

referred to herein as Compound I, or lasmitidan hemisuccinate. The pseudo-polymorphic forms of Compound I described here unexpectedly occurred during the process of manufacturing for commercial scale pharmaceutical production. The pseudo-polymorphic forms described here are useful for activating 5-HT_{1F} receptors and for the treatment or prevention of migraine headache.

In one aspect of the present disclosure, there is provided a di-hydrate of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form D) characterized by an X-ray diffraction characterized by an X-ray diffraction including peaks at 18.7 +/- 0.2 degrees 2 θ , 26.5 +/- 0.2 degrees 2 θ , 27.0 +/- 0.2 degrees 2 θ , 27.5 +/- 0.2 degrees 2 θ , and 27.8 +/- 0.2 degrees 2 θ using Cu-K α radiation.

In a further aspect of the present disclosure, there is provided the di-hydrate disclosed herein, produced by a method comprising wet granulation of amorphous 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide hemisuccinate

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the di-hydrate disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition for use in treating migraine in a mammal comprising an effective amount of the di-hydrate disclosed herein.

In another aspect of the present disclosure, there is provided a use of a di-hydrate disclosed herein in the manufacture of a medicament for treating migraine in a mammal in need thereof.

In embodiments, the disclosure provides Compound I in the form of a solvate. In embodiments, the solvate is a hydrate. In embodiments, the hydrate is a di-hydrate or a tri-hydrate. In embodiments, the disclosure provides a hydrate or dehydrated hydrate characterized by an X-ray powder diffraction (XRPD) pattern substantially similar to one of those set forth in Figure 1.

Figure 1A shows an XRPD pattern of Form D, a di-hydrate, also referred to as Hydrate 1, using Cu-K α radiation. In embodiments, the XRPD pattern for Form D includes at least peaks at about 18.7, 26.5, 27.0, 27.5 and 27.8 degrees 2 θ , +/- 0.2 degrees. In embodiments, the XRPD pattern of Form D includes one or more additional peaks as set forth in Table 2. In embodiments, the disclosure provides Form D characterized by having unit cell parameters at 100 Kelvin of about $a = 25.08 \text{ \AA}$, $b = 10.08 \text{ \AA}$, $c = 20.84 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 123.71$, and $\gamma \text{ angle} = 90^\circ$.

Figure 1B shows an XRPD pattern of Form F, a tri-hydrate. In embodiments, the XRPD pattern of Form F includes the peaks as set forth in Table 4.

Figure 1C shows an XRPD pattern of Form E, a dehydrated Form D. In embodiments, the XRPD pattern for Form E using Cu-K α radiation includes at least peaks at about 9.2 and 10.5 degrees 2 θ , +/- 0.2 degrees. In embodiments, the XRPD pattern of Form E includes the peaks as set forth in Table 3.

In embodiments, the disclosure provides Compound I in the form of a di-hydrate, Form D, a tri-hydrate, Form F, or a dehydrated hydrate of Form D, referred to herein as Form E. In embodiments, the disclosure provides a composition comprising a mixture of Form A and Form D, or a mixture of Form A and Form E, or a mixture of Form D and Form E, or a mixture of Form A, Form D, and Form E.

WE CLAIM:

1. A di-hydrate of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form D) characterized by an X-ray diffraction including peaks at 18.7 ± 0.2 degrees 2θ , 26.5 ± 0.2 degrees 2θ , 27.0 ± 0.2 degrees 2θ , 27.5 ± 0.2 degrees 2θ , and 27.8 ± 0.2 degrees 2θ using $\text{Cu-K}\alpha$ radiation.
2. The di-hydrate of claim 1, wherein the X-ray diffraction includes one or more additional peaks at 8.5, 9.7, 11.9, 13.8, 14.0, 15.4, 15.5, 15.8, 17.0, 17.3, 17.7, 18.0, 18.9, 19.3, 19.8, 20.0, 20.8, 21.4, 21.6, 21.9, 22.4, 22.7, 23.0, 24.1, 24.3, 24.7, 25.6, 25.9, 26.1, 26.4, 28.4, 29.1, 29.6, 29.8 or 31.9 degrees 2θ , ± 0.2 degrees 2θ , using $\text{Cu-K}\alpha$ radiation.
3. The di-hydrate of claim 1, further characterized by having unit cell parameters at 100 Kelvin of $a = 25.08 \text{ \AA}$, $b = 10.08 \text{ \AA}$, $c = 20.84 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 123.71$, and $\gamma \text{ angle} = 90^\circ$.
4. The di-hydrate of claim 1, produced by a method comprising wet granulation of amorphous 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide hemisuccinate.
5. A pharmaceutical composition comprising the di-hydrate of claim 1 and a pharmaceutically acceptable carrier.
6. The pharmaceutical composition of claim 5, wherein said di-hydrate is substantially free from impurities.
7. The pharmaceutical composition of claim 6, wherein said di-hydrate has a chemical purity greater than 98.0% as determined by HPLC.
8. The pharmaceutical composition of claim 5, further comprising an anhydrous solid crystalline form of the hemisuccinate salt of 2,4,6-trifluoro-N-[6-(1-methyl-piperidine-4-carbonyl)-pyridin-2-yl]-benzamide (Form A).
9. A pharmaceutical composition for use in treating migraine in a mammal comprising an effective amount of the di-hydrate of claim 1.
10. The pharmaceutical composition for use of claim 9, wherein the mammal is a human.
11. Use of a di-hydrate of claim 1 in the manufacture of a medicament for treating migraine in a mammal in need thereof.
12. The use of claim 11, wherein the mammal is a human.