[0005] With particular attention to pulmonary disorders, inflammation of the airways is a hallmark symptom of chronic inflammatory lung disorders, which are almost always linked with unfavorable clinical outcomes. Airway neutrophilia is a trait that is shared by all of these disorders, despite the fact that their causes are quite diverse. In the immune system's defense of the lung, mechanisms such as phagocytosis, degranulation, neutrophil extracellular trap formation, exosome secretion, release of cytokines and chemokines, and autophagy are all involved. Neutrophils, as vital regulators linking the innate and adaptive immune systems, are a double-edged sword. Even though neutrophils are an effective line of defense against external pathogens, neutrophils and the components that make up neutrophils have the potential to set off a number of cascades that result in inflammation and fibrogenesis.

[0006] Eczema is a chronic disease that causes inflammation, redness, and irritation of the skin. Atopic dermatitis is the most common form of eczema. The causes of eczema, including atopic dermatitis, remain unclear. Atopic dermatitis is a major global public health problem, affecting 1%-20% of people worldwide. The prevalence of atopic dermatitis in adults is about 1%-3%, and 10%-20%, in children. Atopic dermatitis is the most common form of eczema in childhood. Since 1960s, the prevalence of atopic dermatitis has increased more than 3-fold. The reasons for the rising prevalence are as yet unclear (Lee, J. H., et al. A Comprehensive Review of the Treatment of Atopic Eczema, *Allergy Asthma Immunol. Res.*, **2016** 8(3), 181-190). Atopic dermatitis is a worldwide public health concern with significant financial burden. In addition, atopic dermatitis affects the quality of life of families as well as those affected themselves. Eczema, including atopic dermatitis, remains a challenging condition for physicians and patients.

[0007] Accordingly, there is an ongoing need in the art for compounds, compositions and methods for treating fibrosis, such as idiopathic pulmonary fibrosis (IPF), and atopic dermatitis, along with a variety of other diseases and conditions relating to neutrophil migration.

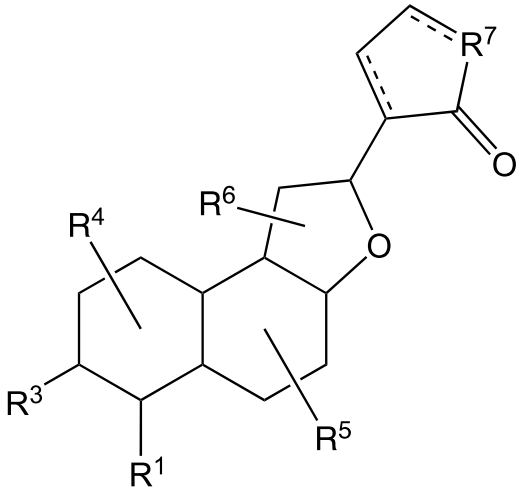
BRIEF SUMMARY

[0008] Examples described herein relate to compounds, compositions, and methods for treating and/or preventing fibrosis and various fibrotic diseases, disorders or conditions. It has been found that compounds described herein, such as a compound of Formula (I) and (II), can be administered to a subject in need thereof to decrease fibrotic symptoms, such as collagen deposition, collagen accumulation, collagen fiber formation, inflammatory cytokine

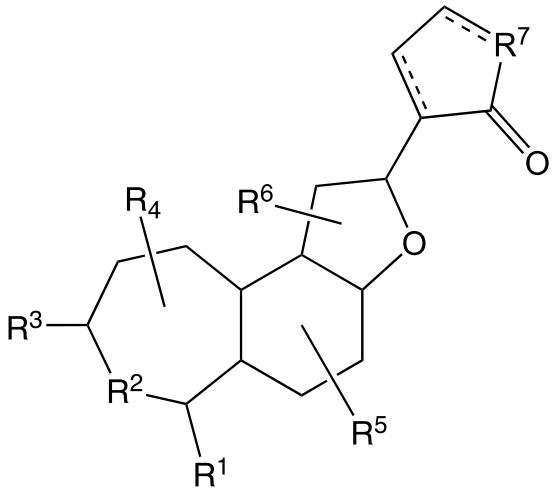
expression, and inflammatory cell infiltration, and treat and/or prevent various fibrotic diseases, disorders, and conditions characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

[0009] In other examples, it has been found that compounds described herein, such as a compound of Formula (I) and (II), can be administered to a subject in need thereof to decrease atopic dermatitis symptoms and treat and/or prevent various dermatological conditions, such as atopic dermatitis.

[0010] A compound of Formula (I) or Formula (II) is provided herein, as follows:



(I),



(II),

or pharmaceutically acceptable salts thereof, wherein:

R^1 is a alkyl, -CN, $-NH_2$, -OH, $-CH_2OH$, -CHO, $-CH_2R^8$, -COOH, $-CONH_2$, $-COR^8$, $-N_3$, $-COR^8$, -SH -S(alkyl), halogen, aryl, heteroaryl, or linked to R^3 to form a 3- to 10-membered cyclic or heterocyclic group, wherein the alkyl, the aryl, the heteroaryl, and the cyclic or heterocyclic group are unsubstituted or substituted with one or more R^8;

R^2 is oxygen or NR^9;

R^3 is a hydroxyl, =O, halogen, -SH, -S(alkyl), $-NR^9R^{10}$, -COOH, $-COOR^9$, $-CONH_2$, -CN, $-N_3$, haloalkyl, or alkoxy;

R^4, R^5, and R^6 are each, independently, hydrogen or an unsubstituted or substituted alkyl;

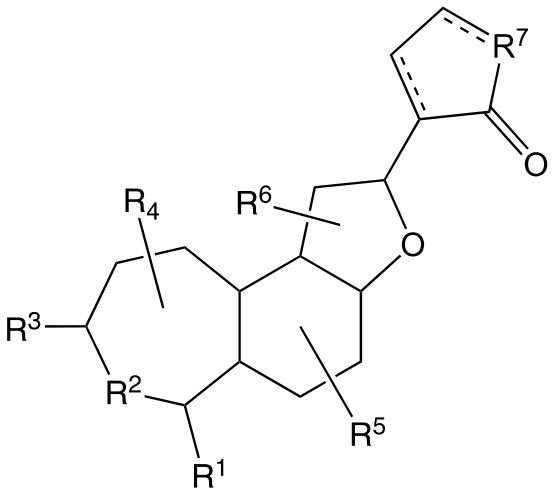
R^7 is oxygen, nitrogen, or NR^9;

each R^8 is, independently, hydroxyl, halogen, -SH, -S(alkyl), $-NR^9R^{10}$, -COOH, $-COOR^9$, $-CONH_2$, $-COR^9$, $-COHR^9R^{10}$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, or aralkyl; and

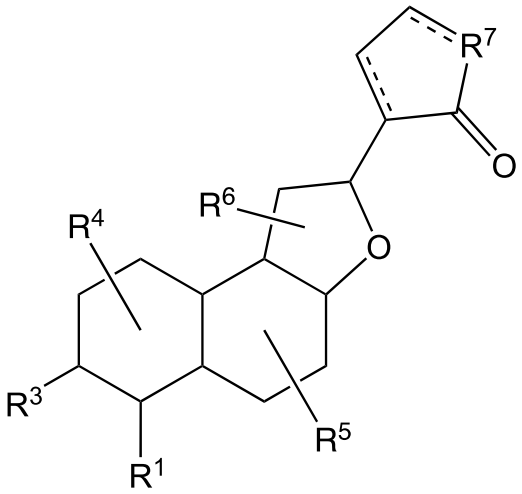
R^9 and R^{10} are each, independently, hydrogen or an unsubstituted or substituted alkyl;

with the proviso that the compound of Formula (I) is not isoandrographolide.

[0010a] In one aspect, the present disclosure refers to a compound of Formula (II) or Formula (I):



(II),



(I),

or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is a C_1-C_6 alkyl, -OH, -CN, $-NH_2$, $-CH_2OH$, -CHO, $-CH_2R^8$, -COOH, $-CONH_2$, $-COR^8$, $-N_3$, -SH -SMe, a halogen atom, aryl, heteroaryl, or linked to R^3 to form a 3- to 10-membered cyclic, heterocyclic, or heteroaromatic group, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, and the cyclic or heterocyclic group are unsubstituted or substituted with one or more oxo or R^8;

R^2 is NR^9 or oxygen;

R^3 is a =O, hydroxyl, =N-OH, halogen, -SH, -SMe, $-NR^9R^{10}$, -COOH, $-COOR^9$, $-OCOR^9$, $-CONH_2$, -CN, $-N_3$, C_1-C_5 haloalkyl, or C_1-C_5 alkoxy;

R^4, R^5, and R^6 are each, independently, hydrogen or a C_1-C_5 unsubstituted or substituted alkyl;

R^7 is oxygen, nitrogen, or NR^9;

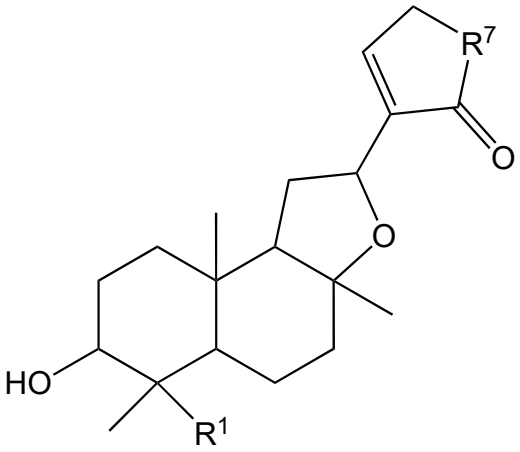
each R^8 is, independently, a hydroxyl, a halogen, -SH, -SMe, $-NR^9R^{10}$, -COOH, $-COOR^9$, $-OCOR^9$, $-CONH_2$, $-COR^9$, $-COHR^9R^{10}$, -CN, $-N_3$, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, aryl, aralkyl, or heterocyclyl; and

R^9 and R^{10} are each, independently, hydrogen, C_3-C_8 cycloalkyl, or C_1-C_5 unsubstituted or substituted alkyl;

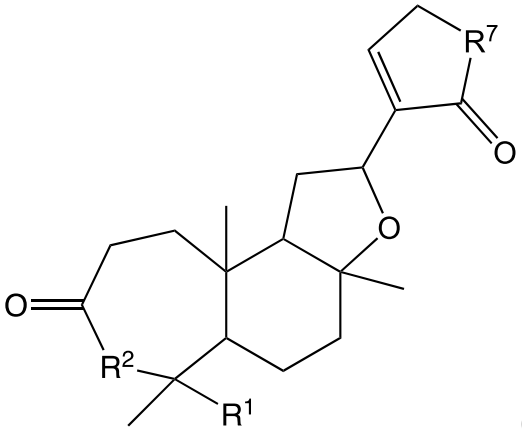
with the proviso that the compound of Formula (I) is not isoandrographolide.

[0011] In some examples, a method of treating or preventing a fibrotic disease, disorder or condition includes administering to a subject in need thereof a therapeutically effect amount of compound of Formula (I) or (II).

[0012] In certain examples, the compound of Formula (I) is Formula (Ia) and the compound of Formula (II) is Formula (IIa), as follows:



(Ia),



(IIa),

or pharmaceutically acceptable salts thereof, wherein:

R^1 is a C_1-C_6 alkyl, -CN, $-NH_2$, -OH, $-CH_2OH$, CHO, $-CH_2R^8$, -COOH, $-CONH_2$, $-COR^8$, $-N_3$, $-COR^8$, -SH -Sme, a halogen atom, aryl, heteroaryl, or linked to R^3 to form a 3- to 10-membered cyclic or heterocyclic group, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, and the cyclic or heterocyclic group are unsubstituted or substituted with one or more R^8;

R^2 is oxygen or NR^9;

R^7 is oxygen, nitrogen, or NR^9;

each R^8 is, independently, a hydroxyl, a halogen, -SH, -Sme, $-NR^9R^{10}$, -COOH, $-COOR^9$, $-CONH_2$, $-COR^9$, $-COHR^9R^{10}$, -CN, $-N_3$, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, aryl, or aralkyl; and

R^9 and R^{10} are each, independently, hydrogen or a C_1-C_5 unsubstituted or substituted alkyl;

with the proviso that the compound of Formula (I) is not isoandrographolide.

[0012a] In another aspect, the present disclosure refers to a method of making a compound as disclosed herein, wherein the compound is of Formula (Iaa), the method comprising:

providing a solution of isoandrographolide and a solvent;

combining 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), tetrabutylammonium iodide (TBAI), N-Chlorosuccinimide (NCS), a salt, and the solution to form a first intermediate;

combining hydroxylamine hydrochloride, pyridine, and the first intermediate to form a second intermediate; and

dehydration into cyanide of the second intermediate to form the compound of Formula (Iaa), optionally, wherein the step of dehydration into cyanide, comprises combining triethylamine, 4-toluenesulfonyl chloride, and the second intermediate to form the compound of Formula (Iaa); or wherein the step of dehydration into cyanide, comprises combining benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and the second intermediate to form the compound of Formula (Iaa).

[0012b] In another aspect, the present disclosure refers to a method of making a compound as disclosed herein, wherein the compound is of Formula (IIaa), the method comprising:

providing a solution of isoandrographolide and a solvent;

combining tert-Butyldimethylsilyl chloride (TBDMSCl), and the solution to form a first intermediate;

combining pyridine, celite, pyridinium chlorochromate, and the first intermediate to form a second intermediate;

combining hydroxylamine hydrochloride, pyridine, and the second intermediate to form a third intermediate; and

combining 4-toluenesulfonyl chloride and the third intermediate followed by treatment with dioxane HCL to form the compound of Formula (IIaa).

[0012c] In another aspect, the present disclosure refers to a method of making a compound as disclosed herein, wherein the compound is of Formula (IIaa), the method comprising:

providing a solution of isoandrographolide and a solvent;

combining Dess-Martin Periodinane (DMP), and the solution to form a first intermediate;

combining hydroxylamine hydrochloride, pyridine, and the first intermediate to form a second intermediate; and

combining triethylamine, 4-methylbenzene-1-sulfonyl chloride, 4-dimethylaminopyridine (DMAP), and the second intermediate, followed by treatment with dioxane HCl to form the compound of Formula (IIaa).**[0013]** In various examples, the compounds of Formula (I) or Formula (II), and their pharmaceutically acceptable compositions, are direct or indirect inhibitors or direct or indirect modulators of one or more of the following therapeutic targets: neutrophil migration, cathepsin D (Cath D), surfactant protein C (SPC), glutathione (GSH), collagen, type I, alpha 1 (COL1A1), pyruvate carboxylase (PC), 90kD heat shock protein (Hsp90β), and transforming growth factor-beta (TGF-β1), and thus are useful for treating or lessening the severity of the variety of diseases, disorders, or conditions described herein.

[0013a] In another aspect, the present disclosure refers to a pharmaceutical composition as disclosed herein, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, and at least one pharmaceutically acceptable carrier.

[0013b] In yet another aspect, the present disclosure refers to a compound as disclosed herein, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition as disclosed herein, for use as a medicament.

[0014] In these and other examples, because the compounds of Formula (I) or Formula (II), and their pharmaceutically acceptable compositions, are direct or indirect inhibitors or direct or indirect modulators of neutrophil migration, the compounds of Formula (I) or Formula (II), and their pharmaceutically acceptable compositions, may be suitable for treating and/or preventing cardiovascular diseases and conditions (*e.g.,* atherosclerosis, acute coronary ischaemia, heart failure, peripheral artery disease, aortic aneurysm, arrythmia, and acute myocardial infarction (AMI)); endocrine diseases and conditions (*e.g.,* CKD, tubulointerstitial fibrosis (TIF), gout, and diabetes); neurological diseases and conditions (*e.g.,* Alzheimer's disease); gastrointestinal diseases and conditions (*e.g.,* pancreatitis IBD, and ulcerative colitis); autoimmune diseases and conditions (*e.g.,* lupus erythematosus (SLE), vasculitis, and rheumatoid arthritis (RA)); hematological diseases and conditions (*e.g.,* sickle cell disease (VOC)), pulmonary diseases and conditions (*e.g.,* COPD, IPF, asthma, type 2-low neutrophilic asthma, and cystic fibrosis), dermatological diseases and conditions (*e.g.,* atopic dermatitis, lupus (SLE), psoriasis, dermatomyositis (indiopathic inflammatory myopathy), hidradenitis suppurativa (HS), sweet syndrome, pyoderma gangrenosum (PG), acne, Schnitzler's syndrome, and adult onset Still's disease); or combinations thereof.

[0014a] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating, or preventing a neutrophil-related condition or disease, optionally, wherein the condition or disease is a cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a dermatological disease or condition, or any combination thereof; or optionally, wherein the treating is ameliorating a neutrophil-related condition or disease in the subject.

[0014b] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating, or preventing a fibrotic condition or disease, optionally, wherein the condition or disease is idiopathic pulmonary fibrosis (IPF); or optionally, wherein the treating is ameliorating a fibrotic condition or disease in the subject.

[0014c] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating, or preventing a dermatological condition or disease, optionally, wherein the condition or disease is atopic dermatitis; or optionally, wherein the treating is ameliorating a dermatological condition or disease in the subject.

[0015] As described herein, the compounds of Formula (I) or Formula (II) are provided as inhibitors or modulators of one or more of the following therapeutic targets: neutrophil migration, cathepsin D (Cath D), surfactant protein C (SPC), glutathione (GSH), collagen, type I, alpha 1 (COL1A1), pyruvate carboxylase (PC), 90kD heat shock protein (Hsp90β), and transforming growth factor-beta (TGF-β1). In relation to, or independent of, this inhibitory or modulatory activity, the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to fibrosis and atopic dermatitis. Accordingly, in another example of the disclosure, pharmaceutically acceptable compositions are provided,

wherein these compositions comprise any of the compounds of Formula (I) or Formula (II) as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain examples, these compositions optionally further comprise one or more additional therapeutic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

[0017] FIGS.1A-1F depict a series of bar graphs illustrating the reduction in fibrotic symptoms in a bleomycin-induced pulmonary fibrosis model upon treatment with either compound 3 or various controls. For each bar graph, the bars, from left to right, denote a normal control, bleomycin (control), pirfenidone (control) at 100 mpk, compound 3 at 1 mpk, compound 3 at 3 mpk, compound 3 at 10 mpk, and compound 3 at 30 mpk.

[0018] FIGS.2A-2D depict a series of bar graphs illustrating the therapeutic effects of compound 3 relative to various controls. For each bar graph, the bars, from left to right, denote a normal control, bleomycin (control), pirfenidone (control) at 100 mpk, compound 3 at 10 mpk (P), compound 3 at 30 mpk (P), compound 3 at 100 mpk (P), and compound 3 at 100 mpk (T).

[0019] FIGS.3A-3G depict a series of histological images illustrating the therapeutic effects of compound 3 relative to various controls.

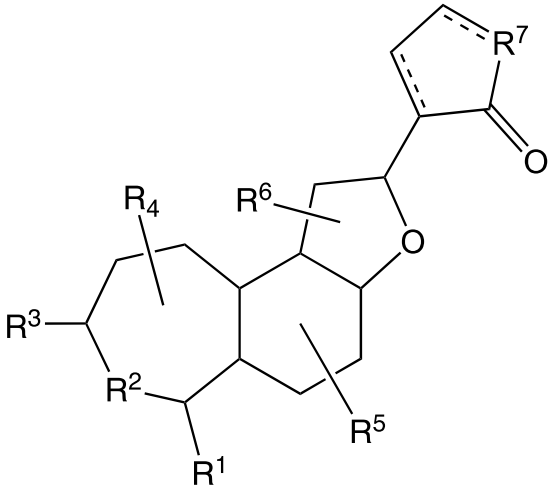
[0020] FIGS.4A-4G depict a series of bar graphs comparing the levels of TNF-α, IL-6, IL-36γ, total cell count (BALF), neutrophils (BALF), neutrophils (blood), and eosinophils (BALF), MIP-2 upon treatment with either compound 3 or various controls. For each bar graph, the bars, from left to right, denote a native control, treatment-free control (LPS), dexamethasone (comparative), and Compound 3 at 30 mpk.

[0021] FIGS.5A-5G depict a series of bar graphs illustrating the effects of compound 3 on inflammatory cytokines in a lipopolysaccharide (LPS)-induced acute lung injury model, relative to various controls. For each bar graph, the bars, from left to right, denote a normal

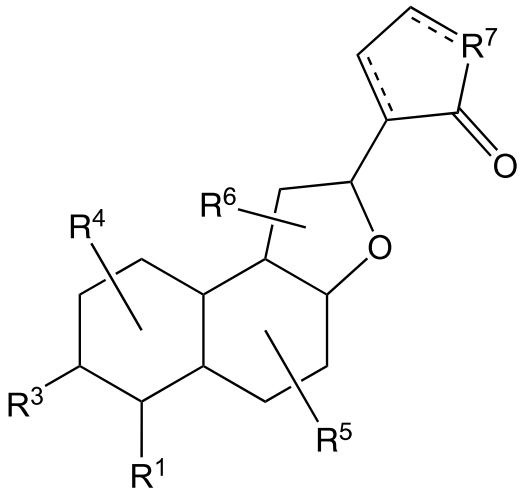
CLAIMS

What is claimed is:

1. A compound of Formula (II) or Formula (I):



(II),



(I),

or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is a C_1-C_6 alkyl, -OH, -CN, $-NH_2$, $-CH_2OH$, -CHO, $-CH_2R^8$, -COOH, $-CONH_2$, $-COR^8$, $-N_3$, -SH -SMe, a halogen atom, aryl, heteroaryl, or linked to R^3 to form a 3- to 10-membered cyclic, heterocyclic, or heteroaromatic group, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, and the cyclic or heterocyclic group are unsubstituted or substituted with one or more oxo or R^8;

R^2 is NR^9 or oxygen;

R^3 is a =O, hydroxyl, =N-OH, halogen, -SH, -SMe, $-NR^9R^{10}$, -COOH, $-COOR^9$, $-OCOR^9$, $-CONH_2$, -CN, $-N_3$, C_1-C_5 haloalkyl, or C_1-C_5 alkoxy;

R^4, R^5, and R^6 are each, independently, hydrogen or a C_1-C_5 unsubstituted or substituted alkyl;

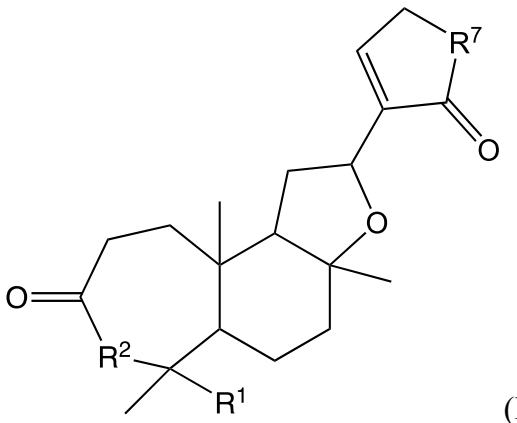
R^7 is oxygen, nitrogen, or NR^9;

each R^8 is, independently, a hydroxyl, a halogen, -SH, -SMe, $-NR^9R^{10}$, -COOH, $-COOR^9$, $-OCOR^9$, $-CONH_2$, $-COR^9$, $-COHR^9R^{10}$, -CN, $-N_3$, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, aryl, aralkyl, or heterocyclyl; and

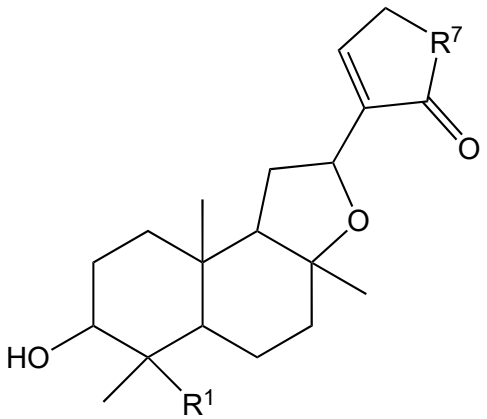
R^9 and R^{10} are each, independently, hydrogen, C_3-C_8 cycloalkyl, or C_1-C_5 unsubstituted or substituted alkyl;

with the proviso that the compound of Formula (I) is not isoandrographolide.

2. The compound of claim 1, wherein the compound of Formula (II) is Formula (IIa) and the compound of Formula (I) is Formula (Ia):



(IIa),



(Ia),

or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is a C_1-C_6 alkyl, -OH, -CN, -NH_2, -CH_2OH, CHO, -CH_2R^8, -COOH, -$CONH_2$, -COR^8, -N_3, -SH -SMe, a halogen atom, aryl, or heteroaryl, wherein the C_1-C_6 alkyl, the aryl, and the heteroaryl are unsubstituted or substituted with one or more R^8;

R^2 is NR^9 or oxygen;

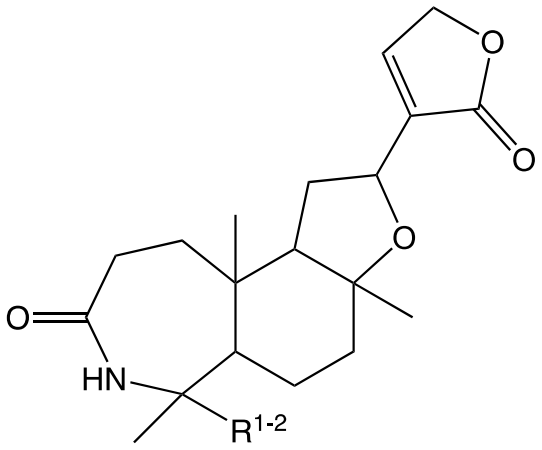
R^7 is oxygen, nitrogen, or NR^9;

each R^8 is, independently, a hydroxyl, a halogen, -SH, -SMe, -NR^9R^{10}, -COOH, -$COOR^9$, -$CONH_2$, -COR^9, -$COHR^9R^{10}$, -CN, -N_3, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, aryl, or aralkyl; and

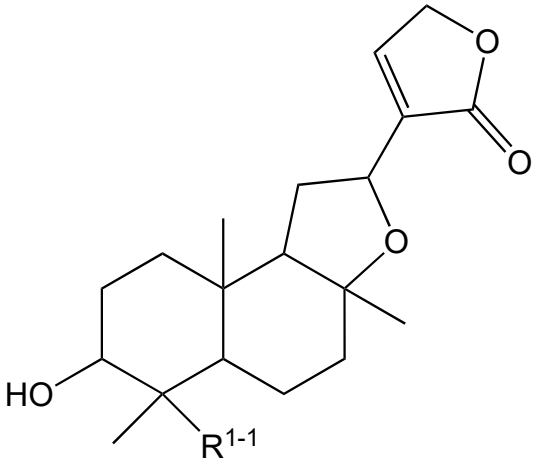
R^9 and R^{10} are each, independently, hydrogen or a C_1-C_5 unsubstituted or substituted alkyl;

with the proviso that the compound of Formula (Ia) is not isoandrographolide,

optionally, wherein the compound of Formula (IIa) is Formula (IIaa)and the compound of Formula (Ia) is Formula (Iaa):



(IIaa),



(Iaa),

or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein:

R^{1-1} is -OH, -CN, -NH_2, -COOH, CHO, -CH_2R^8, -$CONH_2$, -COR^8, -N_3, -SH, -SMe, a halogen atom, aryl, or heteroaryl, wherein the aryl and the heteroaryl are unsubstituted or substituted with one or more R^8;

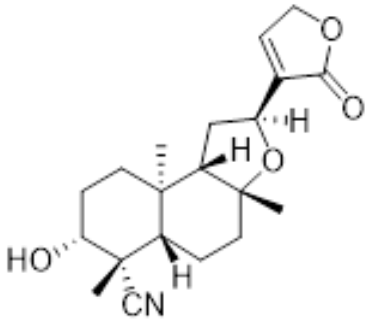
R^{1-2} is a -OH, -CN, C_1-C_6 alkyl, -NH_2, -CH_2OH, -COOH, CHO, -CH_2R^8, -$CONH_2$, -COR^8, -N_3, -COR^8, -SH, -SMe, a halogen atom, aryl, or heteroaryl, wherein the C_1-C_6 alkyl, the aryl, and the heteroaryl are unsubstituted or substituted with one or more R^8;

each R^8 is, independently, a hydroxyl, a halogen, -SH, -SMe, -NR^9R^{10}, -COOH, -$COOR^9$, -$CONH_2$, -COR^9, -$COHR^9R^{10}$, -CN, -N_3, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_5 alkoxy, aryl, or aralkyl; and

R^9 and R^{10} are each, independently, hydrogen or a C_1-C_5 unsubstituted or substituted alkyl.

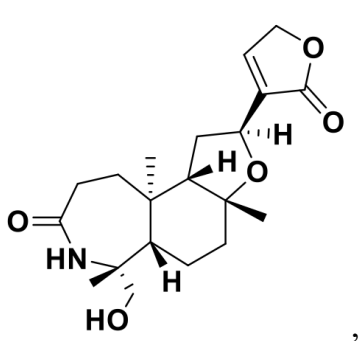
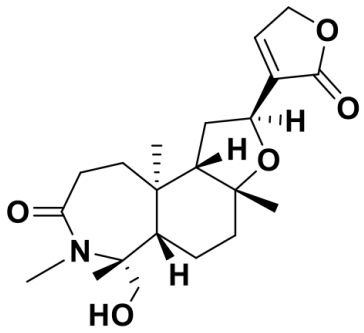
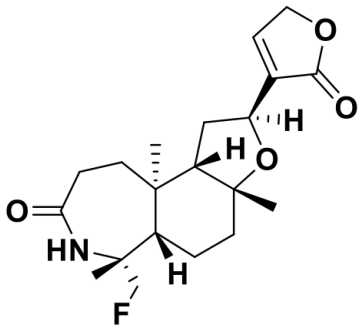
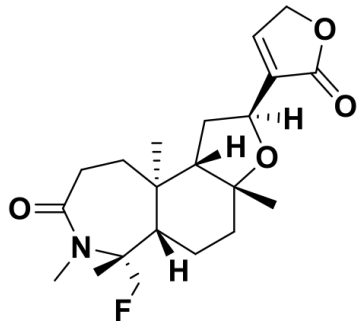
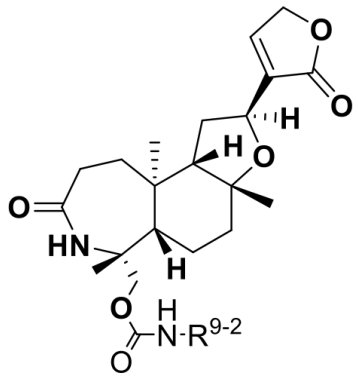
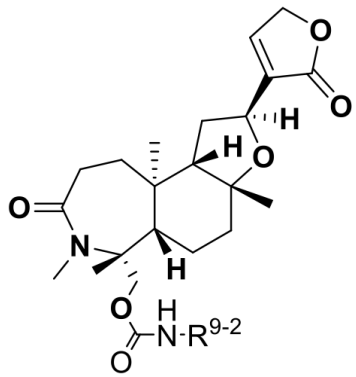
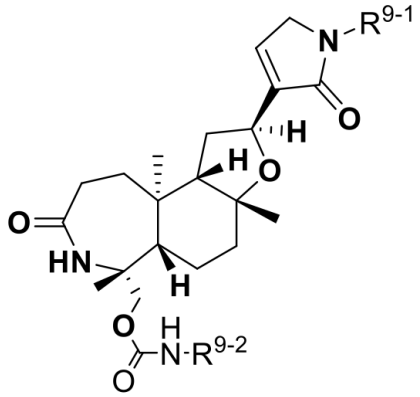
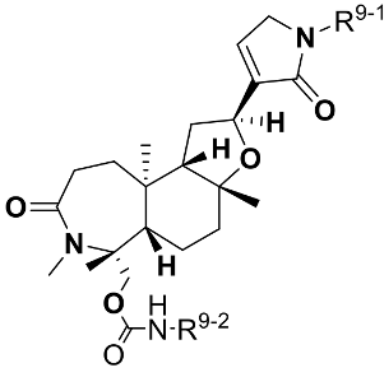
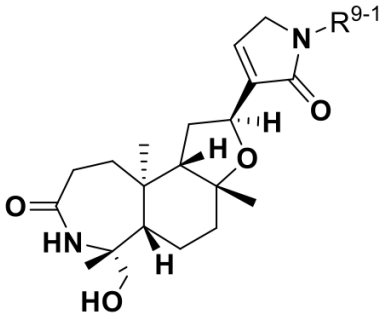
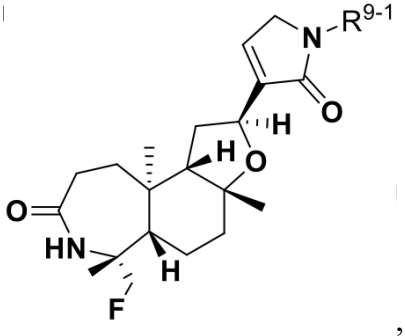
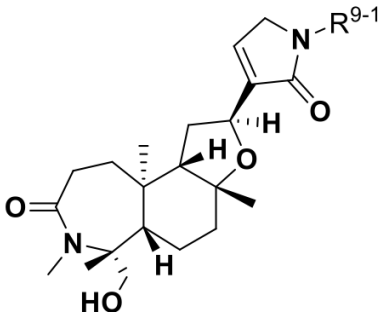
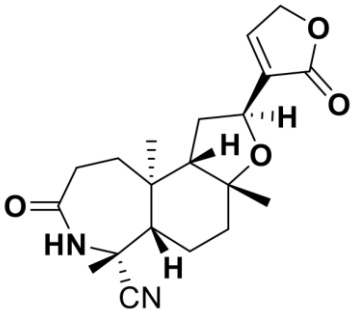
3. The compound of claim 2, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein the compound is of Formula (Iaa), optionally, wherein R^{1-1} is -CN.

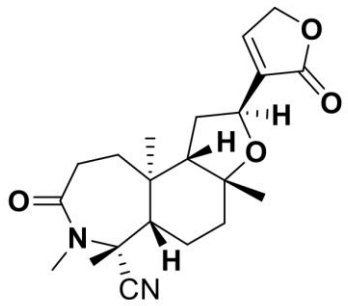
4. The compound of claim 3, wherein the compound of Formula (Iaa) is:

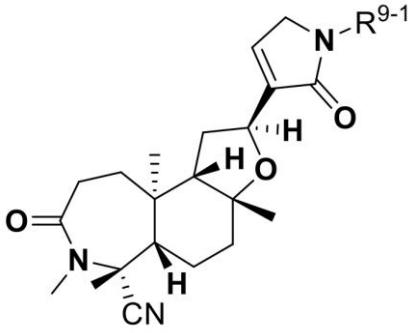


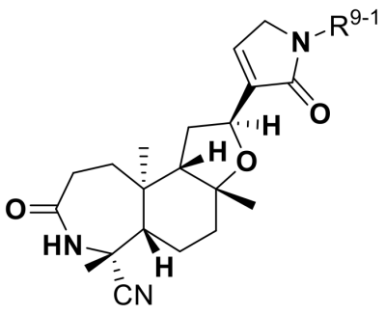
, or a pharmaceutically acceptable salt.

5. The compound of claim 2, wherein the compound is of Formula (IIaa), or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, optionally, wherein the compound of Formula (IIaa) is:


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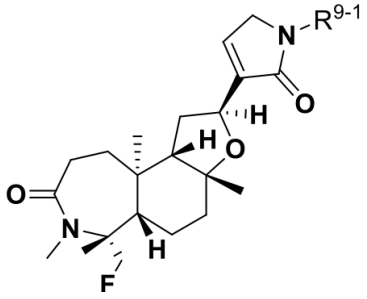


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or

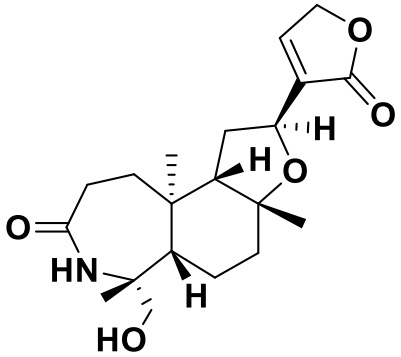


, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein:

R^{9-1} is hydrogen or methyl; and

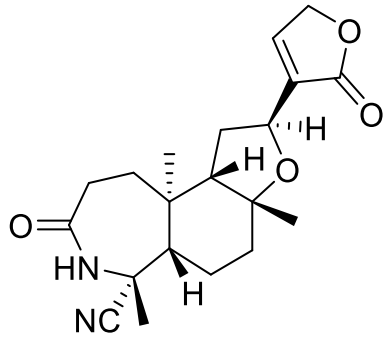
R^{9-2} is methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, secbutyl, or cyclobutyl.

6. The compound of claim 5, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, wherein R^{1-2} is $-CH_2OH$ or -CN, optionally, wherein the compound is:



, or a pharmaceutically acceptable salt; or

the compound is:



, or a pharmaceutically acceptable salt.

7. A method of making a compound of claim 3, wherein the compound is of Formula (Iaa), the method comprising:

providing a solution of isoandrographolide and a solvent;

combining 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), tetrabutylammonium iodide (TBAI), N-Chlorosuccinimide (NCS), a salt, and the solution to form a first intermediate;

combining hydroxylamine hydrochloride, pyridine, and the first intermediate to form a second intermediate; and

dehydration into cyanide of the second intermediate to form the compound of Formula (Iaa),

optionally, wherein the step of dehydration into cyanide, comprises combining triethylamine, 4-toluenesulfonyl chloride, and the second intermediate to form the compound of Formula (Iaa); or wherein the step of dehydration into cyanide, comprises combining benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and the second intermediate to form the compound of Formula (Iaa).

8. A method of making a compound of claim 3, wherein the compound is of Formula (IIaa), the method comprising:

providing a solution of isoandrographolide and a solvent;

combining tert-Butyldimethylsilyl chloride (TBDMSCl), and the solution to form a first intermediate;

combining pyridine, celite, pyridinium chlorochromate, and the first intermediate to form a second intermediate;

combining hydroxylamine hydrochloride, pyridine, and the second intermediate to form a third intermediate; and

combining 4-toluenesulfonyl chloride and the third intermediate followed by treatment with dioxane HCL to form the compound of Formula (IIaa).

9. A method of making a compound of claim 3, wherein the compound is of Formula (IIaa), the method comprising:

providing a solution of isoandrographolide and a solvent;

combining Dess-Martin Periodinane (DMP), and the solution to form a first intermediate;

combining hydroxylamine hydrochloride, pyridine, and the first intermediate to form a second intermediate; and

combining triethylamine, 4-methylbenzene-1-sulfonyl chloride, 4-dimethylaminopyridine (DMAP), and the second intermediate, followed by treatment with dioxane HCl to form the compound of Formula (IIaa).

10. A pharmaceutical composition comprising the compound of any one of claims 1 to 6, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, and at least one pharmaceutically acceptable carrier.

11. A compound of any one of claims 1 to 6, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of claim 10, for use as a medicament.

12. Use of a compound of any one of claims 1 to 6, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of claim 10, in the preparation of a medicament for treating, or preventing a neutrophil-related condition or disease, optionally, wherein the condition or disease is a cardiovascular condition or disease, an endocrine condition or disease, a neurological condition or disease, a gastrointestinal condition or disease, or a dermatological disease or condition, or any combination thereof; or optionally, wherein the treating is ameliorating a neutrophil-related condition or disease in the subject.

13. Use of a compound of any one of claims 1 to 6, or a stereoisomer thereof, or pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of claim 10, in the preparation of a medicament for treating, or preventing a fibrotic condition or disease, optionally, wherein the condition or disease is idiopathic pulmonary fibrosis (IPF); or optionally, wherein the treating is ameliorating a fibrotic condition or disease in the subject.

14. Use of a compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of claim 10, in the preparation of a medicament for treating, or preventing a dermatological condition or disease, optionally, wherein the condition or disease is atopic dermatitis; or optionally, wherein the treating is ameliorating a dermatological condition or disease in the subject.

15. The use of any one of claims 12 to 14, wherein the subject is a human.