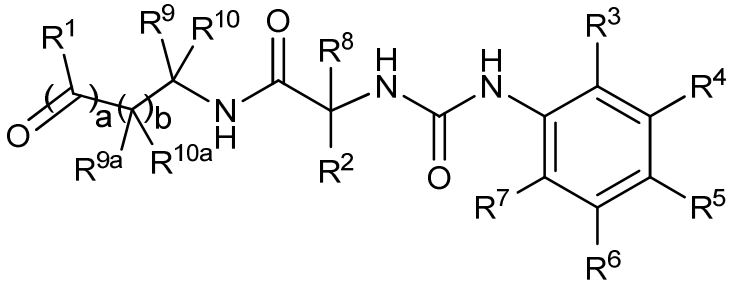
Menezes-de-Lima O Jr, Passos GF, Calixto JB. Molecular mechanisms of topical anti-inflammatory effects of lipoxin A(4) in endotoxin-induced uveitis. *Molecular Pharmacology* 2008; 74: 154-161; Gronert K, Maheshwari N, Khan N, Hassan IR, Dunn M, Schwartzmann ML. A role for the mouse 12/15-lipoxygenase pathways in promoting epithelial wound healing and host defense. Journal of Biological Chemistry 2005; 280: 15267-15278; Leedom A, Sullivan AB, Dong B, Lau D, Gronert K. Endogenous LXA4 circuits are determinants of pathological angiogenesis in response to chronic injury. *American Journal of Pathology* 2010; 176: 74-84; Gronert K. Lipoxins in the eye and their role in wound healing. *Prostaglandins, Leukotrienes and Essential fatty Acids*. 2005; 73: 221-229). Pharmaceutical utility of lipoxin A4 and its analogs are hampered by inherent physicochemical properties of the natural poly-olefinic natural product. Therefore, small molecule anti-inflammatory agonists of FPR2 would have a wide variety of therapeutic benefit in inflammatory disorders especially in the eye. Targeting FPR2 selectively would also have benefits of reduced side effects as compared to more broad acting anti-inflammatories such as steroids or NSAIDs which have significant side effects of elevated IOP and delays in wound healing in the eye. FPR2 is also expressed in ocular tissues in the cornea and also the posterior of eye, in addition to the inflammatory cells that migrate into the ocular tissues. FPR2 thus represents an important novel pro-resolutionary molecular target for the development of new therapeutic agents in ocular diseases with excessive inflammatory responses.

SUMMARY

In one aspect, provided herein is a use of a pharmaceutical composition comprising a compound represented by Formula II or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, or diastereisomer thereof:



Formula II

wherein:

a is 1 and b is 0; or

a is 0 and b is 1; or

a is 1 and b is 1;

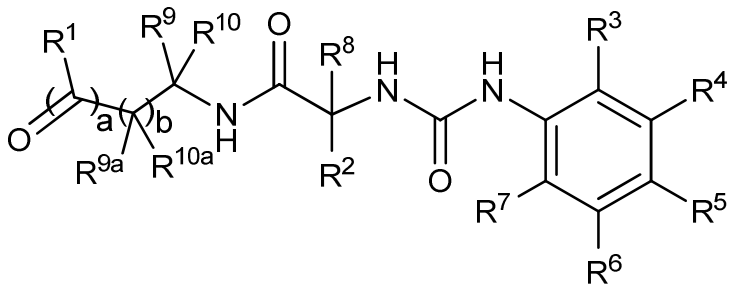
R^1 is optionally substituted C_{1-8} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkenyl, $-NR^{11}R^{12}$ or $-OR^{13}$;
R^2 is optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^3 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;
R^4 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;
R^5 is halogen, $-CF_3$ or $-S(O)_nR^{14}$;
n is 0, 1 or 2;
R^6 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;
R^7 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;
R^8 is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^9 is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{10} is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{9a} is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{10a} is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{11} is hydrogen or optionally substituted C_{1-8} alkyl;
R^{12} is hydrogen or optionally substituted C_{1-8} alkyl;
R^{13} is hydrogen or optionally substituted C_{1-8} alkyl;
R^{14} is hydrogen, CF_3 or optionally substituted C_{1-8} alkyl; and
R^{15} is hydrogen or optionally substituted C_{1-8} alkyl
in the manufacture of a medicament for treating an ocular inflammatory disease.

BRIEF DESCRIPTION OF THE INVENTION

The invention pertains to the ability of FPR2 agonists to exhibit ocular anti-inflammatory activity with chemical stability and suitable for ocular delivery. These FPR2 compounds show good potency at the receptor, a subset of compounds is exemplified in the tables below, and importantly, the FPR2 compounds are active topically, and therefore could be administered in many forms, including but not limited to eye drops. These compounds may also be administered directly or through a local drug delivery device applied to ocular

What is claimed is:

1. Use of a pharmaceutical composition comprising a compound represented by Formula II or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, or diastereisomer thereof:



Formula II

wherein:

a is 1 and b is 0; or

a is 0 and b is 1; or

a is 1 and b is 1;

R^1 is optionally substituted C_{1-8} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkenyl, $-NR^{11}R^{12}$ or $-OR^{13}$;

R^2 is optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;

R^3 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;

R^4 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;

R^5 is halogen, $-CF_3$ or $-S(O)_nR^{14}$;

n is 0, 1 or 2;

R^6 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;

R^7 is hydrogen, optionally substituted C_{1-8} alkyl, halogen, $-COOR^{15}$, $-OR^{13}$, $-NR^{11}R^{12}$, NO_2, optionally substituted heterocycle, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl or optionally substituted C_{3-8} cycloalkenyl;

R^8 is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^9 is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{10} is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{9a} is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{10a} is hydrogen, optionally substituted C_{1-8} alkyl or optionally substituted C_{6-10} aryl;
R^{11} is hydrogen or optionally substituted C_{1-8} alkyl;
R^{12} is hydrogen or optionally substituted C_{1-8} alkyl;
R^{13} is hydrogen or optionally substituted C_{1-8} alkyl;
R^{14} is hydrogen, CF_3 or optionally substituted C_{1-8} alkyl; and
R^{15} is hydrogen or optionally substituted C_{1-8} alkyl
in the manufacture of a medicament for treating an ocular inflammatory disease.

2. The use according to claim 1, wherein the compound represented by Formula II is selected from:
{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino}acetic acid;
{[(2S,3S)-2-{[(4-bromophenyl)carbamoyl]amino}-3-methylpentanoyl]amino}acetic acid;
(2S,3S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-3-methylpentanoic acid;
2-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}-2-methylpropanoic acid;
{[(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-4-methylpentanoyl] amino}acetic acid;
{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}acetic acid;
2-{[(4-bromophenyl)carbamoyl]amino}-N-(2-oxoazepan-3-yl)-3-phenylpropanamide;
{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-3-phenylpropanoyl]amino}acetic acid;
3-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-3-phenylpropanoyl]amino}propanoic acid;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-(2-hydroxyethyl)-3-phenylpropanamide;
{[(2S,3S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-3-methylpentanoyl]amino}acetic acid;
(2S,3S)-N-(2-amino-2-oxoethyl)-2-{[(4-bromophenyl)carbamoyl]amino}-3-methylpentanamide;
(2S,3S)-N-(2-amino-2-oxoethyl)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-3-methylpentanamide;
(2S,3S)-2-{[(4-bromophenyl)carbamoyl]amino}-3-methyl-N-(2-oxopropyl)pentanamide;

(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-N-(2-oxopropyl)-3-phenylpropanamide;
(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-N-(2-hydroxyethyl)-3-phenylpropanamide;
methyl {[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino}acetate;
propan-2-yl {[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino}acetate;
{[(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}pentanoyl]amino}acetic acid;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-(2-hydroxyethyl)-4-methylpentanamide;
(2S)-N-(2-amino-2-oxoethyl)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanamide;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methyl-N-(2-oxopropyl)pentanamide;
(2S)-N-(2-amino-2-oxoethyl)-2-{[(4-bromophenyl)carbamoyl]amino}pentanamide;
(2S)-N-(2-amino-2-oxoethyl)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}pentanamide;
(2S)-N-(2-amino-2-oxoethyl)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-4-methylpentanamide;
(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-4-methyl-N-(2-oxopropyl)pentanamide;
(2S)-2-{[(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}propanoic acid;
(2S)-2-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}propanoic acid;
(2S)-2-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}-3-methylbutanoic acid;
(2S)-N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanamide;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-(2-hydroxy-2-methylpropyl)-4-methylpentanamide;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-(1,3-dihydroxypropan-2-yl)-4-methylpentanamide;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-(2,3-dihydroxypropyl)-4-methylpentanamide;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-[(2R)-1-hydroxypropan-2-yl]-4-methylpentanamide;

tert-butyl
(2S)-2-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}pentanoate;
(2S)-2-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}pentanoic acid;
(2S)-N-[(2S)-1-amino-1-oxopentan-2-yl]-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanamide;
(2S)-{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}(phenyl)ethanoic acid;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methyl-N-(1H-tetrazol-5-ylmethyl)pentanamide;
[(2-{[(4-bromophenyl)carbamoyl]amino}-2,4-dimethylpentanoyl)amino]acetic acid;
[(2-{[(4-bromophenyl)carbamoyl]amino}-2-ethylbutanoyl)amino]acetic acid;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-[(3-hydroxy-1,2-oxazol-5-yl)methyl]-4-methylpentanamide;
(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-[2-(dimethylamino)-2-oxoethyl]-4-methylpentanamide;
{[(2S)-4-methyl-2-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)pentanoyl]amino}acetic acid;
{[(2S)-4-methyl-2-({[4-(methylsulfanyl)phenyl]carbamoyl}amino)pentanoyl]amino}acetic acid;
(2S)-4-methyl-N-(1H-tetrazol-5-ylmethyl)-2-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)pentanamide;
2-methyl-2-{[(2S)-4-methyl-2-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)pentanoyl]amino}propanoic acid;
{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-(methylsulfanyl)butanoyl]amino}acetic acid;
{[2-{[(4-bromophenyl)carbamoyl]amino}-3-(1H-indol-3-yl)propanoyl]amino}acetic acid;
tert-butyl {[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl](methyl)amino}acetate; and
{[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl](methyl) amino}acetic acid.

3. The use according to claim 1 or 2, wherein the ocular inflammatory disease is selected from: uveitis, keratitis, allergic eye disease, infectious keratitis, herpetic keratitis, corneal angiogenesis, lymphangiogenesis, retinitis, choroiditis, acute multifocal placoid pigment epitheliopathy, Behcet's disease,wet and dry age-related macular degeneration (ARMD).