

PHENOXYETHYL PIPERIDINE COMPOUNDS

The present invention relates to novel phenoxyethyl piperidine compounds, to pharmaceutical compositions comprising the compounds, to methods of using the compounds to treat physiological disorders, and to intermediates and processes useful in the synthesis of the compounds.

The present invention is in the field of treatment of inflammatory conditions, such as arthritis, including osteoarthritis and rheumatoid arthritis, and further including pain associated with these conditions. Arthritis affects millions of patients in the United States alone and is a leading cause of disability. Treatments often include NSAIDs (nonsteroidal anti-inflammatory drugs) or COX-2 inhibitors, which may produce untoward cardiovascular and/or gastrointestinal side effects. As such, patients who have a poor cardiovascular profile, such as hypertension, may be precluded from using NSAIDs or COX-2 inhibitors. Thus, there is a need for an alternative treatment of osteoarthritis and rheumatoid arthritis, preferably without the side effects of the current treatments.

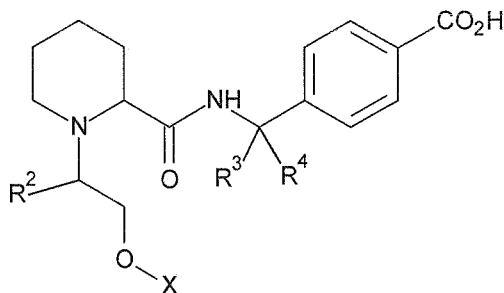
Four prostaglandin E₂ (PGE₂) receptor subtypes have been identified as the following: EP1, EP2, EP3, and EP4. It has been disclosed that EP4 is the primary receptor involved in joint inflammatory pain in rodent models of rheumatoid arthritis and osteoarthritis (See, for example, *J. Pharmacol. Exp. Ther.*, 325, 425 (2008)). Hence, a selective EP4 antagonist may be useful in treating arthritis, including arthritic pain. In addition, it has been suggested that since EP4 antagonism does not interfere with biosynthesis of prostanoids, such as PGI₂ and TxA₂, a selective EP4 antagonist may not possess the potential cardiovascular side effects seen with NSAIDs and COX-2 inhibitors. (See, for example, *Bioorganic & Medicinal Chemistry Letters*, 21, 484 (2011)).

WO 2013/004290 discloses cyclic amine derivatives as EP4 receptor antagonists. US 2005/0250818 discloses certain ortho substituted aryl and heteroaryl amide compounds that are EP4 receptor selective antagonists with analgesic activity. In addition, WO 2011/102149 discloses certain compounds that are selective EP4 antagonists which are useful in treating IL-23 mediated diseases.

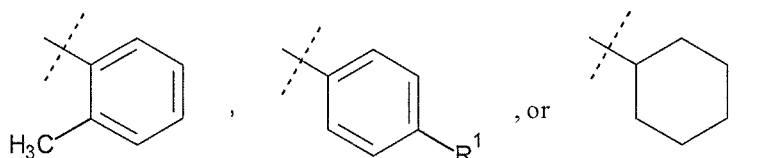
Summary

In a first aspect, the present disclosure provides a compound of the formula:

1a



wherein X is:



R^1 is H, -CN, or F; R^2 is H or methyl; R^3 is H; and R^4 is H, methyl, or ethyl; or R^3 and R^4 joined together form a cyclopropyl ring; or a pharmaceutically acceptable salt thereof.

In a second aspect, the present disclosure provides for use of a compound, or pharmaceutically acceptable salt thereof, as disclosed herein, in the manufacture of a medicament for the treatment of osteoarthritis.

In a third aspect, the present disclosure provides for use of a compound or pharmaceutically acceptable salt thereof, as disclosed herein, in the manufacture of a medicament for the treatment of rheumatoid arthritis.

In a fourth aspect, the present disclosure provides for use of a compound or pharmaceutically acceptable salt thereof, as disclosed herein, in the manufacture of a medicament for the treatment of pain associated with osteoarthritis or rheumatoid arthritis.

In a fifth aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof as disclosed herein for use in therapy.

In a sixth aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof as disclosed herein for use in the treatment of osteoarthritis.

In a seventh aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof as disclosed herein for use in the treatment of rheumatoid arthritis.

In an eighth aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof as disclosed herein for use in the treatment of pain associated with osteoarthritis or rheumatoid arthritis.

In a ninth aspect, the present disclosure provides a pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof as disclosed herein in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The present invention provides novel compounds that are selective inhibitors of EP4 relative to EP1, EP2, and EP3. In addition, the present invention provides novel

8. Use of a compound, or pharmaceutically acceptable salt thereof, as in claims 1 to 7, in the manufacture of a medicament for the treatment of A method of treating osteoarthritis in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound, or pharmaceutically acceptable salt thereof, as in claims 1 to 7.
9. Use of a compound, or pharmaceutically acceptable salt thereof, as in claims 1 to 7, in the manufacture of a medicament for the treatment of A method of treating rheumatoid arthritis in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound or pharmaceutically acceptable salt thereof, as in claims 1 to 7.
10. Use of a compound, or pharmaceutically acceptable salt thereof, as in claims 1 to 7, in the manufacture of a medicament for the treatment of A method of treating pain associated with osteoarthritis or rheumatoid arthritis in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound or a pharmaceutically acceptable salt thereof, as in claims 1 to 7.
11. A compound or pharmaceutically acceptable salt thereof as in claims 1 to 7 for use in therapy.
12. A compound or pharmaceutically acceptable salt thereof as in claims 1 to 7 for use in the treatment of osteoarthritis.
13. A compound or pharmaceutically acceptable salt thereof as in claims 1 to 7 for use in the treatment of rheumatoid arthritis.
14. A compound or pharmaceutically acceptable salt thereof as in claims 1 to 7 for use in the treatment of pain associated with osteoarthritis or rheumatoid arthritis.
15. A pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof as in claims 1 to 7 in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.