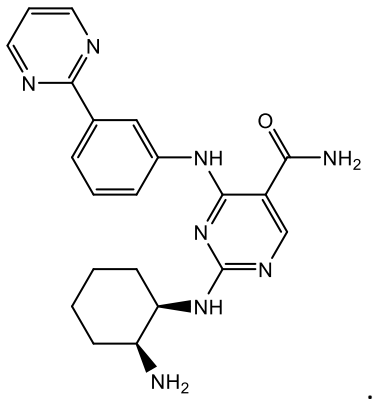
SUMMARY

[0007] Provided herein are methods of using a Syk inhibitor in the treatment of ophthalmic allergic, dry eye, and/or inflammatory diseases. In some examples, provided is a method of treating an ophthalmic disease comprising administering a therapeutically effective amount of a Syk inhibitor topically to an eye of a patient in need thereof.

[0008] In some examples, provided is a method of using 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide, a specific Syk inhibitor, or a salt thereof, in the treatment of ophthalmic diseases.

[0009] 2-((1R,2S)-2-aminocyclohexylamino)-4-(3-(pyrimidin-2-yl)phenylamino)pyrimidine-5-carboxamide (herein also referred to as Compound 1) is of the formula:



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It is described in U.S. Patent 8,318,755, which is incorporated by reference in its entirety.

[0010] In some examples, provided herein is a method for treating an ophthalmic disease or condition comprising administering to a patient in need thereof a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof.

[0011] In some examples, the ophthalmic disease or condition is allergic and/or inflammatory, including one or more of allergic conjunctivitis (also called ocular allergy or eye allergy, including acute allergic conjunctivitis, chronic allergic conjunctivitis, temporary allergic conjunctivitis, persistent allergic conjunctivitis, seasonal allergic conjunctivitis or perennial allergic conjunctivitis), rhinoconjunctivis, dry eye, keratoconjunctivitis, eye inflammation, inflammation of the ocular surface or eyelids (e.g., dry eye, blepharitis, ptyergium, peripheral corneal infiltrate, post corneal transplant, pingueculitis, episcleritis, scleritis, keratitis, fungal keratitis, dermatitis of the eyelids, bacterial and viral conjunctivitis, and atopic

keratoconjunctivitis (AKC), neurotrophic keratitis, GVHD-graft versus host disease), other ocular surface inflammation, irritation, and/or hyperemia, and/or anterior chamber of the eye (e.g., anterior uveitis, post-operative inflammation, iritis), vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC), neurotrophic keratitis, GVHD-graft versus host disease, traumatic and post-surgical iritis, uveitis, pingueculum, pterygium, contact lens induced dry eye, other steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, posterior uveitis, retina diseases such as macular edema associated with cystoid macular edema, diabetic macular edema, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), eye redness, swollen eye/chemosis, eyelid swelling, eyelid congestion, and itchy eye, steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, and ocular conditions for which a corticosteroid is indicated. In some examples, the ophthalmic disease or condition is acute or chronic allergic conjunctivitis, which may be seasonal, perennial, temporary, or persistent allergic conjunctivitis.

[0012] In some examples, the methods treat an anterior segment inflammatory disease. In some examples, the methods treat an ocular surface inflammatory disease, such as dry eye, blepharitis, ptyergium, peripheral corneal infiltrate, post corneal transplant, pingueculitis, episcleritis, scleritis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, fungal keratitis (via effect of TLR signaling), bacterial or viral conjunctivitis (treating the inflammatory component-not necessarily as an anti-infective), steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, and other ocular conditions for which a corticosteroid is indicated. In some examples, the methods treat an anterior chamber inflammatory disease, such as anterior uveitis, post-operative inflammation, or traumatic and post-surgical iritis.

[0013] In some examples, the methods treat one or more signs/symptoms of allergic conjunctivitis, including redness, itchiness, eyelid swelling, conjunctival swelling, discomfort, watery eyes, sensitivity to light, keratitis, corneal staining, conjunctival staining, or markers of inflammation of the eye, etc. In some examples, the methods treat one or more signs and/or symptoms of dry eye including, discomfort, dryness, grittiness, dryness, burning, keratitis, conjunctival redness, conjunctival staining, corneal staining, reduced tearing, reduced tear film break up time, reduced quality of life, reduced visual function.

[0014] In some examples, the methods treat dry eye.

[0015] In some examples, provided herein is a method for treating an ophthalmic disease or condition comprising administering topically to a patient in need thereof about 0.001 mg to about 1 mg of Compound 1 or a pharmaceutically acceptable salt thereof once a day, twice a day, three times a day, or four times a day. In some examples, the method comprises administering about 0.001 mg to about 1 mg of Compound 1 or a pharmaceutically acceptable salt thereof to each eye of the patient.

[0016] In some examples, provided are pharmaceutical compositions, specifically ophthalmic compositions in the form of eyedrops, comprising Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, suitable for treating ophthalmic diseases or conditions.

[0017] In some examples, provided herein are eyedrop ophthalmic compositions comprising Compound 1 or a pharmaceutically acceptable salt thereof, a buffer, a tonicity modifier, and a vehicle such as water. In some examples, the eyedrop ophthalmic compositions further comprise a preservative. In some examples, the eyedrop ophthalmic composition further comprise a demulcent, surfactant, or polymer system.

[0018] The eyedrop ophthalmic compositions described herein can comprise Compound 1 or a pharmaceutically acceptable salt thereof in an amount of about 0.001% to about 10%; about 0.01% to about 10%; about 0.05% to about 10%; about 0.1% to about 10%; about 0.2% to about 7%; about 0.3% to about 5%; about 0.4% to about 2%; or about 0.5% to about 1% w/w. In some examples, the eyedrop ophthalmic compositions comprise about 0.5% to about 1% w/w of Compound 1 or a pharmaceutically acceptable salt thereof. In some examples, the eyedrop ophthalmic compositions comprise about 0.5% or about 1% w/w of Compound 1 or a pharmaceutically acceptable salt thereof. In some examples, the eyedrop ophthalmic compositions comprise Compound 1 HCl salt.

[0019] In some examples, the tonicity modifier is one or more of glycerin (also known as glycerol), NaCl, and KCl. In some examples, the eyedrop ophthalmic compositions comprise about 0.1% to about 5% w/w of a tonicity modifier. In some examples, the eyedrop ophthalmic compositions comprise about 0.2% to about 2% w/w of a tonicity modifier. In some examples, the eyedrop ophthalmic compositions comprise about 0.5% to about 1.5% w/w of

a tonicity modifier. In some examples, the eyedrop ophthalmic compositions comprise about 0.5% w/w of a tonicity modifier. In some examples, the eyedrop ophthalmic compositions comprise about 1.5% w/w of a tonicity modifier. In some examples, the eyedrop ophthalmic compositions comprise about 1% to about 2% w/w of glycerin. In some examples, the eyedrop ophthalmic compositions comprise about 1.5% w/w of glycerin.

[0020] In some examples, the eyedrop ophthalmic compositions comprise about 0.005% to about 0.02% w/w of a preservative. In some examples, the eyedrop ophthalmic compositions comprise about 0.01% w/w of a preservative. In some examples, the preservative is benzalkonium chloride. In some examples, the eyedrop ophthalmic compositions comprise about 0.005% to about 0.02% w/w of benzalkonium chloride. In some examples, the eyedrop ophthalmic compositions comprise about 0.01% w/w of benzalkonium chloride. In some examples the eyedrop ophthalmic composition does not contain a preservative.

[0021] In some examples, the buffer is a phosphate buffer. In some examples, the buffer is an about 5 mM to about 20 mM phosphate buffer. In some examples, the buffer is an about 10 mM phosphate buffer.

[0022] In some examples, the vehicle comprises water and the eyedrop ophthalmic compositions are aqueous ophthalmic compositions.

[0023] In some examples, provided is an aqueous ophthalmic composition comprising about 0.1% to about 2% w/w Compound 1 or a pharmaceutically acceptable salt thereof, about 1% to about 2% w/w of a tonicity modifier, about 0.005% to about 0.02% w/w of a preservative, and a buffer in water, and having a pH of about 5.5 to 7.5.

[0024] In some examples, provided is an aqueous ophthalmic composition comprising about 0.1% to about 2% w/w Compound 1 HCl salt, about 1% to about 2% w/w of a tonicity modifier, about 0.005% to about 0.02% w/w of a preservative, a buffer in water and having a pH of about 5.5 to 7.5.

[0025] In some examples, provided is an aqueous ophthalmic composition comprising about 0.1% to about 2% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about

0.005% to about 0.02% w/w benzalkonium chloride, and a buffer in water, and having a pH of about 5.5 to 7.5.

[0026] In some examples, provided is an aqueous ophthalmic composition comprising about 0.1% to about 2% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a buffer in water, and having a pH of about 6.

[0027] In some examples, provided is an aqueous ophthalmic composition comprising about 0.1% to about 2% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a buffer in water, and having a pH of about 6.

[0028] In some examples, provided is an aqueous ophthalmic composition comprising about 0.5% to about 1% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a phosphate buffer in water, and having a pH of about 5.5 to 7.5.

[0029] In some examples, provided is an aqueous ophthalmic composition comprising about 0.5% to 1% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

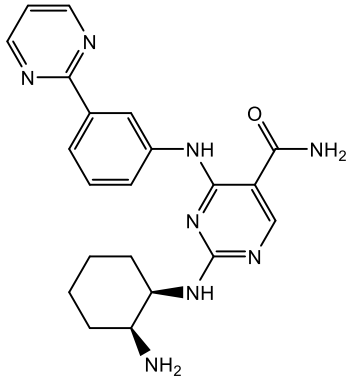
[0030] In some examples, provided is an aqueous ophthalmic composition comprising about 0.5% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

[0031] In some examples, provided is an aqueous ophthalmic composition comprising about 1% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

[0032] In some examples, the aqueous ophthalmic compositions do not comprise a stabilizer.

[0033] In some examples, the aqueous ophthalmic compositions further comprise a stabilizer.

[0033a] In one aspect, the present disclosure provides for an ophthalmic composition comprising about 0.001 % w/w to about 10 % w/w of Compound 1 of the formula:



Compound 1,

or a pharmaceutically acceptable salt thereof.

[0033b] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.01 % w/w to about 10 % w/w of Compound 1 or a pharmaceutically acceptable salt thereof, a tonicity modifier, a buffer and water.

[0033c] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.1 % w/w to about 1 % w/w of Compound 1 or a pharmaceutically acceptable salt thereof, a tonicity modifier, a buffer and water.

[0033d] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.01% to about 1% w/w Compound 1 or a pharmaceutically acceptable salt thereof, about 1% to about 2% w/w of a tonicity modifier, about 0.005% to about 0.02% w/w of a preservative, and a buffer in water, and having a pH of about 5.5 to about 7.5.

[0033e] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.01% to about 5% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a buffer in water and having a pH of about 5.5 to about 7.5.

[0033f] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.1% to about 5% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a phosphate buffer in water, and having a pH of about 5.5 to 7.5.

[0033g] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.1% to 5% w/w Compound 1 HCl salt, about 1.5 % w/w glycerin, about

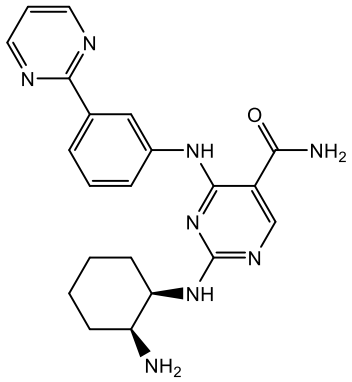
0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

[0033h] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 0.5% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

[0033i] In another aspect, the present disclosure provides for an ophthalmic composition comprising about 1% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

[0033j] In another aspect, the present disclosure provides for use of the ophthalmic composition as described herein in the manufacture of a medicament for treating an ophthalmic disease or condition.

[0033k] In another aspect, the present disclosure provides for use of Compound 1 of the formula:

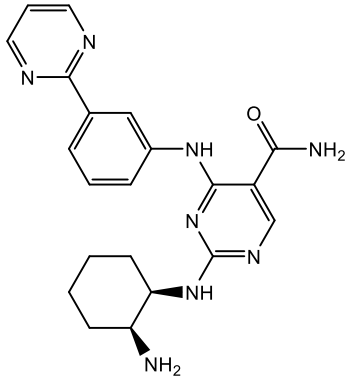


Compound 1,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an ophthalmic disease or condition.

[0033l] In another aspect, the present disclosure provides for the ophthalmic composition as described herein for use as a medicament.

[0033m] In another aspect, the present disclosure provides for Compound 1 of the formula:



Compound 1,

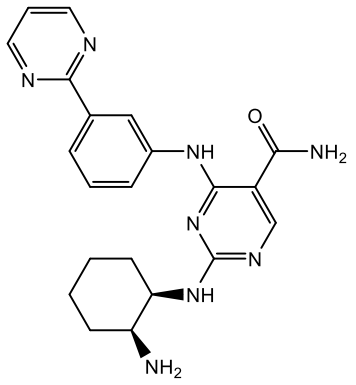
or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0034] Also provided are methods of using and preparing the compositions described herein.

[0035] These and other examples are described in more details in the text that follows.

WHAT IS CLAIMED IS:

1. An ophthalmic composition comprising about 0.001 % w/w to about 10 % w/w of Compound 1 of the formula:



Compound 1,

or a pharmaceutically acceptable salt thereof.

2. An ophthalmic composition comprising about 0.01 % w/w to about 10 % w/w of Compound 1 or a pharmaceutically acceptable salt thereof, a tonicity modifier, a buffer and water.

3. An ophthalmic composition comprising about 0.1 % w/w to about 1 % w/w of Compound 1 or a pharmaceutically acceptable salt thereof, a tonicity modifier, a buffer and water.

4. The ophthalmic composition of any one of claims 1-3, comprising Compound 1 HCl salt.

5. The ophthalmic composition of any one of claims 1-4, comprising about 0.1% to about 5% of a tonicity modifier, about 0.005 to about 0.02% w/w of a preservative, and a buffer, and having a pH of about 5.5 to 7.

6. The ophthalmic composition of any one of claims 1-4, comprising about 0.2% to about 2% w/w of a tonicity modifier, about 0.005 to about 0.02% w/w of a preservative, and a buffer, and having a pH of about 6.

7. The ophthalmic composition of any one of claims 1-4, comprising about 0.5% to about 1.5% w/w of a tonicity modifier, about 0.01% w/w of a preservative, and a buffer, and having a pH of about 6.

8. The ophthalmic composition of any one of claims 5-7, wherein the tonicity modifier is one or more of glycerin, NaCl, and KCl.

9. The ophthalmic composition of any one of claims 5-7, wherein the tonicity modifier is glycerin.

10. The ophthalmic composition of any one of claims 5-9, wherein the preservative is benzalkonium chloride.

11. The ophthalmic composition of any one of claims 5-10, wherein the buffer is a phosphate buffer.

12. The ophthalmic composition of any one of claims 5-10, wherein the buffer is a citrate buffer.

13. An ophthalmic composition comprising about 0.01% to about 1% w/w Compound 1 or a pharmaceutically acceptable salt thereof, about 1% to about 2% w/w of a tonicity modifier, about 0.005% to about 0.02% w/w of a preservative, and a buffer in water, and having a pH of about 5.5 to about 7.5.

14. An ophthalmic composition comprising about 0.01% to about 5% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a buffer in water and having a pH of about 5.5 to about 7.5.

15. An ophthalmic composition comprising about 0.1% to about 5% w/w Compound 1 HCl salt, about 1% to about 2% w/w glycerin, about 0.005% to about 0.02% w/w benzalkonium chloride, and a phosphate buffer in water, and having a pH of about 5.5 to 7.5.

16. An ophthalmic composition comprising about 0.1% to 5% w/w Compound 1 HCl salt, about 1.5 % w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

17. An ophthalmic composition comprising about 0.5% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

18. An ophthalmic composition comprising about 1% w/w Compound 1 HCl salt, about 1.5% w/w glycerin, about 0.01% w/w benzalkonium chloride, and about 10 mM phosphate buffer in water, and having a pH of about 6.

19. Use of the ophthalmic composition of any one of claims 1-18 in the manufacture of a medicament for treating an ophthalmic disease or condition.

20. The use of claim 19, wherein the ophthalmic disease or condition is allergic and/or inflammatory, including signs and/or symptoms of one or more of allergic conjunctivitis (including acute allergic conjunctivitis, chronic allergic conjunctivitis, seasonal allergic conjunctivitis or perennial allergic conjunctivitis), rhinoconjunctivis, dry eye, keratoconjunctivitis, blepharitis, dermatitis of the eyelids, blepharoconjunctivitis, ptyergium, post corneal transplant, pingueculitis, episcleritis, scleritis, keratitis, peripheral corneal infiltrate, fungal keratitis, bacterial and viral conjunctivitis, post-operative inflammation, eye inflammation, inflammation of the ocular surface or eyelids, anterior chamber or posterior chamber of the eye, atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC), neurotrophic keratitis, GVHD-graft versus host disease, traumatic or post-surgical iritis, uveitis, pingueculum, pterygium, contact lens induced dry eye, ocular surface inflammation, irritation, and/or hyperemia, posterior uveitis, retina diseases, diabetic macular edema, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), eye redness, eyelid swelling, eyelid congestion, swelling eye, itchy eye, steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, and ocular conditions for which a corticosteroid is indicated.

21. The use of claim 19, wherein the ophthalmic disease or condition is one or more of dry eye, blepharitis, ptyergium, peripheral corneal infiltrate, post corneal transplant, pingueculitis, episcleritis/scleritis, atopic keratoconjunctivitis, fungal keratitis, allergy, AKC, VKC, GPC,

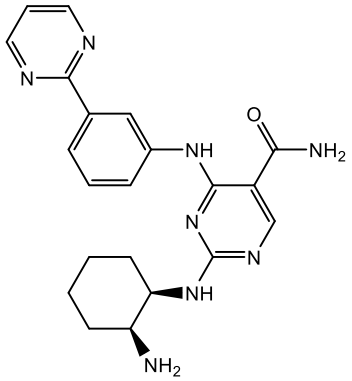
bacterial or viral conjunctivitis, anterior uveitis, traumatic or post-surgical iritis, eyelid swelling, eye redness, irritation, ocular surface inflammation, or post-operative inflammation.

22. The use of claim 19, wherein the ophthalmic disease or condition is chronic allergic conjunctivitis.

23. The use of claim 19, wherein the ophthalmic disease or condition is acute allergic conjunctivitis.

24. The use of any one of claims 19-23, whereby one or more of redness, inflammation, swelling, discomfort, watery eye and itching of the eye, keratitis, corneal staining, conjunctival staining, or markers of inflammation of the eye is reduced or eliminated.

25. Use of Compound 1 of the formula:



Compound 1,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an ophthalmic disease or condition.

26. The use of claim 25, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered in an amount of about 0.01 mg to about 1 mg to an eye.

27. The use of claim 25 or 26, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered once a day.

28. The use of claim 25 or 26, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered twice a day.

29. The use of any one of claims 25-28, wherein the ophthalmic disease or condition is allergic and/or inflammatory, including signs and/or symptoms of one or more of allergic conjunctivitis (including acute allergic conjunctivitis, chronic allergic conjunctivitis, seasonal allergic conjunctivitis or perennial allergic conjunctivitis), irritation, rhinoconjunctivis, dry eye, keratitis, keratoconjunctivitis, blepharitis, blepharoconjunctivitis, ptyergium, post corneal transplant, pingueculitis, episcleritis, scleritis, peripheral corneal infiltrate, fungal keratitis, dermatitis of the eyelids, bacterial or viral conjunctivitis, post-operative inflammation, eye inflammation, inflammation of the ocular surface, eyelids, anterior chamber or posterior chamber of the eye, atopic keratoconjunctivitis (AKC), neurotrophic keratitis, GVHD-graft versus host disease, GPC, vernal keratoconjunctivitis (VKC), viral bacterial fungal or parasitic infection, traumatic and post-surgical iritis, uveitis, pingueculum, pterygium, contact lens induced dry eye, posterior uveitis, anterior uveitis, retina diseases such as macular edema associated with cystoid macular edema, diabetic macular edema, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), eye redness, eyelid swelling, eyelid congestion, swelling eye, itchy eye, discomfort, keratitis, corneal staining, conjunctival staining, markers of inflammation of the eye, steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, and ocular conditions for which a corticosteroid is indicated.

30. The use of any one of claims 25-28, wherein the ophthalmic disease or condition is one or more of dry eye, allergic conjunctivitis, keratoconjunctivitis (sicca), keratitis, blepharitis, ptyergium, peripheral corneal infiltrate, post corneal transplant, pingueculitis, episcleritis/scleritis, atopic keratoconjunctivitis, fungal keratitis, bacterial and viral conjunctivitis, anterior uveitis, or post-operative inflammation, and signs and/or symptoms thereof.

31. The use of any one of claims 25-28, wherein the ophthalmic disease or condition is allergic conjunctivitis.

32. The use of any one of claims 25-28, wherein the ophthalmic disease or condition is acute allergic conjunctivitis.

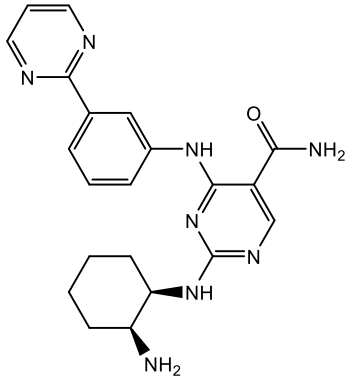
33. The use of any one of claims 25-28, wherein the ophthalmic disease or condition is chronic allergic conjunctivitis.

34. The use of any one of claims 25-28, wherein the ophthalmic disease or condition is dry eye.

35. The use of any one of claims 25-34, whereby one or more of redness, inflammation, swelling, eyelid congestion, watery eye and itching of the eye is reduced or eliminated.

36. The ophthalmic composition of any one of claims 1-18 for use as a medicament.

37. Compound 1 of the formula:



Compound 1,

or a pharmaceutically acceptable salt thereof, for use as a medicament.