

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

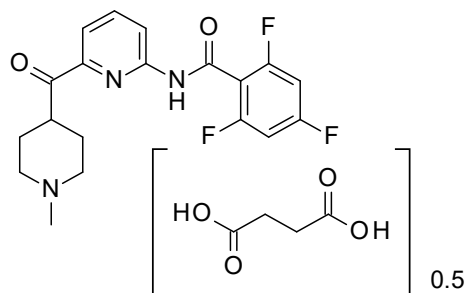
The examples of the present disclosure provide processes for the preparation of lasmiditan hemisuccinate, 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hemisuccinate salt, and/or compositions thereof, and/or particularly useful intermediates for use in these processes. The examples of the present 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 a first aspect of the present disclosure, there is provided a process for preparing a compound of the formula:

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

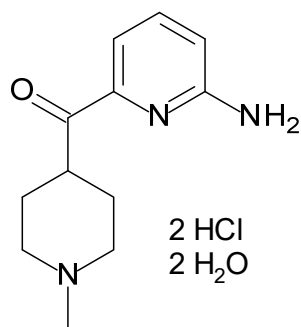


comprising the steps of:

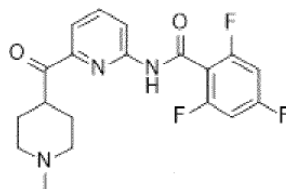
i.) Treatment of piperidine-4-carboxylic acid under reductive amination conditions comprising formaldehyde and formic acid in water with subsequent treatment with aqueous HCl followed by water distillation and acetonitrile addition, with repeated dilution/distillation until the water content is not more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

- 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;
5
- 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;
10
15
- 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.
20

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

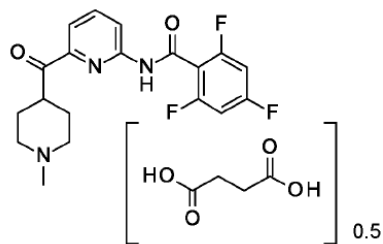


In a fourth aspect of the present disclosure, there is provided the use of the compound
5 of the third aspect in the preparation of a compound of the formula:



or a pharmaceutically acceptable salt thereof.

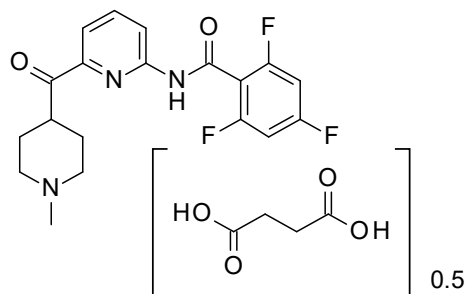
In a fifth aspect of the present disclosure, there is provided the use of the compound of
10 the third aspect in the preparation of a compound of the formula:



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

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;
- 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;
- 20
- 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

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,

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;

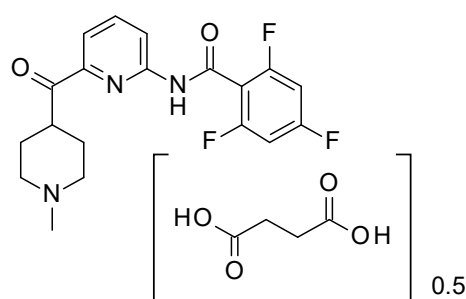
20 xi.) Treatment of 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)-2-pyridyl]benzamide hydrochloride with saturated aqueous Na₂CO₃ in methyl-tert-butyl ether;

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;

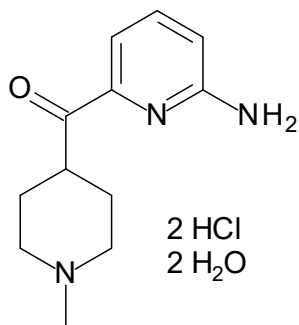
20

 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;

25

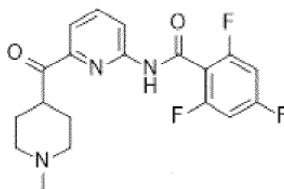
30

- 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 compound of the formula:



9. The compound of Claim 8 which is crystalline, and which is 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).

10. The use of the compound of Claim 8 in the preparation of a compound of the formula:



or a pharmaceutically acceptable salt thereof.

11. The use of the compound of Claim 8 in the preparation of a compound of the formula:

