TOXIC ALDEHYDE RELATED DISEASES AND TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S.S.N. 61/755,613, filed on January 23, 2013, and U.S.S.N. 61/901,796, filed on November 8, 2013, the contents of each of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Metabolic and inflammatory processes in cells generate toxic aldehydes, such as malondialdehyde (MDA), 4-hydroxyl-2-nonenal (4HNE), and 8-hydroxy-2-deoxyguanosine (8-OHdg). These aldehydes are highly reactive to proteins, carbohydrates, lipids and DNA, leading to chemically modified biological molecules, activation of inflammatory mediators such as NF-kappaB, and damages in diverse organs. For example, retinaldehyde can react with phosphatidylethanolamine (PE) to form a highly toxic compound called A2E, which is a component of lipofuscin believed to be involved in the development and progression of Age Related Macular Degeneration (AMD). Many bodily defense mechanisms function to remove or lower the levels of toxic aldehydes. Novel small molecule therapeutics can be used to scavenge "escaped" retinaldehyde in the retina, thus reducing A2E formation and lessening the risk of AMD (Jordan *et al.* (2006)).

Aldehydes are implicated in diverse pathological conditions such as dry eye, cataracts, keratoconus, Fuch's endothelial dystrophy in the cornea, uveitis, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with photorefractive keratectomy (PRK) healing or other corneal healing, conditions associated with tear lipid degradation or lacrimal gland dysfunction, inflammatory ocular conditions such as ocular rosacea (with or without meibomian gland dysfunction), and non-ocular disorders or conditions such as skin cancer, psoriasis, contact dermatitis, atopic dermatitis, acne vulgaris, Sjogren-Larsson Syndrome, ischemic-reperfusion injury, inflammation, diabetes, neurodegeneration (*e.g.*, Parkinson's disease), scleroderma, amyotrophic lateral sclerosis, autoimmune disorders (*e.g.*, lupus), cardiovascular disorders (*e.g.*, atherosclerosis), and conditions associated with the injurious effects of blister agents (Negre-Salvagre *et al.* (2008), Nakamura *et al.* (2007), Batista *et al.* (2012), Kenney *et al.* (2003), Int J Dermatol 43: 494 (2004), Invest Ophthalmol Vis Sci 48: 1552 (2007), Graefe's Clin Exp Ophthalmol 233:

694 (1994), Molecular Vision 18: 194 (2012)). Reducing or eliminating aldehydes should thus ameliorate the symptoms and slow the progression of these pathological conditions.

MDA, HNE and other toxic aldehydes are generated by a myriad of metabolic mechanisms involving: fatty alcohols, sphingolipids, glycolipids, phytol, fatty acids, arachadonic acid metabolism (Rizzo (2007)), polyamine metabolism (Wood *et al.* (2006)), lipid peroxidation, oxidative metabolism (Buddi *et al.* (2002), Zhou *et al.* (2005)), and glucose metabolism (Pozzi *et al.* (2009)). Aldehydes can cross link with primary amino groups and other chemical moieties on proteins, phospholipids, carbohydrates, and DNA, leading in many cases to toxic consequences, such as mutagenesis and carcinogenesis (Marnett (2002)). MDA is associated with diseased corneas, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy corneas (Buddi *et al.* (2002)). Also, skin disorders, *e.g.*, Sjogren-Larsson Syndrome, are likely connected with the accumulation of fatty aldehydes such as octadecanal and hexadecanal (Rizzo *et al.* (2010)). Further, increased lipid peroxidation and resultant aldehyde generation are associated with the toxic effects of blister agents (Sciuto *et al.* (2004) and Pal *et al.* (2009)).

There has been no suggestion in the art for treating the various conditions associated with toxic aldehydes by the administration of small molecule therapeutics acting as a scavenger for aldehydes, such as MDA and/or HNE. Thus, there is a need for treating, preventing, and/or reducing a risk of a disease or disorder in which aldehyde toxicity is implicated in the pathogenesis. The present invention addresses such a need.

SUMMARY OF THE INVENTION

The invention relates to a method of treating, preventing, and/or reducing a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis, by administering a compound (*e.g.*, a primary amine compound) described herein. The invention also relates to the use of a compound (*e.g.*, a primary amine compound) described herein in the manufacture of a medicament for the treatment, prevention, and/or reduction of a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis; or the use of a compound (*e.g.*, a primary amine compound) described herein in treating, preventing, and/or reducing a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis.

In one embodiment, a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis is an ocular disease, disorder, or condition, including, but not

limited to, a corneal disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular conditions associated with high aldehyde levels as a result of inflammation (*e.g.*, uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea (with or without meibomian gland dysfunction)).

In a second embodiment, a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis is a skin disorder or condition or a cosmetic indication. For example, the disease, disorder, or condition includes, but is not limited to, psoriasis, scleroderma, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjogren-Larsson Syndrome and other ichthyosis, and the cosmetic indication is solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, and a skin condition associated burn and/or wound.

In a third embodiment, a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis is a condition associated with the toxic effects of blister agents or burns from alkali agents.

In a fourth embodiment, a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis is an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease. For example, the disease, disorder, or condition includes, but is not limited to, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease, sepsis, atherosclerosis, ischemic-reperfusion injury, Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, diabetes, metabolic syndrome, and fibrotic diseases.

A compound (*e.g.*, a primary amine compound) described herein can be administered topically or systemically, as described in detail below.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present specification, including definitions, will control. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and

materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. A plot showing that Compound 9 rapidly reacts with and traps the two most common pathogenic aldehydes: malondialdehye (MDA) and 4-hydroxynonenal (HNE)

Figure 2. Bar graphs showing that Compound 9 prevents aldehyde-mediated cell death in neurons

Figure 3. A bar graph showing broad downregulation of inflammatory cytokines by a single dose of Compound 9

Figure 4. Bar graphs showing the anti-inflammatory profile of a single-dose of Compound 9 in response to LPS treatment

Figure 5. Bar graphs showing the efficacy of a single dose of Compound 9 in (A) contact dermatitis and (B) allergic dermatitis

Figure 6. (A) a plot and a table showing the mucositis score over time in hamsters subject to 40 Gy irradiation and treated with or without Compound 9, (B) photographs of cheeks of hamsters subject to 40 Gy irradiation and treated with or without Compound 9

Figure 7. A bar plot showing that Compound 9 treatment diminishes radiation induced fibrosis in hamsters subject to 40 Gy irradiation

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to compounds (*e.g.*, a primary amine compound) for the treatment, prevention, and/or reduction of a risk of diseases, disorders, or conditions in which aldehyde toxicity is implicated in the pathogenesis.

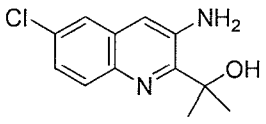
Examples of the diseases, disorders, or conditions in which aldehyde toxicity is implicated include an ocular disease, disorder, or condition, including, but not limited to, a corneal disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing

and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular conditions associated with high aldehyde levels as a result of inflammation (*e.g.*, uveitis, scleritis, ocular Stevens Johnson Syndrome, ocular rosacea (with or without meibomian gland dysfunction)). In one example, the ocular disease, disorder, or condition is not macular degeneration, such as age-related macular degeneration ("AMD"), or Stargardt's disease. In a further example, the ocular disease, disorder, or condition is dry eye syndrome, ocular rosacea, or uveitis.

Examples of the diseases, disorders, conditions, or indications in which aldehyde toxicity is implicated also include non-ocular disorders, including psoriasis, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjogren-Larsson Syndrome and other ichthyosis, solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, a skin condition associated burn and/or wound, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease, sepsis, atherosclerosis, ischemic-reperfusion injury, Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, diabetes, metabolic syndrome, and fibrotic diseases. In a further example, the non-ocular disorder is a skin disease, disorder, or condition selected from contact dermatitis, atopic dermatitis, allergic dermatitis, and. radiation dermatitis. In another example, the non-ocular disorder is a skin disease, disorder, or condition selected from Sjogren-Larsson Syndrome and a cosmetic indication associated burn and/or wound.

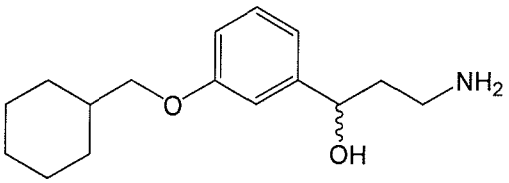
Examples of the diseases, disorders, or conditions in which aldehyde toxicity is implicated further include conditions associated with the toxic effects of blister agents or burns from alkali agents. The compounds described herein reduce or eliminate toxic aldehydes and thus treat, prevent, and/or reduce a risk of these diseases or disorders.

Certain compounds comprising primary amine groups (*e.g.*, compounds described herein) are found to be useful in scavenging toxic aldehydes, such as MDA and HNE. The compounds described herein undergo a Schiff base condensation with MDA, HNE, or other toxic aldehydes, and form a complex with the aldehydes in an energetically favorable reaction, thus reducing or eliminating aldehydes available for reaction with a protein, lipid, carbohydrate, or DNA. Importantly, compounds described herein can react with aldehydes to form a compound having a closed-ring structure that contains the aldehydes, thus trapping the aldehydes and preventing the aldehydes from being released back into the cellular milieu.

For example, Compound 9, , disclosed in PCT publication WO 2006/127945, rapidly traps MDA and HNE, even in the presence of peptides and phospholipids, which are the biological targets of these aldehydes.

In addition, primary amine compounds described in US 2012/0295895 and Maeda *et al.* (2012), the contents of each of which are incorporated herein by reference in their entirety, can reduce levels of all trans-retinal and prevent accumulation of conjugation products in the retina. The primary compounds described therein are thus useful in scavenging and trapping aldehydes, such as MDA and HNE. For example, compounds disclosed therein with an optical coherence tomography (OCT) grade of 2 or less are useful in scavenging and trapping aldehydes, such as MDA and HNE. In a further example, compounds disclosed therein with an OCT grade of 1 or less are useful in scavenging and trapping aldehydes, such as MDA and HNE. Particular examples include 3-(aminomethyl)-5-methylhexanoic acid (both stereoisomers), 6-(trifluromethoxy)benzothiazol-2-amine, and 3-ethyl-5-methyl-2-(aminoethoxy)methyl-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

US 7,982,071, the contents of which are incorporated herein by reference in their entirety, describes certain alkoxy derivatives containing a primary amine group. Those compounds are useful in the treatment of certain ophthalmic disorders, specifically AMD and Stargardt's disease. Compounds described in the 071 patent, particularly Compound (11)



are found to be useful in treating a disease, disorder, or condition described herein, such as an ocular disease, disorder, or condition (*e.g.*, dry eye syndrome, conditions associated with PRK or other corneal healing, uveitis, scleritis, ocular Stevens Johnson syndrome, ocular rosacea (with or without meibomian gland dysfunction), cataracts, keratoconus, bullous and other keratopathy, and endothelial dystrophy and related disorders).

Further, compounds described in PCT Application Nos. PCT/US2013/076592 and PCT/US2014/012356, the contents of each of which are incorporated herein by reference in their entirety, are effective in effective in scavenging and trapping MDA and HNE and other toxic aldehydes. Those compounds are found to be useful in treating a disease, disorder, or condition described herein, such as an ocular disease, disorder, or condition (*e.g.*, dry eye

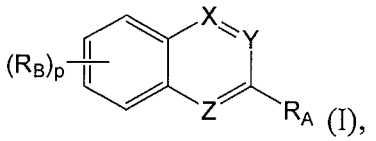
syndrome, conditions associated with PRK or other corneal healing, uveitis, scleritis, ocular Stevens Johnson syndrome, ocular rosacea (with or without meibomian gland dysfunction), cataracts, keratoconus, bullous and other keratopathy, and endothelial dystrophy and related disorders).

In one embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of an ocular disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein. The ocular disease, disorder, or condition includes, but is not limited to, a corneal disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy in the cornea), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular conditions where inflammation leads to high aldehyde levels (*e.g.*, uveitis, scleritis, ocular Stevens Johnson Syndrome, ocular rosacea (with or without meibomian gland dysfunction)). The ocular disease, disorder, or condition does not include macular degeneration, such as AMD, or Stargardt's disease. In one illustration, in the ocular disease, disorder, or condition, the amount or concentration of MDA or HNE is increased in the ocular tissues or cells. For example, the amount or concentration of aldehydes (*e.g.*, MDA or HNE) is increased for at least 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 5 fold, 10 fold as compared to that in normal ocular tissues or cells. Compounds described herein, such as Compound 9, decrease aldehyde (*e.g.*, MDA and HNE) concentration in a time-dependent manner. The amount or concentration of aldehydes (*e.g.*, MDA or HNE) can be measured by methods or techniques known in the art, such as those described in Tukozkan *et al.*, Furat Tip Dergisi 11: 88-92 (2006).

In one class, the ocular disease, disorder, or condition is dry eye syndrome. In a second class, the ocular disease, disorder, or condition is a condition associated with PRK healing and other corneal healing. For example, the invention is directed to advancing PRK healing or other corneal healing, comprising administering to a subject in need thereof a compound described herein. In a third class, the ocular disease, disorder, or condition is an ocular condition associated with high aldehyde levels as a result of inflammation (*e.g.*, uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea (with or without meibomian gland dysfunction). In a fourth class, the ocular disease, disorder, or condition is keratoconus, cataracts, bullous and other keratopathy, Fuchs' endothelial dystrophy, ocular

cicatricial pemphigoid, or allergic conjunctivitis. The compound described herein may be administered topically or systemically, as described herein below.

In a first aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of formula (I):

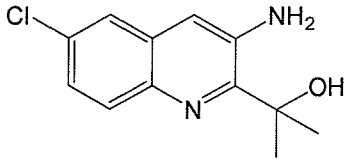


(I),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (I) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (I) described herein.

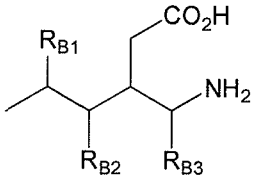
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering Compound (9):



(9),

or a pharmaceutically acceptable salt thereof.

In a second aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of formula (II):



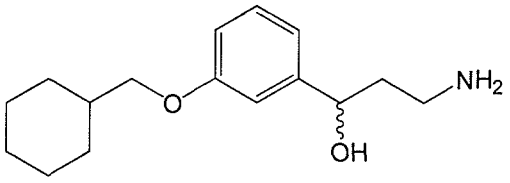
(II),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (II) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (II) described herein.

In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound selected from the compounds listed in Table 2. Preferably, the compound is (S)-3-(aminomethyl)-5-methylhexanoic acid or (R)-3-(aminomethyl)-5-methylhexanoic acid, or pharmaceutically acceptable salts or racemic mixtures thereof.

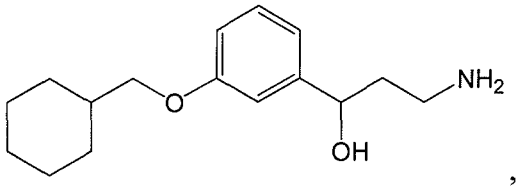
In a third aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering Compound (11):



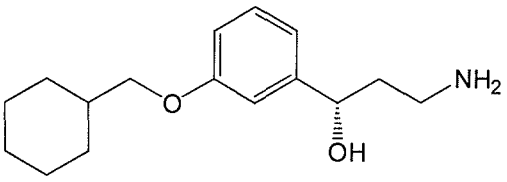
(11),

or a pharmaceutically acceptable salt thereof.

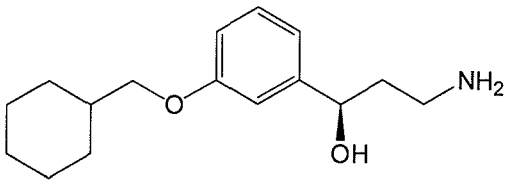
In one illustration of this aspect, the compound is:



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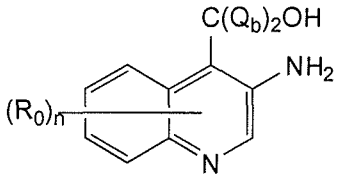


, or

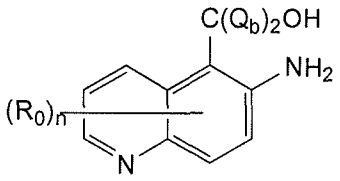


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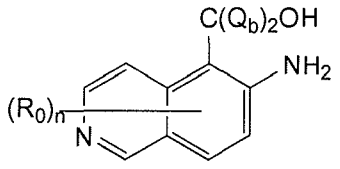
In a fourth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of any one of formulae (IIIa)-(IIIf):



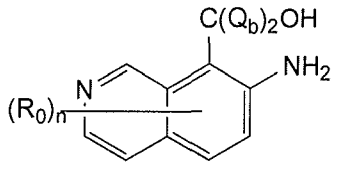
(IIIa),



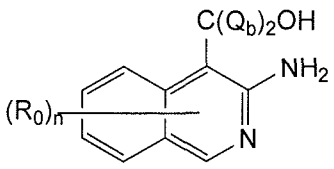
(IIIb),



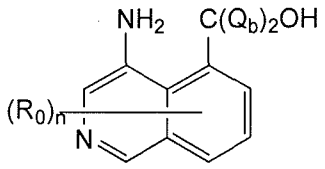
(IIIc),



(IIId),



(IIIe), or

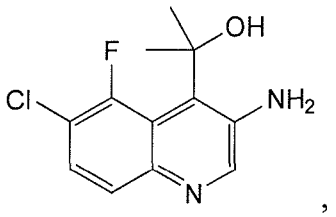


(IIIf),

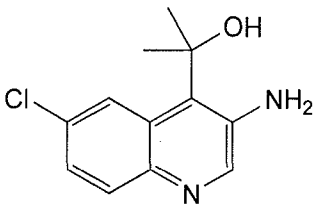
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IIIa)-(IIIf) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formulae (IIIa)-(IIIf) described herein.

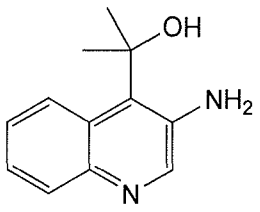
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound selected from Compounds (1)-(8):



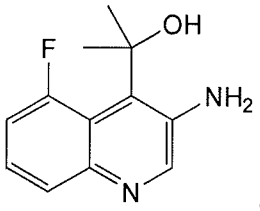
(1),



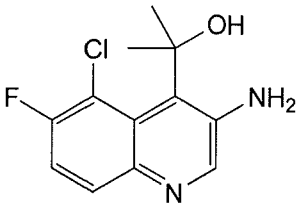
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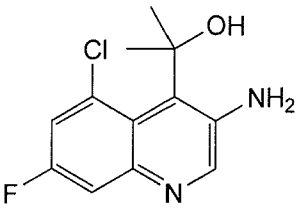
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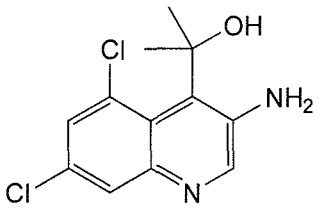
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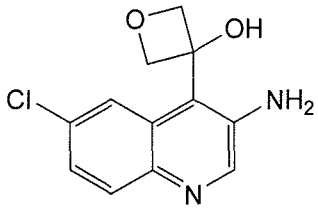
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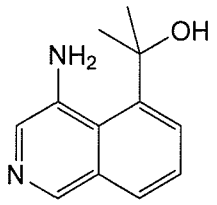
(7), and



(8).

or a pharmaceutically acceptable salt thereof. Preferably, the compound is Compound (1) or (2).

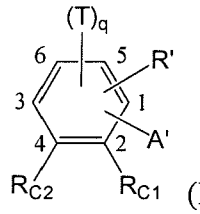
In another specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering Compound (10):



(10),

or a pharmaceutically acceptable salt thereof.

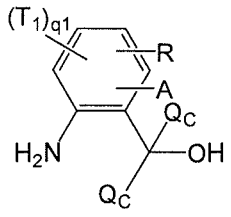
In a fifth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of formula (IV):



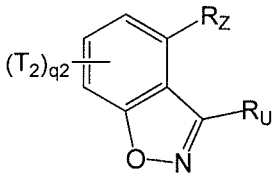
(IV),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (IV) is described in detail below.

In one class of this aspect, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of formula (IVa) or formula (IVb):



(IVa), or

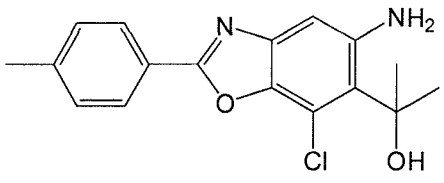


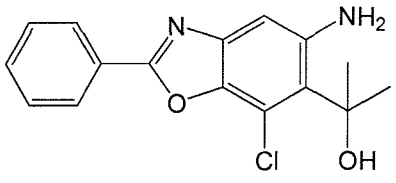
(IVb),

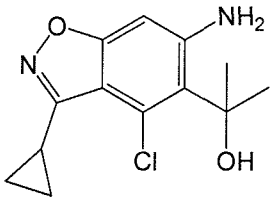
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IVa) and (IVb) is described in detail below.

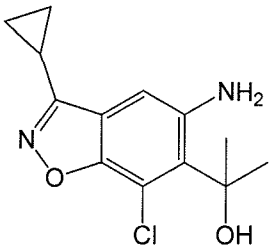
In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formula (IV), (IVa), and (IVb) described herein.

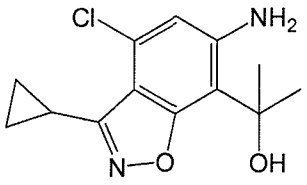
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the ocular diseases, disorders, or conditions described herein, comprising administering a compound selected from Compounds (12)-(18):

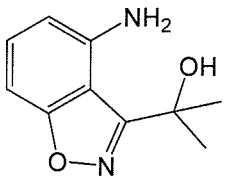

(12),

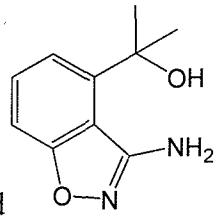

(13),


(14),


(15),


(16),


(17), and


(18),

or a pharmaceutically acceptable salt thereof.

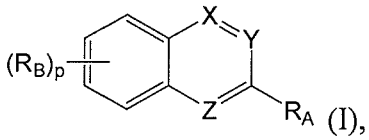
In a second embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of a skin disorder or condition or a cosmetic indication, in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein. The skin disorder or condition includes, but is not limited to, psoriasis, scleroderma, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, and Sjogren-Larsson Syndrome and other ichthyosis, and the cosmetic indication is solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, or a skin condition associated burn and/or wound.

Various skin disorders or conditions, such as atopic dermatitis, topical (discoid) lupus, psoriasis and scleroderma, are characterized by high MDA and HNE levels (Br J Dermatol 149: 248 (2003); JEADV 26: 833 (2012); Clin Rheumatol 25: 320 (2006)). In addition, ichthyosis characteristic of the Sjogren-Larsson Syndrome (SLS) originates from accumulation of fatty aldehydes, which disrupts the normal function and secretion of lamellar bodies (LB) and leads to intercellular lipid deposits in the Strateum Corneum (SC) and a defective water barrier in the skin layer (W.B. Rizzo *et al.* (2010)). The enzyme, fatty aldehyde dehydrogenase, that metabolizes aldehydes is dysfunctional in SLS patients. Thus, compounds that reduce or eliminate aldehydes, such as the compounds described herein, can be used to treat, prevent, and/or reduction of a risk of skin disorders or conditions in which aldehyde toxicity is implicated in the pathogenesis, such as those described herein.

Furthermore, with an improvement to the water barrier and prevention of aldehyde-mediated inflammation (including fibrosis and elastosis (Chairpotto *et al.* (2005)), many cosmetic indications, such as solar elastosis/wrinkles, skin tone, firmness (puffiness), eczema, smoke or irritant induced skin changes and dermal incision cosmesis, and skin conditions associated with burn and/or wound can be treated using the method of the invention. For example, Compound (9) is effective against contact dermatitis in a phorbol myristate acetate model and allergic dermatitis in an oxazolone model.

In one class, the skin disease, disorder, or condition is psoriasis, scleroderma, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, or Sjogren-Larsson Syndrome and other ichthyosis. In one exemplification, the skin disease, disorder, or condition is contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, or Sjogren-Larsson Syndrome and other ichthyosis. In a second class, the cosmetic indication is solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, or a skin condition associated burn and/or wound.

In a first aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of formula (I):

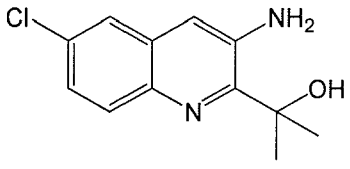


(I),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (I) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (I) described herein.

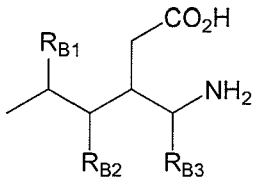
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering Compound (9):



(9),

or a pharmaceutically acceptable salt thereof.

In a second aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of formula (II):



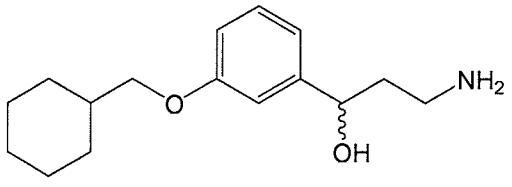
(II),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (II) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (II) described herein.

In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound selected from the compounds listed in Table 2. Preferably, the compound is (S)-3-(aminomethyl)-5-methylhexanoic acid or (R)-3-(aminomethyl)-5-methylhexanoic acid, or pharmaceutically acceptable salts or racemic mixtures thereof.

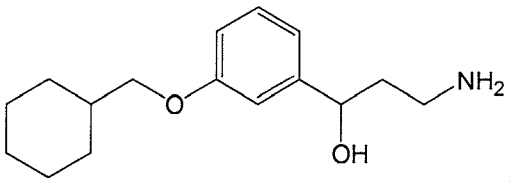
In a third aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering Compound (11):



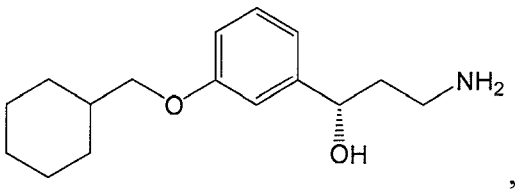
(11),

or a pharmaceutically acceptable salt thereof.

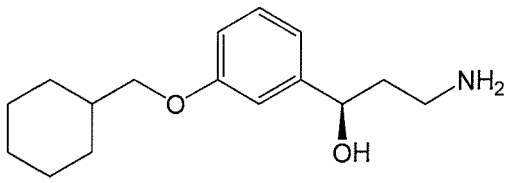
In one illustration of this aspect, the compound is:



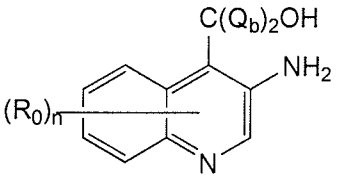
,



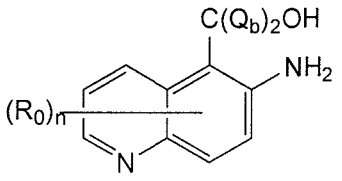
, or



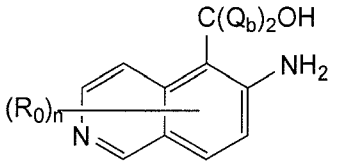
In a fourth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of any one of formulae (IIIa)-(IIIf):



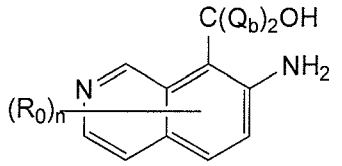
(IIIa),



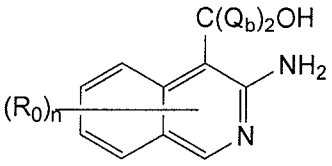
(IIIb),



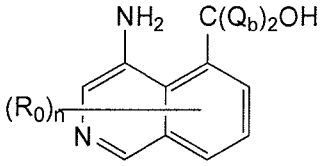
(IIIc),



(IIId),



(IIIe), or

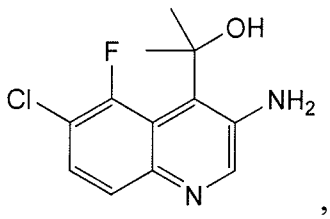


(IIIf),

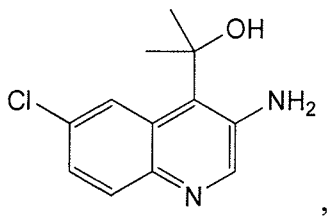
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IIIa)-(IIIf) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formulae (IIIa)-(IIIf) described herein.

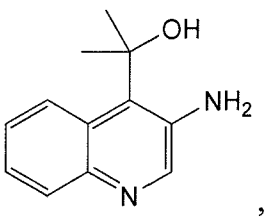
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound selected from Compounds (1)-(8):



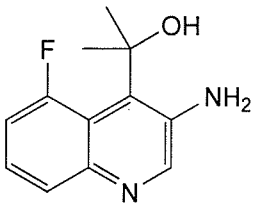
(1),

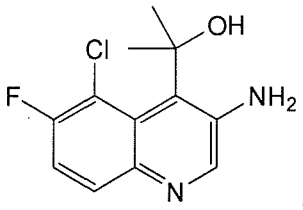


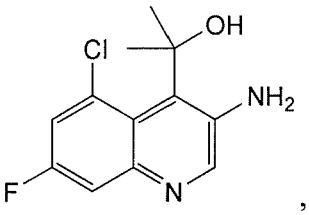
(2),

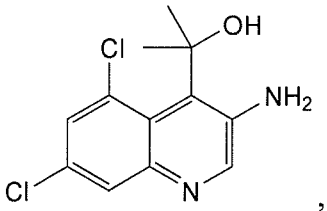


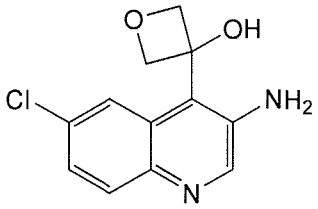
(3),


(4),


(5),

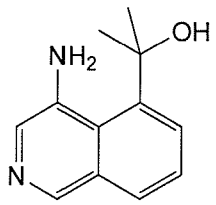

(6),


(7), and


(8).

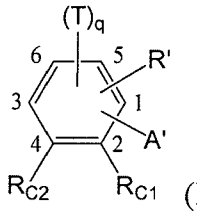
or a pharmaceutically acceptable salt thereof. Preferably, the compound is Compound (1) or (2).

In another specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering Compound (10):


(10),

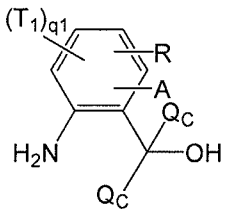
or a pharmaceutically acceptable salt thereof.

In a fifth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of formula (IV):

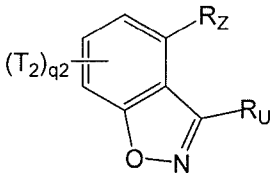

(IV),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (IV) is described in detail below.

In one class of this aspect, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of formula (IVa) or formula (IVb):



(IVa), or

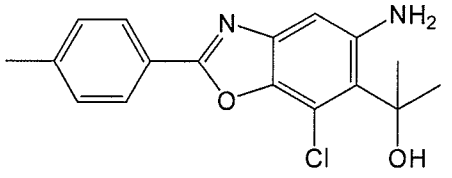


(IVb),

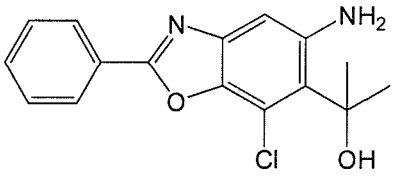
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IVa) and (IVb) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formula (IV), (IVa), and (IVb) described herein.

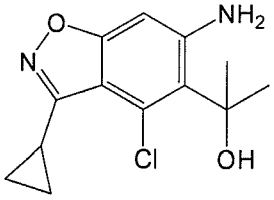
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the skin disorders or conditions or cosmetic indications described herein, comprising administering a compound selected from Compounds (12)-(18):



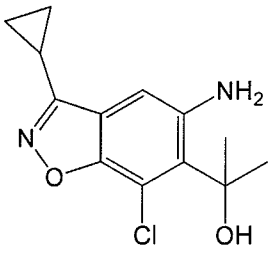
(12),



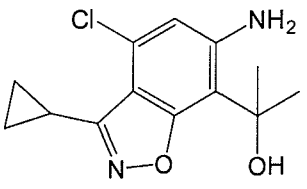
(13),



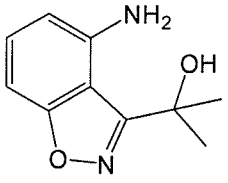
(14),



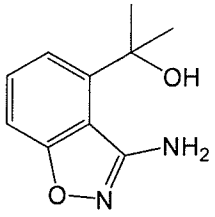
(15),



(16),



(17), and



(18),

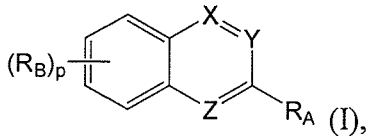
or a pharmaceutically acceptable salt thereof.

In a third embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of a condition associated with the toxic effects of blister agents or burns from alkali agents in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein.

Blister agents include, but are not limited to, sulfur mustard, nitrogen mustard, and phosgene oxime. Toxic or injurious effects of blister agents include pain, irritation, and/or tearing in the skin, eye, and/or mucous, and conjunctivitis and/or corneal damage to the eye. Sulfur mustard is the compound bis(2-chlorethyl) sulfide. Nitrogen mustard includes the compounds bis(2-chlorethyl)ethylamine, bis(2-chlorethyl)methylamine, and tris(2-chlorethyl)amine. Sulfur mustard or its analogs can cause an increase in oxidative stress and in particular in HNE levels, and by depleting the antioxidant defense system and thereby increasing lipid peroxidation, may induce an oxidative stress response and thus increase aldehyde levels (Jafari *et al.* (2010); Pal *et al.* (2009)). Antioxidants, such as Silibinin, when applied topically, attenuate skin injury induced from exposure to sulfur mustard or its analogs, and increased activities of antioxidant enzymes may be a compensatory response to reactive oxygen species generated by the sulfur mustard (Jafari *et al.* (2010); Tewari-Singh *et al.* (2012)). Further, intervention to reduce free radical species was an effective treatment post exposure for phosgene induced lung injury (Sciuto *et al.* (2004)). Thus, compounds that reduce or eliminate aldehydes, such as compounds described herein, can be used to treat, prevent, and/or reduce a risk of a condition associated with the toxic effects of blister agents, such as sulfur mustard, nitrogen mustard, and phosgene oxime.

Alkali agents include, but are not limited to, lime, lye, ammonia, and drain cleaners. Compounds that reduce or eliminate aldehydes, such as compounds described herein, can be used to treat, prevent, and/or reduce a risk of a condition associated with burns from an alkali agent.

In a first aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of formula (I):

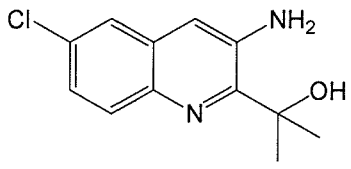


(I),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (I) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (I) described herein.

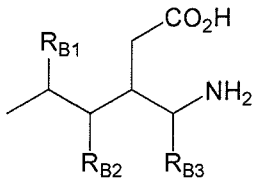
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering Compound (9):



(9),

or a pharmaceutically acceptable salt thereof.

In a second aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of formula (II):



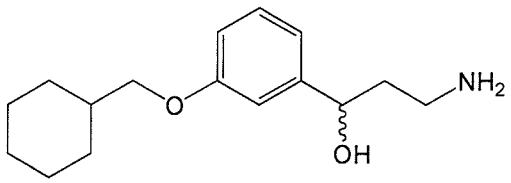
(II),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (II) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (II) described herein.

In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound selected from the compounds listed in Table 2. Preferably, the compound is (S)-3-(aminomethyl)-5-methylhexanoic acid or (R)-3-(aminomethyl)-5-methylhexanoic acid, or pharmaceutically acceptable salts or racemic mixtures thereof.

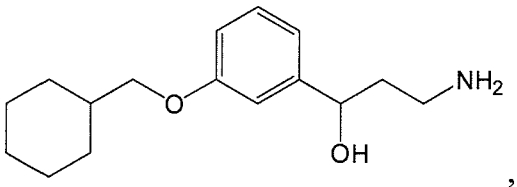
In a third aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering Compound (11):

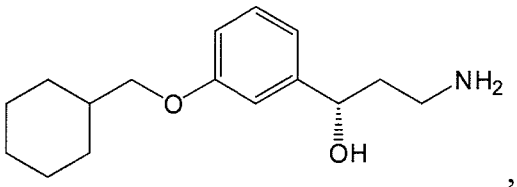


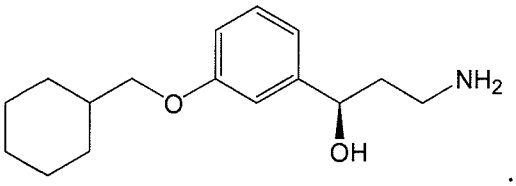
(11),

or a pharmaceutically acceptable salt thereof.

In one illustration of this aspect, the compound is:

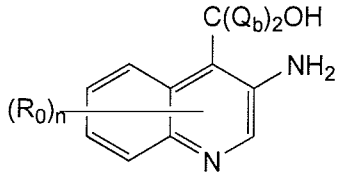


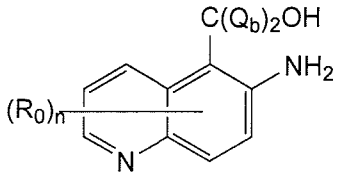
,


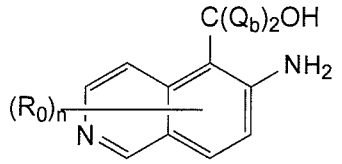
, or


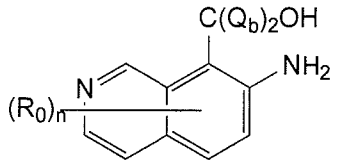
.

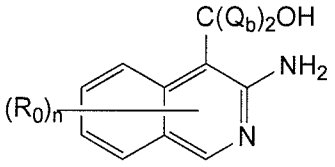
In a fourth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of any one of formulae (IIIa)-(IIIf):

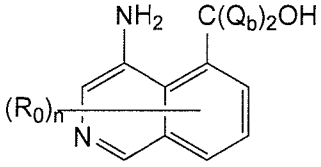


(IIIa),


(IIIb),


(IIIc),


(IIId),


(IIIe), or


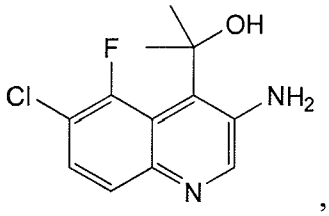
(IIIf),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IIIa)-(IIIf) is described in detail below.

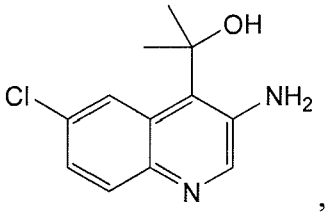
In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formulae (IIIa)-(IIIf) described herein.

In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or

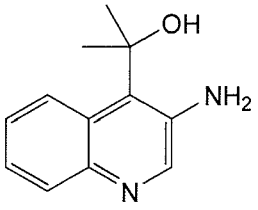
burns from alkali agents described herein, comprising administering a compound selected from Compounds (1)-(8):



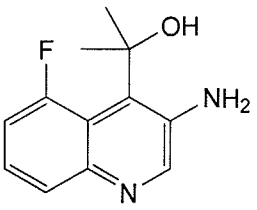
(1),



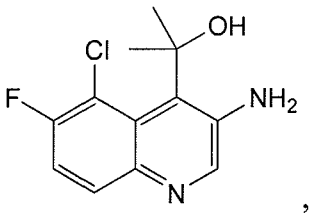
(2),



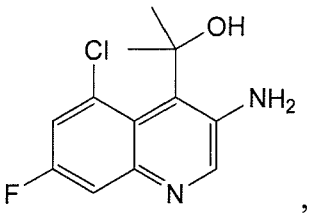
(3),



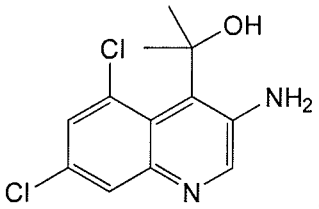
(4),



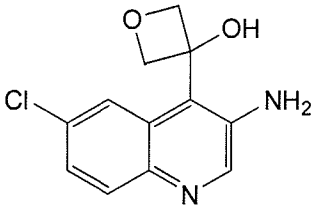
(5),



(6),



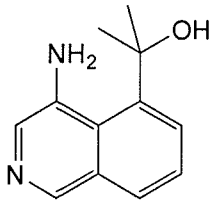
(7), and



(8).

or a pharmaceutically acceptable salt thereof. Preferably, the compound is Compound (1) or (2).

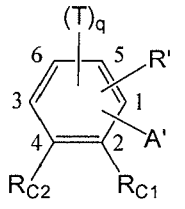
In another specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering Compound (10):



(10),

or a pharmaceutically acceptable salt thereof.

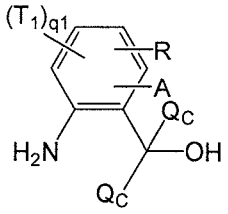
In a fifth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of formula (IV):



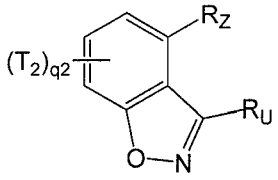
(IV),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (IV) is described in detail below.

In one class of this aspect, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of formula (IVa) or formula (IVb):



(IVa), or

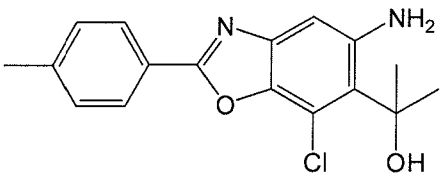


(IVb),

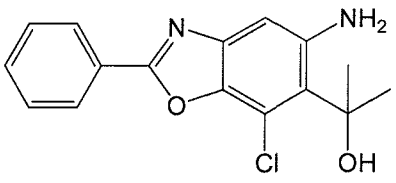
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IVa) and (IVb) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formula (IV), (IVa), and (IVb) described herein.

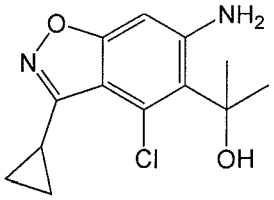
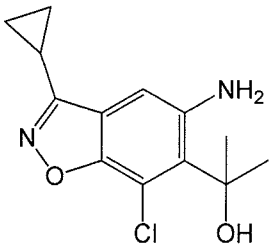
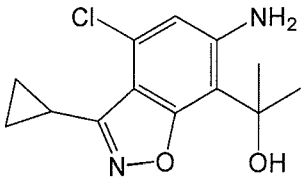
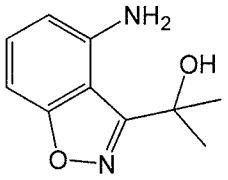
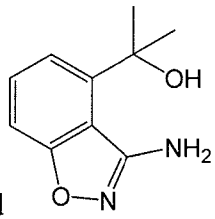
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of the condition associated with the toxic effects of blister agents or burns from alkali agents described herein, comprising administering a compound selected from Compounds (12)-(18):



(12),



(13),


(14),

(15),

(16),

(17), and

(18),

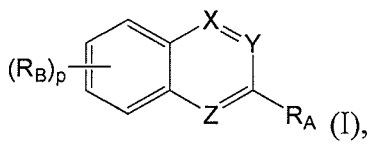
or a pharmaceutically acceptable salt thereof.

In a fourth embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease, disorder, or condition, or metabolic syndrome, or diabetes, in which aldehyde toxicity is implicated in the pathogenesis, comprising administering to a subject in need thereof a compound described herein. The autoimmune or immune-mediated disease, disorder, or condition includes, but is not limited to, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis. The inflammatory disease, disorder, or condition includes, but is not limited to, rheumatoid arthritis, inflammatory bowel disease (*e.g.*, Crohn's disease and ulcerative colitis), sepsis, and fibrosis (*e.g.*, renal, hepatic, pulmonary, and cardiac fibrosis). The cardiovascular disease, disorder, or condition includes, but is not limited to, atherosclerosis and ischemic-reperfusion injury. The neurological disease, disorder, or condition includes, but is not limited to, Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and the neurological aspects of Sjogren-Larsson Syndrome (cognitive delay and spasticity).

A skilled person would understand that the disease, disorder, or condition listed herein may involve more than one pathological mechanisms. For example, a disease, disorder, or condition listed herein may involve dysregulation in the immunological response and inflammatory response. Thus, the above categorization of a disease, disorder, or condition is not absolute, and the disease, disorder, or condition may be considered an immunological, an inflammatory, a cardiovascular, a neurological, and/or metabolic disease, disorder, or condition.

Individuals with deficiencies in aldehyde dehydrogenase are found to have high aldehyde levels and increased risk of Parkinson's disease (PNAS 110:636 (2013)) and Alzheimer's disease (BioChem Biophys Res Commun. 273:192 (2000)). In Parkinson's disease, aldehydes specifically interfere with dopamine physiology (Free Radic Biol Med, 51: 1302 (2011); Mol Aspects Med, 24: 293 (2003); Brain Res, 1145: 150 (2007)). In addition, aldehydes levels are elevated in multiple sclerosis, amyotrophic lateral sclerosis, autoimmune diseases such as lupus, rheumatoid arthritis, lupus, psoriasis, scleroderma, and fibrotic diseases, and increased levels of HNE and MDA are implicated in the progression of atherosclerosis and diabetes (J. Cell. Mol. Med., 15: 1339 (2011); Arthritis Rheum 62: 2064 (2010); Clin Exp Immunol, 101: 233 (1995); Int J Rheum Dis, 14: 325 (2011); JEADV 26: 833 (2012); Clin Rheumatol 25: 320 (2006); Gut 54: 987 (2005); J Am Soc Nephrol 20: 2119 (2009)). MDA is further implicated in the increased formation of foam cells leading to atherosclerosis (Leibundgut *et al.*, Current Opinion in Pharmacology 13: 168 (2013)). Also, aldehyde-related toxicity plays an important role in the pathogenesis of many inflammatory lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD) (Bartoli *et al.*, Mediators of Inflammation 2011, Article 891752). Thus, compounds that reduce or eliminate aldehydes, such as compounds described herein, can be used to treat, prevent, and/or reduce a risk of an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease, disorder, or condition, or metabolic syndrome, or diabetes. For example, compounds described herein, such as Compound 9, prevent aldehyde-mediated cell death in neurons. Further, compounds described herein, such as Compound 9, downregulate a broad spectrum of pro-inflammatory cytokines and/or upregulate anti-inflammatory cytokines, which indicates that compounds described herein are useful in treating inflammatory diseases, such as multiple sclerosis and amyotrophic lateral sclerosis.

In a first aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of formula (I):

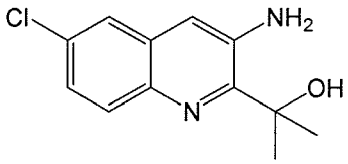


(I),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (I) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (I) described herein.

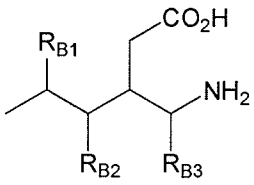
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering Compound (9):



(9),

or a pharmaceutically acceptable salt thereof.

In a second aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of formula (II):



(II),

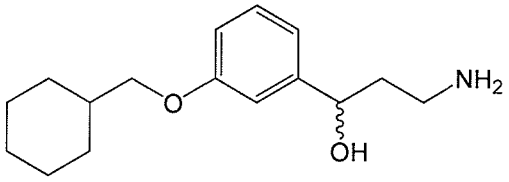
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (II) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of formula (II) described herein.

In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory,

cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound selected from the compounds listed in Table 2. Preferably, the compound is (S)-3-(aminomethyl)-5-methylhexanoic acid or (R)-3-(aminomethyl)-5-methylhexanoic acid, or pharmaceutically acceptable salts or racemic mixtures thereof.

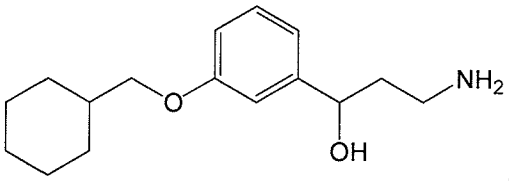
In a third aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering Compound (11):



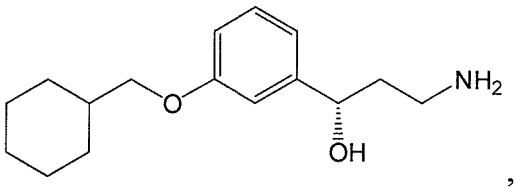
(11),

or a pharmaceutically acceptable salt thereof.

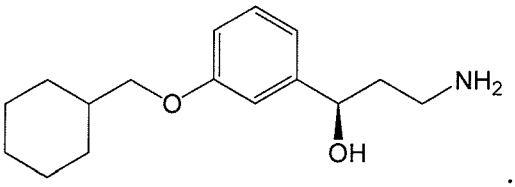
In one illustration of this aspect, the compound is:



,

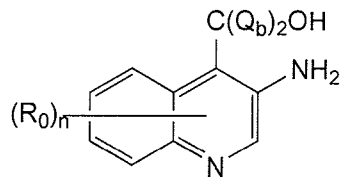


, or

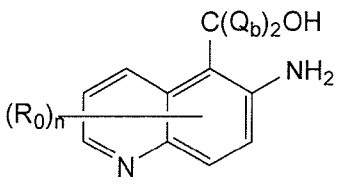


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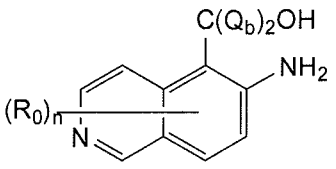
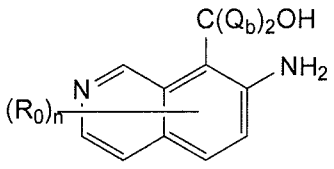
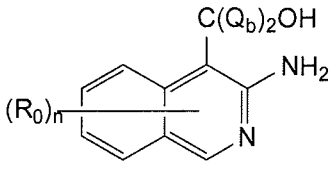
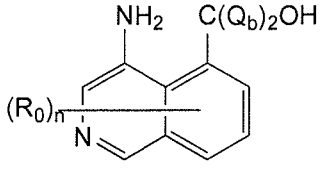
In a fourth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of any one of formulae (IIIa)-(IIIf):



(IIIa),



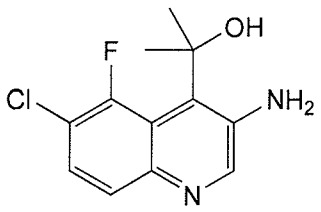
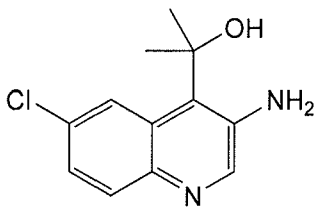
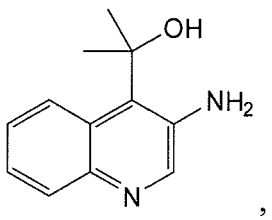
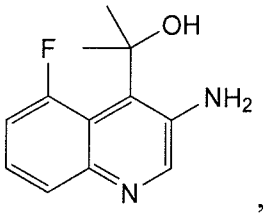
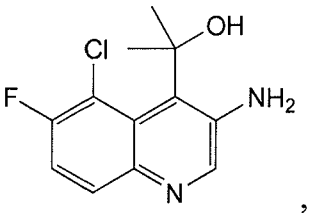
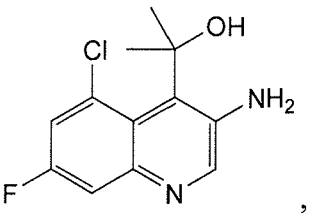
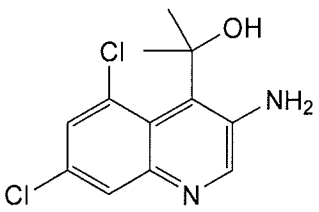
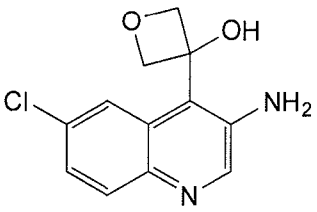
(IIIb),


(IIIc),

(IIId),

(IIIe), or

(IIIf),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IIIa)-(IIIf) is described in detail below.

In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formulae (IIIa)-(IIIf) described herein.

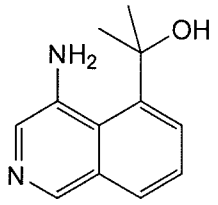
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound selected from Compounds (1)-(8):


(1),

(2),

(3),

(4),

(5),

(6),

, and


(7) (8).

or a pharmaceutically acceptable salt thereof. Preferably, the compound is Compound (1) or (2).

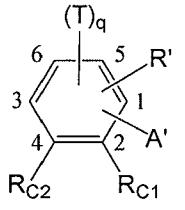
In another specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering Compound (10):



(10),

or a pharmaceutically acceptable salt thereof.

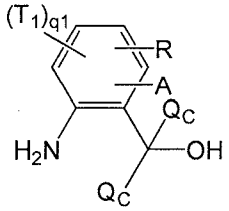
In a fifth aspect of this embodiment, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of formula (IV):



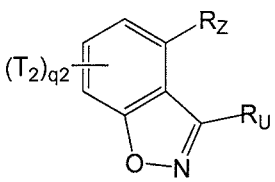
(IV),

or a pharmaceutically acceptable salt thereof, wherein each of the variables in formula (IV) is described in detail below.

In one class of this aspect, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of formula (IVa) or formula (IVb):



(IVa), or

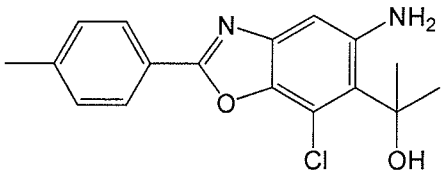


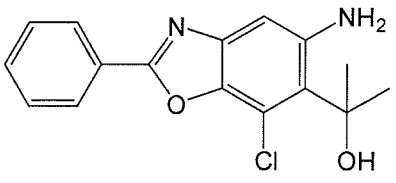
(IVb),

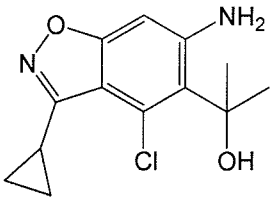
or a pharmaceutically acceptable salt thereof, wherein each of the variables in formulae (IVa) and (IVb) is described in detail below.

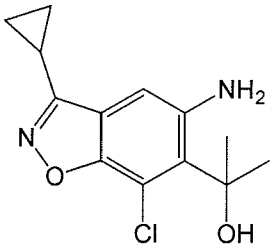
In one exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound of each of the various illustrations and/or examples of the compounds of each of formula (IV), (IVa), and (IVb) described herein.

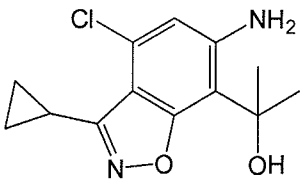
In one specific exemplification, the invention relates to the treatment, prevention, and/or reduction of a risk of each of the autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological diseases, disorders, or conditions, or metabolic syndromes, or diabetes described herein, comprising administering a compound selected from Compounds (12)-(18):

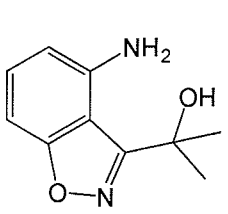

(12),

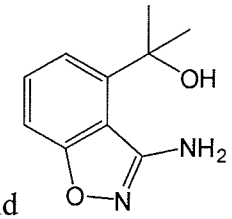

(13),


(14),


(15),


(16),


(17), and


(18),

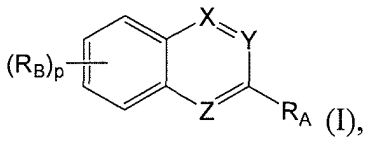
or a pharmaceutically acceptable salt thereof.

Compounds useful in the invention

Compounds that can be used in the invention are compounds that contain one or more primary amine groups and react with aldehydes (*e.g.*, MDA and HNE) to form a complex, for example, through a Schiff base condensation mechanism. Preferably, the aldehyde complex so formed has a closed-ring structure, thus preventing the aldehyde from being released from the complex and back into the cellular milieu, where the aldehyde can react with various cellular targets, such as a protein, lipid, carbohydrate, and DNA, and interfere with numerous normal physiological processes, thus resulting in diseases, disorders, and other undesirable conditions. Thus, compounds that can be used in the invention are compounds which react with and thus decrease or eliminate aldehydes (*e.g.*, MDA and HNE). For example, the compounds decrease the amount or concentration of aldehydes by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%, as compared to the amount or concentration of aldehydes in the absence of the compounds.

In addition, compounds described in the invention may possess activities in addition to reacting with aldehydes. In one example, compounds described herein may affect the expression or amount of chemokines in the cells. In a further example, compounds described herein may downregulate a broad spectrum of pro-inflammatory cytokines, including but not limited to, IL-5 and IL-1β, IL-12, IL-17, and TNF. In another example, compounds described herein may upregulate anti-inflammatory cytokines, including but not limited to, IL-10. In another example, compounds described herein may downregulate other cytokines involved in inflammation, including but not limited to, eotaxin, IP-10, LIF, MCP-1, MIG, MIP, and RANTES. In another example, compounds described herein may prevent aldehyde-mediated death of various types of cells, such as neurons.

In one aspect, compounds that can be used in the invention include a compound of formula (I):



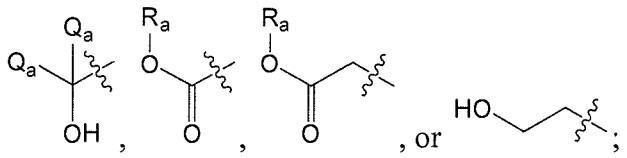
(I),

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently N, CH, or $C(NH_2)$, provided that one of X, Y, and Z is N;

p is 0, 1, 2, or 3;

each R_B is independently halogen, hydroxyl, carbamoyl, amino, or unsubstituted or substituted aryl;

R_A is , or ;

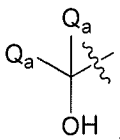
Q_a is C_1-C_6 straight chain alkyl; and

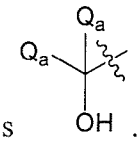
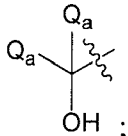
R_a is unsubstituted or substituted C_1-C_8 straight chain or C_3-C_8 branched alkyl.

In one illustration, R_a is C_1-C_8 straight chain or C_3-C_8 branched alkyl substituted with one or more substituents independently selected from alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, NH_2, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, acylamino, alkylcarbonylamino, arylcarbonylamino, carbamoyl, ureido, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, sulfamoyl, sulfonamido, trifluoromethyl, azido, heterocyclyl, alkylaryl, and an aromatic or heteroaromatic moiety.

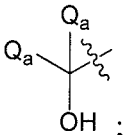
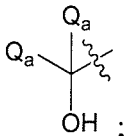
In one illustration, R_B is aryl substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, NH_2, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, acylamino, alkylcarbonylamino, arylcarbonylamino, carbamoyl, ureido, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, and an aromatic or heteroaromatic moiety.

In one illustration, the compounds of formula (I) are the compounds wherein X is CH; Z is N; Y is $C(NH_2)$.

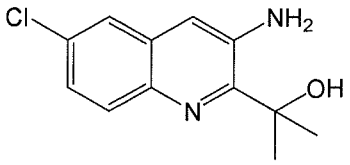
In another illustration, the compounds of formula (I) are the compounds wherein p is 1. In another illustration, the compounds of formula (I) are the compounds wherein R_A is . In a further illustration, the compounds of formula (I) are the compounds wherein

p is 1 and R_A is  . In yet a further illustration, the compounds of formula (I) are the compounds wherein p is 1; R_A is  ; and each Q_a is methyl.

In another illustration, the compounds of formula (I) are the compounds wherein R_B is halogen, hydroxyl, carbamoyl, amino, or aryl.

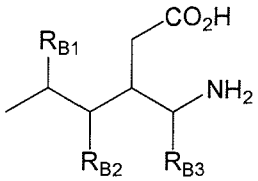
In another illustration, the compounds of formula (I) are the compounds wherein R_B is halogen. In a further illustration, the compounds of formula (I) are the compounds wherein p is 1; R_A is  ; and R_B is halogen. In yet a further illustration, the compounds of formula (I) are the compounds wherein p is 1; R_A is  ; each Q_a is methyl; and R_B is halogen. In one exemplification, R_B is Cl.

In one exemplification, a compound of formula (I) is Compound (9):



(9).

In a second aspect, compounds that can be used in the invention include a compound of formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R_{B1} is unsubstituted or substituted C_1-C_8 straight chain or C_3-C_8 branched alkyl, C_2-C_8 straight chain or C_3-C_8 branched alkenyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_1-C_6 alkyl-C_3-C_7 cycloalkyl, hydroxyl, C_1-C_6 alkylphenoxy, phenyl, or substituted phenyl;

R_{B2} is H, unsubstituted or substituted C_1-C_6 straight chain or C_3-C_6 branched alkyl, phenyl, or substituted phenyl; and

R_{B3} is H, unsubstituted or substituted C_1-C_6 straight chain or branched C_3-C_6 alkyl, or carboxyl.

In one illustration, the compounds of formula (II) are the compounds wherein R_{B3} is H.

In one illustration, the compounds of formula (II) are the compounds wherein R_{B2} is H. In another illustration, the compounds of formula (II) are the compounds wherein R_{B2} is unsubstituted C_1-C_6 straight chain alkyl. In a further illustration, the compounds of formula (II) are the compounds wherein R_{B2} is unsubstituted methyl. In another illustration, the compounds of formula (II) are the compounds wherein R_{B2} is unsubstituted C_3-C_6 branched alkyl. In another illustration, the compounds of formula (II) are the compounds wherein R_{B2} is unsubstituted phenyl.

In one illustration, the compounds of formula (II) are the compounds wherein R_{B1} is unsubstituted C_1-C_8 straight chain or C_3-C_8 branched alkyl, or C_1-C_8 straight chain or C_3-C_8 branched alkyl substituted with one or more substituents independently selected from

hydroxyl, F, Cl,

unsubstituted C_1-C_6 alkoxy, C_1-C_6 alkoxy substituted with halogen or phenyl,

unsubstituted phenyl, phenyl substituted with one or more substituents independently selected from F, Cl, and unsubstituted C_1-C_6 alkoxy,

unsubstituted phenoxy, and phenoxy substituted with one or more substituents independently selected from F, Cl, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with F or Cl, unsubstituted C_1-C_6 alkoxy, and nitro.

In another illustration, the compounds of formula (II) are the compounds wherein R_{B1} is unsubstituted C_1-C_6 alkoxy, or C_1-C_6 alkoxy substituted with F or Cl.

In another illustration, the compounds of formula (II) are the compounds wherein R_{B1} is unsubstituted phenyl, or phenyl substituted with one or more substituents independently selected from F, Cl, unsubstituted C_1-C_6 alkoxy, and nitro.

In another illustration, the compounds of formula (II) are the compounds wherein R_{B1} is unsubstituted phenoxy, or phenoxy substituted with one or more substituents independently selected from F, Cl, unsubstituted C_1-C_6 alkoxy, and nitro.

In another illustration, the compounds of formula (II) are the compounds wherein R_{B1} is unsubstituted C_3-C_6 cycloalkyl.

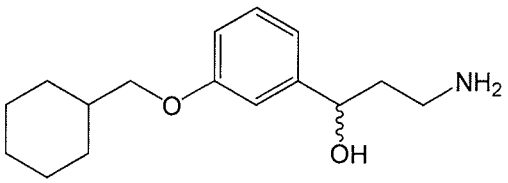
In another illustration, the compounds of formula (II) are the compounds wherein R_{B1} is unsubstituted C_2-C_8 straight chain alkenyl.

In a further illustration, the compounds of formula (II) are the compounds wherein R_{B3} is H; R_{B2} is H; and R_{B1} is one of the substituents described above.

In a further illustration, the compounds of formula (II) are the compounds wherein R_{B3} is H; R_{B2} is unsubstituted C_1-C_6 straight chain alkyl or unsubstituted phenyl; and R_{B1} is unsubstituted methyl.

Specific examples of the compounds of formula (II) include the compounds in Table 2. Yet further the compounds of formula (II) are (S)-3-(aminomethyl)-5-methylhexanoic acid and (R)-3-(aminomethyl)-5-methylhexanoic acid, or pharmaceutically acceptable salts or racemic mixtures thereof.

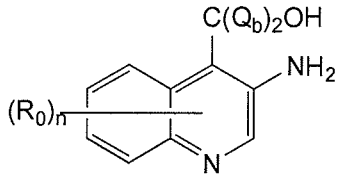
In a third aspect, compounds that can be used in the invention include Compound (11):



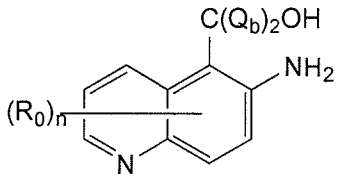
(11),

or a pharmaceutically acceptable salt thereof.

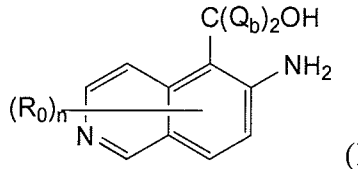
In a fourth aspect, compounds that can be used in the invention include a compound of one of formulae (IIIa)-(IIIf):



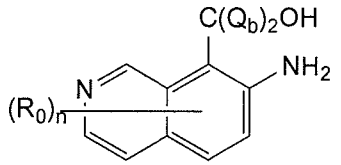
(IIIa),



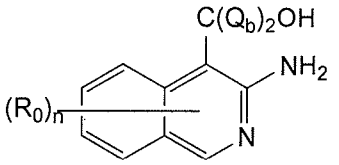
(IIIb),



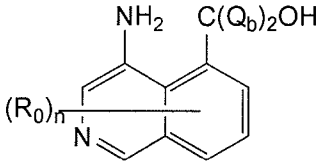
(IIIc),



(IIId),



(IIIe), and

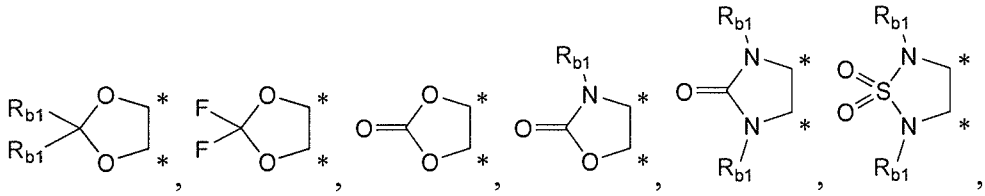


(IIIf),

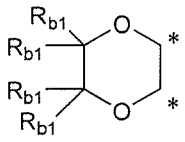
or a pharmaceutically acceptable salt thereof, wherein:

each R_0 is independently halogen, CF_2H, CF_3, R_{b2}, OR_{b1}, $COOR_{b1}$, $CON(R_{b1})_2$, $N(R_{b2})_2$, $NR_{b1}COR_{b1}$, $NR_{b1}COOR_{b2}$, $NR_{b1}CON(R_{b1})_2$, $NR_{b1}SO_2R_{b2}$, SO_2R_{b2}, $SO_2N(R_{b1})_2$,

unsubstituted phenyl, or phenyl substituted with 1-3 substituents independently selected from F, Cl, CF_2H, CF_3, OR_{b1}, and R_{b2}, or two such substituents, together with the carbon atoms of the phenyl rings to which they are attached, form a five-or six-membered ring having a structure selected from

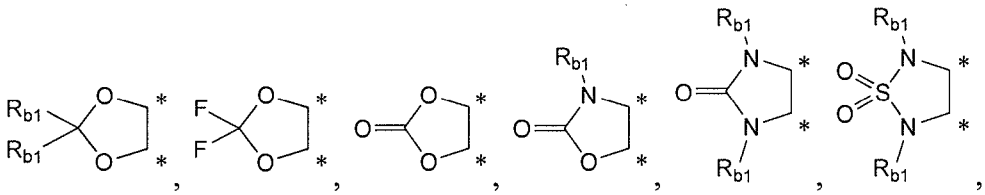


, and

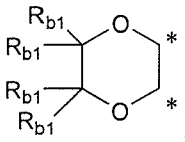


, wherein "*" denotes the positions of the carbon atoms to which the substituents are attached on the phenyl ring, or

alternatively, when attached to adjacent atoms, any two R_0, together with the atoms to which they are attached, form a five- or six-membered ring having a structure selected from



, and



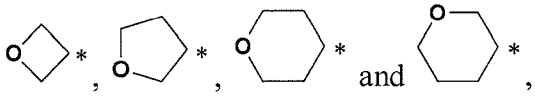
, wherein "*" denotes the positions of the atoms to which the two R_0 are attached, or

each R_{b1} is independently H, C_1-C_6 straight chain or C_3-C_6 branched alkyl, or C_3-C_6 cycloalkyl;

each R_{b2} is independently C_1-C_6 straight chain or C_3-C_6 branched alkyl, or C_3-C_6 cycloalkyl;

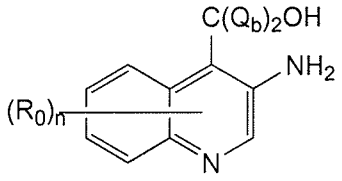
each R_{b3} is independently H, C_1-C_6 straight chain or C_3-C_6 branched alkyl, or halogen;

each Q_b is independently H, C_1-C_6 straight chain or C_3-C_6 branched alkyl, or C_1-C_6 straight chain or C_3-C_6 branched alkyl substituted with 1-6 F, or

both Q_b, together with the carbon atom to which they are attached, form a C_3-C_6 carbocycle or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which both Q_b are attached, wherein the carbocycle or the heterocycle is optionally substituted with one or more R_{b3}; and

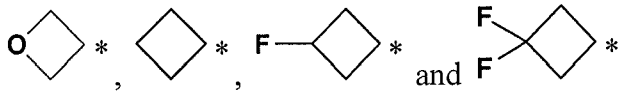
n is 0,1, 2, or 3.

One class of this aspect are the compounds of formula (IIIa):

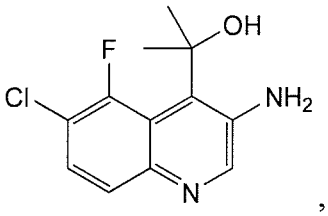


(IIIa),

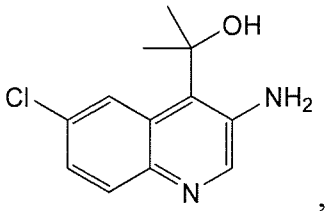
or a pharmaceutically acceptable salt thereof.

Further illustrating this exemplification are the compounds of formula (IIIa), wherein n is 0, 1 or 2. Yet a further illustration includes the compounds of formula (IIIa) wherein R_0, which can be attached to either ring of formula (IIIa), is F or Cl. Further defining formula (IIIa) are the compounds wherein Q_b is selected from C_1-C_6 straight chain or C_3-C_6 branched alkyl, or wherein both Q_b, together with the carbon atom to which they are attached, form a ring selected from  and wherein "*" denotes the position of the carbon atom to which both Q_b are attached.

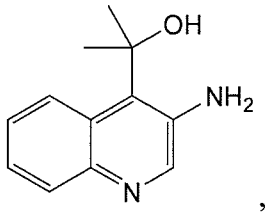
Specific examples of formula (IIIa) include Compounds (1)–(8) and pharmaceutically acceptable salts thereof:



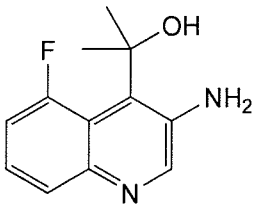
(1),



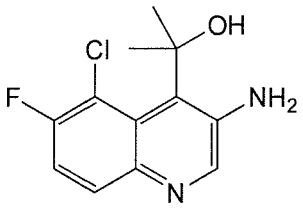
(2),



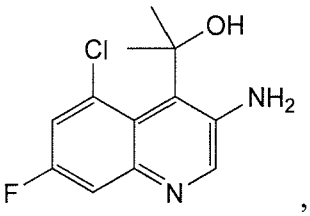
(3),



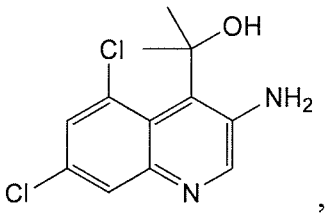
(4),



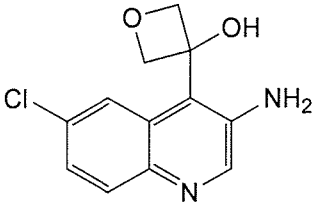
(5),



(6),



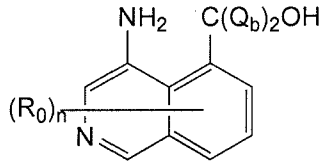
(7), and



(8).

Preferably, the compound is Compound (1) or (2).

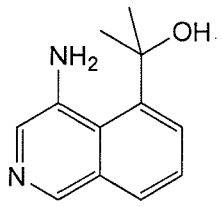
Another class of this aspect are the compounds of formula (IIIf):



(IIIf),

or a pharmaceutically acceptable salt thereof.

Specific examples of formula (IIIf) include Compound (10) and pharmaceutically acceptable salts thereof:



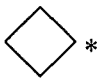
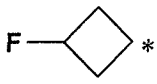
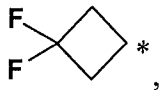
(10).

Examples of the compounds of this aspect include a compound of any one of formulae (IIIa)-(IIIf), wherein n is 0, 1 or 2. For example, n is 1.

Examples of the compounds of this aspect include a compound of any one of formulae (IIIa)-(IIIf), wherein each R_0 is independently selected from F, Cl, Br, CF_2H, CF_3, R_{b2}, OR_{b1}, $COOR_{b1}$, $CON(R_{b1})_2$, $N(R_{b2})_2$, $NR_{b1}COR_{b1}$, $NR_{b1}COOR_{b2}$, $NR_{b1}CON(R_{b1})_2$, $NR_{b1}SO_2R_{b2}$, SO_2R_{b2}, $SO_2N(R_{b1})_2$, unsubstituted phenyl, and phenyl substituted with 1-3 substituents as listed above. For example, each R_0 is independently selected from F, Cl, Br, CF_2H, CF_3 and R_{b2}. For example, each R_0 is independently selected from F, Cl and Br. For example, n is 0, 1 or 2 and each R_0 is independently selected from F, Cl, Br, CF_2H, CF_3, R_{b2}, OR_{b1}, $COOR_{b1}$, $CON(R_{b1})_2$, $N(R_{b2})_2$, $NR_{b1}COR_{b1}$, $NR_{b1}COOR_{b2}$, $NR_{b1}CON(R_{b1})_2$, $NR_{b1}SO_2R_{b2}$, SO_2R_{b2}, $SO_2N(R_{b1})_2$, unsubstituted phenyl, and phenyl substituted with 1-3 substituents as listed above. For example, n is 0, 1 or 2 and each R_0 is independently selected from F, Cl, Br, CF_2H, CF_3 and R_{b2}. For example, n is 0, 1 or 2 and each R_0 is independently selected from F, Cl and Br.

Examples of the compounds of this aspect include a compound of any one of formulae (IIIa)-(IIIf), wherein at least one Q_b is C_1-C_6 straight chain alkyl. For example, in certain compounds, at least one Q_b is methyl, ethyl or propyl. For example, each Q_b is methyl. For example, n is 0, 1 or 2 and at least one Q_b is C_1-C_6 straight chain alkyl (*e.g.*, methyl, ethyl and propyl). For example, n is 0, 1 or 2 and each Q_b is methyl. In another example, at least one Q_b is C_1-C_6 straight chain alkyl substituted with 1-6 F. For example, in certain compounds, at least one Q_b is methyl, ethyl or propyl substituted with 1-6 F. For example, at least one Q_b is CH_2F, CHF_2, or CF_3. For example, each Q_b is CF_3. For example, n is 0, 1 or 2 and at least one Q_b is C_1-C_6 straight chain alkyl substituted with 1-6 F (*e.g.*,

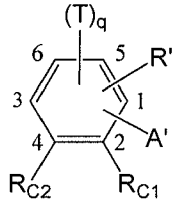
methyl, ethyl or propyl substituted with 1-6 F). For example, n is 0, 1 or 2 and each Q_b is CF_3.

Examples of the compounds of this aspect include a compound of any one of formula (IIIa)-(IIIf), wherein both Q_b, together with the carbon atom to which they are attached, form a C_3-C_6 carbocycle or a saturated heterocycle, each of which is optionally substituted with one or more R_{b3}, wherein each R_{b3} is independently methyl, ethyl, propyl, fluorine, chlorine or bromine (*e.g.*, each R_{b3} is independently methyl or fluorine). For example, both Q_b, together with the carbon atom to which they are attached, form , ,  or , wherein "*" denotes the position of the carbon atom to which the two Q_b are attached.

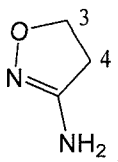
Examples of the compounds of this aspect include a compound of any one of formula (IIIa)-(IIIf), wherein each R_{b1} is independently H or C_1-C_6 straight chain alkyl. For example, each R_{b1} is independently H, methyl, ethyl or propyl.

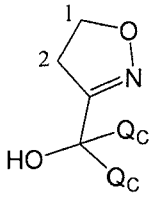
Examples of the compounds of this aspect include a compound of any one of formula (IIIa)-(IIIf), wherein each R_{b2} is independently methyl, ethyl or propyl.

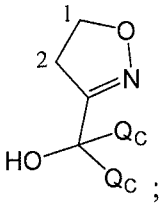
In a fifth aspect, compounds that can be used in the invention include a compound of formula (IV):

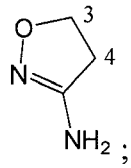
 (IV),

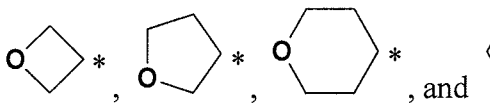
or a pharmaceutically acceptable salt thereof, wherein:

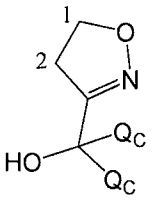
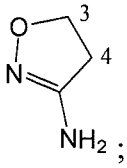
A' and R', together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with R_C', wherein "1", "2", "3", "4", "5", and "6" denote the points of attachment of the heteroaryl ring to the phenyl ring, provided that when the heteroaryl ring is , then R_{C1} is $C(Q_C)_2OH$, R_{C2} is absent, and R_C' is absent, and

that when the heteroaryl ring is , then R_{C1} is absent, R_{C2} is NH_2, and R_C' is absent;

R_{C1} is $C(Q_C)_2OH$, or R_{C1} is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form ;

R_{C2} is NH_2, or R_{C2} is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form ;

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached;

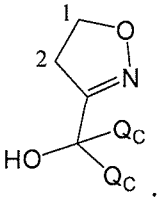
R_C' is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_1-C_6 alkyl, or C_1-C_6 alkoxy, or R_C' is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form  or ;

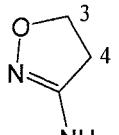
q is 0, 1, or 2, provided that when R_C' is phenyl, q is not 0; and

each T is independently halogen, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano.

In one example, A' and R', together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with R_C'. In one example, R_C' is C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl), aryl (*e.g.*, phenyl), or aryl (*e.g.*, phenyl) substituted with C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, R_C' is phenyl, phenyl substituted with methyl, cyclopropyl, or cyclobutyl. In another example, R_C' is C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, R_C' is C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, and propoxy).

In one example, R_{C1} is $C(Q_C)_2OH$ and R_{C2} is NH_2. In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

In one example, A' and R', together with the two adjacent carbon atoms to which they are attached, form 

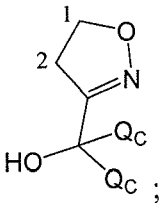
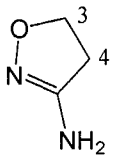
. In another example, A' and R', together with the two adjacent carbon atoms to which they are attached, form 

. In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

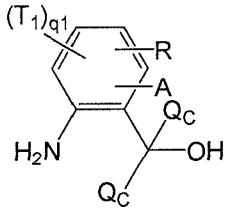
In one example, q is 1 or 2. In a further example, q is 1.

In one example, each T is independently halogen (*e.g.*, F, Cl, and Br). In a further example, each T is independently F or Cl. In another example, each T is independently C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, each T is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

In one example, A' and R', together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with R_C'; R_C' is aryl, aryl substituted with methyl, or cyclopropyl; q is 1; T is Cl; R_{C1} is $C(Q_C)_2OH$; R_{C2} is NH_2; and each Q_C is methyl.

In a further example of formula (IV), A' and R', together with the two adjacent carbon atoms to which they are attached, form ; R_{C2} is NH_2; each Q_C is methyl; and q is 0. In another further example of formula (IV), A' and R', together with the two adjacent carbon atoms to which they are attached, form ; R_{C1} is $C(Q_C)_2OH$; each Q_C is methyl; and q is 0.

In one class of this aspect, the compounds of formula (IV) are the compounds of formula (IVa):


(IVa),

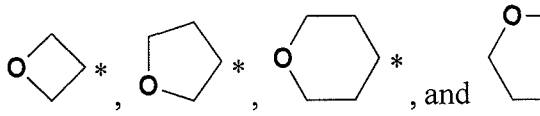
or a pharmaceutically acceptable salt thereof, wherein:

A and R, together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with R_C;

R_C is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_1-C_6 alkyl, or C_1-C_6 alkoxy;

q_1 is 1 or 2;

each T_1 is independently halogen, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached.

In one example, R_C is C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl), aryl (*e.g.*, phenyl), or aryl (*e.g.*, phenyl) substituted with C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and

butyl). In a further example, R_C is phenyl, phenyl substituted with methyl, cyclopropyl, or cyclobutyl. In yet another example, R_C is C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, R_C is C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, and propoxy).

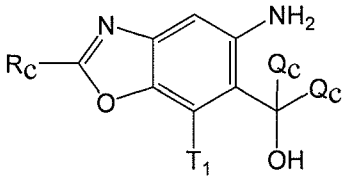
In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

In one example, q_1 is 1.

In one example, each T_1 is independently halogen (*e.g.*, F, Cl, and Br). In a further example, each T_1 is independently F or Cl. In another example, each T_1 is independently C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, each T_1 is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

In a further example of formula (IVa), R_C is aryl, aryl substituted with methyl, or cyclopropyl; q_1 is 1; T_1 is Cl; and each Q_C is methyl.

One illustration of this class are the compounds of formula (IVa1):

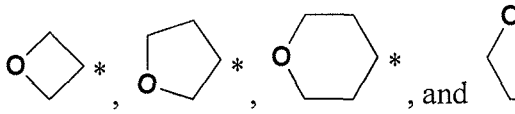


(IVa1),

or a pharmaceutically acceptable salt thereof, wherein:

R_C is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_2-C_6 alkyl, or C_1-C_6 alkoxy;

T_1 is F, Cl, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached.

In one example, R_C is C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl), aryl (*e.g.*, phenyl), or aryl (*e.g.*, phenyl) substituted with C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further embodiment, R_C is phenyl, phenyl substituted with methyl, cyclopropyl,

or cyclobutyl. In a further embodiment, R_C is phenyl or phenyl substituted with methyl. In another example, R_C is C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, R_C is C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, and propoxy).

In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

In one example, T_1 is Cl. In another example, T_1 is C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, T_1 is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

In a further example of formula (IVa1), R_C is aryl or aryl substituted with methyl; T_1 is Cl; and each Q_C is methyl.

Further defining the compounds of formula (IVa1) are the compounds wherein:

R_C is C_3-C_6 cycloalkyl, aryl, or aryl substituted with C_1-C_6 alkyl;

T_1 is F, Cl, methyl, cyclopropyl, cyclobutyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl,

or a pharmaceutically acceptable salt thereof.

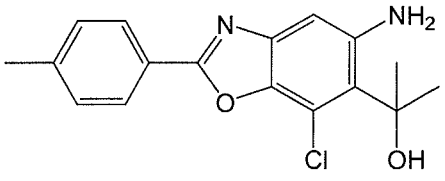
In one subclass are the compounds wherein:

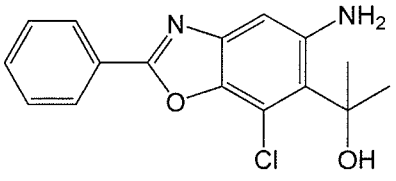
T_1 is F, Cl, methyl, or cyano; and

Q_C is methyl,

or a pharmaceutically acceptable salt thereof.

Further illustrating the compounds of formula (IVa1) are compounds 12 and 13:

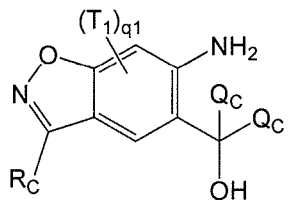


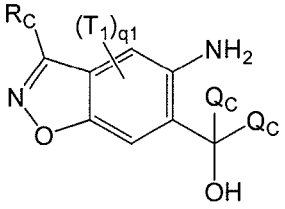
(12) and


(13),

or a pharmaceutically acceptable salt thereof.

Another illustration of this class are the compounds of formula (IVa2) or (IVa3):



(IVa2) or


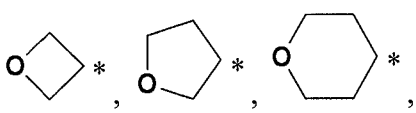
(IVa3),

or a pharmaceutically acceptable salt thereof, wherein:

R_C is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_1-C_6 alkyl, or C_1-C_6 alkoxy;

q_1 is 1 or 2;

each T_1 is independently F, Cl, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached.

In one example, R_C is C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl), aryl (*e.g.*, phenyl), or aryl (*e.g.*, phenyl) substituted with C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further embodiment, R_C is phenyl, phenyl substituted with methyl, cyclopropyl, or cyclobutyl. In a further example, R_C is cyclopropyl or cyclobutyl. In another example, R_C is C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, R_C is C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, and propoxy).

In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

In one example, q_1 is 1.

In one example, each T_1 is Cl. In another example, each T_1 is independently C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, each T_1 is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

In a further example of formula (IVa2) or (IVa3), R_C is cyclopropyl; q_1 is 1; T_1 is Cl; and each Q_C is methyl.

Further defining the compounds of formulae (IVa2) and (IVa3) are the compounds wherein:

R_C is C_3-C_6 cycloalkyl, aryl, or aryl substituted with C_1-C_6 alkyl;

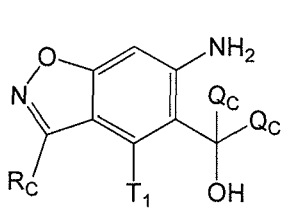
q_1 is 1;

T_1 is F, Cl, methyl, cyclopropyl, cyclobutyl, or cyano; and

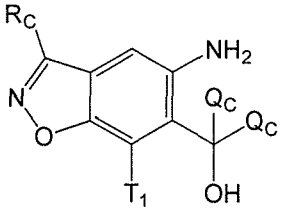
each Q_C is independently C_1-C_6 alkyl or C_1-C_6 cycloalkyl,

or a pharmaceutically acceptable salt thereof.

Further illustrating the compounds of formula (IVa2) or (IVa3) are the compounds of formula (IVa2A) or (IVa3A):



(IVa2A) or



(IVa3A),

or a pharmaceutically acceptable salt thereof, wherein R_C, T_1, and Q_C are defined above in formula (IVa2) or (IVa3).

Further defining the compounds of formula (IVa2A) or (IVa3A) are the compounds wherein:

R_C is C_3-C_6 cycloalkyl, aryl, or aryl substituted with C_1-C_6 alkyl;

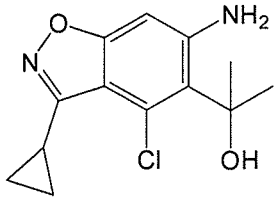
T_1 is F, Cl, methyl, cyclobutyl, cyclopropyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_1-C_6 cycloalkyl,

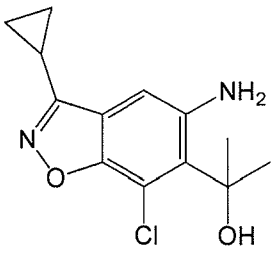
or a pharmaceutically acceptable salt thereof.

For example, R_C is cyclopropyl or cyclobutyl; T_1 is F or Cl; and each Q_C is independently C_1-C_6 alkyl.

Further illustrating the compounds of formula (IVa2) or (IVa3) are compounds 14 and 15:



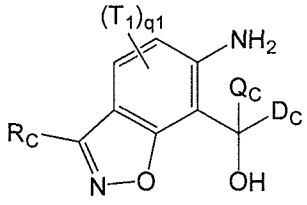
(14) and



(15),

or a pharmaceutically acceptable salt thereof.

A third illustration of this class are the compounds of formula (IVa4):



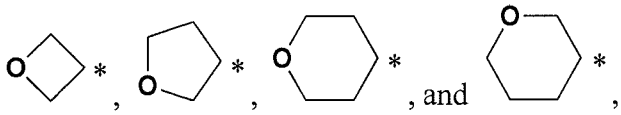
(IVa4),

or a pharmaceutically acceptable salt thereof, wherein:

R_C is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_1-C_6 alkyl, or C_1-C_6 alkoxy;

q_1 is 1 or 2;

each T_1 is independently F, Cl, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached.

In one example, R_C is C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl), aryl (*e.g.*, phenyl), or aryl (*e.g.*, phenyl) substituted with C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further embodiment, R_C is phenyl, phenyl substituted with methyl, cyclopropyl, or cyclobutyl. In a further embodiment, R_C is cyclopropyl or cyclobutyl. In another example, R_C is C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, R_C is C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, and propoxy).

In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

In one example, q_1 is 1.

In one example, each T_1 is Cl. In another example, each T_1 is independently C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, each T_1 is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

In a further example of formula (IVa4), R_C is cyclopropyl; q_1 is 1; T_1 is Cl; and each Q_C is methyl.

Further defining the compounds of formula (IVa4) are the compounds wherein:

R_C is C_3-C_6 cycloalkyl, aryl, or aryl substituted with C_1-C_6 alkyl;

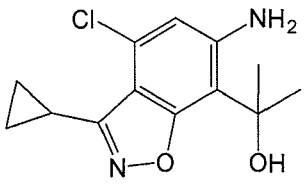
q_1 is 1;

T_1 is F, Cl, methyl, cyclopropyl, cyclobutyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_1-C_6 cycloalkyl,

or a pharmaceutically acceptable salt thereof.

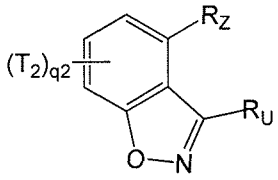
Further illustrating this class is compound 16:



(16),

or a pharmaceutically acceptable salt thereof.

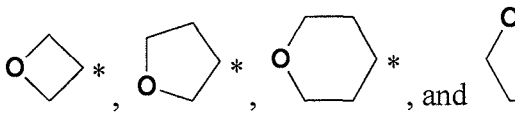
In a second class of this aspect, the compounds of formula (IV) are the compounds of formula (IVb):



(IVb),

or a pharmaceutically acceptable salt thereof, wherein:

one of R_U and R_Z is $C(Q_C)_2OH$, and the other is NH_2;

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached;

q_2 is 0, 1, or 2; and

each T_2 is independently halogen, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano.

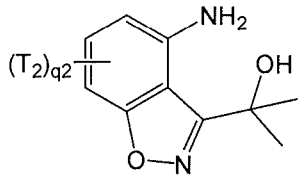
In one example, each Q_C is independently C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and butyl). In a further example, each Q_C is methyl.

In one example, q_2 is 0 or 1. In a further example, q_2 is 0.

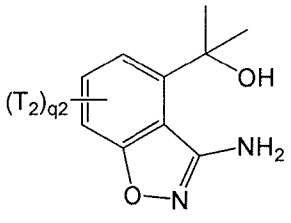
In one example, each T_2 is independently halogen (*e.g.*, F, Cl, and Br). In a further example, each T_2 is independently F or Cl. In another example, each T_2 is independently C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, each T_2 is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

In a further example of formula (IVb), q_2 is 0; and each Q_C is methyl.

One illustration of this class are the compounds of formula (IVb1) or (IVb2):



(IVb1) or



(IVb2),

or a pharmaceutically acceptable salt thereof, wherein:

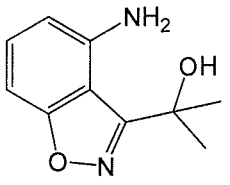
q_2 is 0, 1, or 2; and

each T_2 is independently F, Cl, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano.

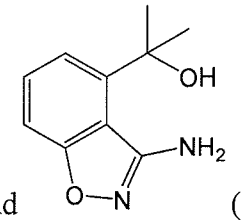
In one example, q_2 is 0 or 1. In a further example, q_2 is 0.

In one example, each T_2 is Cl. In another example, each T_2 is independently C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) or C_1-C_{10} alkyl (*e.g.*, methyl, ethyl, propyl, and butyl) substituted with C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl). In another example, each T_2 is independently C_3-C_6 cycloalkyl (*e.g.*, cyclopropyl and cyclobutyl).

Further illustrating the compounds of formula (IVb1) or (IVb2) are compounds 17 and 18:



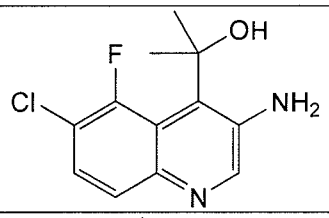
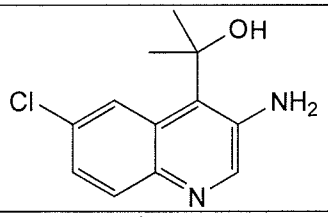
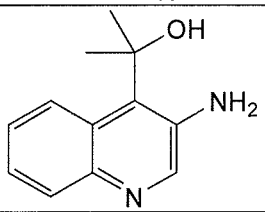
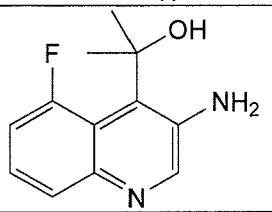
(17) and



(18).

Compounds that can be used in the invention include the compounds listed in Tables 1 and 2.

Table 1

Compound #		Compound #	
1		2	
3		4	

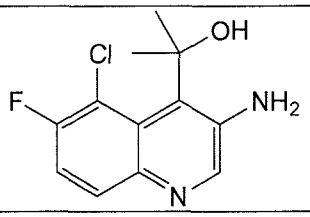
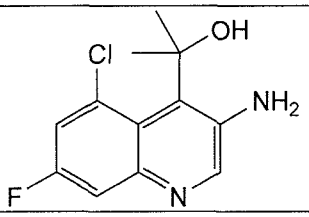
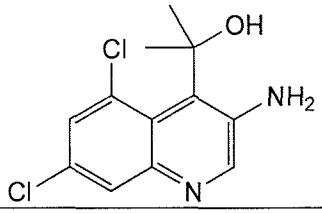
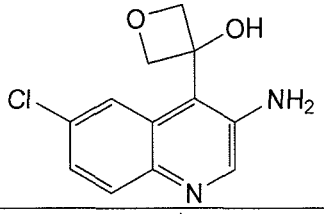
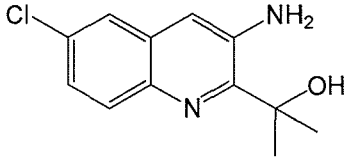
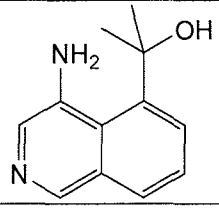
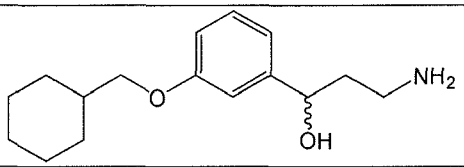
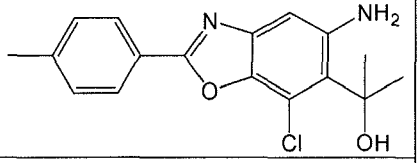
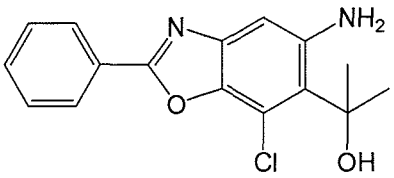
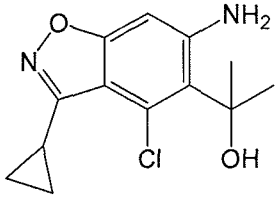
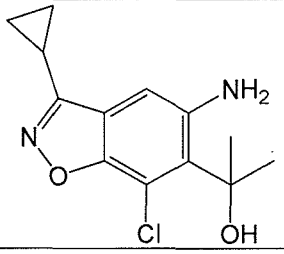
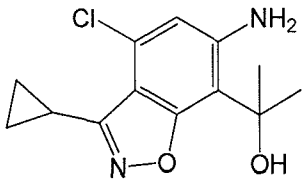
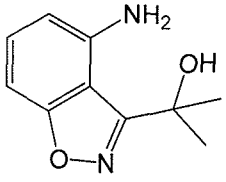
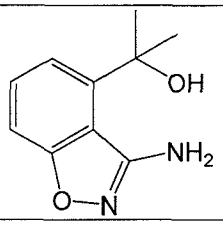
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	

Table 2

3-aminomethyl-5-methylhexanoic acid, 3-aminomethyl-5-methylheptanoic acid, 3-aminomethyl-5-methyl-octanoic acid, 3-aminomethyl-5-methyl-nonanoic acid, 3-aminomethyl-5-methyl-decanoic acid, 3-aminomethyl-5-methyl-undecanoic acid, 3-aminomethyl-5-methyl-dodecanoic acid, 3-aminomethyl-5-methyl-tridecanoic acid, 3-aminomethyl-5-cyclopropyl-hexanoic acid, 3-aminomethyl-5-cyclobutyl-hexanoic acid, 3-

aminomethyl-5-cyclopentyl-hexanoic acid, 3-aminomethyl-5-cyclohexyl-hexanoic acid, 3-aminomethyl-5-trifluoromethyl-hexanoic acid, 3-aminomethyl-5-phenyl-hexanoic acid, 3-aminomethyl-5-(2-chlorophenyl)-hexanoic acid, 3-aminomethyl-5-(3-chlorophenyl)-hexanoic acid, 3-aminomethyl-5-(4-chlorophenyl)-hexanoic acid, 3-aminomethyl-5-(2-methoxyphenyl)-hexanoic acid, 3-aminomethyl-5-(3-methoxyphenyl)-hexanoic acid, 3-aminomethyl-5-(4-methoxyphenyl)-hexanoic acid, 3-aminomethyl-5-benzyl-hexanoic acid, (S)-3-aminomethyl-5-methylhexanoic acid, (R)-3-aminomethyl-5-methylhexanoic acid, (3R,4S)-3-aminomethyl-4,5-dimethyl-hexanoic acid, 3-aminomethyl-4,5-dimethyl-hexanoic acid, (3R,4S)-3-aminomethyl-4,5-dimethyl-hexanoic acid MP; (3S,4S)-3-aminomethyl-4,5-dimethyl-hexanoic acid, (3R,4R)-3-aminomethyl-4,5-dimethyl-hexanoic acid MP; 3-aminomethyl-4-isopropyl-hexanoic acid, 3-aminomethyl-4-isopropyl-heptanoic acid, 3-aminomethyl-4-isopropyl-octanoic acid, 3-aminomethyl-4-isopropyl-nonanoic acid, 3-aminomethyl-4-isopropyl-decanoic acid, 3-aminomethyl-4-phenyl-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-ethoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-propoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-isopropoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-tert-butoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-fluoromethoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-fluoro-ethoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3,3,3-trifluoro-propoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-phenoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-chloro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-chloro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-chloro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-fluoro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-fluoro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-fluoro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-methoxy-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-methoxy-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-methoxy-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-6-hydroxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-methoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-ethoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-propoxy-hexanoic acid, (3S,5S)-3-aminomethyl-6-isopropoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-tert-butoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-fluoromethoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-fluoro-ethoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-(3,3,3-trifluoro-propoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-phenoxy-

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phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-phenyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-chloro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-chloro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-chloro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-methoxy-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-methoxy-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-methoxy-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-fluoro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-fluoro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-fluoro-phenyl)-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-5-methyl-7-phenyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(4-chloro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(3-chloro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(2-chloro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(4-methoxy-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(3-methoxy-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(2-methoxy-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(4-fluoro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(3-fluoro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(2-fluoro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-5-methyl-oct-7-enoic acid, (3S,5R)-3-aminomethyl-5-methyl-non-8-enoic acid, (E)-(3S,5S)-3-aminomethyl-5-methyl-oct-6-enoic acid, (Z)-(3S,5S)-3-aminomethyl-5-methyl-oct-6-enoic acid, (Z)-(3S,5S)-3-aminomethyl-5-methyl-non-6-enoic acid, (E)-(3S,5S)-3-aminomethyl-5-methyl-non-6-enoic acid, (E)-(3S,5R)-3-aminomethyl-5-methyl-non-7-enoic acid, (Z)-(3S,5R)-3-aminomethyl-5-methyl-non-7-enoic acid, (Z)-(3S,5R)-3-aminomethyl-5-methyl-dec-7-enoic acid, (E)-(3S,5R)-3-aminomethyl-5-methyl-undec-7-enoic acid, (3S,5S)-3-aminomethyl-5,6,6-trimethyl-heptanoic acid, (3S,5S)-3-aminomethyl-5,6-dimethyl-heptanoic acid, (3S,5S)-3-aminomethyl-5-cyclopropyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-cyclobutyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-cyclopentyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-cyclohexyl-hexanoic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-5-methyl-nonanoic acid, (3S,5R)-3-aminomethyl-5-methyl-decanoic acid, (3S,5R)-3-aminomethyl-5-methyl-undecanoic acid, (3S,5R)-3-aminomethyl-5-methyl-dodecanoic acid, (3S,5R)-3-aminomethyl-5,9-dimethyl-decanoic acid, (3S,5R)-3-aminomethyl-5,7-dimethyl-octanoic acid, (3S,5R)-3-aminomethyl-5,8-dimethyl-nonanoic acid, (3S,5R)-3-aminomethyl-6-cyclopropyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-6-cyclobutyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-6-cyclopentyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-6-cyclohexyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-7-cyclopropyl-

5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-cyclobutyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-cyclopentyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-cyclohexyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-8-cyclopropyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-8-cyclobutyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-8-cyclopentyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-8-cyclohexyl-5-methyl-octanoic acid, (3S,5S)-3-aminomethyl-6-fluoro-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-7-fluoro-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-8-fluoro-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-9-fluoro-5-methyl-nonanoic acid, (3S,5S)-3-aminomethyl-7,7,7-trifluoro-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-8,8,8-trifluoro-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-5-methyl-8-phenyl-octanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-phenyl-hexanoic acid, (3S,5R)-3-aminomethyl-5-methyl-7-phenyl-heptanoic acid.

Compounds described in the invention can be prepared by methods known in the art. For examples, compounds described in the invention can be prepared according to the methods described in PCT Publication WO 2006/127945 and PCT Application Nos. PCT/US2013/076592 and PCT/US2014/012356, the contents of each of which are incorporated herein by reference in their entirety.

Compounds within the scope of the instant invention may contain chiral centers and thus are capable of existing as racemates, racemic mixtures, diastereomers and single enantiomers. All such forms should be understood as within the scope of this invention.

As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl.

In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

As used herein, the term "cycloalkyl", "C_3, C_4, C_5, C_6, C_7 or C_8 cycloalkyl" or "C_3-C_8 cycloalkyl" is intended to include hydrocarbon rings having from three to eight carbon atoms in their ring structure. In one embodiment, a cycloalkyl group has five or six carbons in the ring structure.

The term "substituted alkyl" refers to alkyl moieties having substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, NH_2, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, acylamino (the term "acylamino" includes alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, sulfamoyl, sulfonamido, trifluoromethyl, azido, heterocyclyl, alkylaryl, and an aromatic or heteroaromatic moiety.

"Alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), branched alkenyl groups, cycloalkenyl (*e.g.*, alicyclic) groups (*e.g.*, cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from five to eight carbon atoms in their ring structure, and in one embodiment, cycloalkenyl groups have five or six carbons in the ring structure. The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

"Aryl" includes groups with aromaticity, including "conjugated", or multicyclic, systems with at least one aromatic ring. Examples include phenyl, benzyl, etc.

"Heteroaryl" groups are aryl groups, as defined above, having from one to four heteroatoms in the ring structure, and may also be referred to as "aryl heterocycles" or "heteroaromatics". As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms

may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic (*e.g.*, 2,3-dihydroindole), although all of the rings may be aromatic (*e.g.*, quinoline). The second ring can also be fused or bridged.

The aryl or heteroaryl aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, alkyl, alkenyl, akynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to,

fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

As used herein, "carbocycle" or "carbocyclic ring" is intended to include any stable monocyclic, bicyclic or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. For example, a C_3-C_{14} carbocycle is intended to include a monocyclic, bicyclic or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane and [2.2.2]bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In one embodiment, bridge rings are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (*e.g.*, naphthyl, tetrahydronaphthyl) and spiro rings are also included.

As used herein, "heterocycle" includes any ring structure (saturated or partially unsaturated) which contains at least one ring heteroatom (*e.g.*, N, O or S). Examples of heterocycles include, but are not limited to, morpholine, pyrrolidine, tetrahydrothiophene, piperidine, piperazine and tetrahydrofuran. Examples of heterocyclic groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol5(4H)-one, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole,

pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

The term "substituted", as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

When any variable (*e.g.*, R_1) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R_1 moieties, then the group may optionally be substituted with up to two R_1 moieties and R_1 at each occurrence is selected independently from the definition of R_1. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

The present invention is also directed to the use of a compound described herein in the manufacture of a medicament for the treatment, prevention, and/or reduction of a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis. More specifically this aspect of the invention is directed to the use of a compound described herein in the manufacture of a medicament for the treatment, prevention, and/or reduction of a risk of (1) an ocular disease, disorder, or condition, including, but not limited to, a corneal

disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular conditions associated with high aldehyde levels as a result of inflammation (*e.g.*, uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea (with or without meibomian gland dysfunction)), (2) a skin disorder or condition or a cosmetic indication. For example, the disease, disorder, or condition includes, but is not limited to, psoriasis, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjogren-Larsson Syndrome and other ichthyosis, solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, and a skin condition associated burn and wound, (3) a condition associated with the toxic effects of blister agents or burns from alkali agents, or (4) an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease (*e.g.*, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease, sepsis, atherosclerosis, ischemic-reperfusion injury, Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, diabetes, metabolic syndrome, and fibrotic diseases).

A "patient," "subject," or "host" to be treated by the subject method may mean either a human or non-human animal, such as primates, mammals, and vertebrates.

The terms "administering of" or "administering a" should be understood to mean providing a compound or a salt thereof or a pharmaceutical composition to a patient in need of treatment, prevention, or reduction in risk or a symptom.

The term "treating" is art-recognized and includes inhibiting a disease, disorder or condition in a subject, *e.g.*, impeding its progress; and relieving the disease, disorder or condition, *e.g.*, causing regression of the disease, disorder and/or condition. Treating the disease, disorder or condition includes ameliorating at least one symptom of the particular disease, disorder or condition, even if the underlying pathophysiology is not affected.

The term "preventing" is art-recognized and includes stopping a disease, disorder or condition from occurring in a subject which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it. Preventing a condition related to a disease includes stopping the condition from occurring after the disease has been diagnosed but before the condition has been diagnosed.

The term "reducing the risk of" means that the likelihood of a subject to suffer from a disease, disorder or condition is decreased, for example, from between 50% and 100% to between 0 and 90%, between 0 and 80%, between 0 and 70%, between 0 and 60%, or between 0 and 50%, or decreased by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

The term "alleviate" is meant to describe a process by which the severity of a sign or symptom of a disorder is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. In a preferred embodiment, the administration of pharmaceutical compositions of the invention leads to the elimination of a sign or symptom, however, elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom.

The term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non-health-care professionals.

The present invention is also directed to the use of a compound described herein in treating, preventing, and/or reducing a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in the pathogenesis. More specifically this aspect of the invention is directed to the use of a compound described herein in treating, preventing, and/or reducing a risk of (1) an ocular disease, disorder, or condition, including, but not limited to, a corneal disease (*e.g.*, dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, and Fuch's endothelial dystrophy), other ocular disorders or conditions (*e.g.*, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, and conditions associated with tear lipid degradation or lacrimal gland dysfunction), and other ocular conditions associated with high aldehyde levels as a result of inflammation (*e.g.*, uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea (with or without meibomian gland dysfunction)), (2) a skin disorder or condition or a cosmetic indication. For example, the disease, disorder, or condition includes, but is not limited to, psoriasis, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjogren-Larsson Syndrome and other ichthyosis, solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, and a skin condition associated burn and wound, (3) a condition associated with the toxic effects of blister agents or burns from alkali agents, or (4) an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease (*e.g.*, lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD),

rheumatoid arthritis, inflammatory bowel disease, sepsis, atherosclerosis, ischemic-reperfusion injury, Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, diabetes, metabolic syndrome, and fibrotic diseases).

The term "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salts" is art-recognized, and includes relatively non-toxic, inorganic and organic acid addition salts, and inorganic and organic base addition salts, including without limitation, the compounds described herein. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric acid and sulfuric acid, and those derived from organic acids, such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like. Examples of suitable inorganic bases for the formation of salts include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc and the like. Salts may also be formed with suitable organic bases, including those that are non-toxic and strong enough to form such salts. For purposes of illustration, the class of such organic bases may include mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and triethylamine; mono-, di- or trihydroxyalkylamines such as mono-, di-, and triethanolamine; amino acids, such as arginine and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; (trihydroxymethyl)aminoethane; and the like. *See*, for example, J. Pharm. Sci. 66:1-19 (1977).

The compounds described herein may be administered in the parent form or as a pharmaceutically acceptable salt. A compound described herein should be understood to include both. Pharmaceutically acceptable salts can be prepared from a parent compound that contains basic or acidic moieties by conventional chemical methods. Acid addition salts would include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds described herein can form

pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For reviews on pharmaceutically acceptable salts see S. M. Berge, L. D. Bighley and D. C. Monkhouse, Pharmaceutical salts, J. Pharm. Sci., 66, 1-19 (1977) and P. H. Stahl and C. G. Wermuth (eds.), Pharmaceutical Salts: Properties, Selection, and Use, Weinheim, Germany: Wiley and Zürich: Verlag Helvetica Chimica Acta, 2002 [ISBN 3-906390-26-8], incorporated herein by reference. Reference to the parent compound or a salt thereof should be understood to include all hydrates of the compound and all polymorphic forms of the parent compound.

The phrase "pharmaceutically acceptable carrier" is art-recognized, and includes, for example, pharmaceutically acceptable materials, compositions or vehicles, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of a subject composition and not injurious to the patient. In certain embodiments, a pharmaceutically acceptable carrier is non-pyrogenic. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A "pharmaceutical composition" is a formulation containing the disclosed compounds in a form suitable for administration to a subject. In a preferred embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a tablet, a capsule, an IV bag, a vial, or a single pump on an aerosol inhaler. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salts thereof) in a unit dose of composition is an effective amount and

is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. In a preferred embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and optionally with any preservatives, buffers, or propellants that may be required.

The compounds described herein may be administered with a pharmaceutically acceptable carrier in a pharmaceutical composition. The pharmaceutical compositions of the present invention encompass any composition made by admixing a therapeutically effective amount of a compound described herein with a pharmaceutically acceptable carrier. The administration may be by systemic means.

"Systemic administration" or "administered systemically" refers to a route of administration of the compounds or pharmaceutical compositions described therein such that the effect associated with the administration of the compounds or pharmaceutical composition is felt throughout the body, and is not limited to a specific location at which or a particular means by which the compounds or pharmaceutical compositions are administered. For example, a systemic administration includes, but is not limited to, an oral, a nasal, a parenteral, a subcutaneous, an intraocular, an intradermal, an intramuscular, an intravenous, an intraperitoneal, an intrathecal, intra-vesicular, intra-ventricular, intra-peritoneal, intra-parenchymal, a transdermal, and a transmucosal administration.

The compounds described herein can also be administered topically, such as directly to the eye, *e.g.*, as an eye-drop or ophthalmic ointment. Eye drops typically comprise an effective amount of at least one compound described herein and a carrier capable of being safely applied to an eye. For example, the eye drops are in the form of an isotonic solution, and the pH of the solution is adjusted so that there is no irritation of the eye. In many instances, the epithelial barrier interferes with penetration of molecules into the eye. Thus, most currently used ophthalmic drugs are supplemented with some form of penetration enhancer. These penetration enhancers work by loosening the tight junctions of the most superior epithelial cells (Burstein, Trans Ophthalmol Soc UK 104: 402 (1985); Ashton *et al.*, J Pharmacol Exp Ther 259: 719 (1991); Green *et al.*, Am J Ophthalmol 72: 897 (1971)). The most commonly used penetration enhancer is benzalkonium chloride (Tang *et al.*, J Pharm Sci 83: 85 (1994); Burstein *et al*, Invest Ophthalmol Vis Sci 19: 308 (1980)), which also works as preservative against microbial contamination.

Topical administration may be in the form of a cream, suspension, emulsion, ointment, drops, oil, lotion, patch, tape, inhalant, spray, or controlled release topical formulations including gels, films, patches, and adhesives. Intra-ocular administration may take the form of subconjunctival, subtenon's capsule, retrobulbar or intravitreal injections, depots or implants. Compounds administered by these routes may be in solution or suspension form. Administration of compounds by depot injection may contain pharmaceutically acceptable carriers or excipients; these may be natural or synthetic and may be biodegradable or non-biodegradable and facilitate drug release in a controlled manner. Implants used for controlled release of compound may be composed of natural or synthetic, biodegradable or non-biodegradable materials. The carrier is acceptable in that it is compatible with the other components of the composition and is not injurious to the patient. Some examples of carriers include (1) sugars such as lactose glucose and sucrose, (2) starches such as corn starch and potato starch, (3) cellulose and (4) cyclodextrins. A useful topical formulation is described in PCT publication WO 2011/072141, the contents of which are herein incorporated by reference.

Formulations for topical administration to the skin can include, for example, ointments, creams, gels and pastes comprising the primary amine compound in a pharmaceutical acceptable carrier. The formulation of the primary amine compound for topical use includes the preparation of oleaginous or water-soluble ointment bases, as is well known to those in the art. For example, these formulations may include vegetable oils, animal fats, and, for example, semisolid hydrocarbons obtained from petroleum. Particular components used may include white ointment, yellow ointment, cetyl esters wax, oleic acid, olive oil, paraffin, petrolatum, white petrolatum, spermaceti, starch glycerite, white wax, yellow wax, lanolin, anhydrous lanolin and glyceryl monostearate. Various water-soluble ointment bases may also be used, including glycol ethers and derivatives, polyethylene glycols, polyoxyl 40 stearate and polysorbates.

The formulations for topical administration may contain the compound used in the present application at a concentration in the range of 0.001-10%, 0.05-10%, 0.1-10%, 0.2-10%, 0.5-10%, 1-10%, 2-10%, 3-10%, 4-10%, 5-10%, or 7-10% (weight/volume), or in the range of 0.001-2.0%, 0.001-1.5%, or 0.001-1.0%, (weight/volume), or in the range of 0.05-2.0%, 0.05-1.5%, or 0.05-1.0%, (weight/volume), or in the range of 0.1-5.0%, 0.1-2.0%, 0.1-1.5%, or 0.1-1.0% (weight/volume), or in the range of 0.5-5.0%, 0.5-2.0%, 0.5-1.5%, or 0.5-1.0% (weight/volume), or in the range of 1-5.0%, 1-2.0%, or 1-1.5%(weight/volume). The formulations for topical administration may also contain the compound used in the present

application at a concentration in the range of 0.001-2.5%, 0.01-2.5%, 0.05-2.0%, 0.1-2.0%, 0.2-2.0%, 0.5-2.0%, or 1-2.0% (weight/weight), or in the range of 0.001-2.0%, 0.001-1.5%, 0.001-1.0%, or 0.001-5% (weight/weight).

In an eye drop formulation the composition may contain the active compound at a concentration of 0.01-20%, 0.02-15%, 0.04-10%, 0.06-5%, 0.08-1%, or 0.09-0.5% (weight/volume) with or without pH and/or osmotic adjustment to the solution. More particularly, the eye drop formulation may contain a compound described herein at a concentration of 0.09-0.5% (weight/volume), such as 0.1%.

In one exemplification, the pharmaceutical compositions encompass a composition made by admixing a therapeutically effective amount of a compound described herein with an oligomeric or a polymeric carrier such as a cyclodextrin, or chemically modified cyclodextrin, including trimethyl-β-cyclodextrin, 2-hydroxyethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, 3-hydroxypropyl-β-cyclodextrin, and β-cyclodextrin sulfobutylether sodium salt (or potassium salt). Exemplifying an oligomeric or a polymeric carrier is β-cyclodextrin sulfobutylether sodium salt. The amount of β-cyclodextrin sulfobutylether sodium salt in the composition may range from about 0.01% to 30% weight/volume. In one illustration, the concentration of β-cyclodextrin sulfobutylether sodium salt is 5-25% weight/volume. Further illustrating the concentration of β-cyclodextrin sulfobutylether sodium salt is 6-20% weight/volume. In one exemplification the concentration of β–cyclodextrin sulfobutylether is 6-12% weight/volume. Further exemplifying the concentration of β–cyclodextrin sulfobutylether is 9-10% weight/volume, including 9.5% weight/volume. The amount of the compound described herein in the composition may range 0.01-20%, 0.02-15%, 0.04-10%, 0.06-5%, 0.08-1%, or 0.09-0.5% (weight/volume). More particularly, the composition may contain a compound described herein at a concentration of 0.09-0.5% (weight/volume), such as 0.1%.

The compounds described herein may be administered orally and as such the pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

For oral administration in the form of a tablet or capsule (*e.g.*, a gelatin capsule), the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, magnesium aluminum silicate, starch paste, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum starches, agar, alginic acid or its sodium salt, or effervescent mixtures, croscarmellose or its sodium salt, and the like. Diluents, include, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A therapeutically effective dose, of a compound described herein in an oral formulation, may vary from 0.01 mg/kg to 50 mg/kg patient body weight per day, more particularly 0.01 to 10 mg/kg, which can be administered in single or multiple doses per day. For oral administration the drug can be delivered in the form of tablets or capsules containing 1 mg to 500 mg of the active ingredient specifically, 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 100 mg, 250 mg, and 500 mg, or in the forms of tables or capsules containing at least 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50% (w/w) of the active ingredient. For example, the capsules may contain 50 mg of the active ingredient, or 5-10% (w/w) of the active ingredient. For example, the tablets may contain 100 mg of the active ingredient, or 20-50% (w/w) of the active ingredient. For example, the tablet may contain, in addition to the active ingredient, a disintegrant (*e.g.*, croscarmellose or its sodium salt and methyl cellulose), a diluent (*e.g.*,

microcrystalline cellulose), and a lubricant (*e.g.*, sodium stearate and magnesium stearate). The drug can be administered on a daily basis either once, twice or more per day.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

Parenteral formulations comprising a compound described herein can be prepared in aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. The formulations may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. The compositions are prepared according to conventional methods, and may contain about 0.1 to 75%, preferably about 1 to 50%, of a compound described herein.

The phrases "parenteral administration" and "administered parenterally" are art-recognized terms, and include modes of administration other than enteral and topical administration, such as injections, and include, without limitation, intravenous, intramuscular, intrapleural, intravascular, intrapericardial, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

EXAMPLES

Example 1

Primary rat cortical cultures were placed in an incubator for 24 or 48 hours and treated with various concentrations of Compound 9. Then 20 μL of the culture media was removed for an LDH assay as described in Bergmeyer *et al.*, Methods of Enzymatic Analysis, 3rd ed. (1983). As shown in Figure 2, Compound 9 prevented aldehyde-mediated cell death in neurons.

Example 2

Male C57BI/6 mice were dosed with Compound 9 30 minutes before they were exposed to LPS (20 mg/kg). Two hours after the LPS exposure, blood was collected from the mice and an ELISA was conducted to determine the amount of circulating cytokines. As shown in Figures 3 and 4, Compound 9 treatment led to reduction in proinflammatory cytokines, such as IL-5 and IL-1β, IL-17, and TNF. Also, Figure 4 shows that Compound 9 treatment resulted in elevated anti-inflammatory cytokines, such as IL-10. In addition, various other chemokines, such as eotaxin, IL-12, IP-10, LIF, MCP-1, MIG, MIP, and RANTES, were also decreased by Compound 9 treatment.

Example 3

To determine the efficacy of Compound 9 in treating contact dermatitis, phorbol myristate acetate ("PMA") was applied topically (2.5 μg in 20 μL) to both the anterior and posterior portions of the right pinna of mice (N=10 per group). As a control, the left pinna received 20 μL of ethanol (PMA excipient) to both the anterior and posterior portions. Six hours after the PMA application, both the right and left pinna thickness was determined. Measurements were determined at least twice from the same region of both ears, with care taken not to include hair or folded pinna. The results are shown in Figure 5A.

Example 4

To measure the efficacy of Compound 9 in treating allergic dermatitis, oxazolone ("OXL") was applied (1.5%, 100 μL in acetone) to the shaved abdomens of mice. Seven days later, the thickness of the pinna of the OXL treated mice was determined. Then Compound 9 (100 mg/kg) or the vehicle (*i.e.*, Captisol) was administered intraperitoneally to mice followed by topical application of OXL (1%, 20 μL) 30 min later to both the anterior and posterior portions of the right pinna. As a control, the left pinna received 20 μL of acetone (OXL excipient) to both the anterior and posterior portions. The thickness of the pinna of both ears was measured again 24 hours later. N=10 per group. The results are shown in Figure 5B.

Example 5

To five separate reaction vials was added Compounds 1, 2, 12, 14, and 16, respectively (0.064 mmol), MDA salt (22.7 % MDA, 0.064 mmol), and glyceryl trioleate (600 mg). To the mixture was added 20 wt% Capitsol in aqueous PBS (~2.5 ml), followed by linoleic acid (600 mg). The reaction mixture was stirred vigorously at ambient temperature and monitored by LC/MS. The Compounds quickly react with MDA to form

MDA adducts. For Compounds 1, 12, 14, and 16, a majority of the adducts were bis-oxaminal. Other MDA adducts were also formed at different time points of the reactions.

Compound 9 also reacted with MDA and formed MDA adducts, in both the imine form and the oxaminal form.

Thus, each of Compounds 1, 2, 9, 12, 14, and 16 reacts and traps MDA.

Example 6. Synthesis of 2-(3-amino-6-chloro-5-fluoroquinolin-4-yl)propan-2-ol (Compound (1))

(*E*)- and (*Z*)-3-chloro-2-fluoro-6-(2-nitrovinylamino)benzoic acid (1-1). 37.19 g crude wet methazonic acid (prepared by the method of G.B. Bachman *et al.*, *J. Am. Chem. Soc.* 69, 365-371 (1947)) was mixed with 50 g 6-amino-3-chloro-2-fluorobenzoic acid (Butt Park Ltd., Camelford, Cornwall, UK) and 750 mL acetone and shaken until a clear solution was formed. To the solution was added sequentially 200 mL water and 200 mL 12 N HCl, and the solution was kept 3 days at room temperature. The mixture was diluted with 2 L water and filtered. The filtrate was evaporated to remove acetone and filtered. The combined solids were washed with water (4×200 mL) and dried at 60 °C under high vacuum to afford **1-1** as a 4.5:1 mixture of *E*- and *Z*-isomers.

^{1}H NMR (400 MHz, DMSO-d_6) δ : *E*-isomer 6.79 (d, 1H, J = 6.4 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.83 (t, 1H, J = 8.4 Hz), 7.99 (dd, 1H, J = 6.4, 13.2 Hz), 12.34 (d, 1H, NH, J = 13.2 Hz), 14.52 (br, 1H, OH). *Z*-isomer 7.39 (d, 1H, J = 11.2 Hz), 7.42 (d, 1H, J = 9.6 Hz), 7.71 (t, 1H, J = 8.4 Hz), 8.49 (t, 1H, J = 11.6 Hz), 10.24 (d, 1H, NH, J = 12.4 Hz), 14.52 (br, 1H, OH). LC-MS: 259 [(M-H)$^-$].

6-chloro-5-fluoro-3-nitroquinolin-4-ol (1-2). A mixture of 62.0 g (**1-1**), 55.2 g *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 30.1 g *N*-hydroxysuccinimide (HOSu) in 1 L absolute dimethylformamide (DMF) was stirred at room temperature for 1 h. 4-dimethylaminopyridine (DMAP, 38.7 g) was added and the mixture was stirred at room temperature for 2 h. The mixture was filtered, and the solid was washed with 10% HOAc (4×200 mL), air-dried overnight, and then dried at 60 °C under high vacuum to give (**1-2**) as a pale yellow powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 7.52 (dd, 1H, J = 0.8, 8.8 Hz), 7.91 (dd, 1H, J = 7.2, 8.8 Hz), 9.15 (s, 1H), 13.0 (br, 1H, OH). LC-MS: 242.9 (MH)$^+$, 264.9 (MNa)$^+$.

4-bromo-6-chloro-5-fluoro-3-nitroquinoline (1-3). A mixture of 40 g (**1-2**) and 71 g $POBr_3$ in 150 mL dry DMF was stirred at 80 °C for 1 h. The mixture was cooled to room temperature, diluted with 2 L CH_2Cl_2, and transferred to a separatory funnel containing 1.5 L

ice water. The organic layer was separated, washed with ice water (3×1.5 L), dried with $MgSO_4$, and evaporated to give crude (**1-3**) as a light brown solid, which was used without further purification.

^1H NMR (400 MHz, $CDCl_3$) δ : 4.70 (br, 2H, NH_2), 7.42 (dd, 1H, J = 6.0, 9.0 Hz), 7.73 (dd, 1H, J = 1.8, 8.8 Hz). LC-MS: 274.8 $(MH)^+$, 276.8 $[(M+2)H]^+$, 278.8 $[(M+4)H]^+$.

4-bromo-6-chloro-5-fluoroquinolin-3-amine (1-4). Crude (**1-3**) (51.2 g) was dissolved in 40 mL glacial HOAc under Ar, 3 g Fe powder was added, and the mixture was stirred at 60 °C for 10 min. The mixture was diluted with 200 mL EtOAc, filtered through Celite, and the Celite was washed thoroughly with EtOAc. The combined filtrates were passed through a short silica gel column, and the column was washed with EtOAc until all (**1-4**) was recovered. The combined EtOAc fractions were evaporated to dryness to give crude (**1-4**) which was crystallized from hexanes-EtOAc to provide (**1-4**) as a pale brown solid.

^1H NMR (400 MHz, $CDCl_3$) δ : 4.70 (br, 2H, NH_2), 7.42 (dd, 1H, J = 6.0, 9.0 Hz), 7.73 (dd, 1H, J = 1.8, 8.8 Hz). LC-MS: 274.8 $(MH)^+$, 276.8 $[(M+2)H]^+$, 278.8 $[(M+4)H]^+$.

2-(3-amino-6-chloro-5-fluoroquinolin-4-yl)propan-2-ol (Compound (1)). A dry 1 L round bottom flask was flushed with argon and cooled to –78°C in a dry ice/acetone bath. Dry tetrahydrofuran (THF, 300 mL) was injected, followed by 72.6 mL 2.5 M *n*-BuLi/hexanes. (**1-4**) (20 g) in 300 mL dry THF was added dropwise with vigorous stirring over 2 h, affording a dark red solution of the 4-quinolinelithium. Ultra dry acetone (27 mL) was added dropwise over 10 min, and the solution was stirred for an additional 10 min. A solution of 20 g NH_4Cl in 100 mL water was added and the mixture was warmed to room temperature, transferred to a separatory funnel containing 300 mL EtOAc, and shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×250 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and evaporated to a dark brown residue which was partially purified by chromatography on a silica gel column eluted with hexanes-EtOAc to afford a mixture containing 6-chloro-5-fluoroquinolin-3-amine and **Compound (1)**. **Compound (1)** was isolated by crystallization from hexanes-EtOAc.

^1H NMR (400 MHz, CD_3OD) δ : 1.79 (s, 3H), 1.80 (s, 3H), 7.36 (dd, 1H, J = 7.2, 8.8 Hz), 7.61 (dd, 1H, J = 1.6, 9.0 Hz), 8.35 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ : 29.8, 29.9, 76.7, 120.4 (d, J_{C-F} = 12 Hz), 120.5 (d, J_{C-F} = 4 Hz), 125.4, 126.1 (d, J_{C-F} = 3 Hz), 126.6 (d, J_{C-F} = 3 Hz), 143.1, 143.2 (d, J_{C-F} = 5 Hz), 148.3, 152.7 (d, J_{C-F} = 248 Hz). LC-MS: 254.9 $(MH)^+$, 256.9 $[(M+2)H]^+$.

Example 7. Synthesis of 2-(3-amino-6-chloroquinolin-4-yl)propan-2-ol (Compound (2))

6-chloro-3-nitroquinolin-4-ol (2-1). A mixture of *cis*- and *trans*-5-chloro-2-(2-nitrovinylamino)benzoic acid (68.4 g, Sus *et al.*, Liebigs Ann. Chem. 583: 150 (1953)), 73 g EDC and 35.7 g HOSu in 1 L dry DMF was stirred at room temperature for 1 h. After adding 45.8 g DMAP the mixture was stirred at room temperature for 2 h. To the stirred mixture was slowly added 1 L 10% HOAc, and the resulting suspension was poured into 2 L 10% HOAc. The solid was filtered off, washed with 10% HOAc (4×400 mL) and dried at 80 °C under high vacuum to give (**2-1**) as a tan powder .

4-bromo-6-chloro-quinolin-3-amine (2-2). A mixture of 25 g (**2-1**) and 50 g $POBr_3$ in 100 mL dry DMF was stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with 2 L CH_2Cl_2, and transferred to a separatory funnel containing 1 L ice water. The organic layer was separated, washed with ice water (3×1 L), dried with $MgSO_4$, and evaporated to provide crude 4-bromo-6-chloroquinolin-4-ol as a light brown solid (38 g, 100% crude yield). The quinolinol was dissolved in 750 mL glacial HOAc, 36 g iron powder was added, and the stirred mixture was heated under Ar at 60°C until the color turned to grey. The mixture was diluted with 2 L EtOAc, filtered through Celite, and the Celite was washed with EtOAc. The combined filtrates were passed through a short silica gel column which was washed with EtOAc until all (**2-2**) was recovered. The combined fractions were evaporated to dryness and the residue was crystallized from hexanes-EtOAc to provide (**2-2**) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.47 (br, 2H, NH_2), 7.41 (dd, 1H, J = 2.4, 8.8 Hz), 7.89 (d, 1H, J = 9.2 Hz), 7.96 (d, 1H, J = 2.4 Hz), 8.45 (s, 1H). LC-MS: 256.7 $(MH)^+$, 258.7 $[(M+2)H]^+$, 260.7 $[(M+4)H]^+$.

Synthesis of 2-(3-amino-6-chloroquinolin-4-yl)propan-2-ol (Compound (2)). A mixture of 20 g (**2-2**) and 800 mL dioxane was stirred at 60°C until a solution formed, cooled to room temperature, and sparged with dry HCl for 5 min. The solvent was evaporated, and 500 mL dioxane was added and evaporated to provide 4-bromo-6-chloroquinolin-3-aminium hydrochloride. The product was mixed with 100 g NaI and 600 mL dry MeCN and refluxed overnight. The solvent was evaporated and the residue was partitioned between 500 mL EtOAc and a solution of 10 g $NaHCO_3$ in 500 mL water. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×200 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to provide 6-chloro-4-iodoquinolin-3-amine as a tan solid . A dry 1 L round bottom flask was flushed with Ar and cooled to -78°C in a dry

ice/acetone bath. Dry THF (350 mL) was added followed by 188 mL 1.7 M *t*-BuLi/pentane with vigorous stirring. A solution of 25.8 g crude 6-chloro-4-iodoquinolin-3-amine in 350 mL dry THF was added dropwise to the stirred mixture. When addition was complete the reaction mixture was stirred at -78°C for 5 min. Ultra dry acetone (50 mL) was added dropwise and the solution was stirred at -78°C for 10 min after addition was complete. A solution of 20 g NH_4Cl in 200 mL water was added and the mixture was warmed up to room temperature, transferred to a separatory funnel containing 300 mL EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (2×250 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to a dark brown residue. The residue was partially purified by column chromatography on silica gel eluted with hexanes-EtOAc. All fractions containing (**2-3**) were combined and evaporated to give crude (**2-3**) as a red oil. A batch of crude ii) (*ca.* 2 g) obtained from a separate synthesis was added to this product, and the combined batches were dissolved in 50 mL EtOAc and filtered. The filtrate and washings were combined and concentrated to an oil which was diluted with 10 mL hot hexanes, treated dropwise with EtOAc until a clear solution formed, and allowed to evaporate at room temperature overnight in the fume hood. The oily mother liquor was removed and the solid was washed with minimum volumes of 3:1 hexanes-EtOAc. After recrystallization twice from hexanes-EtOAc, a first crop of pure (**Compound (2)**) was obtained as off-white crystals. All the mother liquor and washings were pooled and EtOAc (*ca.* 50 mL) was added to form a clear solution which was extracted with 0.5 N aq. HCl (4×100 mL). The aqueous layers were pooled and neutralized with 20% NaOH to pH 8. The resulting suspension was extracted with EtOAc (3×50 mL) and the combined organic layers were dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography and two crystallizations from hexanes-EtOAc to provide a second crop of (**2-3**). A third crop (**2-3**) was obtained by fractional crystallization of the combined mother liquor and washings from hexanes-EtOAc.

^1H NMR (400 MHz, $CDCl_3$) δ : 1.93 (s, 6H), 3.21 (br, 1H, OH), 5.39 (br, 2H, NH_2), 7.29 (dd, 1H, J = 2.0, 8.8 Hz), 7.83 (d, 1H, J = 8.8 Hz), 7.90 (d, 1H, J = 2.0 Hz), 8.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.5, 76.5, 123.2, 124.6, 125.7, 127.5, 131.5, 131.9, 138.8, 141.5, 146.5. LC-MS: 236.9 $(MH)^+$, 238.9 $[(M+2)H]^+$.

Example 8. Synthesis of 2-(5-amino-7-chloro-2-*p*-tolylbenzoxazol-6-yl)propan-2-ol (Compound (12))

3-Methoxy-4-(trifluoroacetylamino)benzoic acid (12-1). To a suspension of 5.0 g 4-amino-3-methoxybenzoic acid in 200 mL EtOAc was added under stirring a solution of 5.0 mL $(CF_3CO)_2O$ in 50 mL of EtOAc. After complete addition, the reaction mixture was further stirred at room temperature for 2 h. The solution was filtered, and the filtrate was evaporated to dryness. The residue was dissolved and evaporated twice in EtOAc. The final residue was dried under high vacuum to afford pure (**12-1**) as a white solid.

5-Methoxy-2-nitro-4-(trifluoroacetylamino)benzoic acid (12-2). A suspension of 7.55 g (**12-1**) in 80 mL 96% H_2SO_4 was stirred at room temperature until a homogeneous solution was formed. The solution was cooled with an ice bath under stirring while a solution of 2.03 g 90.6% fuming HNO_3 in 20 mL 96% H_2SO_4 was added dropwise under cooling. The temperature was maintained below 10 °C. After complete addition, the mixture was further stirred for 10 min, and then slowly added onto 200 g ice under vigorous stirring. The mixture was saturated with NaCl and extracted with EtOAc (3×100 mL). The combined organic layer was washed with brine (2×50 mL), dried with Na_2SO_4, and then evaporated to give pure (**12-2**) as a light brown solid.

4-Amino-5-hydroxy-2-nitrobenzoic acid (12-3). A mixture of 6.94 g (**12-2**) in 35 mL 20% aqueous NaOH was stirred under argon at 100 °C overnight. The mixture was cooled to room temperature. To it was added dropwise 20 mL 12 N HCl under ice bath cooling. After complete addition, the solution was evaporated, and the residue was extracted with 200 mL absolute EtOH. The solid NaCl was filtered off, and the filtrate was evaporated to give the crude HCl salt of (**12-3**) as a dark grey solid.

4-Amino-5-hydroxy-2-nitrobenzoic acid ethyl ester (12-4). The above 6.95 g crude HCl salt of (**12-3**) was dissolved in 250 mL absolute EtOH. The solution was purged with dry HCl to nearly saturation, and then stirred at 80 °C for 36 h. The solvent was evaporated, and the residue was partitioned between 200 mL EtOAc and 200 mL brine. The aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layer was dried with Na_2SO_4, acidified with 2 mL of HOAc, and then passed through a short silica gel column. The column was eluted with 1% HOAc/EtOAc. The combined yellow fraction was evaporated to give crude (**12-4**) as a red viscous oil.

5-Hydroxy-4-(4-methylbenzoylamino)-2-nitrobenzoic acid ethyl ester (12-5). A mixture of 2.26 crude (**12-4**) and 2.1 g *p*-toluoyl chloride in 25 mL 1,4-dioxane was stirred at 95 °C for 1.5 h. The solvent was removed, and the residue was evaporated twice with EtOH and

then evaporated twice with EtOAc. The final residue was dried at 60 °C under high vacuum to give crude (**12-5**) as a tan solid.

2-Chloro-3-hydroxy-4-(4-methylbenzoylamino)-6-nitrobenzoic acid ethyl ester (12-6). A suspension of 3.35 g (**12-5**) in 100 mL dioxane was stirred until a clear solution was formed, and then 70 μL diisopropylamine (DIPA) was added. The solution was stirred at 50 °C while 1.96 mL SO_2Cl_2 was added. The reaction mixture was stirred under argon at 50 °C for 1 h, cooled to room temperature, diluted with 200 mL EtOAc, washed with water (3×100 mL), and dried with $MgSO_4$. The solvent was evaporated and the residue was dried at 60 °C under high vacuum to give crude (**12-6**) as a brown solid.

7-Chloro-5-nitro-2-(*p*-tolyl)benzoxazole-6-carboxylic acid ethyl ester (12-7). A mixture of 4.35 g crude (**12-6**) and 3.93 g Ph_3P in 50 mL dry THF was stirred at room temperature until a solution was formed. To the solution was added 6.7 mL 40% DEAD/toluene, and the mixture was stirred at 70 °C for 1 h. The mixture was diluted with 50 mL EtOH and evaporated. The residue was separated by silica gel column chromatography with hexane-EtOAc as eluent to give pure (**12-7**) as a white solid.

5-Amino-7-chloro-2-(*p*-tolyl)benzoxazole-6-carboxylic acid ethyl ester (12-8). A mixture of 1.17 g (**12-7**), 1.07 g iron powder and 25 mL glacial HOAc was heated at 60 °C under vigorous stirring for 3 h. The reaction mixture was diluted with 200 mL EtOAc. The slurry was passed through a celite pellet, and the celite was washed with EtOAc. The combined filtrates were passed through a short silica gel column, and the column was eluted with EtOAc. The combined yellow fractions were evaporated, and the residue was crystallized from hexanes-EtOAc to give pure (**12-8**) as a bright yellow solid.

2-(5-Amino-7-chloro-2-(*p*-tolyl)benzoxazol-6-yl)propan-2-ol (Compound (12)). A mixture of 7.0 mL 3.0 M MeMgCl/THF and 6 mL THF was protected under argon, and cooled in an ice bath with vigorous stirring. To it was added dropwise a solution of 886 mg (**12-8**) in 50 mL THF. After compete addition, the mixture was stirred at 0 °C for 5 min. To the mixture was added 100 mL saturated NH_4Cl with ice bath cooling and vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (DCM) (3×100 mL). The combined organic layers were dried with $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with MeOH-DCM as eluent and then crystallized from heptane/DCM to give pure (**Compound (12)**) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.89 (s, 6H), 2.41 (s, 3H), 4.45 (br, 3H, NH_2 and OH), 6.81 (s, 1H), 7.27 (d, 1H, J = 8.8 Hz), 8.07 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 21.7, 31.0, 76.9, 106.2, 113.5, 124.0, 126.8, 127.6, 129.6, 140.9, 142.2, 142.9, 145.3, 164.1. LC-MS: 317.0 $(MH)^+$, 319.0 $[(M+2)H]^+$.

Example 9. Synthesis of 2-(5-amino-7-chloro-2-phenylbenzoxazol-6-yl)propan-2-ol (Compound (13))

4-Benzoylamino-5-hydroxy-2-nitrobenzoic acid ethyl ester (13-1). A mixture of 2.26 g crude 4-amino-5-hydroxy-2-nitrobenzoic acid ethyl ester (**12-4**) and 1.91 g benzoyl chloride in 25 mL 1,4-dioxane was stirred at 95 °C for 1 h. The solvent was removed and the residue was evaporated twice with EtOH. The residue was further evaporated twice with EtOAc, and then was dried at 60 °C under high vacuum to give crude (**13-1**) as a tan solid.

4-Benzoylamino-2-chloro-3-hydroxy-6-nitrobenzoic acid ethyl ester (13-2). A suspension of 3.23 g (**13-1**) in 100 mL dioxane was stirred until a clear solution was formed. To the solution was added 70 μL DIPA, and the solution was stirred to 50 °C, followed by addition of 2.03 mL SO_2Cl_2. The reaction mixture was stirred under argon at 50 °C for 1 h, cooled to room temperature, diluted with 200 mL EtOAc, washed with water (3×100 mL), and then dried with $MgSO_4$. The solvent was evaporated and the residue was dried at 60 °C under high vacuum to give crude (**13-2**) as a brown solid.

7-Chloro-5-nitro-2-phenylbenzoxazole-6-carboxylic acid ethyl ester (13-3). A mixture of crude 3.74 g (**13-2**) and 3.93 g Ph_3P in 50 mL dry THF was stirred at room temperature until a solution was formed. To the solution was added 6.7 mL 40% DEAD/toluene, and the mixture was stirred at 70 °C for 1 h. The mixture was diluted with EtOH and evaporated. The residue was separated by silica gel column chromatography with hexane-EtOAc as eluent to give (**13-3**) as a white solid.

5-Amino-7-chloro-2-phenylbenzoxazole-6-carboxylic acid ethyl ester (13-4). A mixture of 0.89 g (**13-3**), 2.0 g iron powder and 25 mL glacial HOAc was heated at 60 °C under vigorous stirring for 1.5 h. The mixture was diluted with 200 mL EtOAc. The slurry was passed through a celite pellet, and the celite was washed with EtOAc. The combined filtrates were pass through a short silica gel column, and the column was eluted with EtOAc. The combined yellow fractions were evaporated, and the residue was crystallized from hexanes-EtOAc to give pure (**13-4**) as a bright yellow solid.

2-(5-Amino-7-chloro-2-phenylbenzoxazol-6-yl)propan-2-ol (Compound (13)). A mixture of 6 mL 3.0 M MeMgCl/THF and 6 mL THF was protected under argon, and cooled in an ice

bath with vigorous stirring. To it was added dropwise a solution of 638 mg (**13-4**) in 50 mL THF. After complete addition, the mixture was stirred at 0 °C for 5 min. To the mixture was added 100 mL saturated NH_4Cl with cooling and vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with DCM (3×100 mL). The combined organic layers were dried with $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with MeOH-DCM as eluent, and then crystallized from heptane-DCM to give pure (**Compound (13)**) as a pale yellow solid.

^1H NMR (400 MHz, $CDCl_3$) δ : 1.92 (s, 6H), 4.69 (br, 3H, NH_2 and OH), 6.87 (s, 1H), 7.48-7.54 (3H), 8.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.0, 77.0, 106.3, 113.6, 126.8, 126.9, 127.7, 128.9, 131.6, 140.9, 143.0, 145.4, 163.9. LC-MS: 303.1 $(MH)^+$, 305.0 $[(M+2)H]^+$.

Example 10. Synthesis of 2-(6-amino-4-chloro-3-cyclopropylbenzisoxazol-5-yl)propan-2-ol (Compound (14))

(2-Chloro-4,6-dimethoxyphenyl)cyclopropylmethanone (14-1). A solution of 28.28 g 1-chloro-3,5-dimethoxybenzene and 17.8 mL cyclopropanecarbonyl chloride in 300 mL dry 1,2-dichloroethane (DCE) was protected with argon, and cooled in a dry ice/acetone bath to –30 to –40 °C. To it was added in portions 32.4 g $AlCl_3$ powder under vigorous stirring. After complete addition, the solution was stirred at –30 to –40 °C for 30 min, and then allowed to warm up to room temperature. After further stirring at room temperature for 20 min, the mixture was added onto 1 kg ice under stirring. The mixture was extracted with ether (3×300 mL). The combined organic layers were dried with $MgSO_4$ and evaporated. The residue was separated by column chromatography with hexanes/EtOAc as eluent to give pure (**14-1**) as a white solid.

(2-Chloro-6-hydroxy-4-methoxyphenyl)cyclopropylmethanone (14-2). A solution of 13.45 g (**14-1**) in 100 mL dry DCM was protected with argon, and cooled at –78 °C (dry ice/acetone bath) under stirring. To it was added 62 mL 1 M BBr_3/DCM. After complete addition, the mixture was further stirred at –78 °C for 1 h.. To the mixture was slowly injected 50 mL MeOH under dry ice/acetone bath cooling and vigorous stirring. After complete injection, the mixture was further stirred at –78 °C for 10 min, and then allowed to warm up to room temperature. The mixture was partitioned between 500 mL DCM and 500 mL brine. The organic layer was separated, washed with brine (2×100 mL), and then mixed with a solution of 4.0 g NaOH in 300 mL water. After stirring at room temperature for 1 h, the mixture was acidified with 10 mL 12 N aqueous HCl with stirring. The organic layer was

separated, dried with $MgSO_4$, and evaporated. The residue was separated by silica gel column chromatography with hexanes-EtOAc as eluent to give (**14-2**) as a white solid.

(*E*)- and (*Z*)-(2-Chloro-6-hydroxy-4-methoxyphenyl)cyclopropylmethanone oxime (14-3). A mixture of 10.38 g (**14-2**) and 15.95 g NH_2OH•HCl in 150 mL dry pyridine was protected under argon, and stirred at 80 °C for 20 h. The solvent was evaporated, and the residue was partitioned between 400 mL 0.1 N HCl/brine and 400 mL Et_2O. The organic layer was separated, washed with water (2×50 mL), dried with $MgSO_4$ and evaporated. The residue was crystallized from heptane-EtOAc to give pure (**14-3**) as a white solid.

(*E*)- and (*Z*)-(2-Chloro-6-hydroxy-4-methoxyphenyl)cyclopropylmethanone *O*-acetyl oxime (14-4). To a suspension of 9.75 g (**14-3**) in 40 mL EtOAc was added 6.5 mL Ac_2O under stirring at room temperature. After complete addition, the mixture was stirred at room temperature for 1 h. To the mixture was added 50 mL MeOH and 20 mL pyridine, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the residue was partitioned between 300 mL 1 N HCl/brine and 300 mL EtOAc. The organic layer was separated, washed with water (2×50 mL), dried with $MgSO_4$ and evaporated to give crude (**14-4**) as a light brown oil.

4-Chloro-3-cyclopropyl-6-methoxybenzisoxazole (14-5). Crude (**14-4**) was protected under argon, and heated in an oil bath at 150 °C for 3 h. The crude product was purified by silica gel column chromatography using hexanes-EtOAc as eluent to give pure (**14-5**) as a light tan solid.

4-Chloro-3-cyclopropylbenzisoxazol-6-ol (14-6). A solution of 7.61 g (**14-5**) in 75 mL dry DCM was protected under argon, and cooled to –78 °C in a dry ice/acetone bath. To it was added dropwise 80 mL 1 M BBr_3 in DCM with vigorous stirring. After compete addition, the mixture was allowed to warm to room temperature, and then stirred at room temperature for 1 h. The mixture was again cooled to –78 °C in a dry ice/acetone bath. To the mixture was added 20 mL MeOH under vigorous stirring. After complete addition, the reaction mixture was allowed to warm to room temperature, and then partitioned between 1.5 L brine and 1.5 L EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×300 mL). The combined organic layers were dried with $MgSO_4$, and passed through a short silica gel column that was eluted with EtOAc. The combined fractions were evaporated to give pure (**14-6**) as a light brown oil, which solidified upon standing.

4-Chloro-3-cyclopropylbenzisoxazol-6-yl trifluoromethanesulfonate (14-7). A mixture of 6.88 g (**14-6**) and 4 mL pyridine in 50 mL DCM was protected under argon and stirred at 0 °C in an ice bath. To it was added dropwise 6.73 mL Tf_2O with vigorous stirring. After

complete addition, the mixture was allowed to warm up to room temperature. After further stirring for 10 min at room temperature, the mixture was partitioned between 200 mL 1 N HCl and 300 mL DCM. The organic layer was separated, washed sequentially with 100 mL 1 N HCl, 100 mL brine, 100 mL 5% aqueous $NaHCO_3$ and 100 mL brine, dried with $MgSO_4$ and then evaporated. The residue was purified by column chromatography with hexanes-EtOAc as eluent to give pure (**14-7**) as an off-white solid.

***tert*-Butyl (4-chloro-3-cyclopropylbenzisoxazol-6-yl)carbamate (14-8).** A mixture of 8.02 g (**14-7**), 2.87 g *tert*-butyl carbamate, 2.37 g *t*BuONa, 1.08 g tris(dibenzylideneacetone) dipalladium(0) (Pd_2dba_3), 2.0 g 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (*t*-butyl Xphos) and 7 g 4 Å molecular sieves in 120 mL dry toluene was purged with argon, and then heated at 110 °C with vigorous stirring for 20 min. The reaction mixture was diluted with 300 mL EtOAc, and passed through a celite pellet which was then washed with EtOAc. The combined solutions were evaporated and the residue was separated by silica gel column chromatography with hexanes-EtOAc as eluent to give crude (**14-8**) as a light brown oil.

6-Amino-4-chloro-3-cyclopropylbenzisoxazole (14-9). The 4.09 g crude (**14-8**) was dissolved in 10 mL DCM, followed by addition of 10 mL TFA. The mixture was stirred at room temperature for 30 min. The solvent was removed, and the residue was partitioned between 200 mL DCM and 200 mL 10% $NaHCO_3$. The organic layer was separated, washed with water (2×50 mL), dried with $MgSO_4$ and evaporated. The residue was separated by silica gel column chromatography with hexanes-EtOAc as eluent to give pure (**14-9**) as a white solid.

5-Bromo-4-chloro-3-cyclopropylbenzisoxazol-6-ylamine (14-10) and 7-bromo-4-chloro-3-cyclopropylbenzisoxazol-6-ylamine (16-1). To a solution of 1.96 g (**14-9**) in 100 mL DCM was added 1.67 g solid NBS in small portions under vigorous stirring at room temperature. After complete addition, the mixture was further stirred at room temperature for 30 min, diluted with 100 mL DCM, washed sequentially with 10% aqueous $NaHSO_3$ (200 mL) and water (2×200 mL), dried with $MgSO_4$, and evaporated to give a 1:1 mixture of (**14-10**) and (**16-1**) as a tan oil, which solidified on standing.

6-Amino-4-chloro-3-cyclopropylbenzisoxazole-5-carbonitrile (14-11) and 6-amino-4-chloro-3-cyclopropylbenzisoxazole-7-carbonitrile (16-2). A suspension of 2.72 g of a mixture of (**14-10**) and (**16-1**), 1.70 g CuCN and 3.62 g CuI in 25 mL dry DMF was purged with argon, and then heated at 110 °C in an oil bath with vigorous stirring for 15 h. The mixture was cooled to room temperature. To it was added 100 mL 30% aqueous NH_3. After stirring at room temperature for 1 h, the mixture was diluted with 300 mL water, and

extracted with EtOAc (2×500 mL). The combined organic layers were washed with water (3×200 mL), dried with $MgSO_4$ and evaporated. The residue was separated by silica gel column chromatography with hexanes-EtOAc as eluent to give (**14-11**) as a light yellow solid, and (**16-2**) as a light tan solid.

4-Chloro-5-cyano-3-cyclopropyl-6-(tritylamino)benzisoxazole (14-12). To a mixture of 435 mg (**14-11**) and 700 μL TEA in 20 mL DCM was added 1.09 g solid trityl chloride in small portions under stirring at room temperature. After complete addition, the mixture was further stirred at room temperature for 30 min. The reaction mixture was diluted with 300 mL DCM, washed with water (4×200 mL), dried with $MgSO_4$ and then evaporated. The residue was separated by silica gel column chromatography with DCM as eluent to give pure (**14-12**) as a white solid.

4-Chloro-3-cyclopropyl-6-(tritylamino)benzisoxazole-5-carbaldehyde (14-13). A solution of 481 mg (**14-12**) in 13 mL dry THF was cooled in an ice bath with stirring. To the solution was added dropwise 7 mL 1 M DIBAL/toluene. After complete addition, the reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched with 100 mL 1% aqueous tartaric acid, and the mixture was extracted with DCM (3×100 mL). The organic layer was washed with water (3×100 mL), dried with $MgSO_4$ and evaporated. The residue was dissolved in DCM and adsorbed onto silica gel. The mixture was air-dried and separated by silica gel column chromatography with hexanes-EtOAc as eluent to give crude (**14-13**) as a yellow solid.

1-[4-Chloro-3-cyclopropyl-6-(tritylamino)benzisoxazol-5-yl]ethanol (14-14). The above 257.8 mg crude (**14-13**) was dissolved in 10 mL dry THF, and the solution was added to a mixture of 2.0 mL 3 M MeMgCl/THF and 2 mL dry THF at 0 °C (ice bath) with stirring. After complete addition, the mixture was further stirred at 0 °C for 5 min, and then quenched with 100 mL 5% NH_4Cl under ice bath cooling. The mixture was extracted with DCM (3×100 mL), dried with $MgSO_4$ and evaporated. The residue was separated by silica gel column chromatography with hexanes-EtOAc as eluent to give pure (**14-14**) as a white solid.

1-[4-Chloro-3-cyclopropyl-6-(tritylamino)benzisoxazol-5-yl]ethanone (14-15). To a solution of 150.5 mg (**14-14**) in 20 mL dry DCM was added 271 mg solid Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, DMP) in small portions at room temperature under vigorous stirring. After complete addition, the reaction mixture was further stirred at room temperature for 10 min. The reaction mixture was diluted with 300 mL DCM, washed with water (4×200 mL), dried with $MgSO_4$ and evaporated. The

residue was separated by silica gel column chromatography with hexanes-EtOAc as eluent to give pure (**14-15**) as a pale yellow solid.

1-(6-Amino-4-chloro-3-cyclopropylbenzisoxazol-5-yl)ethanone (14-16). To a solution of 182 mg (**14-15**) in 20 mL dry DCM was added dropwise 2 mL TFA under stirring at room temperature. The solution was stirred at room temperature for 10 min, diluted with 200 mL DCM, washed with water (4×100 mL), dried with $MgSO_4$ and evaporated to give crude (**14-16**) as a white solid.

2-(6-Amino-4-chloro-3-cyclopropylbenzisoxazol-5-yl)propan-2-ol (Compound (14)). The 174.7 mg crude (**14-16**) was dissolved in 20 mL dry THF, and the solution was added dropwise to a well stirred mixture of 2.5 mL 3M MeMgCl/THF and 2 mL THF at 0 °C (ice bath). After complete addition, the mixture was further stirred at 0 °C for 5 min. To it was added dropwise 100 mL 5% aqueous NH_4Cl under ice bath cooling and stirring. The mixture was extracted with DCM (3×100 mL), dried with $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with MeOH-DCM as eluent and then crystallized from heptane-DCM to give pure (**Compound (14)**) as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ : 1.10 (m, 2H), 1.20 (m, 2H), 1.91 (s, 6H), 2.18 (m, 1H), 4.28 (br, 2H, NH_2), 6.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 8.68, 9.35, 30.0, 77.4, 97.4, 121.2, 125.1, 133.1, 145.7, 149.3, 166.4. LC-MS: 266.9 $(MH)^+$, 269.0 $[(M+2)H]^+$.

Example 11. Synthesis of 2-(5-amino-7-chloro-3-cyclopropylbenzisoxazol-6-yl)propan-2-ol (Compound (15))

Cyclopropanecarboxylic acid methoxymethylamide (15-1). A suspension of 9.75 g *N,O*-dimethylhydroxylamine hydrochloride and 9.7 mL pyridine in 200 mL DCM was stirred at room temperature for 10 min, and then cooled in an ice bath with stirring. To the suspension was added dropwise a solution of 9.03 mL cyclopropanecarbonyl chloride in 40 mL DCM with vigorous stirring. After complete addition, the mixture was stirred at 0 °C for 30 min, and then at room temperature for 1 h. The solution was diluted with 100 mL DCM, washed with brine (3×200 mL), and dried with $MgSO_4$. The solvent was evaporated, and the residue vacuum distilled. The fraction collected at 43-45 °C/1 mmHg gave (**15-1**) as a colorless liquid.

2-(3-Chloro-4-fluorophenyl)-1,1,1,3,3,3-hexamethyldisilazane (15-2). A solution of 7.3 g 3-chloro-4-fluoroaniline in 100 mL dry THF was protected under argon and cooled at –78 °C (dryice/acetone bath). To the solution was slowly added 21 mL 2.5 M *n*BuLi in hexanes with vigorous stirring. After complete addition, the suspension was further stirred at –78 °C for 10

min. To the latter was slowly added 6.65 mL chlorotrimethylsilane (TMSCl) under vigorous stirring. After complete addition, the mixture was further stirred at –78 °C for 30 min. To the latter was again added 24 mL 2.5 M *n*BuLi, followed by 7.65 mL TMSCl under vigorous stirring. The mixture was stirred at –78 °C for 30 min, and then allowed to warm to room temperature. The solvent was removed and the residue was vacuum distilled. The fractions collected below 95 °C/1mmHg were pooled to give (**15-2**) as a colorless liquid.

(5-Amino-3-chloro-2-fluorophenyl)(cyclopropyl)methanone (15-3). A solution of 9.11 g (**15-2**) in 100 mL dry THF was cooled to –78 °C in a dry ice/acetone bath under argon. To it was added dropwise 15.7 mL 2.5 M *n*BuLi in hexanes under vigorous stirring. After complete addition, the mixture was stirred at –78 °C for 2 h. To the mixture was added slowly 5.2 g (**15-1**) under stirring. After complete addition, the reaction mixture was stirred at –78 °C for 1 h, and then allowed to warm up to room temperature. The reaction mixture was poured into 400 mL cold 1:1 MeOH/1 N HCl under stirring. After further stirring for 30 min, the mixture was extracted with DCM (3×200 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to give crude (**15-3**) as a light brown oil.

***N*-[3-Chloro-5-(cyclopropylcarbonyl)-4-fluorophenyl]acetamide (15-4).** Crude (**15-3**) (6.09 g) was dissolved in 100 mL DCM. To it were added sequentially 6 mL acetic anhydride (Ac_2O) and 9.6 mL triethylamine (TEA) with ice bath cooling and vigorous stirring. After complete addition, the reaction mixture was further stirred at room temperature for 1 h, diluted with 200 mL DCM, and washed with 0.1 N HCl (3×200 mL). The organic layer was dried with $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with hexanes-EtOAc as eluent and then crystallized from hexanes-EtOAc to give pure (**15-4**) as a white solid.

(*E*)- and (*Z*)- *N*-{3-Chloro-5-[cyclopropyl(hydroxyimino)methyl]-4-fluorophenyl} acetamide (15-5). A mixture of 2.28 g (**15-4**), 3.1 g NH_2OH•HCl, 30 mL pyridine and 30 mL EtOH was stirred at 50 °C for 22 h. EtOH was evaporated, and the residue was partitioned between 200 mL Et_2O and 200 mL 1 N HCl/brine. The organic layer was separated, washed with water (2×20 mL), dried with $MgSO_4$ and evaporated to give pure (**15-5**) as an off-white amorphous solid.

***N*-(7-Chloro-3-cyclopropylbenzisoxazol-5-yl)acetamide (15-6).** A solution of 2.01 g (**15-5**) in 40 mL dry DMF was protected with argon and stirred with ice bath cooling. To the solution was added in portions 1.48 g 60% NaH in mineral oil under vigorous stirring. After complete addition, the reaction mixture was stirred at room temperature for 1.5 h, and then was carefully added into a mixture of 300 mL saturated $NaHCO_3$ and 300 mL EtOAc under

stirring. The organic layer was separated, washed with water (3×50 mL), dried with $MgSO_4$ and evaporated. The residue was separated by column chromatography with hexanes-EtOAc as eluent to give pure (**15-6**) as a white solid.

***tert*-Butyl acetyl(7-chloro-3-cyclopropylbenzisoxazol-5-yl)carbamate (15-7).** A mixture of 789.3 mg (**15-6**), 808 mg Boc_2O and 38 mg DMAP in 40 mL dry DCM was stirred at room temperature for 1 h. Solvent was evaporated to give crude (**15-7**) as a white solid.

***tert*-Butyl (7-chloro-3-cyclopropylbenzisoxazol-5-yl)carbamate (15-8).** The above crude (**15-7**) was dissolved in 100 mL MeOH. The solution was basified with 0.1 mL 25 wt. % NaOMe/MeOH, and then stirred at room temperature for 30 min. To the solution was added 1 g solid NH_4Cl, and the solvent was evaporated. The residue was partitioned between 300 mL 0.1 N HCl/brine and 300 mL EtOAc. The organic layer was separated, washed sequentially with 100 mL 0.1 N HCl/brine, 100 mL water, 100 mL saturated $NaHCO_3$ and 100 mL water, dried with $MgSO_4$ and evaporated. The residue was crystallized from heptane-EtOAc to give pure (**15-8**) as a white solid.

5-[(*tert*-Butoxycarbonyl)amino]-7-chloro-3-cyclopropylbenzisoxazole-6-carboxylic acid (15-9). A solution of 770 mg (**15-8**) in 50 mL dry THF was protected under argon, and stirred with dry ice/acetone bath cooling. To the solution was added dropwise 5.9 mL 1.7 M *t*BuLi/pentane under vigorous stirring. After complete addition, the mixture was further stirred at –78 °C for 5 min. To the latter was added all at once 7.2 g freshly crushed dry ice under vigorous stirring. The mixture was stirred at –78 °C for 5 min, and then allowed to warm up to room temperature. The reaction mixture was partitioned between 300 mL 1 N HCl/brine and 300 mL EtOAc. The organic layer was separated, washed with 100 mL 0.1 N HCl/brine, dried with $MgSO_4$ and evaporated. The residue was separated by silica gel column chromatography with hexanes/EtOAc/HOAc as eluent to give (**15-9**) as an off-white foam.

Methyl 5-[(*tert*-butoxycarbonyl)amino-7-chloro-3-cyclopropylbenzisoxazole-6-carboxylate (15-10). A solution of 815 mg (**15-9**) and 5 mL MeOH in 10 mL DCM was stirred with ice bath cooling. To the solution was added dropwise 2.31 mL 2 M trimethylsilyldiazomethane ($TMSCHN_2$) in hexanes under stirring. After complete addition, the solution was stirred at room temperature for 10 min and evaporated. The residue was dissolved in 100 mL DCM, and the solution was passed through a short silica gel column. The column was eluted with MeOH-DCM, and the combined fractions were evaporated to give (**15-10**) as an off-white solid.

Methyl 5-amino-7-chloro-3-cyclopropylbenzisoxazole-6-carboxylate (15-11). A solution of 813 mg (**15-10**) in 10 mL DCM was stirred with ice bath cooling. To it was added dropwise 10 mL TFA with stirring. After complete addition, the mixture was stirred at room temperature for 30 min and evaporated. The residue was partitioned between 200 mL saturated $NaHCO_3$ and 200 mL EtOAc. The organic layer was separated, washed with water (2×50 mL), dried with $MgSO_4$, and evaporated to give (**15-11**) as a yellow oil, which solidified on standing.

2-(5-Amino-7-chloro-3-cyclopropylbenzisoxazol-6-yl)propan-2-ol (Compound (15)). A solution of 7.73 mL 3M MeMgCl/THF in 6 mL dry THF was protected under argon and stirred with ice bath cooling. To it was added dropwise a solution of 620 mg (**15-11**) in 50 mL dry THF under vigorous stirring. After complete addition, the mixture was allowed to warm and then stirred at room temperature for 1 h. The mixture was added carefully into 300 mL saturated aqueous NH_4Cl under stirring and ice bath cooling. The mixture was extracted with DCM (3×100 mL), dried with $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with MeOH-DCM as eluent, and then crystallized from heptane-DCM to give pure (**Compound (15)**) as an off-white solid.

^1H NMR (400 MHz, $CDCl_3$) δ : 1.10 (m, 2H), 1.15 (m, 2H), 1.91 (s, 6H), 2.09 (m, 1H), 4.33 (br, 3H, NH_2 and OH), 6.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 7.11, 7.25, 30.7, 77.1, 105.6, 113.7, 120.4, 132.5, 144.4, 155.4, 160.5. LC-MS: 267.1 $(MH)^+$, 269.1 $[(M+2)H]^+$.

Example 12. Synthesis of 2-(6-amino-4-chloro-3-cyclopropylbenzisoxazol-7-yl)propan-2-ol (Compound (16))

1-(6-Amino-4-chloro-3-cyclopropyl-benzisoxazol-7-yl)ethanone (16-3). To a mixture of 636 mg (**16-2**) and 43 mg CuI was slowly added 8.16 mL 3 M MeMgCl/THF under stirring and ice bath cooling. The suspension was protected under argon, and heated at 70 °C in an oil bath for 15 min. The mixture was cooled to 0 °C in an ice bath. To it was added 136 mL MeOH, followed by 2.17 g solid NH_4Cl and 13.6 mL water. The mixture was warmed to room temperature with stirring to give a clear solution, which was adsorbed on silica gel, air-dried and separated by silica gel column chromatography with hexanes-EtOAc as eluent to give (**16-3**) as a yellow solid.

2-(6-Amino-4-chloro-3-cyclopropylbenzisoxazol-7-yl)propan-2-ol (Compound (16)). A mixture of 1.54 mL 3 M MeMgCl/THF and 5 mL dry THF was protected under argon and stirred with ice bath cooling. To it was added a solution of 387.1 mg (**16-3**) in 15 mL dry THF under vigorous stirring. After complete addition, the solution was further stirred at 0 °C

for 20 min. To the solution was added 100 mL saturated aqueous NH_4Cl with ice bath cooling and vigorous stirring. The mixture was warmed to room temperature and extracted with DCM (3×100 mL). The combined organic layers were dried with $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with MeOH-DCM as eluent, and crystallized from heptane-DCM to give pure (**Compound (16)**) as a light tan solid.

^1H NMR (400 MHz, $CDCl_3$) δ : 1.12 (m, 2H), 1.18 (m, 2H), 1.78 (s, 6H), 2.17 (m, 1H), 4.86 (br, 2H, NH_2), 6.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 8.81, 9.26, 30.1, 74.1, 112.7, 114.4, 121.8, 131.3, 143.8, 148.6, 166.1. LC-MS: 267.0 $(MH)^+$, 268.9 $[(M+2)H]^+$.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the present invention.

All patents, patent applications, and literature references cited herein are hereby expressly incorporated by reference.

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CLAIMS

1. A method of treating, preventing, or reducing a risk of a disease, disorder, condition, or cosmetic indication in which aldehyde toxicity is implicated in a subject in need thereof, comprising administering topically or systemically to the subject a compound comprising a primary amine, provided that the disease, disorder, or condition is not macular degeneration or Stargardt disease.

2. The method of claim 1, wherein the disease, disorder, or condition is an ocular disorder, provided that the ocular disorder is not macular degeneration or Stargardt disease.

3. The method of claim 2, wherein the ocular disorder is selected from the group consisting of dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, Fuch's endothelial dystrophy, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, conditions associated with tear lipid degradation or lacrimal gland dysfunction, uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea.

4. The method of claim 3, wherein the ocular disorder is dry eye syndrome.

5. The method of claim 3, wherein the ocular disorder is a condition associated with PRK healing and other corneal healing.

6. The method of claim 3, wherein the ocular disorder is selected from the group consisting of uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea.

7. The method of claim 6, wherein the ocular disorder is ocular rosacea or uveitis.

8. The method of claim 3, wherein the ocular disorder is selected from the group consisting of keratoconus, cataracts, bullous and other keratopathy, Fuchs' endothelial dystrophy, ocular cicatricial pemphigoid, and allergic conjunctivitis.

9. The method of claim 1, wherein the disease, disorder, or condition is a skin disease, disorder, or condition selected from the group consisting of psoriasis, topical (discoid) lupus,

contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjogren-Larsson Syndrome and other ichthyosis, and the cosmetic indication is selected from the group consisting of solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, and a skin condition associated burn or wound.

10. The method of claim 9, wherein the skin disease, disorder, or condition is selected from the group consisting of psoriasis, scleroderma, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, and Sjogren-Larsson Syndrome and other ichthyosis.

11. The method of claim 10, wherein the skin disease, disorder, or condition is contact dermatitis, atopic dermatitis, allergic dermatitis, or radiation dermatitis.

12. The method of claim 10, wherein the skin disease, disorder, or condition is Sjogren-Larsson Syndrome.

13. The method of claim 9, wherein the cosmetic indication is selected from the group consisting of solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, and a skin condition associated burn or wound.

14. The method of claim 1, wherein the disease, disorder, or condition is a condition associated with the toxic effects of blister agents or burns from alkali agents.

15. The method of claim 14, wherein the blister agent is sulfur mustard, nitrogen mustard, or phosgene oxime.

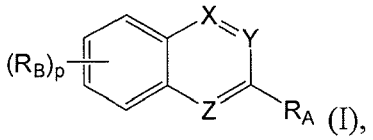
16. The method of claim 14, wherein the alkali agent is lime, lye, ammonia, or a drain cleaner.

17. The method of claim 1, wherein the disease, disorder, or condition is an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease, or diabetes, metabolic syndrome, or a fibrotic disease.

18. The method of claim 17, wherein the disease, disorder, or condition is selected from the group consisting of lupus, scleroderma, asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease, sepsis, atherosclerosis, ischemic-reperfusion injury, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis.

19. The method of claim 17, wherein the fibrotic disease is a renal, hepatic, pulmonary, or cardiac fibrosis.

20. The method of any one of claims 1 to 19, wherein the compound is a compound of formula (I):



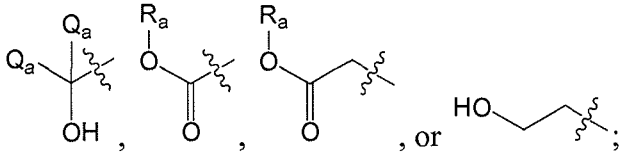
(I),

or a pharmaceutically acceptable salt thereof, wherein:

X, Y, and Z are each independently N, CH, or $C(NH_2)$, provided that one of X, Y, and Z is N;

p is 0, 1, 2, or 3;

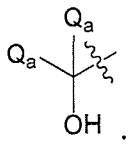
each R_B is independently halogen, hydroxyl, carbamoyl, amino, or unsubstituted or substituted aryl;

R_A is ;

Q_a is C_1-C_6 straight chain alkyl; and

R_a is unsubstituted or substituted C_1-C_8 straight chain or C_3-C_8 branched alkyl.

21. The method of claim 20, wherein p is 1.

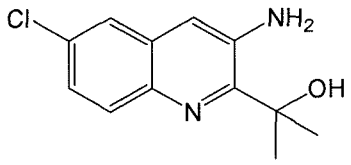
22. The method of claim 20, wherein R_A is .

23. The method of claim 20, wherein R_B is halogen, hydroxyl, carbamoyl, amino, or aryl.

24. The method of claim 23, wherein R_B is halogen.

25. The method of claim 24, wherein R_B is chlorine.

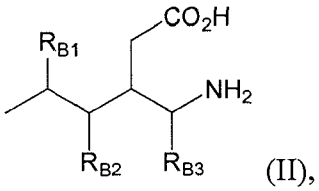
26. The method of claim 20, wherein the compound is



(9),

or a pharmaceutically acceptable salt thereof.

27. The method of any one of claims 1 to 19, wherein the compound is a compound of formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R_{B1} is unsubstituted or substituted C_1-C_8 straight chain or C_3-C_8 branched alkyl, C_2-C_8 straight chain or C_3-C_8 branched alkenyl, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, C_1-C_6 alkyl-C_3-C_7 cycloalkyl, hydroxyl, C_1-C_6 alkylphenoxy, phenyl, or substituted phenyl;

R_{B2} is H, unsubstituted or substituted C_1-C_6 straight chain or C_3-C_6 branched alkyl, phenyl, or substituted phenyl; and

R_{B3} is H, unsubstituted or substituted C_1-C_6 straight chain or branched C_3-C_6 alkyl, or carboxyl.

28. The method of claim 27, wherein the compound is selected from the group consisting of:

3-aminomethyl-5-methylhexanoic acid, 3-aminomethyl-5-methylheptanoic acid, 3-aminomethyl-5-methyl-octanoic acid, 3-aminomethyl-5-methyl-nonanoic acid, 3-aminomethyl-5-methyl-decanoic acid, 3-aminomethyl-5-methyl-undecanoic acid, 3-aminomethyl-5-methyl-dodecanoic acid, 3-aminomethyl-5-methyl-tridecanoic acid, 3-aminomethyl-5-cyclopropyl-hexanoic acid, 3-aminomethyl-5-cyclobutyl-hexanoic acid, 3-aminomethyl-5-cyclopentyl-hexanoic acid, 3-aminomethyl-5-cyclohexyl-hexanoic acid, 3-

aminomethyl-5-trifluoromethyl-hexanoic acid, 3-aminomethyl-5-phenyl-hexanoic acid, 3-aminomethyl-5-(2-chlorophenyl)-hexanoic acid, 3-aminomethyl-5-(3-chlorophenyl)-hexanoic acid, 3-aminomethyl-5-(4-chlorophenyl)-hexanoic acid, 3-aminomethyl-5-(2-methoxyphenyl)-hexanoic acid, 3-aminomethyl-5-(3-methoxyphenyl)-hexanoic acid, 3-aminomethyl-5-(4-methoxyphenyl)-hexanoic acid, 3-aminomethyl-5-benzyl-hexanoic acid, (S)-3-aminomethyl-5-methylhexanoic acid, (R)-3-aminomethyl-5-methylhexanoic acid, (3R,4S)-3-aminomethyl-4,5-dimethyl-hexanoic acid, 3-aminomethyl-4,5-dimethyl-hexanoic acid, (3R,4S)-3-aminomethyl-4,5-dimethyl-hexanoic acid MP; (3S,4S)-3-aminomethyl-4,5-dimethyl-hexanoic acid, (3R,4R)-3-aminomethyl-4,5-dimethyl-hexanoic acid MP; 3-aminomethyl-4-isopropyl-hexanoic acid, 3-aminomethyl-4-isopropyl-heptanoic acid, 3-aminomethyl-4-isopropyl-octanoic acid, 3-aminomethyl-4-isopropyl-nonanoic acid, 3-aminomethyl-4-isopropyl-decanoic acid, 3-aminomethyl-4-phenyl-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-ethoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-propoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-isopropoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-tert-butoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-fluoromethoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-fluoro-ethoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3,3,3-trifluoro-propoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-phenoxy-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-chloro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-chloro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-chloro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-fluoro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-fluoro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-fluoro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-methoxy-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-methoxy-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-methoxy-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(4-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(3-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-(2-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-6-hydroxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-methoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-ethoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-propoxy-hexanoic acid, (3S,5S)-3-aminomethyl-6-isopropoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-tert-butoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-fluoromethoxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-fluoro-ethoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-(3,3,3-trifluoro-propoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-phenoxy-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-chloro-phenoxy)-5-methyl-hexanoic acid,

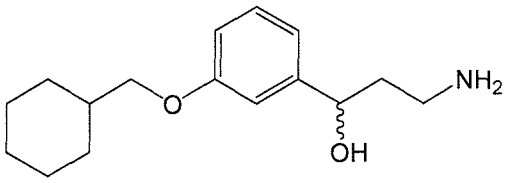
(3S,5S)-3-aminomethyl-6-(3-chloro-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-chloro-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-fluoro-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-fluoro-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-fluoro-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-methoxy-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-methoxy-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-methoxy-phenoxy)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl 6-(4-trifluoromethyl-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl 6-(3-trifluoromethyl-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl 6-(2-trifluoromethyl-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl 6-(4-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl 6-(3-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-5-methyl 6-(2-nitro-phenoxy)-hexanoic acid, (3S,5S)-3-aminomethyl-6-benzyloxy-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-7-hydroxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-methoxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-ethoxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-propoxy-heptanoic acid, (3S,5S)-3-aminomethyl-7-isopropoxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-tert-butoxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-fluoromethoxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(2-fluoro-ethoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(3,3,3-trifluoro-propoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-7-benzyloxy-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-phenoxy-heptanoic acid, (3S,5S)-3-aminomethyl-7-(4-chloro-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(3-chloro-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(2-chloro-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(4-fluoro-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(3-fluoro-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(2-fluoro-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(4-methoxy-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(3-methoxy-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-7-(2-methoxy-phenoxy)-5-methyl-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(4-trifluoromethyl-phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(3-trifluoromethyl-phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(2-trifluoromethyl-phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(4-nitro-phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(3-nitro-phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-7-(2-nitro-phenoxy)-heptanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-phenyl-hexanoic acid, (3S,5S)-

3-aminomethyl-6-(4-chloro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-chloro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-chloro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-methoxy-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-methoxy-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-methoxy-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(4-fluoro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(3-fluoro-phenyl)-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-6-(2-fluoro-phenyl)-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-5-methyl-7-phenyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(4-chloro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(3-chloro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(2-chloro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(4-methoxy-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(3-methoxy-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(2-methoxy-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(4-fluoro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(3-fluoro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-(2-fluoro-phenyl)-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-5-methyl-oct-7-enoic acid, (3S,5R)-3-aminomethyl-5-methyl-non-8-enoic acid, (E)-(3S,5S)-3-aminomethyl-5-methyl-oct-6-enoic acid, (Z)-(3S,5S)-3-aminomethyl-5-methyl-oct-6-enoic acid, (Z)-(3S,5S)-3-aminomethyl-5-methyl-non-6-enoic acid, (E)-(3S,5S)-3-aminomethyl-5-methyl-non-6-enoic acid, (E)-(3S,5R)-3-aminomethyl-5-methyl-non-7-enoic acid, (Z)-(3S,5R)-3-aminomethyl-5-methyl-non-7-enoic acid, (Z)-(3S,5R)-3-aminomethyl-5-methyl-dec-7-enoic acid, (E)-(3S,5R)-3-aminomethyl-5-methyl-undec-7-enoic acid, (3S,5S)-3-aminomethyl-5,6,6-trimethyl-heptanoic acid, (3S,5S)-3-aminomethyl-5,6-dimethyl-heptanoic acid, (3S,5S)-3-aminomethyl-5-cyclopropyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-cyclobutyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-cyclopentyl-hexanoic acid, (3S,5S)-3-aminomethyl-5-cyclohexyl-hexanoic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-5-methyl-nonanoic acid, (3S,5R)-3-aminomethyl-5-methyl-decanoic acid, (3S,5R)-3-aminomethyl-5-methyl-undecanoic acid, (3S,5R)-3-aminomethyl-5-methyl-dodecanoic acid, (3S,5R)-3-aminomethyl-5,9-dimethyl-decanoic acid, (3S,5R)-3-aminomethyl-5,7-dimethyl-octanoic acid, (3S,5R)-3-aminomethyl-5,8-dimethyl-nonanoic acid, (3S,5R)-3-aminomethyl-6-cyclopropyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-6-cyclobutyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-6-cyclopentyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-6-cyclohexyl-5-methyl-hexanoic acid, (3S,5R)-3-aminomethyl-7-cyclopropyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-cyclobutyl-5-methyl-heptanoic acid,

(3S,5R)-3-aminomethyl-7-cyclopentyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-7-cyclohexyl-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-8-cyclopropyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-8-cyclobutyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-8-cyclopentyl-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-8-cyclohexyl-5-methyl-octanoic acid, (3S,5S)-3-aminomethyl-6-fluoro-5-methyl-hexanoic acid, (3S,5S)-3-aminomethyl-7-fluoro-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-8-fluoro-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-9-fluoro-5-methyl-nonanoic acid, (3S,5S)-3-aminomethyl-7,7,7-trifluoro-5-methyl-heptanoic acid, (3S,5R)-3-aminomethyl-8,8,8-trifluoro-5-methyl-octanoic acid, (3S,5R)-3-aminomethyl-5-methyl-8-phenyl-octanoic acid, (3S,5S)-3-aminomethyl-5-methyl-6-phenyl-hexanoic acid, and (3S,5R)-3-aminomethyl-5-methyl-7-phenyl-heptanoic acid,
or a pharmaceutically acceptable salt thereof.

29. The method of claim 28, wherein the compound is (S)-3-(aminomethyl)-5-methylhexanoic acid or (R)-3-(aminomethyl)-5-methylhexanoic acid, or a pharmaceutically acceptable salt or racemic mixture thereof.

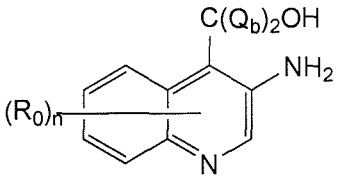
30. The method of any one of claims 1 to 19, wherein the compound is



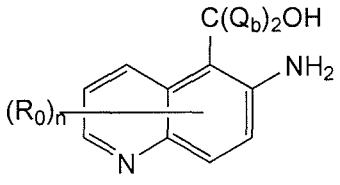
(11),

or a pharmaceutically acceptable salt thereof.

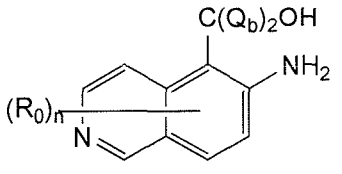
31. The method of any one of claims 1 to 19, wherein the compound is a compound of one of formula (IIIa)-(IIIf):



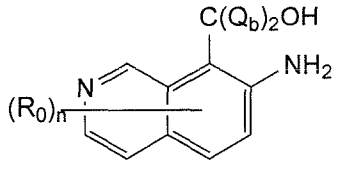
(IIIa),



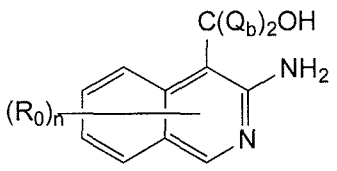
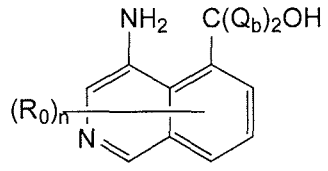
(IIIb),



(IIIc),

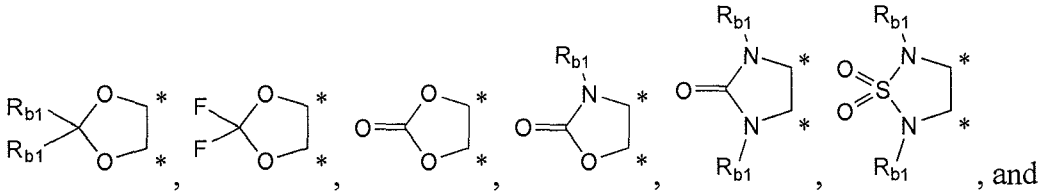
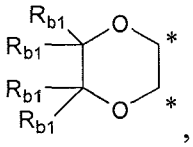


(IIId),

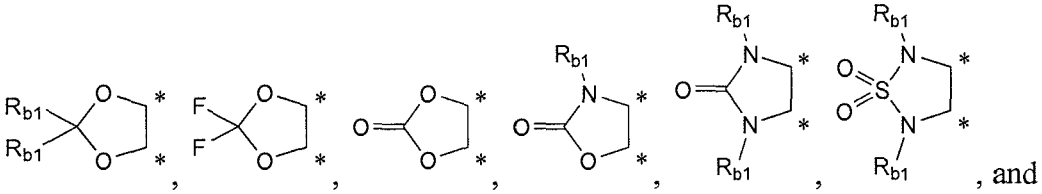
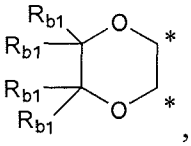

(IIIe), and

(IIIf),

or a pharmaceutically acceptable salt thereof, wherein:

each R_0 is independently halogen, CF_2H, CF_3, R_{b2}, OR_{b1}, $COOR_{b1}$, $CON(R_{b1})_2$, $N(R_{b2})_2$, $NR_{b1}COR_{b1}$, $NR_{b1}COOR_{b2}$, $NR_{b1}CON(R_{b1})_2$, $NR_{b1}SO_2R_{b2}$, SO_2R_{b2}, $SO_2N(R_{b1})_2$, unsubstituted phenyl, or phenyl substituted with 1-3 substituents independently selected from F, Cl, CF_2H, CF_3, OR_{b1}, and R_{b2}, or two such substituents, together with the carbon atoms of the phenyl rings to which they are attached, form a five-or six-membered ring having a structure selected from


, and

, wherein "*" denotes the positions of the carbon atoms to which the substituents are attached on the phenyl ring, or

alternatively, when attached to adjacent atoms, any two R_0, together with the atoms to which they are attached, form a five- or six-membered ring having a structure selected from

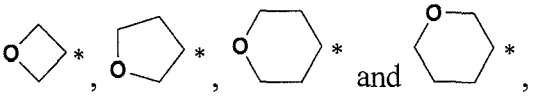

, and

, wherein "*" denotes the positions of the atoms to which the two R_0 are attached, or

each R_{b1} is independently H, C_1-C_6 straight chain or C_3-C_6 branched alkyl, or C_3-C_6 cycloalkyl;

each R_{b2} is independently C_1-C_6 straight chain or C_3-C_6 branched alkyl, or C_3-C_6 cycloalkyl;

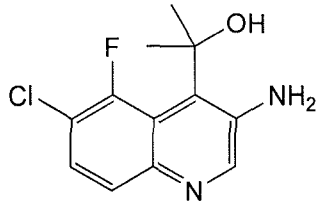
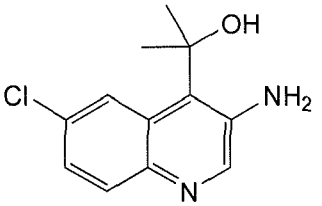
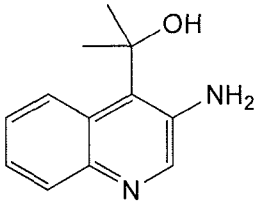
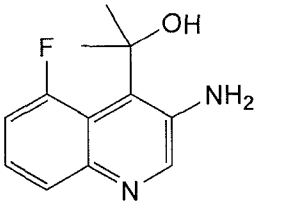
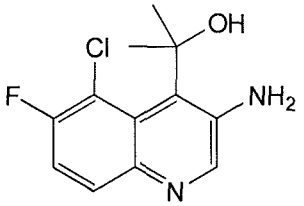
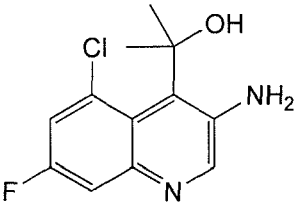
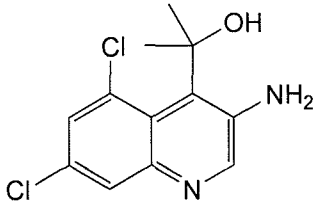
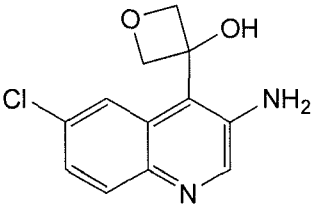
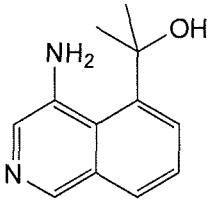
each R_{b3} is independently H, C_1-C_6 straight chain or C_3-C_6 branched alkyl, or halogen;

each Q_b is independently H, C_1-C_6 straight chain or C_3-C_6 branched alkyl, or C_1-C_6 straight chain or C_3-C_6 branched alkyl substituted with 1-6 F, or

both Q_b, together with the carbon atom to which they are attached, form a C_3-C_6 carbocycle or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which both Q_b are attached, wherein the carbocycle or the heterocycle is optionally substituted with one or more R_{b3}; and

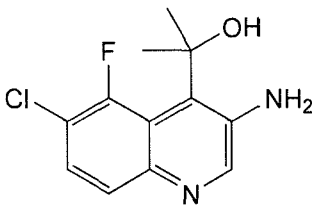
n is 0,1, 2, or 3.

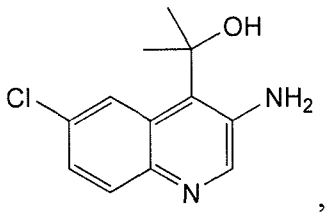
32. The method of claim 31, wherein the compound is selected from the group consisting of:

, ,
, ,
, ,
, , and
,

or a pharmaceutically acceptable salt thereof.

33. The method of claim 32, wherein the compound is

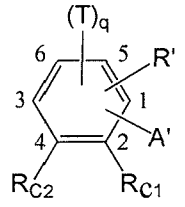


or


,

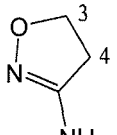
or a pharmaceutically acceptable salt thereof.

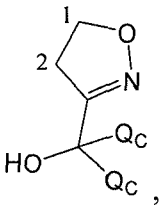
34. The method of any one of claims 1 to 19, wherein the compound is a compound of formula (IV):



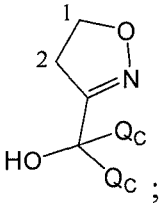
(IV),

or a pharmaceutically acceptable salt thereof, wherein:

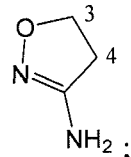
A' and R', together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with R_C', wherein "1", "2", "3", "4", "5", and "6" denote the points of attachment of the heteroaryl ring to the phenyl ring, provided that when the heteroaryl ring is 

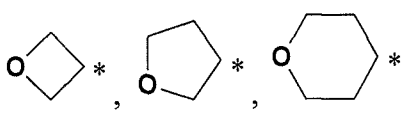
, then R_{C1} is $C(Q_C)_2OH$, R_{C2} is absent, and R_C' is absent, and that when the heteroaryl ring is 

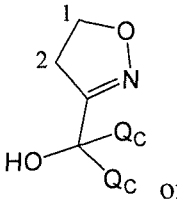
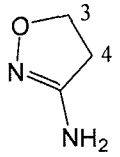
, then R_{C1} is absent, R_{C2} is NH_2, and R_C' is absent;

R_{C1} is $C(Q_C)_2OH$, or R_{C1} is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form 

;

R_{C2} is NH_2, or R_{C2} is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form ;

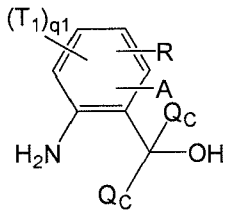
each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached;

R_C' is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_1-C_6 alkyl, or C_1-C_6 alkoxy, or R_C' is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form  or ;

q is 0, 1, or 2, provided that when R_C' is phenyl, q is not 0; and

each T is independently halogen, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano.

35. The method of claim 34, wherein the compound is a compound of formula (IVa):


(IVa),

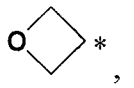
or a pharmaceutically acceptable salt thereof, wherein:

A and R, together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with R_C;

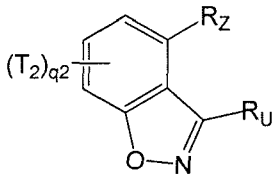
R_C is C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, aryl, aryl substituted with C_1-C_6 alkyl, or C_1-C_6 alkoxy;

q_1 is 1 or 2;

each T_1 is independently halogen, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano; and

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached.

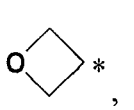
36. The method of claim 34, wherein the compound is a compound of formula (IVb):



(IVb),

or a pharmaceutically acceptable salt thereof, wherein:

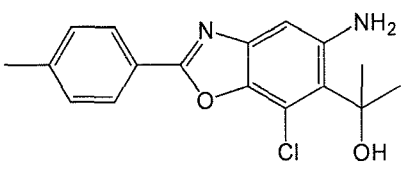
one of R_U and R_Z is $C(Q_C)_2OH$, and the other is NH_2;

each Q_C is independently C_1-C_6 alkyl or C_3-C_6 cycloalkyl, or two Q_C, together with the carbon atom to which they are attached, form a C_3-C_6 carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two Q_C are attached;

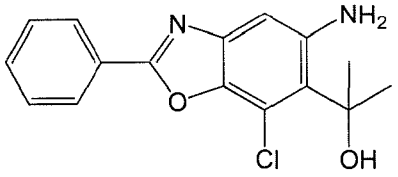
q_2 is 0, 1, or 2; and

each T_2 is independently halogen, C_1-C_{10} alkyl, C_1-C_{10} alkyl substituted with C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl, or cyano.

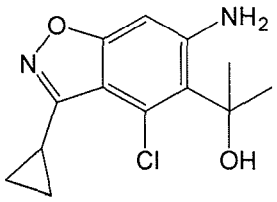
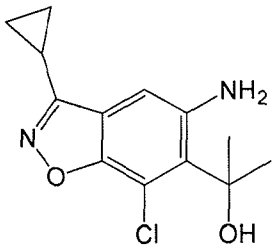
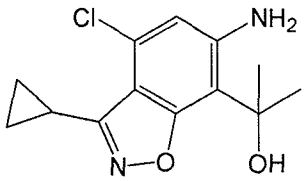
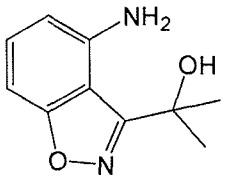
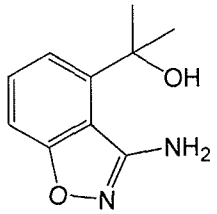
37. The method of claim 34, wherein the compound is a compound selected from the group consisting of:



,

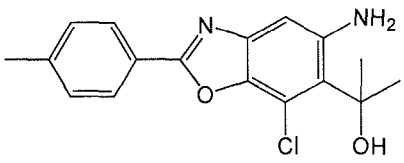
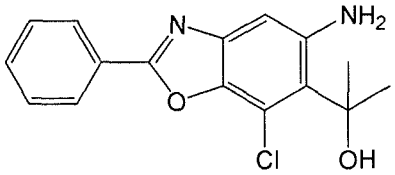
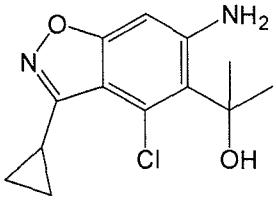
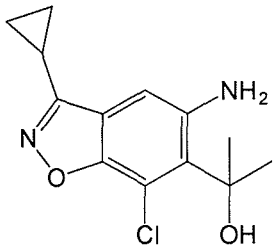
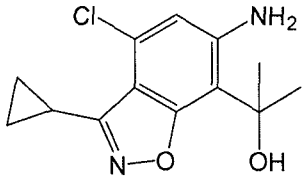


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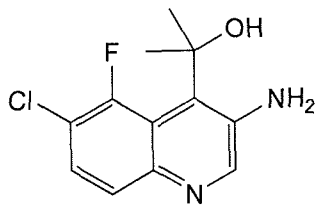
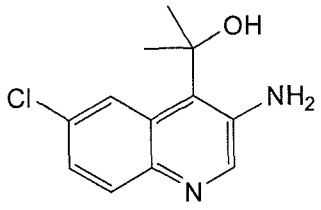
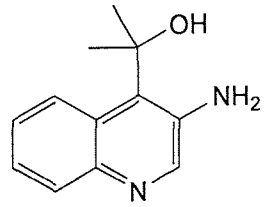
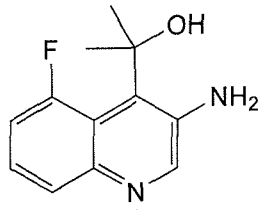
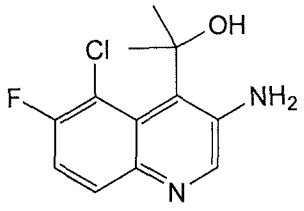
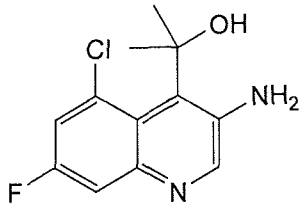
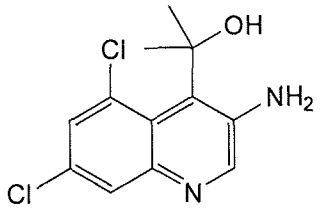
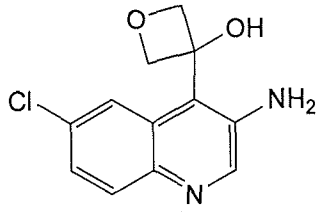
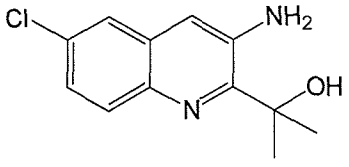
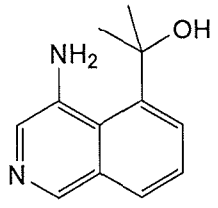
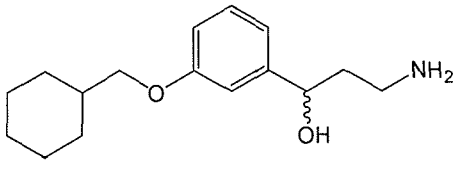
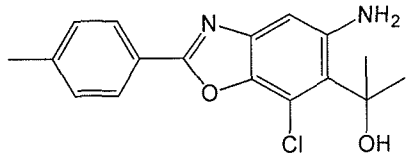
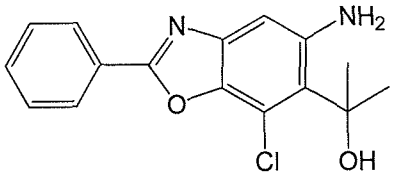
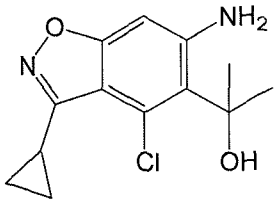
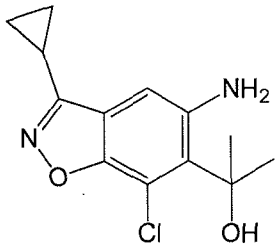
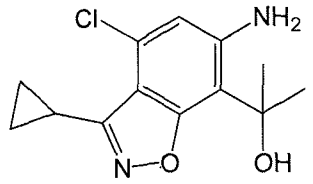
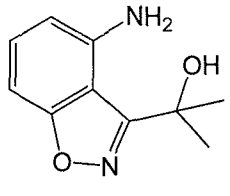
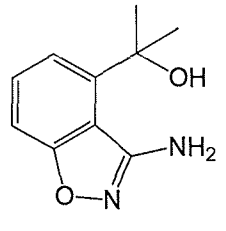
or a pharmaceutically acceptable salt thereof.

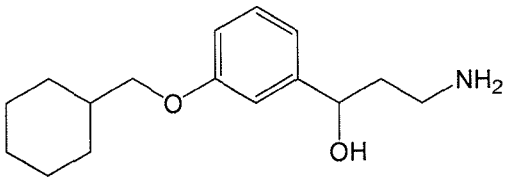
38. The compound of claim 37, wherein the compound is

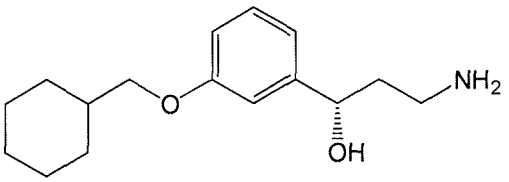






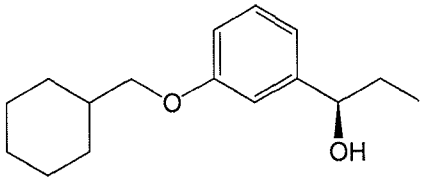
or a pharmaceutically acceptable salt thereof.

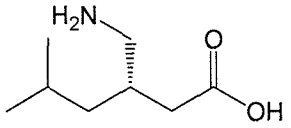
39. A method of treating, preventing, or reducing a risk of a disease, disorder, or condition in which aldehyde toxicity is implicated in a subject in need thereof, comprising administering topically or systemically to the subject a compound selected from the group consisting of:

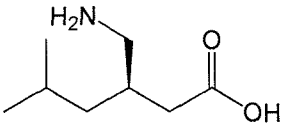





















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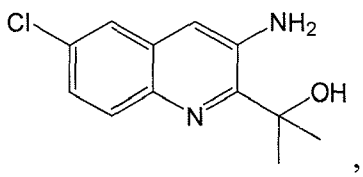
or a pharmaceutically acceptable salt thereof, wherein the disease, disorder, or condition is selected from the group consisting of:

an ocular disorder selected from the group consisting of dry eye syndrome, cataracts, keratoconus, bullous and other keratopathy, Fuch's endothelial dystrophy, allergic conjunctivitis, ocular cicatricial pemphigoid, conditions associated with PRK healing and other corneal healing, conditions associated with tear lipid degradation or lacrimal gland dysfunction, uveitis, scleritis, ocular Stevens Johnson Syndrome, and ocular rosacea,

a skin disease, disorder, or condition selected from the group consisting of psoriasis, topical (discoid) lupus, contact dermatitis, atopic dermatitis, allergic dermatitis, radiation dermatitis, acne vulgaris, Sjogren-Larsson Syndrome and other ichthyosis, and a cosmetic indication selected from the group consisting of solar elastosis/wrinkles, skin tone firmness, puffiness, eczema, smoke or irritant induced skin changes, dermal incision, and a skin condition associated burn or wound,

a condition associated with the toxic effects of blister agents or burns from alkali agents, and

an autoimmune, immune-mediated, inflammatory, cardiovascular, or neurological disease, diabetes, metabolic syndrome, and a fibrotic disease.

40. The method of claim 39, wherein the compound is 

, or a pharmaceutically acceptable salt thereof.

41. Use of a compound comprising a primary amine in the manufacture of a medicament for the treatment, prevention, or reduction of a risk of a disease, disorder, condition, or a cosmetic indication in which aldehyde toxicity is implicated in a subject, provided that the disease, disorder or condition is not macular degeneration or Stargradt disease.

42. Use of a compound comprising a primary amine in treating, preventing, or reducing a risk of a disease, disorder, condition, or a cosmetic indication in which aldehyde toxicity is implicated in a subject, provided that the disease, disorder or condition is not macular degeneration or Stargradt disease.