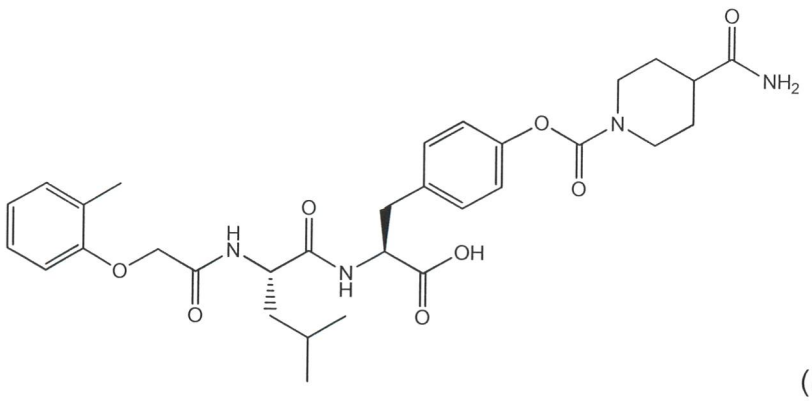
Integrins are heterodimeric glycoproteins consisting of one α- and one β-subunit. Expressed on the cell surface of leukocytes, integrins play a role in their recruitment to sites of inflammation. The association of a specific α- and β-subunit determines the ligand specificity of the integrin. The α4 integrin subunit (CD49d) is a constituent of Very Late Antigen-4, VLA-4 (integrin α4β1; CD49d/CD29) and α4β7 (CD49d/CD103). In the case of integrin α4β1, the corresponding ligands are the immunoglobulin superfamily adhesion molecule vascular cell adhesion molecule 1 (VCAM-1) on vascular endothelial cells and the extracellular matrix glycoprotein fibronectin, which are responsible for the homing, trafficking, differentiation, priming, activation, proliferation and survival of integrin α4β1 expressing cells. Integrin α4β1 is expressed on lymphocytes, monocytes, macrophages, NK cells and eosinophils. Integrin α4β7 and its corresponding ligand, MAdCAM (Mucosal Addressin Cell Adhesion Molecule-1), regulate leukocyte trafficking to the gut, but their involvement in DED cannot be ruled out.

Natalizumab, an antibody directed against the integrin α4 subunit, has been shown to profoundly inhibit inflammation and improve clinical outcomes in both multiple sclerosis (Cross and Naismith, 2014) and Crohn's disease (Cohen et al., 2014) which are also T cell mediated pathologies. Lifitegrast, a small molecule antagonist, directed against a different adhesion molecule (LFA-1, integrin αLβ2), has been shown to reduce corneal staining and improve symptoms when delivered topically to dry eye patients (Sheppard et al., 2014). Furthermore, a specific small molecule antagonist to integrin α4β1, BIO-8809, had been shown to decrease corneal fluorescein staining, conjunctival T cell infiltrates and TNFα expression in cornea and conjunctiva in a murine dry eye model (Ecoiffier et al., 2008). Taken together these considerations provided a rationale for further exploring the blockade of integrin α4 in an animal model of DED.

SUMMARY

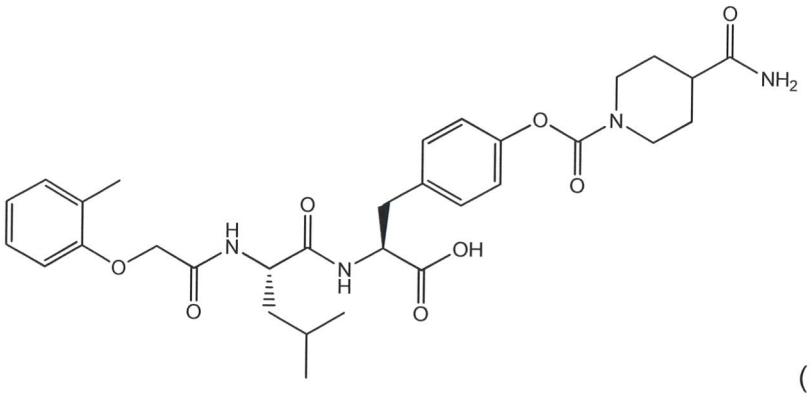
Disclosed is a method for treating an ocular inflammatory condition in a mammal in need thereof, comprising ocularly administering to the mammal a therapeutically effective amount of a compound of formula I



(I)

or a pharmaceutically acceptable salt, ester, anhydride, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof (collectively referred to as therapeutic agent **A**). In certain embodiments, therapeutic agent **A** is applied topically. Topical administration may be to the cornea, the conjunctival sac, and/or the eyelid. In certain other embodiments, therapeutic agent **A** is applied locally, e.g., subconjunctivally, intracamerally, intravitreally, subtenon, subretinally, subchoroidally, or suprachoroidally.

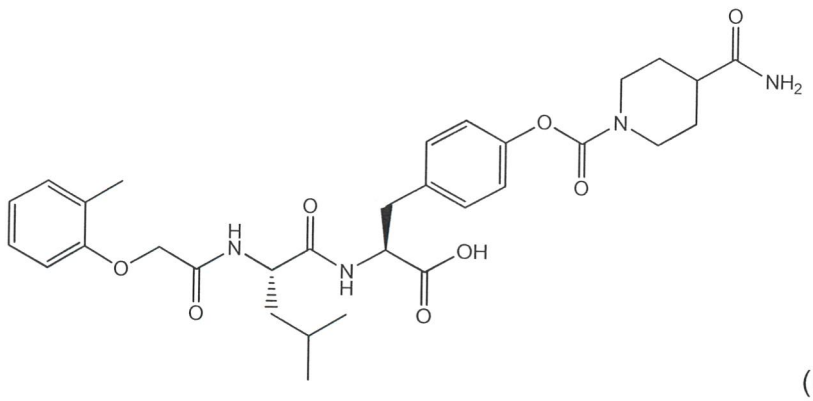
Disclosed is a compound of formula I



(I)

or a pharmaceutically acceptable salt, ester, anhydride, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof (collectively referred to as therapeutic agent **A**) for use in treating an ocular inflammatory condition. In certain embodiments, therapeutic agent **A** is provided in a pharmaceutically acceptable vehicle, such as a pharmaceutically acceptable ophthalmic vehicle.

Disclosed is a pharmaceutical composition comprising a compound of formula I



(I)

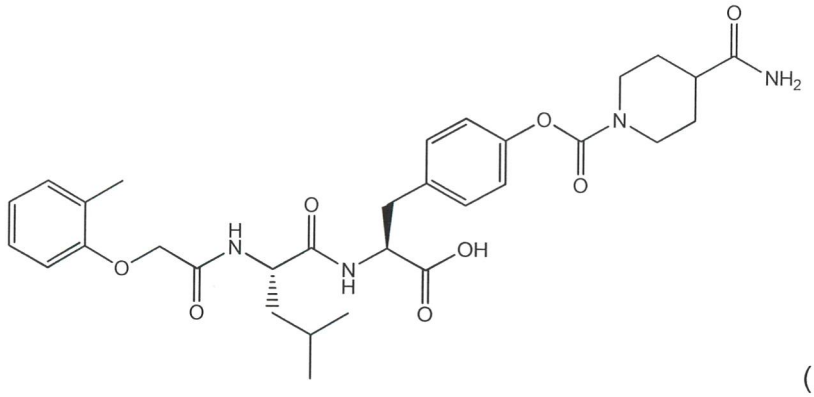
or a pharmaceutically acceptable salt, ester, anhydride, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof (collectively referred to as therapeutic agent **A**) and one or more pharmaceutically acceptable excipients, wherein the composition is useful for treating an ocular inflammatory condition. In certain embodiments, the pharmaceutical composition is suitable for ocular administration. In some such embodiments, the pharmaceutical composition is suitable to be applied topically. In certain embodiments, the pharmaceutical composition is suitable to be applied to the conjunctival sac or to the eyelid. In certain other embodiments, the pharmaceutical composition is suitable to be applied subconjunctivally, intracamerally, intravitreally, subtenon, subretinally, subchoroidally, or suprachoroidally.

Disclosed is a pharmaceutical composition comprising therapeutic agent **A** and one or more pharmaceutically acceptable excipients, wherein the composition is useful for treating an ocular inflammatory condition when applied in the form of an eye drop, spray or mist.

Disclosed is a pharmaceutical composition comprising therapeutic agent **A** and one or more pharmaceutically acceptable excipients, wherein the composition is useful for treating an ocular inflammatory condition when applied as a topical ophthalmic formulation.

Disclosed is a method for treating an ocular inflammatory condition in a mammal (which mammal may be a human) in need thereof by preventing or reducing the migration of antigen-presenting cells to the lymph nodes. Such method comprises administering to said mammal (which mammal may be a human) a therapeutically effective amount of therapeutic agent **A**.

Disclosed is a pharmaceutical composition comprising a compound of formula I



(I)

or a pharmaceutically acceptable salt, ester, anhydride, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof and one or more pharmaceutically acceptable excipients.

IDisclosed is a method for treatment of an ocular inflammatory condition, such as DED, in a mammal (which mammal may be a human) in need thereof comprising administering to said mammal/human a therapeutically effective amount of: (a) a pharmaceutical composition comprising therapeutic agent **A**; (b) cyclosporin A; and (c) one or more pharmaceutically acceptable excipients.

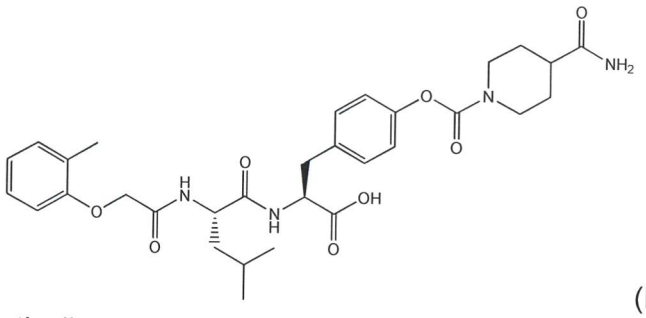
Disclosed is a method for treatment of an ocular inflammatory condition, such as DED, in a mammal (which mammal may be a human) in need thereof comprising administering to said mammal/human a therapeutically effective amount of: (a) a pharmaceutical composition comprising therapeutic agent **A**; (b) a topical steroid selected from the group consisting of dexamethasone base and phosphate, difluprednate, fluocinolone, fluorometholone base and acetate, loteprednol, prednisolone acetate and phosphate, rimexolone, and triamcinolone acetonide; and (c) one or more pharmaceutically acceptable excipients.

Disclosed is a method for treatment of an ocular inflammatory condition, such as DED, in a mammal (which mammal may be a human) in need thereof comprising administering to said mammal/human a therapeutically effective

amount of: (a) a pharmaceutical composition comprising therapeutic agent **A**; (b) a non-steroidal anti-inflammatory drug selected from the group consisting of bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac; and (c) one or more pharmaceutically acceptable excipients.

Disclosed is a method for treatment of an ocular inflammatory condition, such as DED, in a mammal (which mammal may be a human) in need thereof comprising administering to said mammal/human a therapeutically effective amount of: a) a pharmaceutical composition comprising therapeutic agent **A**; (b) an LFA-1 integrin antagonist such as lifitegrast; and (c) one or more pharmaceutically acceptable excipients.

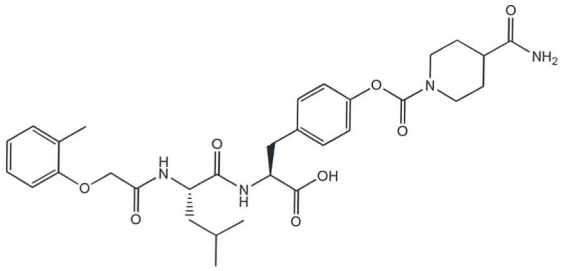
Disclosed is the use of a compound of formula I



(I)

or a pharmaceutically acceptable salt, ester, anhydride, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof in the manufacture of a medicament for the treatment of an ocular inflammatory condition.

In one aspect, there is provided use of a compound of formula I



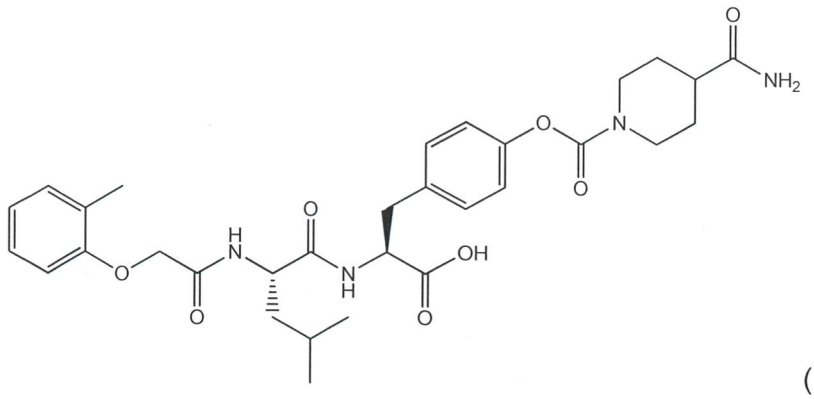
(I)

or a pharmaceutically acceptable salt, ester, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof, in the manufacture of a medicament for treating dry eye disease in a human subject through ocular administration, wherein the medicament is to be administered at a dosing of the compound suitable to primarily act locally.

In certain embodiments of any of the aforementioned aspects, the ocular inflammatory condition is dry eye disease. In other embodiments of each aspect, the ocular inflammatory condition is non-infectious uveitis (anterior, intermediate, posterior, pan), non-infectious conjunctivitis, iritis, or scleritis.

What is claimed is:

1. Use of a compound of formula I



(I)

or a pharmaceutically acceptable salt, ester, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof, in the manufacture of a medicament for treating dry eye disease in a human subject through ocular administration, wherein the medicament is to be administered at a dosing of the compound suitable to primarily act locally.

2. The use according to claim 1, wherein the medicament is to be administered to the human subject at a dosing concentration in the range of 1 mg/mL to 30 mg/mL of the compound.

3. The use according to claim 1 or claim 2, wherein the medicament is to be administered to the human subject at a dosing concentration of 1 mg/mL, 3 mg/mL, 10 mg/mL, or 30 mg/mL of the compound.

4. The use according to any one of claims 1-3, wherein the medicament is formulated as an eye drop, gel, ointment, spray, or mist.

5. The use according to any one of claims 1-4, wherein the medicament is formulated as an ophthalmic solution.

6. The use according to claim 5, wherein the ophthalmic solution contains 1 mg/mL, 3 mg/mL, 10 mg/mL, or 30 mg/mL of the compound of formula I or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, optical isomer, racemate, diastereoisomer or enantiomer thereof.

7. The use according to any one of claims 1-6, wherein the medicament is for use in combination with one or more additional therapeutic agents selected from the group

consisting of (a) cyclosporin A; (b) a steroid selected from the group consisting of dexamethasone base, dexamethasone phosphate, difluprednate, fluocinolone, fluorometholone base, fluorometholone acetate, loteprednol, prednisolone acetate, prednisolone phosphate, rimexolone, and triamcinolone acetonide; and (c) a non-steroidal anti-inflammatory agent selected from the group consisting of bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac.