

AZETIDINYLOXYPHENYLPYRROLIDINE COMPOUNDS

The invention provides certain azetidinyloxyphenylpyrrolidine compounds, pharmaceutical compositions thereof, methods of using the same, and processes for preparing the same.

5 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.

10 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.

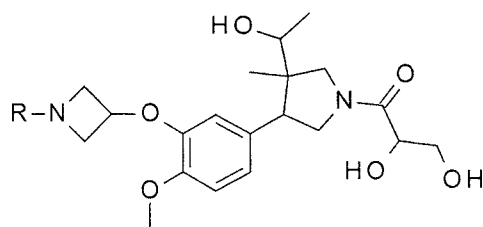
 Cyclic nucleotides (cAMP and cGMP) are important secondary messengers that
15 modulate the contractility of smooth muscle. Cyclic nucleotide phosphodiesterases (PDEs) hydrolyse cyclic nucleotides and are important in regulating the level and duration of action of cyclic nucleotides inside cells. Compounds 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
20 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).

 International Application Publication WO 01/47905 discloses certain pyrrolidine
25 derivative compounds as inhibitors of phosphodiesterase, in particular, phosphodiesterase 4 (PDE4), and recites the compounds as useful in treating a number of diseases including asthma.

Summary

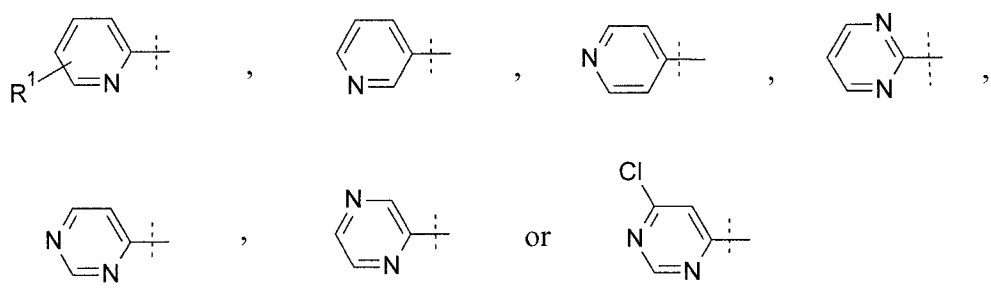
30 In a first aspect of the present disclosure, there is provided a compound of the formula

1a



wherein

R is



5 R¹ is CH₃, CD₃, CN, Cl or CF₃;

provided when R¹ is CH₃ it is not attached at the 5 position;

or a pharmaceutically acceptable salt thereof.

10 In a second aspect of the present disclosure, there is provided a compound which is (2S)-3-[(3S,4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-[[1-(5-chloropyridin-2-yl)azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol.

In a third aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound according to the first or second aspects, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

15 In a fourth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a first component which is a compound according to the first or second aspects, or a pharmaceutically acceptable salt thereof, and a second component which is tadalafil, and a pharmaceutically acceptable carrier, diluent or excipient.

In a fifth aspect of the present disclosure, there is provided a use of a compound according to the first or second aspects, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating overactive bladder.

5 In a sixth aspect of the present disclosure, there is provided a use of a compound according to the first or second aspects, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of tadalafil in the manufacture of a medicament for treating overactive bladder

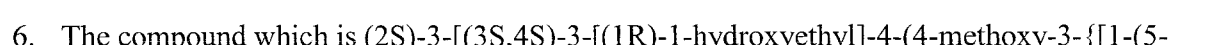
10 In a seventh aspect of the present disclosure, there is provided a compound according to the first or second aspects, or a pharmaceutically acceptable salt thereof, for use in therapy.

In an eighth aspect of the present disclosure, there is provided a compound according to the first or second aspects, or a pharmaceutically acceptable salt thereof, for use in the treatment of overactive bladder.

15 In a ninth aspect of the present disclosure, there is provided a compound according to the first or second aspects for simultaneous, separate or sequential use in combination with tadalafil in the treatment of overactive bladder.

Description

20 The present invention provides certain novel compounds which are inhibitors of PDE4 and as such, are useful in treatment of overactive bladder, including relief of associated symptoms such as frequency and urgency, and other disorders.



11. A compound as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in therapy.
12. A compound as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the treatment of overactive bladder.
13. A compound as claimed in any one of claims 1 to 6 for simultaneous, separate or sequential use in combination with tadalafil in the treatment of overactive bladder.