

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.

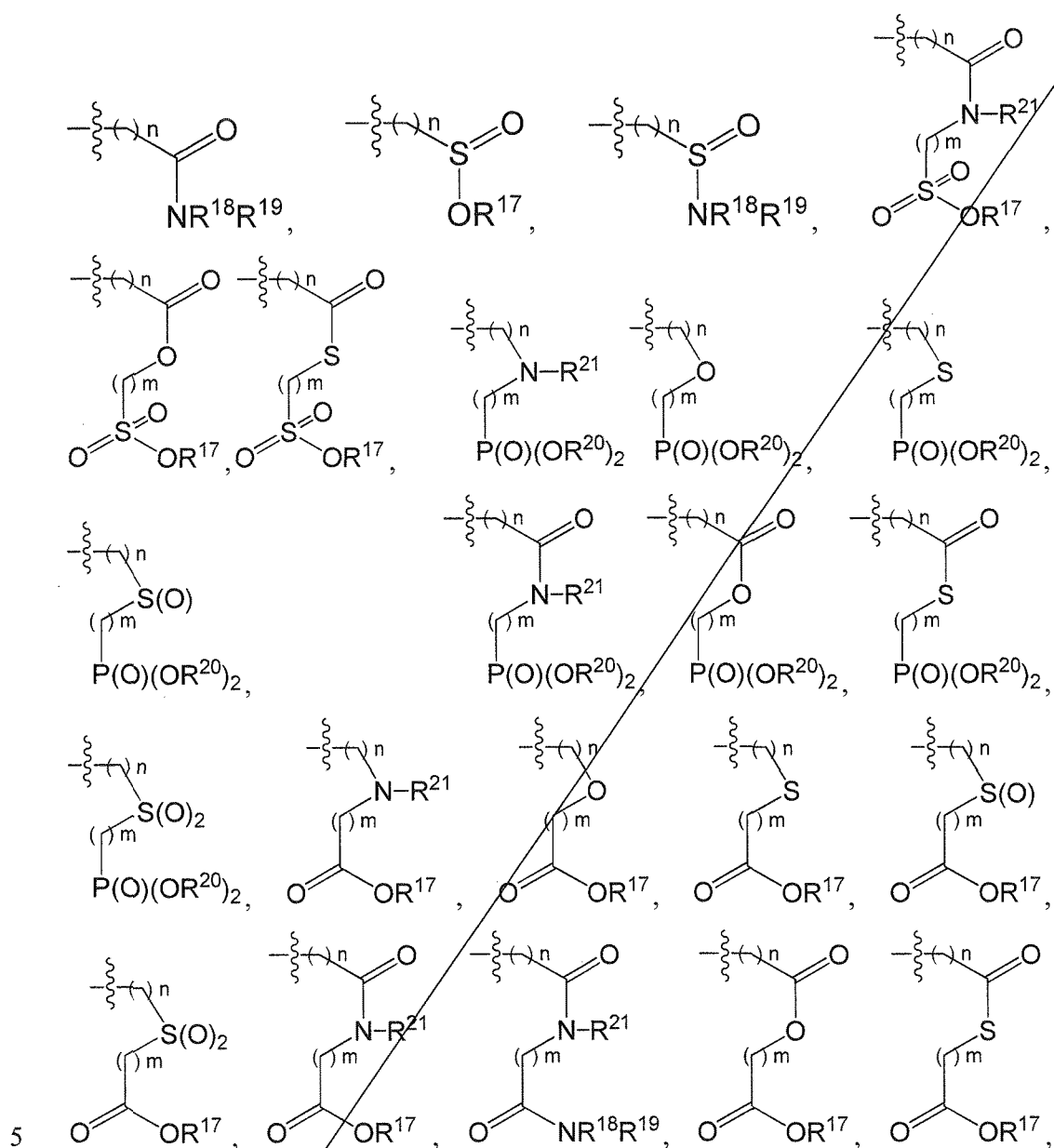
BRIEF DESCRIPTION OF THE INVENTIONDISCLOSURE

In one aspect, there is provided the use of a pharmaceutical composition comprising a therapeutically effective amount of at least one agonist of Formyl peptide receptor 2 in the manufacture of a medicament treating an ocular inflammatory disease in a subject in need of such treatment.

The ~~invention~~ disclosure 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

and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, 5 uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone 10 dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal 15 disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, and intraocular lymphoid tumors; and 20 miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigment epitheliitis, post-surgical corneal inflammation, blepharitis, MGD, glaucoma, branch vein occlusion, Best's vitelliform macular degeneration, retinitis 25 pigmentosa, proliferative vitreoretinopathy (PVR), and any other degenerative diseases of either the photoreceptors or the retinal pigment epithelial (RPE).

| In another ~~aspect~~ embodiment these compounds will be useful for the treatment of ocular inflammatory diseases associated with CNS disorders such as Alzheimer's disease, arthritis, sepsis, inflammatory bowel disease, 30 cachexia, angina pectoris, rheumatoid arthritis and related inflammatory disorders, alopecia, systemic inflammatory diseases such as stroke, coronary artery disease, obstructive airway diseases, HIV-mediated retroviral infections,



optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, or together with R^5 forms a spiro monocyclic or polycyclic, carbocyclic or heterocyclic, saturated or unsaturated 5 to 10 member ring which is optionally substituted;

- 10 R^5 is hydrogen, optionally substituted C_{1-8} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, or together with R^4 forms a spiro monocyclic or polycyclic carbocyclic or heterocyclic, saturated or unsaturated 5

to 10 member ring which is optionally substituted or together with R³ forms a 5 or 6 member ring which is optionally substituted;

R⁶ is halogen, hydrogen, optionally substituted C₁₋₈ alkyl, OR⁹, C(O)R¹⁰, NO₂, NR¹³R¹⁴, CN, SR¹⁵ or SO₂R¹⁶;

- 5 R⁷ is halogen, hydrogen, optionally substituted C₁₋₈ alkyl, OR⁹, C(O)R¹⁰, NO₂, NR¹³R¹⁴, CN, SR¹⁵ or SO₂R¹⁶;

R⁸ is halogen, hydrogen, optionally substituted C₁₋₈ alkyl, OR⁹, C(O)R¹⁰, NO₂, NR¹³R¹⁴, CN, SR¹⁵ or SO₂R¹⁶;

R⁹ is hydrogen, C(O)(C₁₋₈ alkyl) or optionally substituted C₁₋₈ alkyl;

- 10 R¹⁰ is hydrogen, optionally substituted C₁₋₈ alkyl, O(C₁₋₈ alkyl), NR¹¹R¹² or OH;
R¹¹ is hydrogen, optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

R¹² is hydrogen, optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

- 15 R¹³ is hydrogen, optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

R¹⁴ is hydrogen, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₈ alkyl, C(O)(C₁₋₈ alkyl) or SO₂(C₁₋₈ alkyl);

R¹⁵ is hydrogen, optionally substituted C₁₋₈ alkyl or O(C₁₋₈ alkyl);

- 20 R¹⁶ is OH, O(C₁₋₈ alkyl), (C₁₋₈ alkyl) or NR¹¹R¹²;

R¹⁷ is hydrogen, optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

R¹⁸ is hydrogen, C(O)(C₁₋₈ alkyl), optionally substituted C₆₋₁₀ aryl, or optionally substituted C₁₋₈ alkyl;

- 25 R¹⁹ is hydrogen, C(O)(C₁₋₈ alkyl), optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

R²⁰ is hydrogen, optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

R²¹ is hydrogen, optionally substituted C₆₋₁₀ aryl or optionally substituted C₁₋₈ alkyl;

- 30 n is 1, 2, 3, 4, or 5;
m is 1, 2, 3, 4, or 5.

5 8. The method according to claim 7, wherein the FPR2 agonist is selected from:

1-(4-bromophenyl)-3-[4-ethyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]urea;

10 1-(4-bromophenyl)-3-[4-ethyl-2,5-dioxo-4-(propan-2-yl)imidazolidin-1-yl]urea;

1-(4-bromophenyl)-3-(4,4-diethyl-2,5-dioxoimidazolidin-1-yl)urea;

1-(4-bromo-2-fluorophenyl)-3-(4,4-diethyl-2,5-dioxoimidazolidin-1-yl)urea;

1-(4-bromophenyl)-3-(2,4-dioxo-1,3-diazaspiro[4.5]dec-3-yl)urea;

15 1-(4-bromophenyl)-3-[4-methyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]urea;

1-(4-bromophenyl)-3-[4-methyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]urea;

1-(4-bromo-2-fluorophenyl)-3-[4-ethyl-2,5-dioxo-4-(propan-2-yl)imidazolidin-1-yl]urea;

20 1-(4-bromophenyl)-3-[2,5-dioxo-4,4-di(propan-2-yl)imidazolidin-1-yl]urea;

1-(4-bromophenyl)-3-(4,4-dicyclopropyl-2,5-dioxoimidazolidin-1-yl)urea;

1-(4-bromophenyl)-3-[4-ethyl-2,5-dioxo-4-(propan-2-yl)imidazolidin-1-yl]urea;

25 1-(4-bromophenyl)-3-[4-ethyl-2,5-dioxo-4-(propan-2-yl)imidazolidin-1-yl]urea;

1-(4-bromo-2-fluorophenyl)-3-[4-ethyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]urea;

1-(4-bromophenyl)-3-{4-[2-(furan-2-yl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;

30 1-(4-bromophenyl)-3-{4-[2-(4-fluorophenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;

- 1-(4-bromophenyl)-3-{4-[2-(3-fluorophenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 1-(4-bromophenyl)-3-{4-[2-(4-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 5 1-(4-bromophenyl)-3-{4-methyl-2,5-dioxo-4-[2-(thiophen-2-yl)ethyl]imidazolidin-1-yl}urea;
- 1-(4-bromo-2-fluorophenyl)-3-{4-[2-(4-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 1-(4-bromophenyl)-3-{4-methyl-4-[2-(5-methylfuran-2-yl)ethyl]-2,5-dioxoimidazolidin-1-yl}urea;
- 10 1-(4-bromo-2-fluorophenyl)-3-{4-[2-(3-fluoro-4-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 1-(4-bromophenyl)-3-{4-[2-(3-fluoro-4-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 15 1-(4-bromo-2-fluorophenyl)-3-{4-[2-(2-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 1-(4-bromo-2-fluorophenyl)-3-{4-[2-(3-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 1-(4-bromophenyl)-3-{4-[2-(3-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 20 1-(4-bromophenyl)-3-{4-[2-(2-hydroxyphenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea;
- 1-(4-bromophenyl)-3-[4-(hydroxymethyl)-2,5-dioxo-4-(propan-2-yl)imidazolidin-1-yl]urea;
- 25 2-[1-{[(4-bromophenyl)carbamoyl]amino}-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]-N-(2-hydroxyethyl)acetamide;
- methyl 2-[2-(1-{[(4-bromophenyl)carbamoyl]amino}-4-ethyl-2,5-dioxoimidazolidin-4-yl)ethyl]benzoate;
- 2-[1-{[(4-bromophenyl)carbamoyl]amino}-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]-N-(1,3-dihydroxypropan-2-yl)acetamide;
- 30 2-[2-(1-{[(4-bromophenyl)carbamoyl]amino}-4-ethyl-2,5-dioxoimidazolidin-4-yl)ethyl]benzoic acid;

2-[2-(1-[[[4-bromo-2-fluorophenyl]carbamoyl]amino]-4-ethyl-2,5-dioxoimidazolidin-4-yl)ethyl]benzoic acid;

3-([1-[[[4-bromophenyl]carbamoyl]amino]-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]acetyl)amino)propanoic acid;

5 2-[1-[[[4-bromo-2-fluorophenyl]carbamoyl]amino]-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]-N-(2-hydroxyethyl)acetamide;

2-[2-[1-[[[4-bromophenyl]carbamoyl]amino]-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]ethyl]benzoic acid;

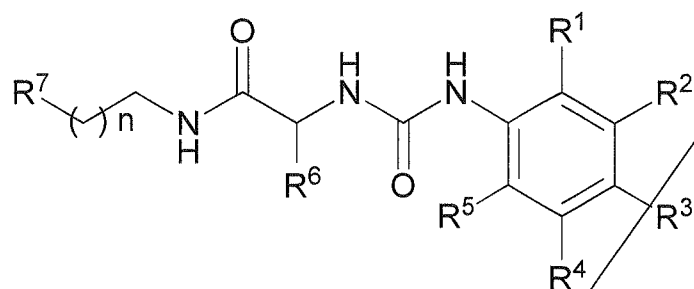
10 diethyl [2-([1-[[[4-bromophenyl]carbamoyl]amino]-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]acetyl)amino)ethyl]phosphonate;

ethyl 3-[[[4-bromophenyl]carbamoyl]amino]-2,4-dioxo-1,3-diazaspiro[4.5]decane-8-carboxylate;

1-(4-bromophenyl)-3-{4-[2-(2-fluorophenyl)ethyl]-4-methyl-2,5-dioxoimidazolidin-1-yl}urea; and

15 3-([1-[[[4-bromo-2-fluorophenyl]carbamoyl]amino]-2,5-dioxo-4-(propan-2-yl)imidazolidin-4-yl]acetyl)amino)propanoic acid.

9. The method according to claim 1, wherein the agonist of FPR2 is represented by Formula VII :



Formula VII

wherein:

n is 0 or 1;

R¹ is hydrogen, substituted or unsubstituted C₁₋₈ alkyl, halogen, -NR⁸R⁹, -
10 NC(O)R²⁰, -OR¹⁰, -OC(O)R²¹, -SR¹¹, -C(O)R¹², CN or NO₂;

R² is hydrogen, substituted or unsubstituted C₁₋₈ alkyl, halogen, -NR⁸R⁹, -
NC(O)R²⁰, -OR¹⁰, -OC(O)R²¹, -SR¹¹, -C(O)R¹², CN or NO₂;

R³ is hydrogen, substituted or unsubstituted C₁₋₈ alkyl, halogen, -NR⁸R⁹, -
NC(O)R²⁰, -OR¹⁰, -OC(O)R²¹, -SR¹¹, -C(O)R¹², CN, NO₂, CF₃, S(O)R¹⁵ or
15 S(O)₂R¹⁶;

R⁴ is hydrogen, substituted or unsubstituted C₁₋₈ alkyl, halogen, -NR⁸R⁹, -
NC(O)R²⁰, -OR¹⁰, -OC(O)R²¹, -SR¹¹, -C(O)R¹², CN or NO₂;

R⁵ is hydrogen, substituted or unsubstituted C₁₋₈ alkyl, halogen, -NR⁸R⁹, -
NC(O)R²⁰, -OR¹⁰, -OC(O)R²¹, -SR¹¹, -C(O)R¹², CN or NO₂;

20 R⁶ is hydrogen, substituted or unsubstituted C₁₋₈ alkyl, substituted or
unsubstituted heterocycle, substituted or unsubstituted C₃₋₈ cycloalkyl,
substituted or unsubstituted C₆₋₁₀ aryl, substituted or unsubstituted C₃₋₈
cycloalkenyl or -CH₂R¹⁹;

R⁷ is substituted or unsubstituted heterocycle, -SR¹¹, -NR⁸R⁹, -
25 N(H)C(O)N(H)S(O)₂R¹⁹, -BR¹³R¹⁴, -S(O)R¹⁵, -C(O)N(H)(CN), -
C(O)N(H)S(O)₂R¹⁹, -S(O)(N)(PO₃H₂)-, -S(O)₂R¹⁶ or -P(O)R¹⁷R¹⁸;

- R^8 is hydrogen, substituted or unsubstituted C_{1-8} alkyl substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted heterocycle, or substituted or unsubstituted C_{6-10} aryl;
- R^9 is hydrogen, substituted or unsubstituted C_{1-8} alkyl substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted heterocycle, or substituted or unsubstituted C_{6-10} aryl;
- R^{10} is hydrogen or substituted or unsubstituted C_{1-8} alkyl ;
- R^{11} is hydrogen , substituted or unsubstituted C_{1-8} alkyl or $-CF_3$;
- R^{12} is hydrogen, substituted or unsubstituted C_{1-8} alkyl, hydroxyl, $-OR^{24}$ or -
- NR^8R^9 ;
- R^{13} is $-OR^{22}$;
- R^{14} is $-OR^{23}$;
- R^{15} is substituted or unsubstituted C_{1-8} alkyl;
- R^{16} is substituted or unsubstituted C_{1-8} alkyl, $-NR^8R^9$, $-NHS(O)_2R^{19}$ or hydroxyl;
- R^{17} is OR^{10} or NR^8R^9 ;
- R^{18} is OR^{10} or NR^8R^9 ;
- R^{19} is substituted or unsubstituted heterocycle, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{6-10} aryl or substituted or unsubstituted C_{3-8} cycloalkenyl;
- R^{20} is hydrogen, substituted or unsubstituted C_{1-8} alkyl substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted heterocycle, or substituted or unsubstituted C_{6-10} aryl;
- R^{21} is hydrogen, substituted or unsubstituted C_{1-8} alkyl substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted heterocycle, or substituted or unsubstituted C_{6-10} aryl;
- R^{22} is hydrogen, substituted or unsubstituted C_{1-8} alkyl, or together with R^{23} can form a cycle;
- R^{23} is hydrogen, substituted or unsubstituted C_{1-8} alkyl, or together with R^{22} can form a cycle;
- R^{24} is hydrogen, substituted or unsubstituted C_{1-8} alkyl substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted heterocycle, or substituted or unsubstituted C_{6-10} aryl.

10. The method of claim 9, wherein the FPR2 agonist is selected from:

{[(2S)-2-[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino}acetic acid;

5 2-[(4-bromophenyl)carbamoyl]amino}-N-(2-oxazepan-3-yl)-3-phenylpropanamide;

ethyl hydrogen ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino)methyl)phosphonate;

10 diethyl ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}-4-methylpentanoyl]amino)methyl)phosphonate;

diethyl ({[(2S,3S)-2-[(4-bromophenyl)carbamoyl]amino}-3-methylpentanoyl]amino)methyl)phosphonate;

ethyl hydrogen ({[(2S,3S)-2-[(4-bromophenyl)carbamoyl]amino}-3-methylpentanoyl]amino)methyl)phosphonate;

15 diethyl ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino)methyl)phosphonate;

diethyl ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}-3-phenylpropanoyl]amino)methyl)phosphonate;

20 diethyl (2-[(2S)-2-[(4-bromophenyl)carbamoyl]amino]-4-methylpentanoyl]amino)ethyl)phosphonate;

ethyl hydrogen ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino)methyl)phosphonate;

dipropyl ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino)methyl)phosphonate;

25 ethyl hydrogen ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino}-3-phenylpropanoyl]amino)methyl)phosphonate;

{[(2S)-2-[(4-bromophenyl)carbamoyl]amino]-4-methylpentanoyl]amino}methanesulfonic acid;

30 propan-2-yl hydrogen {[2-[(4-bromophenyl)carbamoyl]amino}pentanoyl]amino)methyl)phosphonate;

dipropyl ({[(2S)-2-[(4-bromophenyl)carbamoyl]amino]-4-methylpentanoyl]amino)methyl)phosphonate;

diethyl (((2S)-4-methyl-2-((4-(trifluoromethyl)phenyl)carbamoyl)amino)pentanoyl)amino)methyl)phosphonate;
ethyl hydrogen (((2S)-4-methyl-2-((4-(trifluoromethyl)phenyl)carbamoyl)amino)pentanoyl) amino)methyl)phosphonate;
5 (((2S)-4-methyl-2-((4-(trifluoromethyl)phenyl)carbamoyl)amino)pentanoyl)amino)methanesulfonic acid; and
diethyl (((2S)-4-methyl-2-((4-(methylsulfanyl)phenyl)carbamoyl)amino)pentanoyl)amino)methyl)phosphonate.

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11. The method of claim 1, wherein the FPR2 agonist is selected from:

2-(((4-chlorophenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
(2S)-2-(((4-methoxyphenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
15 (2S)-3-phenyl-2-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino]propanoic acid;
acid;
(2S)-2-(((3,4-dichlorophenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
(2S)-2-(((4-nitrophenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
3-phenyl-2-(((4-(trifluoromethoxy)phenyl)amino)carbonyl)amino]propanoic acid;
20 2-(((3,4-dimethoxyphenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
methyl 2-(((4-iodophenyl)amino)carbonyl)amino)-3-phenylpropanoate;
(2S)-2-(((4-bromophenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
(2R)-2-(((4-bromophenyl)amino)carbonyl)amino)-3-phenylpropanoic acid;
3-phenyl-2-((pyridin-3-ylamino)carbonyl)amino]propanoic acid;
25 (2S,3S)-2-(((4-bromophenyl)amino)carbonyl)amino)-3-methylpentanoic acid;
(2S)-(((4-bromophenyl)amino)carbonyl)amino)(phenyl)acetic acid;
2-(((4-bromophenyl)amino)carbonyl)amino)-3-(1H-indol-3-yl)propanoic acid;
(2S)-2-(((4-bromophenyl)amino)carbonyl)amino)-3-methylbutanoic acid;
(2S)-2-(((4-bromo-2-fluorophenyl)amino)carbonyl)amino)-3-methylbutanoic
30 acid;
1-(4-chlorophenyl)-3-(2,4-dioxo-1,3-diazaspiro[4,5]decan-3-yl) urea;
1-(4-chlorophenyl)-3-(4-ethyl-4-methyl-2,5-dioxoimidazolidin-1-yl)urea;

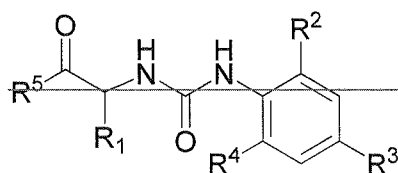
- 1-[4-methyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]-3-phenylurea;
1-(8-methyl-2,4-dioxo-1,3-diazaspiro[4,5]decan-3-yl)-3-(p-tolyl)urea;
1-(2-fluorophenyl)-3-[4-methyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]urea;
- 5 N-(4-bromophenyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)acetamide;
N-(4-bromophenyl)-2-(4,4-diethyl-2,5-dioxoimidazolidin-1-yl)acetamide;
N-(4-bromophenyl)-2-(2,4-dioxo-1,3-diazaspiro[4.5]dec-3-yl)acetamide
N-(4-bromophenyl)-2-(2,5-dioxo-4,4-dipropylimidazolidin-1-yl)acetamide;
N-(4-bromophenyl)-2-(4-ethyl-2,5-dioxo-4-phenylimidazolidin-1-yl)acetamide;
- 10 N-(4-bromophenyl)-2-(4-cyclopropyl-4-methyl-2,5-dioxoimidazolidin-1-yl)acetamide;
N-(4-bromophenyl)-2-(2,4-dioxo-1,3-diazaspiro[4.4]non-3-yl)acetamide
N-(4-bromophenyl)-2-(4-ethyl-4-methyl-2,5-dioxoimidazolidin-1-yl)acetamide;
N-(4-chlorophenyl)-2-(4,4-diethyl-2,5-dioxoimidazolidin-1-yl)acetamide;
- 15 2-(4,4-diethyl-2,5-dioxoimidazolidin-1-yl)-N-(4-fluorophenyl)acetamide;
N-(4-bromophenyl)-2-[4-methyl-2,5-dioxo-4-(2-phenylethyl)imidazolidin-1-yl]acetamide;
N-(4-bromophenyl)-2-(2,4-dioxo-1,3-diazaspiro[4.6]undec-3-yl)acetamide
N-(4-bromophenyl)-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-
- 20 isoindole-2-acetamide; and
N-(4-bromophenyl)-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-2H-isoindole-2-acetamide.

What is claimed is:

1. ~~A method of treating an ocular inflammatory disease in a subject in need of such treatment, which comprises administering~~ Use of a pharmaceutical composition comprising a therapeutically effective amount of at least one agonist of Formyl peptide receptor 2 in the manufacture of a medicament treating an ocular inflammatory disease in a subject in need of such treatment.

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

3. ~~The method of claim 1, wherein the agonist of FPR2 is represented by~~ Formula I:



Formula I

wherein:

~~R¹ is sec-butyl, C₆₋₁₀-aryl, -CH₂-(C₆₋₁₀)aryl, -CH₂-heterocycle, C₄₋₈-cycloalkyl or C₃₋₈-cycloalkenyl or heterocycle;~~

~~R² is halogen or methyl;~~

~~R³ is halogen;~~

~~R⁴ is H, methyl or halogen;~~

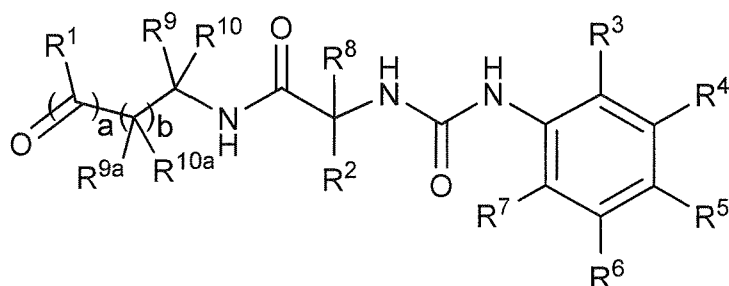
~~R⁵ is OR⁶ or NH₂; and~~

~~R⁶ is H or C₂₋₄-alkyl.~~

4. ~~The method of claim 3, wherein the agonist of FPR2 is selected from:~~ (2S,3S)-2-[[[(4-bromo-2-fluorophenyl)carbonyl]amino]-3-methylpentanoic acid;

(2S)-2-(((4-bromophenyl)carbamoyl)amino)-4-methylpentanoic acid;
 (2S)-2-(((4-bromophenyl)carbamoyl)amino)pentanoic acid;
 (2S)-2-(((4-iodophenyl)carbamoyl)amino)-4-methylpentanoic acid; and
 (2S)-4-methyl-2-(((4-(methylsulfonyl)phenyl)carbamoyl)amino)pentanoic
 acid.

5.3. The method use of claim 1, wherein the agonist of FPR2 is
 represented by Formula II :



Formula II

wherein:

a is 1 and b is 0;

a is 0 and b is 1;

a is 1 and b is 1;

R¹ is optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, -NR¹¹R¹² or -OR¹³;

R² is optionally substituted C₁₋₈ alkyl or optionally substituted C₆₋₁₀ aryl;

R³ is hydrogen, optionally substituted C₁₋₈ alkyl, halogen, -COOR¹⁵, -OR¹³, -NR¹¹R¹², NO₂, optionally substituted heterocycle, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;

R⁴ is hydrogen, optionally substituted C₁₋₈ alkyl, halogen, -COOR¹⁵, -OR¹³, -NR¹¹R¹², NO₂, optionally substituted heterocycle, optionally substituted C₃₋₈

cycloalkyl, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;

R⁵ is halogen, -CF₃ or -S(O)_nR¹⁴;

n is 0, 1 or 2;

- 5 R⁶ is hydrogen, optionally substituted C₁₋₈ alkyl, halogen, - COOR¹⁵, - OR¹³, - NR¹¹R¹², NO₂, optionally substituted heterocycle, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;

- 10 R⁷ is hydrogen, optionally substituted C₁₋₈ alkyl, halogen, - COOR¹⁵, - OR¹³, - NR¹¹R¹², NO₂, optionally substituted heterocycle, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;

R⁸ is hydrogen, optionally substituted C₁₋₈ alkyl or optionally substituted C₆₋₁₀ aryl;

- 15 R⁹ is hydrogen, optionally substituted C₁₋₈ alkyl or optionally substituted C₆₋₁₀ aryl;

R¹⁰ is hydrogen, optionally substituted C₁₋₈ alkyl or optionally substituted C₆₋₁₀ aryl;

- 20 R^{9a} is hydrogen, optionally substituted C₁₋₈ alkyl or optionally substituted C₆₋₁₀ aryl;

R^{10a} is hydrogen, optionally substituted C₁₋₈ alkyl or optionally substituted C₆₋₁₀ aryl;

R¹¹ is hydrogen or optionally substituted C₁₋₈ alkyl;

R¹² is hydrogen or optionally substituted C₁₋₈ alkyl;

- 25 R¹³ is hydrogen or optionally substituted C₁₋₈ alkyl;

R¹⁴ is hydrogen, CF₃ or optionally substituted C₁₋₈ alkyl; and

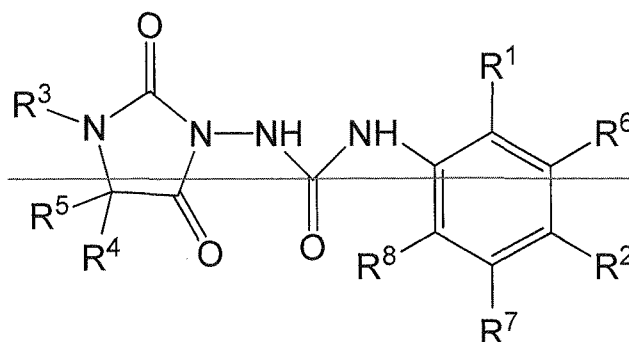
R¹⁵ is hydrogen or optionally substituted C₁₋₈ alkyl.

- 30 | 6.4. The method use of claim 53, wherein the agonist of FPR2 is selected from:

{[(2S)-2-[[[(4-bromophenyl)carbamoyl]amino]pentanoyl]amino}acetic acid;

{[(2S)-2-[[[4-bromophenyl]carbamoyl]amino]-4-methylpentanoyl](methyl)amino}acetic acid.

7. The method of claim 1, wherein the agonist of FPR2 is represented by
Formula III:



Formula III

- 10 R^1 is halogen, hydrogen, optionally substituted C_{1-8} alkyl, OR^9 , $C(O)R^{10}$, NO_2 , $NR^{13}R^{14}$, CN , SR^{15} or SO_2R^{16} ;
 R^2 is halogen, optionally substituted C_{1-8} alkyl, CF_3 , OR^9 , $C(O)R^{10}$, NO_2 , $NR^{13}R^{14}$, CN , SR^{15} or SO_2R^{16} ;
 R^3 is hydrogen, optionally substituted C_{1-8} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{6-10} aryl, optionally substituted heterocycle, or together with R^5 forms a 10- or 11-membered polycyclic ring which is optionally substituted;

R^4 is hydrogen, optionally substituted C_{1-8} alkyl,

