

Crystalline (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-{[1-(5-methylpyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol

The invention provides crystalline (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-{[1-(5-methylpyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol, pharmaceutical compositions thereof, methods of using the same, and processes for preparing the same.

Overactive bladder (OAB) is a symptomatically defined medical condition referring to the symptoms of urinary frequency and urgency, with or without urge incontinence. OAB is a condition that adversely affects the quality of life and social functioning of approximately 17 percent of the adult population. In spite of progress made for OAB treatment, many patients suffer with OAB for years without resolution. The first-line treatment for OAB are antimuscarinic drugs which have a good initial response, but experience diminishing patient compliance over the long term due to adverse effects and decreasing efficacy. There remains a significant unmet need for safe and effective OAB treatments.

Cyclic nucleotides (cAMP and cGMP) are important secondary messengers that modulate the contractility of smooth muscle. Cyclic nucleotide phosphodiesterases (PDEs) hydrolyse cyclic nucleotides and are important in regulating the level and duration of action of cyclic nucleotides inside cells. Compounds which inhibit PDE elevate cellular levels of cyclic nucleotides and thereby relax many types of smooth muscle. Previous studies have shown that relaxation of bladder smooth muscle is mainly mediated by agents that elevate cAMP. Phosphodiesterase 4 (PDE4) is cAMP specific and abundantly expressed in bladder. As such, PDE4 has been implicated in the control of bladder smooth muscle tone *in vitro* and in animal models of overactive bladder (Kaiho, Y. et al. *BJU International* **2008**, 101(5), 615-620).

Summary

In one aspect of the present disclosure, there is provided crystalline (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-{[1-(5-methylpyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol.

In another aspect of the present disclosure, there is provided crystalline (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-{[1-(5-methylpyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol characterized by an X-ray powder diffraction pattern using CuK α radiation having a diffraction peak at
5 diffraction angle 2-theta of 18.5° in combination with one or more of the peaks selected from the group consisting of 16.2°, 20.2°, and 14.4°; with a tolerance for the diffraction angles of 0.2 degrees. In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, diluent or excipient.

10 In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a first component which is a disclosed herein, and a second component which is tadalafil, and a pharmaceutically acceptable carrier, diluent or excipient.

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

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in combination with tadalafil, in the manufacture of a medicament for treating overactive bladder.

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

In a another aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of overactive bladder.

In a further aspect of the present disclosure, there is provided a compound disclosed herein for simultaneous, separate or sequential use in combination with tadalafil in the
25 treatment of overactive bladder.

Description

The compounds of the present invention are inhibitors of phosphodiesterase 4 (PDE4) and demonstrate selectivity for PDE4. As such, compounds of the present

invention are believed to be useful for the treatment of conditions in which PDE4 plays a role such as overactive bladder, including relief of associated symptoms such as frequency and urgency. Further, the present invention, a crystalline form of (2S)-3-

We claim:

1. Crystalline (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-{[1-(5-methylpyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol.
2. Crystalline (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-{[1-(5-methylpyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol characterized by an X-ray powder diffraction pattern using CuK α radiation having a diffraction peak at diffraction angle 2-theta of 18.5° in combination with one or more of the peaks selected from the group consisting of 16.2°, 20.2°, and 14.4°; with a tolerance for the diffraction angles of 0.2 degrees.
3. A pharmaceutical composition comprising a compound according to claims 1 or 2, and a pharmaceutically acceptable carrier, diluent or excipient.
4. A pharmaceutical composition comprising a first component which is a compound according to claims 1 or 2, and a second component which is tadalafil, and a pharmaceutically acceptable carrier, diluent or excipient.
5. Use of a compound according to claims 1 or 2 in the manufacture of a medicament for treating overactive bladder.
6. Use of a compound according to claims 1 or 2, in combination with tadalafil, in the manufacture of a medicament for treating overactive bladder.
7. A compound as claimed in claims 1 or 2 for use in therapy.
8. A compound as claimed in claims 1 or 2 for use in the treatment of overactive bladder.
9. A compound as claimed in claims 1 or 2 for simultaneous, separate or sequential use in combination with tadalafil in the treatment of overactive bladder.