R^1 is ~~optionally substituted~~ C_{1-8} alkyl optionally substituted by hydroxyl, ~~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 C_{1-8} alkyl optionally substituted by C_{6-10} aryl, amide, or heterocycle, said heterocycle is 3-10-member aromatic ring comprising at least one heteroatom selected from N; wherein one methylene group of the alkyl may be substituted by sulfur or sulfonyl~~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, wherein a therapeutically efficient amount of the compound is between about 0.001 and about 5% (w/v) in a liquid formulation.

In one aspect, provided herein is a use of a pharmaceutical composition comprising a compound in the manufacture of a medicament for treating an ocular inflammatory disease, wherein the compound is selected from:

(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methyl-N-(1H-tetrazol-5-ylmethyl)pentanamide;

(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-[(3-hydroxy-1,2-oxazol-5-yl)methyl]-4-methylpentanamide;

(2S)-4-methyl-N-(1H-tetrazol-5-ylmethyl)-2-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)pentanamide;

(2S,3S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-3-methylpentanoic 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,

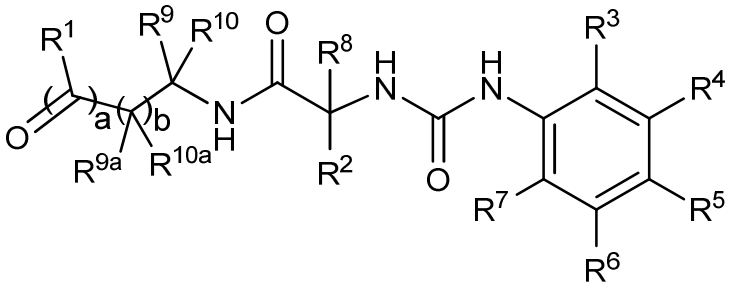
wherein a therapeutically efficient amount of the compound is between about 0.001 and about 5% (w/v) in a liquid formulation.

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 by hydroxyl, ~~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~~C_{1-8} alkyl optionally substituted by C_{6-10} aryl, amide, or heterocycle, said heterocycle is 3-10-member aromatic ring comprising at least one heteroatom selected from N; wherein one methylene group of the alkyl may be substituted by sulfur or sulfonyl;

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, wherein a therapeutically efficient amount of the compound is between about 0.001 and about 5% (w/v) in a liquid formulation.

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;

and

{[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).

4. The use according to claim 1, wherein the compound represented by Formula II is {[(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}acetic acid.

5. The use according to claim 1, wherein the compound represented by Formula II is {[(2S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-4-methylpentanoyl]amino}acetic acid.

6. The use according to claim 1, wherein the compound represented by Formula II is {[(2S,3S)-2-{[(4-bromophenyl)carbamoyl]amino}-3-methylpentanoyl]amino}acetic acid.

7. Use of a pharmaceutical composition comprising a compound in the manufacture of a medicament for treating an ocular inflammatory disease, wherein the compound is selected from:

(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-4-methyl-N-(1H-tetrazol-5-ylmethyl)pentanamide;

(2S)-2-{[(4-bromophenyl)carbamoyl]amino}-N-[(3-hydroxy-1,2-oxazol-5-yl)methyl]-4-methylpentanamide;

(2S)-4-methyl-N-(1H-tetrazol-5-ylmethyl)-2-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)pentanamide;

(2S,3S)-2-{[(4-bromo-2-fluorophenyl)carbamoyl]amino}-3-methylpentanoic 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,

wherein a therapeutically efficient amount of the compound is between about 0.001 and about 5% (w/v) in a liquid formulation.

8. The use according to claim 7, 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).