ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Selective EP4 Antagonist May Be Useful in Treating Arthritis and Arthritic Pain

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Title:	Phenoxyethyl Piperidine Compounds		
Patent Application Number:	WO 2014/004229 Al	**Publication date:**	3 January 2014
Priority Application:	US 61/665,951; US 61/779,099	**Priority date:**	29 June 2012 13 March 2013
Inventors:	Schiffler, M. A.; York, J. S.		
Assignee Company:	Eli Lilly and Company; Lilly Corporate Center, Indianapolis, Indiana 46285, United States		
Disease Area:	Inflammatory conditions, such as arthritis, including osteoarthritis and rheumatoid arthritis, and pain associated with these conditions.	**Biological Target:**	Prostaglandin E receptor 4 (EP4)

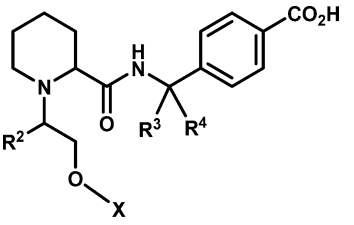
Summary:

The invention in this patent application relates to *N*-phenoxyethyl piperidine derivatives represented generally by formula (II). These compounds are selective prostaglandin E receptor 4 (EP4) antagonists and may be useful for the treatment of inflammatory conditions such as arthritis, including osteoarthritis and rheumatoid arthritis, and pain associated with these conditions.

Arthritis is a form of joint disorder that involves inflammation of one or more joints, and it is a leading cause of disability. It affects millions of patients in the United States and worldwide. This disorder is often treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors. However, these drugs may cause cardiovascular and/or gastrointestinal adverse effects that limit their use with patients suffering from poor cardiovascular conditions such as hypertension. Thus, there is a need for an alternative treatment of osteoarthritis and rheumatoid arthritis, preferably without the side effects of the current treatments.

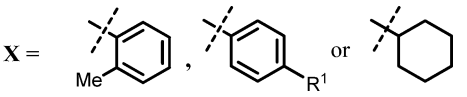
Prostaglandin E2 (PGE2) is an inflammatory mediator that is released at the site of tissue inflammation. Its activities are mediated by four G-protein-coupled EP receptors named EP1, EP2, EP3, and EP4. Researchers have identified EP4 as the primary receptor involved in joint inflammatory pain in rodent models of rheumatoid arthritis and osteoarthritis. Therefore, the use of EP4 antagonists such as the compounds introduced in this invention may potentially be useful in treating arthritis, including arthritic pain. Since EP4 antagonism does not interfere with biosynthesis of prostanoids, thus a selective EP4 antagonist may not cause the cardiovascular side effects seen with NSAIDs and COX-2 inhibitors.

Important Compound Classes:



Formula (II)

Definitions:



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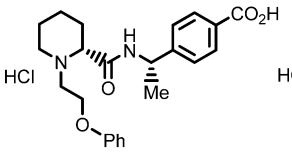
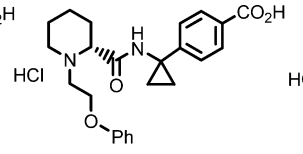
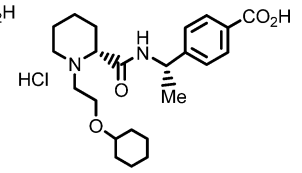
Key Structures: The inventors reported the synthesis and structures of 9 examples including the following three compounds:



Example 1



Example 4



Example 8

Biological Assay:

- In vitro binding to human EPl, EP2, EP3, and EP4
- In vitro human EP4 functional antagonist activity
- In vitro rat EP4 functional antagonist activity
- In vitro antagonist activity in human whole blood

Biological Data: The inventors mentioned testing all 9 examples, but specific assay results were reported only for **example 1** (structure above). Binding assays results for **example 1** are listed in Table 1:

Table 1: In Vitro Binding of Example 1 to Human EPl, EP2, EP3, and EP4

Test	hEP1	hEP2	hEP3	hEP4
K_i (nM)	>17500	1550 ± 1860 (n = 3)	>14000	54 ± 27 (n = 7)

Other test assays results for **example 1** are listed in Table 2:

Table 2: In Vitro Antagonist Activities of Example 1

Test	In vitro human EP4 functional antagonist activity	In vitro rat EP4 functional antagonist activity	In vitro antagonist activity in human whole blood
IC_{50} (nM)	6.9 ± 2.5 (n = 5)	15	123 ± 88 (n = 12)

Recent Review Articles:

Gomez, I.; Foudi, N.; Longrois, D.; Norel, X. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2013**, *89* (2−3), 55−63.

Borriello, M.; Stasi, L. P. *Pharm. Pat. Anal.* **2013**, *2* (3), 387−397.

Konya, V.; Marsche, G.; Schuligoi, R.; Heinemann, A. *Pharmacol. Ther.* **2013**, *138* (3), 485−502.

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Notes

The authors declare no competing financial interest.