DIMETHYL-BENZOIC ACID COMPOUNDS

The present invention relates to novel dimethyl-benzoic acid 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 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.

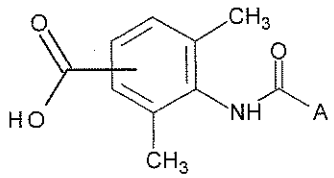
Four prostaglandin E_2 (PGE_2) receptor subtypes have been identified as the following: EP1, EP2, EP3 and EP4. It has been disclosed that EP4 is the primary receptor involved in joint inflammatory pain in rodent models of rheumatoid arthritis and osteoarthritis (See *J. Pharmacol. Exp. Ther.*, 325, 425 (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 PGI_2 and TxA_2, 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 96/02509 discloses certain quinoline derivatives which are selective, non-peptide NK3 antagonists useful in treating a variety of disorders including, for example, pulmonary disorders, CNS disorders, neurogenic inflammation, and inflammatory pain. In addition, U.S. Patent No. 7,705,035 discloses certain indoline amide derivatives useful as EP4 ligands, agonists, or antagonists useful in treating various disorders, such as osteoarthritis, rheumatoid arthritis, and acute and chronic pain.

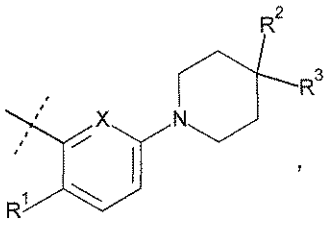
The present ~~invention~~disclosure provides certain novel compounds that are selective inhibitors of EP4 relative to EP1, EP2, and EP3. In addition, the present ~~invention~~ disclosure

provides certain novel compounds with the potential for reduced cardiovascular or gastrointestinal side effects in comparison to traditional NSAIDs.

In one aspect, there is provided a compound of the formula:



wherein A is:



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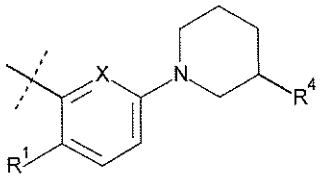

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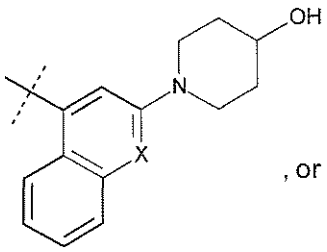

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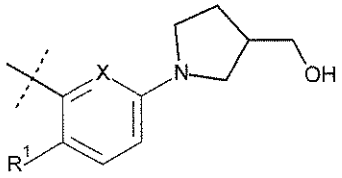


;

R^1 is CH_3, CF_3, or F;

R^2 is H, CH_3, or F;

R^3 is CH_3, OCH_3, OH, F;

R^4 is OH or CH_2OH; and

X is CH or N;

or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a hydrated compound as defined above.

In another aspect, there is provided the use of a compound or pharmaceutically acceptable salt thereof as defined above in the manufacture of a medicament for treating osteoarthritis in a patient.

In another aspect, there is provided the use of a compound or pharmaceutically acceptable salt thereof as defined above in the manufacture of a medicament for treating rheumatoid arthritis in a patient.

In another aspect, there is provided the use of a compound or pharmaceutically acceptable salt thereof as defined above in the manufacture of a medicament for treating pain associated with osteoarthritis or rheumatoid arthritis in a patient.

In another aspect, there is provided a compound or pharmaceutically acceptable salt thereof as defined above for use in therapy.

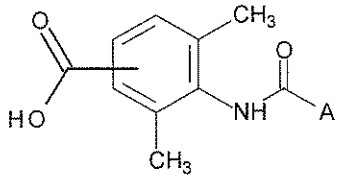
In another aspect, there is provided a compound or pharmaceutically acceptable salt thereof as defined above for use in the treatment of osteoarthritis.

In another aspect, there is provided a compound or pharmaceutically acceptable salt thereof as defined above for use in the treatment of rheumatoid arthritis.

In another aspect, there is provided a compound or pharmaceutically acceptable salt thereof as defined above for use in the treatment of pain associated with osteoarthritis or rheumatoid arthritis.

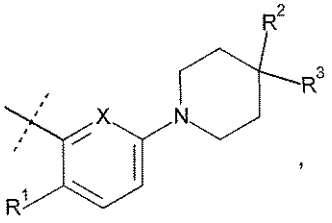
In another aspect, there is provided a pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof as defined above in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Accordingly, the present ~~invention~~disclosure provides a compound of the Formula II:



Formula II

wherein A is:



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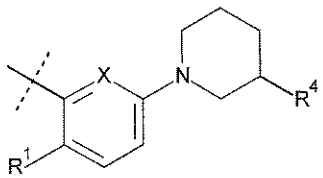

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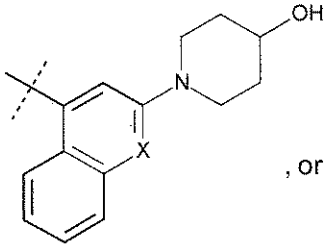
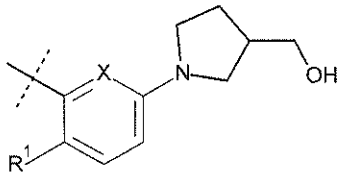


, or



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R^1 is CH_3, CF_3, or F;

R^2 is H, CH_3, or F;

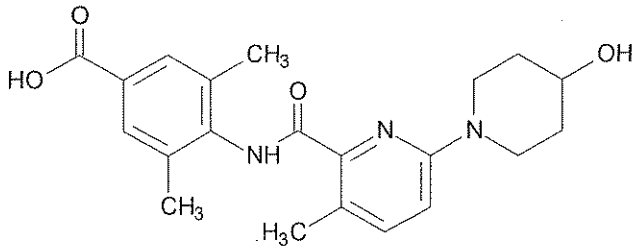
R^3 is CH_3, OCH_3, OH, F;

R^4 is OH or CH_2OH; and

X is CH or N;

or a pharmaceutically acceptable salt thereof.

The present ~~invention~~disclosure further provides a compound of the Formula I:



Formula I

or a pharmaceutically acceptable salt thereof.

The ~~invention~~disclosure further provides a hydrated compound of Formula I.

The present ~~invention~~disclosure also provides a method of treating arthritis in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof. The present ~~invention~~disclosure also provides a method of treating osteoarthritis in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof. In addition, the present ~~invention~~disclosure provides 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 of Formula I or Formula II, or a pharmaceutically acceptable salt thereof. The present ~~invention~~disclosure also provides a method of treating pain associated with arthritis in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof. The present ~~invention~~disclosure further provides 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 of Formula I or Formula II, or a pharmaceutically acceptable salt thereof.

Furthermore, the ~~invention~~disclosure provides a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof for use in therapy, in particular for the treatment of osteoarthritis. In addition, the ~~invention~~disclosure provides a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof for use in the treatment of rheumatoid arthritis. The ~~invention~~disclosure also provides a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof for use in the treatment of pain associated with

osteoarthritis or rheumatoid arthritis. Furthermore, the ~~invention~~disclosure provides the use of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of osteoarthritis. The ~~invention~~disclosure provides the use of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of rheumatoid arthritis. The present ~~invention~~disclosure also provides the use of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of pain associated with osteoarthritis or rheumatoid arthritis.

The ~~invention~~disclosure further provides a pharmaceutical composition comprising a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients. In a particular embodiment, the composition further comprises one or more other therapeutic agents. This ~~invention~~disclosure also encompasses novel intermediates and processes for the synthesis of the compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof.

In addition, the ~~invention~~disclosure includes a method of treating inflammatory conditions such as arthritis, including osteoarthritis and rheumatoid arthritis, in a patient, comprising administering to a patient in need of such treatment an effective amount of an antagonist of a proinflammatory prostaglandin, such as an EP4 antagonist, in combination with an effective amount of a modulator of a lipoxin or resolvin receptor, such as a modulator of BLT-1, BLT-2, ALX/FPR1, GPR32, CysLT1, CysLT2, or ChemR23.

A further ~~aspect~~embodiment of the ~~invention~~disclosure includes a method of treating inflammatory disease such as arthritis, including osteoarthritis and rheumatoid arthritis, in a patient, comprising administering to a patient in need of such treatment an effective amount of an inhibitor of a proinflammatory prostaglandin synthase, such as an mPGES-1 inhibitor, in combination with an effective amount of a modulator of a lipoxin or resolvin receptor, such as a modulator of BLT-1, BLT-2, ALX/FPR1, GPR32, CysLT1, CysLT2, or ChemR23.

As used herein, the terms "treating" or "to treat" includes restraining, slowing, stopping, or reversing the progression or severity of an existing symptom or disorder.

2-theta selected from the group consisting of 5.8°, 8.5°, 9.8°, 11.6°, 11.8°, 17.5°, and 24.2°.

10. The use of a compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 in the manufacture of a medicament for ~~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, according to claims 1 to 9~~.

11. The use of a compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 in the manufacture of a medicament for ~~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, according to claims 1 to 9~~.

12. The use of a compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 in the manufacture of a medicament for ~~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, according to claims 1 to 9~~.

13. A compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 for use in therapy.

14. A compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 for use in the treatment of osteoarthritis.

15. A compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 for use in the treatment of rheumatoid arthritis.

16. A compound or pharmaceutically acceptable salt thereof according to claims 1 to 9 for use in the treatment of pain associated with osteoarthritis or rheumatoid arthritis.

17. A pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof according to claims 1 to 9 in