysis, to obtain solid 1-methylpiperidine-4-carboxylic acid hydrochloride;

- ii.) Treatment of 1-methylpiperidine-4-carboxylic acid hydrochloride with a chlorinating agent such as thionyl chloride in chlorobenzene obtain 1-methylpiperidine-4-carboxylic acid chloride;
- 5 iii.) Treatment of 1-methylpiperidine-4-carboxylic acid chloride with N,N-diethylamine in chlorobenzene containing triethylamine with subsequent base wash and subsequent treatment with aqueous HCl in isopropanol to obtain solid N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride;
- 10 iv.) Treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride with a mineral base such as aqueous NaOH in a non-polar solvent such as methyl-tert-butyl ether with subsequent water wash, phase separation, and distillation of the organic solvent until the water content is
- 15 not more than 0.1 weight % by Karl Fischer analysis to obtain N,N-diethyl-1-methyl-piperidine-4-carboxamide;
- 20 v.) Subsequent treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide with (6-bromo-2-pyridyl)lithium in a non-polar organic solvent such as methyl-tert-butyl ether with subsequent extraction of the resulting mixture with water and a suitable organic solvent such as *n*-butanol, phase separation, and repeated distillation of the organic solvent until the water content is not more than 0.2 weight % by Karl-Fischer analysis, to obtain
- 25 (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone;
- 30 vi.) Treatment of (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone with aqueous HBr and subsequent extraction with *n*-butanol followed by repeated distillation of the organic solvent until the water content is not more than 0.3% by Karl-Fischer analysis, to obtain solid (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone hydrobromide;

vii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone hydrobromide in a biphasic mixture of water and toluene with solid KOH for about 3 hr with subsequent separation of the organic layer and evaporation of the solvent to obtain of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone;

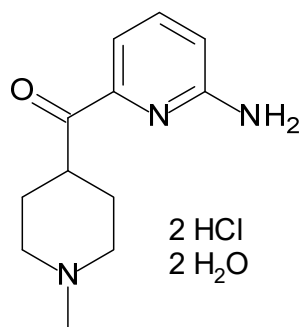
viii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone with 2,4,6-trifluorobenzamide in toluene containing K₂CO₃, water, Pd(OAc)₂, and Xantphos at about 70 °C for about 12 hr, until the (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone content is not more than 0.1% by HPLC, with subsequent dilution of the reaction mixture with water and EtOAc, subsequent treatment with thiourea-modified silica gel at 60 °C for about 8 hr, with subsequent filtration to obtain a solution of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide;

ix.) Treatment of a solution of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide in EtOAc with a solution of about 0.5 equivalents of succinic acid dissolved in EtOH at 55 °C for about 3 hr, with subsequent cooling to RT over about 10 hr, and collection of the resulting solids by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

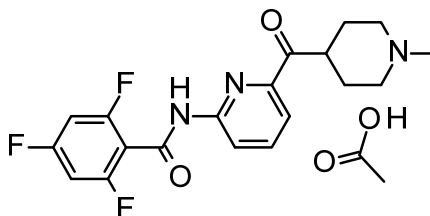
In a further aspect of the present disclosure, there is provided a tablet produced by the process disclosed herein wherein the tablet comprises 50 mg of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

In another aspect of the present disclosure, there is provided a tablet produced by the process disclosed herein wherein the tablet comprises 100 mg of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

In a further aspect of the present disclosure, there is provided a compound of the formula:



In another aspect of the present disclosure, there is provided a compound of the
5 formula:



In a further aspect of the present disclosure, there is provided a crystalline form of the compound disclosed herein.

In another aspect of the present disclosure, there is provided a pharmaceutical
10 composition comprising a compound disclosed herein with one or more pharmaceutically acceptable carriers, diluents, or excipients.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating migraine in a patient.

In another aspect of the present disclosure, there is provided a compound disclosed
15 herein for use in therapy.

In one aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of migraine.

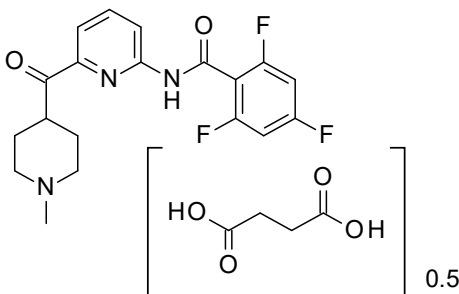
In one ~~embodiment~~example, referred to as Route I, the present ~~invention~~disclosure provides a process for preparing a compound of the formula:

collection of the solid by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

5 In the process of Route I above, preferably the reactions are performed using batch processing methodology. In an embodimentexample the batches by Route I are produced at process scale. In an embodimentexample the batches by Route I are produced in at least 1 kilogram. In an embodimentexample the batches by Route I are produced in at least 10 kilograms. In an embodimentexample the batches by Route I are produced in at least 100 kilograms.

10 In the process of Route I above, the use of chlorobenzene avoids degradation which occurs under alternative methods, such as THF, which reacts with the acid chloride under scale (e.g., 100 kg) resulting in essentially no yield of the acid chloride.

In another embodimentexample, referred to as Route II, the present
15 inventiondisclosure provides a process for preparing a compound of the formula:



comprising the steps of:

20 i.) Treatment of piperidine-4-carboxylic acid under reductive amination conditions comprising formaldehyde and formic acid in water with subsequent treatment with aqueous HCl followed by water distillation and acetonitrile addition, with repeated dilution/distillation until the water content is not more than 0.2% by Karl-Fischer analysis, to obtain solid 1-methylpiperidine-4-carboxylic acid hydrochloride;

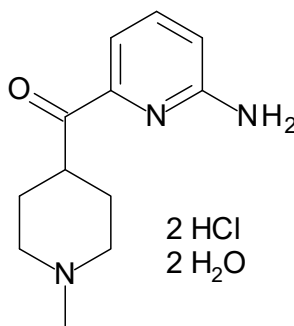
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- vii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone hydrobromide in a biphasic mixture of water and toluene with solid KOH for about 3 hr with subsequent separation of the organic layer and evaporation of the solvent to obtain of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone;
- viii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone with 2,4,6-trifluorobenzamide in toluene containing K_2CO_3 , water, $Pd(OAc)_2$, and Xantphos at about 70 °C for about 12 hr, until the (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone content is not more than 0.1% by HPLC, with subsequent dilution of the reaction mixture with water and EtOAc, subsequent treatment with thiourea-modified silica gel at 60 °C for about 8 hr, with subsequent filtration to obtain a solution of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide;
- ix.) Treatment of a solution of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide in EtOAc with a solution of about 0.5 equivalents of succinic acid dissolved in EtOH at 55 °C for about 3 hr, with subsequent cooling to RT over about 10 hr, and collection of the resulting solids by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

In the process of Route II above, preferably the reactions are performed using batch processing methodology. In an embodimentexample the batches by Route II are produced at process scale. In an embodimentexample the batches by Route II are produced in at least 1 kilogram. In an embodimentexample the batches by Route II are produced in at least 10 kilograms. In an embodimentexample the batches by Route II are produced in at least 100 kilograms.

In the process of Route II above, the use of chlorobenzene avoids degradation which occurs under alternative methods, such as THF, which reacts with the acid chloride under scale (e.g. 100 kg) resulting in essentially no yield of the acid chloride.

In another ~~embodiment~~example the present ~~invention~~disclosure provides:



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which can be named as (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride. Preferably this compound is crystalline. (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride is particularly useful in the preparation of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide

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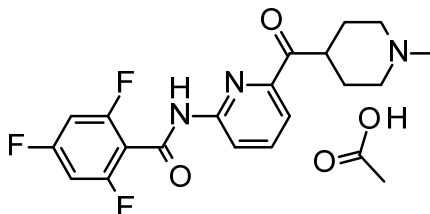
hemisuccinate, and processes which employ (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride may provide advantageous process characteristics, including but not limited to the purity of intermediate and/or final materials. (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate

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dihydrochloride is believed to be a new stable hydrated form of 6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone. The process to isolate (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride described herein provides improved impurity rejection and an improved controlled crystallization process. Form and chemical stability studies showed (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride is generally stable, and drying studies show that over-drying to remove

20 water of hydration is difficult, even under forcing conditions. Use of this intermediate provides advantageously high purity product at expected yield.

In another ~~embodiment~~example the present disclosure provides lasmiditan acetate, which can be represented by the formula:



In another embodimentexample the inventiondisclosure provides lasmiditan acetate in crystalline form, and further provides lasmiditan acetate in crystalline form characterized by an X-ray powder diffraction pattern using CuK α radiation having an intense peak at
5 diffraction angle 2-theta of 26.2° in combination with one or more of the peaks selected from the group consisting of 20.4°, 14.0°, and 17.9° ($\pm$ 0.2° respectively). In another embodimentexample the present inventiondisclosure provides a pharmaceutical composition comprising lasmiditan acetate according to the above embodimentexamples with one or more pharmaceutically acceptable carriers, diluents, or excipients. Preferably the pharmaceutical
10 composition comprises acetic acid. Preferably the pharmaceutical composition comprises acetic acid and is for subcutaneous administration.

In another embodimentexample the inventionpresent disclosure provides a method of treating migraine in a patient comprising administering to a patient in need of such treatment an effective amount of lasmiditan acetate. In another embodimentexample the
15 inventionpresent disclosure provides a method of treating migraine in a patient comprising administering to a patient in need of such treatment an effective amount of lasmiditan acetate with one or more pharmaceutically acceptable carriers, diluents, or excipients. In another embodimentexample the inventionpresent disclosure provides a method of treating migraine in a patient comprising administering to a patient in need of such treatment an effective
20 amount of lasmiditan acetate with one or more pharmaceutically acceptable carriers, diluents, or excipients wherein the composition comprises acetic acid.

In another embodimentexample the inventionpresent disclosure provides lasmiditan acetate for use in therapy. In another embodimentexample the inventionpresent disclosure provides a pharmaceutical composition of lasmiditan acetate with one or more
25 pharmaceutically acceptable carriers, diluents, or excipients for use in therapy. In another embodimentexample the inventionpresent disclosure provides a pharmaceutical composition of lasmiditan acetate with one or more pharmaceutically

acceptable carriers, diluents, or excipients, wherein the composition comprises acetic acid for use in therapy.

In another embodimentexample the inventionpresent disclosure provides lasmiditan acetate for use in the treatment of migraine. In another embodimentexample the
5 inventionpresent disclosure provides a pharmaceutical composition of lasmiditan acetate with one or more pharmaceutically acceptable carriers, diluents, or excipients for use in the treatment of migraine. In another embodimentexample the inventionpresent disclosure provides a pharmaceutical composition of lasmiditan acetate with one or more pharmaceutically acceptable carriers, diluents, or excipients, wherein the composition
10 comprises acetic acid for use in the treatment of migraine.

In another embodimentexample the present disclosure provides lasmiditan acetate, and pharmaceutical compositions comprising a high concentration of lasmiditan acetate, *e.g.*, about 10-200 mg/ml free base equivalent, in an aqueous carrier. In embodimentexamples, the pharmaceutical composition comprises about 10-200 mg/ml free base equivalent lasmiditan
15 in a buffered aqueous solution. In embodimentexamples, the buffered aqueous solution is at a pH of between pH 6.0 - 7.5 at 37 °C. In embodimentexamples, the buffered aqueous solution comprises acetic acid.

In addition to an aqueous carrier, preferably sterile, deionized, distilled water, the pharmaceutical compositions described herein may further comprise one or more
20 pharmaceutically acceptable excipients or cosolvents. The term “pharmaceutically acceptable” refers to excipients and cosolvents which are suitable for use in contact with the tissues of human beings without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Pharmaceutical compositions and processes for preparing the same are well known in the art (see, *e.g.*,
25 Remington: The Science and Practice of Pharmacy (A. Gennaro, et al., eds., 21st ed., Mack Publishing Co., 2005)).

A pharmaceutical composition of lasmiditan acetate can be provided in bulk or in dosage unit form. It is especially advantageous to formulate pharmaceutical compositions of lasmiditan acetate in dosage unit form for ease of administration and uniformity of dosage.
30 The term “dosage unit form” as used herein refers to physically discrete units suitable as unitary dosages for the subject to be treated; each unit containing a

predetermined quantity of active compound lasmiditan calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. A dosage unit form can be, *e.g.*, an ampoule, a vial, or a syringe.

In [embodimentexamples](#), the disclosure provides a pharmaceutical composition comprising an amount of lasmiditan acetate as described herein wherein the amount is from 10 mg to 200 mg per dose. In [embodimentexamples](#), the disclosure provides a pharmaceutical composition comprising an amount of lasmiditan acetate as described herein wherein the amount is 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 100 mg, or 200 mg per dose. The forgoing doses are based on an adult human of average weight. Smaller doses would be acceptable for individuals of lighter weight, for example the elderly or children. Therefore, in [embodimentexamples](#), the pharmaceutical composition may comprise a smaller dose, such as 5, 10, or 15 mg.

As described herein, the highly concentrated aqueous solutions of lasmiditan acetate enables the administration of a single therapeutically effective dose by injection of a high concentration aqueous solution of lasmiditan, for example, by an intravenous, subcutaneous, or intramuscular route.

In [embodimentexample](#), the disclosure provides high concentration aqueous solutions of lasmiditan acetate. In [embodimentexamples](#), the high concentration aqueous solution of lasmiditan acetate is formulated as a parenteral dosage form. In [embodimentexamples](#), the high concentration aqueous solution contains 10-200 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the high concentration aqueous solution of lasmiditan acetate is in the form of a parenteral dosage form. In [embodimentexamples](#), the parenteral dosage form is a buffered aqueous solution of 10-200 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the parenteral dosage form is a buffered aqueous solution of 10, 20, 30, 40, 50, 100 or 200 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the parenteral dosage form is suitable for subcutaneous or intramuscular injection. Preferably the parenteral dosage form is for subcutaneous injection. In [embodimentexamples](#), the pH of the buffered solution is between pH 6.0-7.5 at 37°C.

In [embodimentexamples](#), the buffered aqueous solution comprises a buffering system based on an organic acid. In [embodimentexamples](#), the organic acid is a di- or tri-carboxylic acid.

In [embodimentexamples](#), the di- or tri-carboxylic acid is selected from the group consisting of acetic acid and citric acid. In [embodimentexamples](#), the organic acid is succinic acid. In [embodimentexamples](#), the buffer is an acetic acid buffer. In [embodimentexamples](#), the buffered aqueous solution is free of organic solvents. In [embodimentexamples](#), the buffered aqueous solution is free of organic solvents and surfactants. In a preferred [embodimentexample](#) the buffered aqueous solution comprises lasmiditan acetate, and acetic acid, and sodium hydroxide, adjusted to pH between 6.0-7.5 at 37°C.

In [embodimentexamples](#), the parenteral dosage form of lasmiditan acetate is provided in the form of a pre-filled syringe suitable for administration by a subcutaneous route. In [embodimentexamples](#), the pre-filled syringe comprises 10-50 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the pre-filled syringe comprises 10, 20, 30, 40, 50 or 100 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the lasmiditan is provided in a buffered aqueous solution having a pH 6.0-7.5 at 37 °C. In [embodimentexamples](#), the pre-filled syringe is suitable for at-home use, for example, for those migraine sufferers who might face an extreme and rapid onset of headache. In [embodimentexamples](#), the pre-filled syringe is contained in a package with instructions for parenteral administration, preferably by subcutaneous injection. In [embodimentexamples](#), the pre-filled syringe is in the form of an autoinjector with instructions for subcutaneous injection.

In [embodimentexamples](#), the parenteral dosage form of lasmiditan acetate is provided in the form of a vial containing 10-50 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the parenteral dosage form of lasmiditan acetate is provided in the form of a vial containing 10, 20, 30, 40, 50 or 100 mg/ml free base equivalent of lasmiditan. In [embodimentexamples](#), the lasmiditan is provided in a buffered aqueous solution having a pH 6.0-7.5 at 37 °C.

The disclosure also provides methods for acute treatment of migraine headache attacks, the methods comprising administering a therapeutically effective dose of lasmiditan acetate as described herein. In [embodimentexamples](#), the parenteral solution is administered by subcutaneous injection. In [embodimentexamples](#), the parenteral solution comprises 10-50 mg/ml free base equivalent of lasmiditan acetate in a buffered aqueous solution at pH 6.0-7.5 at 37 °C. In [embodimentexamples](#), the parenteral solution comprises 10, 20,

30, 40, 50 or 100 mg/ml free base equivalent of lasmiditan. In embodimentexamples, the methods comprise administering a single therapeutically effective dose of lasmiditan acetate in a volume of less than or equal to 1 ml, such as from about 0.5 to 1 ml, for example by a single subcutaneous injection. In embodimentexamples, the injection volume is about 1 ml. In 5 embodimentexamples, the injection volume is about 0.5 ml.

The present inventiondisclosure provides a method for the treatment of migraine, in a patient in need thereof, comprising administering to the patient 20-200 mg per subcutaneous dose of lasmiditan acetate and a pharmaceutically acceptable diluent or carrier. The present inventiondisclosure provides a method for treatment of migraine, in a patient in need thereof, 10 comprising administering to the patient 20 mg per subcutaneous dose of lasmiditan acetate and a pharmaceutically acceptable diluent or carrier. The present inventiondisclosure provides a method for the treatment of migraine, in a patient in need thereof, comprising administering to the patient 50 mg per subcutaneous dose of lasmiditan acetate and a pharmaceutically acceptable diluent or carrier. The present inventiondisclosure provides a method for the 15 treatment of migraine, in a patient in need thereof, comprising administering to the patient 75 mg per subcutaneous dose of lasmiditan acetate and a pharmaceutically acceptable diluent or carrier. The present inventiondisclosure provides a method for the treatment of migraine, in a patient in need thereof, comprising administering to the patient 100 mg per subcutaneous dose of lasmiditan acetate and a pharmaceutically acceptable diluent or carrier. The present 20 inventiondisclosure provides a method for the treatment of migraine, in a patient in need thereof, comprising administering to the patient 150 mg per subcutaneous dose of lasmiditan acetate and a pharmaceutically acceptable diluent or carrier. The present inventiondisclosure provides a method for the treatment of migraine, in a patient in need thereof, comprising administering to the patient 200 mg per subcutaneous dose of lasmiditan acetate and a 25 pharmaceutically acceptable diluent or carrier.

In some embodimentexamples, a patient is a human who has been diagnosed as having a condition or disorder in need of prevention with a pharmaceutical composition described herein. In some embodimentexamples, a patient is a human that is characterized as being at risk of a condition or disorder for which administration with a pharmaceutical 30 composition described herein is indicated. In those instances where the disorders which can be treated

by the methods of the present ~~invention~~disclosure are known by established and accepted classifications, such as migraine, episodic headache, chronic headache, chronic cluster headaches, and/or episodic cluster headaches, their classifications can be found in various sources. For example, at present, the fourth edition of the Diagnostic and Statistical

5 Manual of Mental Disorders (DSM-IVTM) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool for identifying many of the disorders described herein. Also, the International Classification of Diseases, Tenth Revision (ICD-10), provides classifications for many of the disorders described herein. The skilled

10 artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for disorders described herein, including those as described in the DSM-IV and ICD-10, and that terminology and classification systems evolve with medical scientific progress. Migraine patients can further be diagnosed with migraine, with or without aura (1.1 and 1.2), as defined by International Headache Society (IHS) International Classification of Headache Disorders, 3rd edition, (ICHD-3) beta version

15 (The International Classification of Headache Disorders, 3rd edition (beta version), Cephalalgia 2013; 33: 629–808). In some ~~embodiment~~examples, the human patient has been diagnosed with episodic migraine prior to receiving chronic administration of lasmiditan, preferably nightly, to prevent migraine. In some ~~embodiment~~examples, the human patient has been diagnosed with chronic migraine prior to receiving the antibody.

20 In some ~~embodiment~~examples, the human patient experiences auras with their migraine headaches. In some ~~embodiment~~examples, the human patient does not experience auras with their migraine headaches.

As used herein “migraine” includes but is not limited to migraine attacks. As used herein “migraine attack” refers to the following description. Symptoms may overlap

25 within various phases of a migraine attack and not all patients experience the same clinical manifestations. In the prodrome phase, the majority of patients have premonitory symptoms that may precede the headache phase by up to 72 hours. These include changes in mood and activity, irritability, fatigue, food cravings, repetitive yawning, stiff neck, and phonophobia. These symptoms may endure well into the aura, headache, and

30 even postdrome phases. Some patients experience an aura phase, wherein about one-third

administration to the patient, provides the desired pharmacological effect in the patient, for example an amount capable of activating 5-HT_{1F} receptors. In a preferred ~~embodiment~~example, “effective amount” means an amount of lasmiditan acetate that upon acute administration is capable of rendering a patient migraine attack free following administration. A “dose” refers to a predetermined quantity of lasmiditan acetate calculated to produce the desired therapeutic effect in a patient. As used herein “mg” refers to milligram. As used herein, doses described in mg, refer to the active pharmaceutical ingredient lasmiditan, as free-base equivalent by mass, for instance a “100 mg” dose, refers to 100 mg of the active pharmaceutical ingredient lasmiditan as free-base equivalent. As used herein, a given dose may be interpreted to describe doses of about the indicated amount, in that doses which are up to 10 percent higher or lower than the indicated dose are likewise contemplated to provide useful regimens in a manner similar to the indicated dose.

Brief Description of the Figures

- 15 Figure 1: Graphical representation of an ¹H NMR spectrum (400 MHz, DMSO-d₆) of lasmiditan acetate containing maleic acid (internal standard).

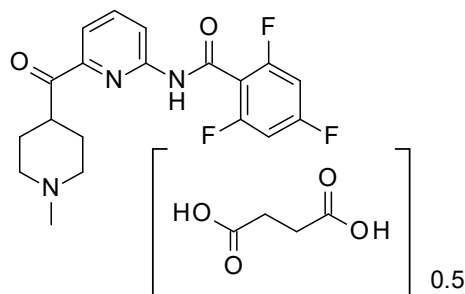
Detailed Description

The reactions described herein may be performed via standard techniques known to the skilled artisan by employing routine glassware or may be performed on pilot and/or production scale in equipment designed for such transformations. Further, each of these reactions described may be executed via either a batch process, or where applicable, a flow reaction methodology. The term “batch process” as used herein refers to a process in which raw materials are combined in a reactor or vessel and product is removed at the end of the reaction.

Additionally, certain intermediates described in the following preparations may contain one or more nitrogen protecting groups. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are well known to the skilled artisan and are described in the literature (See for

WE CLAIM:

1. A process for preparing a compound of the formula:



5 comprising the steps of:

- i.) Treatment of piperidine-4-carboxylic acid under reductive amination conditions comprising formaldehyde and formic acid in water with subsequent treatment with aqueous HCl followed by water distillation and acetonitrile addition, with repeated dilution/distillation until the water content is not more than 0.2% by Karl-Fischer analysis, to obtain solid 1-methylpiperidine-4-carboxylic acid hydrochloride;
- ii.) Treatment of 1-methylpiperidine-4-carboxylic acid hydrochloride with a chlorinating agent such as thionyl chloride in chlorobenzene to obtain 1-methylpiperidine-4-carboxylic acid chloride;
- iii.) Treatment of 1-methylpiperidine-4-carboxylic acid chloride with N,N-diethylamine in chlorobenzene containing triethylamine with subsequent base wash and subsequent treatment with aqueous HCl in isopropanol to obtain solid N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride;
- iv.) Treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride with a mineral base such as aqueous NaOH in a non-polar

solvent such as methyl-tert-butyl ether with subsequent water wash, phase separation, and distillation of the organic solvent until the water content is not more than 0.1 weight t% by Karl Fischer analysis to obtain N,N-diethyl-1-methyl-piperidine-4-carboxamide;

5

v.) Subsequent treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide with (6-bromo-2-pyridyl)lithium in a non-polar organic solvent such as methyl-tert-butyl ether with subsequent extraction of the resulting mixture with water and a suitable organic solvent such as *n*-butanol, phase separation, and repeated distillation of the organic solvent until the water content is not more than 0.2 weight % by Karl-Fischer analysis, to obtain (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone;

10

vi.) Treatment of (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone with aqueous HBr and subsequent extraction with *n*-butanol followed by repeated distillation of the organic solvent until the water content is not more than 0.3% by Karl-Fischer analysis, to obtain solid (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone hydrobromide;

15

vii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone hydrobromide with a solution of NH₃ in ethylene glycol in the presence of Cu₂O catalyst at about 80 °C for about 2 hr, with subsequent washes with water, saturated aqueous NaCl, and 20% aqueous NaOH and subsequent extraction with a non-polar aprotic solvent such as methyl-tert-butyl ether, phase separation, and treatment of the organic phase with 5 weight % carbon;

20

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viii.) Filtration of the above mixture, dilution with a suitable polar alcoholic solvent such as isopropanol, and repeated distillation of the organic solvent until the water content is not more than 0.2% by Karl-Fischer analysis,

30

5 with subsequent treatment of the resulting residue with isopropanol, water, and 20 weight % HCl, wherein the water concentration of the resulting slurry is at least 2%, filtration of the resulting slurry, and drying under vacuum at 40 °C for 16-24 hr to obtain solid (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride;

10 ix.) Treatment of (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone dihydrate dihydrochloride in chlorobenzene with 6 weight/weight % NaOH in water at about 54 °C for about 30 min, with subsequent phase separation and vacuum distillation of the aqueous solution to obtain (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone;

15 x.) Subsequent treatment of (6-amino-2-pyridyl)-(1-methyl-4-piperidyl)methanone with 2,4,6-trifluorobenzoic acid chloride in chlorobenzene at about 100 °C for about 4 hr, with subsequent cooling, charging with acetonitrile and heating the resulting slurry to 80 °C for about 1 hr, and subsequent collection of the resulting solid by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hydrochloride;

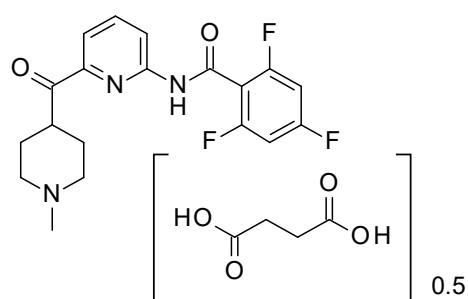
20 xi.) Treatment of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hydrochloride with saturated aqueous Na₂CO₃ in methyl-tert-butyl ether;

25 xii.) Treatment of the mixture of step xi above with SiO₂ with subsequent filtration, treatment with carbon, filtration, and evaporation, dilution with ethanol, and distillation until the water content is not more than 1% by Karl-Fischer analysis, to obtain 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide;

30

- xiii.) Treatment of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide in ethanol with a solution of 0.5 equivalents succinic acid in ethanol at about 55 °C for not less than 3 hr at RT, and subsequent collection of the solid by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.

2. A process for preparing a compound of the formula:



comprising the steps of:

- i.) Treatment of piperidine-4-carboxylic acid under reductive amination conditions comprising formaldehyde and formic acid in water with subsequent treatment with aqueous HCl followed by water distillation and acetonitrile addition, with repeated dilution/distillation until the water content is not more than 0.2% by Karl-Fischer analysis, to obtain solid 1-methylpiperidine-4-carboxylic acid hydrochloride;
- ii.) Treatment of 1-methylpiperidine-4-carboxylic acid hydrochloride with a chlorinating agent such as thionyl chloride in chlorobenzene obtain 1-methylpiperidine-4-carboxylic acid chloride;
- iii.) Treatment of 1-methylpiperidine-4-carboxylic acid chloride with N,N-diethylamine in chlorobenzene containing triethylamine with subsequent base wash and subsequent treatment with aqueous HCl in isopropanol to

obtain solid N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride;

5 iv.) Treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide hydrate hydrochloride with a mineral base such as aqueous NaOH in a non-polar solvent such as methyl-tert-butyl ether with subsequent water wash, phase separation, and distillation of the organic solvent until the water content is not more than 0.1 weight % by Karl Fischer analysis to obtain N,N-diethyl-1-methyl-piperidine-4-carboxamide;

10

 v.) Subsequent treatment of N,N-diethyl-1-methyl-piperidine-4-carboxamide with (6-bromo-2-pyridyl)lithium in a non-polar organic solvent such as methyl-tert-butyl ether with subsequent extraction of the resulting mixture with water and a suitable organic solvent such as *n*-butanol, phase separation, and repeated distillation of the organic solvent until the water content is not more than 0.2 weight % by Karl-Fischer analysis, to obtain (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone;

15

 vi.) Treatment of (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone with aqueous HBr and subsequent extraction with *n*-butanol followed by repeated distillation of the organic solvent until the water content is not more than 0.3% by Karl-Fischer analysis, to obtain solid (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone hydrobromide;

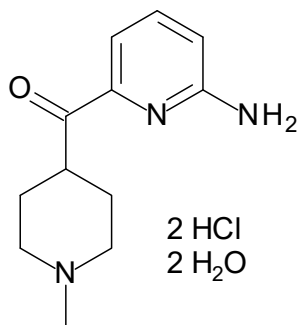
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 vii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone hydrobromide in a biphasic mixture of water and toluene with solid KOH for about 3 hr with subsequent separation of the organic layer and evaporation of the solvent to obtain of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone;

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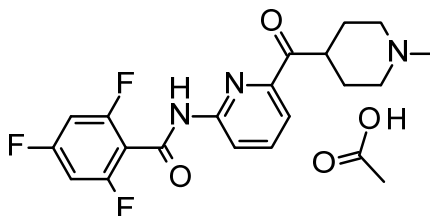
- viii.) Treatment of (6-bromo-2-pyridyl-1-methyl-4-piperidyl)methanone with 2,4,6-trifluorobenzamide in toluene containing K_2CO_3 , water, $Pd(OAc)_2$, and Xantphos at about 70 °C for about 12 hr, until the (6-bromo-2-pyridyl)-(1-methyl-4-piperidyl)methanone content is not more than 0.1% by HPLC, with subsequent dilution of the reaction mixture with water and EtOAc, subsequent treatment with thiourea-modified silica gel at 60 °C for about 8 hr, with subsequent filtration to obtain a solution of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide;
- ix.) Treatment of a solution of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide in EtOAc with a solution of about 0.5 equivalents of succinic acid dissolved in EtOH at 55 °C for about 3 hr, with subsequent cooling to RT over about 10 hr, and collection of the resulting solids by filtration, to obtain solid 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.
3. A process of Claim 1 or 2 wherein the reactions are performed using batch processing methodology.
4. A process of Claim 3 wherein the batch produced is at process scale.
5. A process of Claim 4 wherein the batch produced is at least 1 kilogram.
6. A process of Claim 4 wherein the batch produced is at least 10 kilograms.
7. A process of Claim 4 wherein the batch produced is at least 100 kilograms.
8. A tablet produced by the process of any one of claims 1 - 7 wherein the tablet comprises 50 mg of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.
9. A tablet produced by the process of any one of claims 1 - 7 wherein the tablet comprises 100 mg of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate.
10. A compound of the formula:



11. The compound of Claim 10 which is crystalline.

5 12. The compound according to claim 11 characterized by an X-ray powder diffraction pattern using CuK α radiation having an intense peak at diffraction angle 2-theta of 8.3° in combination with one or more of the peaks selected from the group consisting of 16.6°, 23.5°, and 33.7° ($\pm$ 0.2° respectively).

13. A compound of the formula:



14. A crystalline form of the compound according to claim 13.

15 15. The compound according to claim 14 characterized by an X-ray powder diffraction pattern using CuK α radiation having an intense peak at diffraction angle 2-theta of 26.2° in combination with one or more of the peaks selected from the group consisting of 20.4°, 14.0°, and 17.9° ($\pm$ 0.2° respectively).

16. A pharmaceutical composition comprising a compound according to any one of claims 13 to 15 with one or more pharmaceutically acceptable carriers, diluents, or excipients.
- 5 17. The pharmaceutical composition of claim 16 further comprising acetic acid.
18. Use of a compound according to any one of claims 13 to 15 in the manufacture of a medicament for ~~A method of~~ treating migraine in a patient ~~comprising administering to a patient in need of such treatment an effective amount of a~~
10 ~~compound according to any one of claims 13 to 15.~~
19. A compound according to any one of claims 13 to 15 for use in therapy.
20. A compound according to any one of claims 13 to 15 for use in the treatment of
15 migraine.