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is specifically disclosed in these applications as demonstrating mu opioid receptor antagonist activity.

To effectively use this compound as a therapeutic agent, it would be desirable to have a solid-state form that can be readily manufactured and that has acceptable chemical and physical stability. For example, it would be highly desirable to have a physical form that is thermally stable, for example at temperatures exceeding about 160 °C or about 180 °C, and is not deliquescent, thereby facilitating processing and storage of the material. Crystalline solids are generally preferred over amorphous forms, for enhancing purity and stability of the manufactured product.

No crystalline forms of compound **1** have previously been reported. Accordingly, a need exists for a stable, crystalline form of compound **1** that is not deliquescent, and exhibits favorable thermal stability.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure provides two distinct crystalline solid forms of (S)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid (**1**) and a crystalline hydrochloride salt of compound **1**.

In a first aspect, there is provided a crystalline solid form of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid in Form I which is characterized by an x-ray powder diffraction pattern having diffraction peaks at 2θ values of 6.92±0.20 and 15.34±0.20, and having two or more diffraction peaks at 2θ values selected from 10.24±0.20, 11.48±0.20, 12.32±0.20, 13.46±0.20, 14.04±0.20, 17.30±0.20, 18.06±0.20, 20.30±0.20, 21.42±0.20, 23.48±0.20, 25.54±0.20, 26.96±0.20, 29.30±0.20, and 30.72±0.20.

In a second aspect, there is provided a crystalline solid form of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid in Form II, which is characterized by an x-ray powder diffraction pattern having diffraction peaks at 2θ values of 9.05±0.20 and 16.52±0.20, and having two or more diffraction peaks at 2θ values selected from 9.80±0.20, 12.44±0.20, 12.92±0.20, 14.21±0.20, 15.62±0.20, 17.27±0.20, 19.04±0.20, 19.85±0.20, 21.29±0.20, 22.43±0.20, 23.48±0.20, 23.99±0.20, and 26.09±0.20.

In a third aspect, there is provided a crystalline hydrochloride salt of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid which is characterized by an x-ray powder diffraction pattern having two or more diffraction peaks at 2θ values selected from 6.80±0.20, 9.80±0.20, 12.71±0.20, 13.31±0.20, 15.14±0.20, 19.97±0.20, 21.44±0.20, 22.64±0.20, 23.27±0.20, 24.44±0.20, and 25.37±0.20.

Surprisingly, one form of crystalline compound **1** has been found to exhibit no significant thermal events below a temperature of about 162 °C and to exhibit a weight change of less than about 2.5 % when exposed to a range of relative humidity between about 2 % and about 90 % at room temperature. Furthermore, neither crystalline compound **1** nor the crystalline hydrochloride salt of compound **1** is deliquescent when exposed to up to about 90 % relative humidity at room temperature.

Among other uses, the crystalline solid forms of the ~~invention~~present disclosure are expected to be useful for preparing pharmaceutical compositions for treating or ameliorating medical conditions mediated by mu opioid receptor activity. Accordingly, in another of its composition ~~aspect~~embodiments, the ~~invention~~present disclosure provides a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-

diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid or the present crystalline hydrochloride salt.

In a further aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the crystalline solid form according to the first, second and third aspects.

The ~~invention~~present disclosure also provides a method of treating or ameliorating a disease or condition ameliorated by treatment with a mu opioid receptor antagonist, e.g. a disorder of reduced motility of the gastrointestinal tract, the method comprising administering to the mammal, a therapeutically effective amount of crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid (**1**) or a crystalline hydrochloride salt of compound **1**.

The ~~invention~~present disclosure further provides a method of treating opioid-induced bowel dysfunction or post-operative ileus, the method comprising administering to the mammal, a therapeutically effective amount of crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid (**1**) or a crystalline hydrochloride salt of compound **1**.

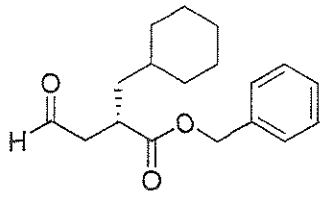
In another method ~~aspect~~embodiment, the ~~invention~~present disclosure provides a process for preparing a crystalline compound **1** in Form I, the process comprising dispersing (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid (**1**) in a polar diluent comprising between about 3 % and about 20 % water to form a crystallization process mixture; holding the process mixture for at least about 12 hours; and isolating the resulting crystals from the process mixture.

In yet another method ~~aspect~~embodiment, the ~~invention~~present disclosure provides a process for preparing crystalline compound **1** in Form I, the process comprising deprotecting the protected intermediate, (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester by catalytic hydrogenolysis in the presence of a polar diluent comprising between about 10 % and about 20 % water to form crystalline compound **1**.

In an aspect, there is provided a process for preparing crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid (compound **1**), the process comprising deprotecting (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester by catalytic hydrogenolysis in the presence of a polar diluent comprising between 10 % and 20 % water to form crystalline compound **1.**

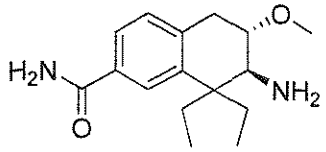
In another aspect, there is provided a process for preparing crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid (compound **1**), the process comprising:

(a) reacting (*S*)-2-cyclohexylmethyl-4-oxo-butyric acid benzyl ester (**4**)



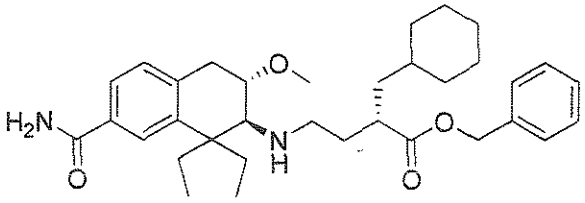
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with (6*S*,7*S*)-7-amino-8,8-diethyl-6-methoxy-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid amide (**3**)



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to provide (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester (**2**)



2 and

(b) deprotecting the compound of formula **2** by catalytic hydrogenolysis in the presence of a polar diluent comprising between 10 % and 20 % water to provide crystalline compound **1.**

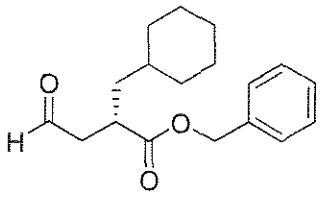
In another aspect, there is provided a process for preparing crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid, the process comprising:

(a) dispersing (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid in a polar diluent comprising between 3 % and 20 % water to form a mixture;

(b) holding the mixture for at least 12 hours; and

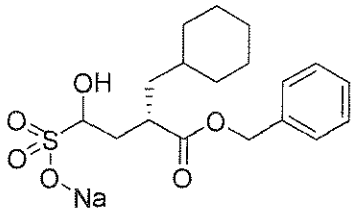
(c) isolating the crystalline (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid from the mixture.

In another aspect, there is provided a compound of formula **4**



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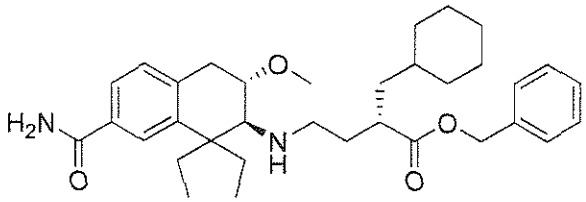
denoted by the chemical name (*S*)-2-cyclohexylmethyl-4-oxo-butyric acid benzyl ester; or a bisulfite adduct thereof of formula **5**



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denoted by the chemical name sodium (*S*)-3-benzyloxycarbonyl-4-cyclohexyl-1-hydroxy-butane-1-sulfonate.

In another aspect, there is provided a compound of formula **2**



2

denoted by the chemical name (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester or a hydrochloride salt thereof.

In another aspect, there is provided a crystalline hydrochloride salt of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester.

In another aspect, there is provided a process for preparing (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid, the process comprising:

(a) reacting (*S*)-2-cyclohexylmethyl-4-oxo-butyric acid benzyl ester (**4**) with (6*S*,7*S*)-7-amino-8,8-diethyl-6-methoxy-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid amide (**3**) to provide (*S*)-4-((2*S*,3S)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester (**2**); and

(b) deprotecting compound **2** by catalytic hydrogenolysis to provide (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid.

In related composition ~~aspect~~embodiments, the ~~invention~~present disclosure provides (S)-4-((2S,3S)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid benzyl ester and the bisulfite adduct, sodium; (*S*)-3-benzyloxycarbonyl-4-cyclohexyl-1-hydroxy-butane-1-sulfonate, which is useful for the preparation of the above protected precursor to compound **1**.

The ~~invention~~present disclosure also provides crystalline solid forms of the ~~invention~~present disclosure as described herein for use in therapy or as a medicament, as well as the use of a crystalline solid form of the ~~invention~~present disclosure in the manufacture of a medicament, especially for the manufacture of a

medicament for treating a disorder associated with mu opioid receptor activity in a mammal.

In another aspect, there is provided a crystalline solid form according to the first, second and third aspects for use in the treatment of a disease or medical condition in a mammal ameliorated by treatment with a mu opioid receptor antagonist.

In another aspect, there is provided a crystalline solid form according to the first, second and third aspects for use in reducing or preventing a side effect associated with use of an opioid agent in a mammal.

In another aspect, there is provided the use of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and the crystalline solid form according to the first, second and third aspects in the manufacture of a medicament for treating a mammal having a medical condition ameliorated by treatment with a mu opioid receptor antagonist.

In another aspect, there is provided the use of the crystalline solid form according to the first, second and third aspects in the manufacture of a medicament for use in combination with an opioid agent for reducing a side effect associated with use of the opioid agent in a mammal.

In another aspect, there is provided the use of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and the crystalline solid form according to the first, second and third aspects in the manufacture of a medicament for enhancing motility of the gastrointestinal tract in a mammal.

In another aspect, there is provided the use of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and the crystalline solid form according to the first, second and third aspects in the manufacture of a medicament for antagonizing a mu opioid receptor in a mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the present invention are illustrated by reference to the accompanying drawings.

Figure 1 shows an x-ray powder diffraction (XRPD) pattern of crystalline Form I (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 2 shows a differential scanning calorimetry (DSC) trace (right side vertical axis) and a thermal gravimetric analysis (TGA) trace (left side vertical axis) of crystalline Form I (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 3 shows a dynamic moisture sorption (DMS) trace of crystalline Form I (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 4 shows an x-ray powder diffraction (XRPD) pattern of crystalline Form II (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 5 shows a differential scanning calorimetry (DSC) trace of crystalline Form II (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 6 shows an x-ray powder diffraction (XRPD) pattern of a crystalline hydrochloride salt of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 7 shows a differential scanning calorimetry (DSC) trace (right side vertical axis) and a thermal gravimetric analysis (TGA) trace (left side vertical axis) of a crystalline hydrochloride salt of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)-2-cyclohexylmethyl-butyric acid of the invention.

Figure 8 shows an x-ray powder diffraction (XRPD) pattern of a crystalline hydrochloride salt of (*S*)-4-((2*S*,3*S*)-7-carbamoyl-1,1-diethyl-3-methoxy-1,2,3,4-