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(54) Title: METHOD OF STIMULATING IMMUNE CELL MIGRATION

(57) Abstract: The present invention provides methods of stimulating the migration of an immune cell, methods of stimulating an immune response and methods of increasing immune cell deformability comprising administering an effective amount of a compound having the Formula (I).

METHOD OF STIMULATING IMMUNE CELL MIGRATION

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/782,130 filed March 14, 2013. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

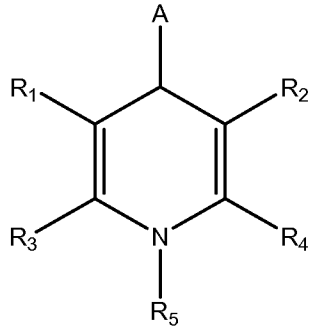
The migration of immune cells to a target site is a major step in eliciting an immune response. Cell migration therefore plays an important role in the ability of immune cells to respond to infection, allergy, inflammation and other conditions that elicit an immune response. The migration of cells is dependent on a number of factors including, for example, chemotactic factors, cell adhesion, as well as mechanical properties of the cells, such as the ability to deform or elongate in order to pass through the microvasculature (Lautenschlager, et al., The regulatory role of cell mechanics for migration of differentiating myeloid cells, *PNAS,* 106 (37): 15696-15701; Saito, et al. (2005) Journal of Leukocyte Biology, 78: 777-784).

It would therefore be useful to identify agents that stimulate the migration of immune cells and/or stimulate in an immune response in a subject in need thereof.

SUMMARY OF THE INVENTION

The present invention provides methods of stimulating the migration of an immune cell, methods of stimulating an immune response and methods of increasing immune cell deformability comprising administering an effective amount of a compound having the Formula (I) shown below.

In one embodiment, the invention is directed to a method of stimulating the migration of an immune cell comprising exposing said immune cell to an effective amount of a compound having the Formula (I):



(I);

or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof;

wherein;

A is optionally substituted aryl or optionally substituted heteroaryl;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$;

or R_1 and R_3 and R_2 and R_4, are each independently taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

each R_c is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

R_5 is selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; and each n is 0, 1 or 2. In some embodiments, the immune cell is selected from the group consisting of lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mast cells. In additional embodiments, the migration of the immune cell is stimulated in a subject in need thereof, wherein the subject is suffering from a condition that can be ameliorated by stimulation of an immune cell.

The invention also encompasses a method of stimulating an immune response in a patient in need thereof comprising administering to said patient an effective amount of a compound having the Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof. In some embodiments, the compound is co-administered with a vaccine. In additional embodiments, the patient is suffering from cancer or an infection. In certain

aspects, the infection is selected from the group consisting of a viral infection, a bacterial infection, a fungal infection, and a protozoal infection.

The invention also encompasses a method of increasing immune cell deformability in a patient in need thereof comprising administering to said patient an effective amount of a compound having the Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof. In some embodiments, the patient is suffering from an inflammatory condition. In additional aspects, the patient is suffering from a condition selected from the group consisting of disseminated intravascular coagulation, sepsis, septic shock, adult respiratory distress syndrome, cystic fibrosis, idiopathic pulmonary fibrosis, systemic sclerosis, gout, disseminated intravascular coagulopathy, and granuloma.

These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the drawings and the detailed description of the embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawing in which like reference characters refer to the same parts throughout the different views. The drawing is not necessarily to scale, emphasis instead being placed upon illustrating the principles of the invention.

The figure is a plot of the number of cells (neutrophils and PBMCs) per well of chemoattraction (CA; left side) and chemorepulsion (CR; right side) of 0.03, 0.30, 3 and 30 uM of Compound 2 using transmigration assay. The two plots at the bottom represent cells per well of chemokinesis for 0.015, 0.15, 1.5 and 15 uM (half the amount used for of CA and CR described above). Chemoattraction is a measure of immune cell migration response toward an agent whereas Chemorepulsion is a measure of immune cell migration response away from an agent. Chemokinesis measure assesses if an increase in random migration is the cause for what otherwise would be a chemoattractive or chemorepulsive response.

DETAILED DESCRIPTION OF THE INVENTION

A description of the embodiments of the invention follows.

As used herein, “a” or “an” are taken to mean one or more unless otherwise specified.

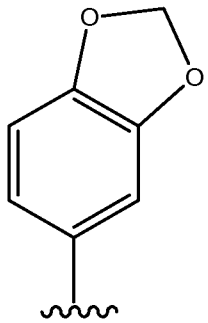
The present invention is based on the discovery that certain dihydropyridine compounds can stimulate the migration of immune cells. Various dihydropyridine

compounds have been described in the literature as calcium channel blockers. However, the present invention is based on the discovery of a class of dihydropyridine compounds that stimulate immune cell migration. It has been found that this activity (to stimulate immune cell migration) does not correlate with calcium channel activity. The present invention provides methods of stimulating the migration of an immune cell, methods of stimulating an immune response and methods of increasing immune cell deformability comprising the use of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

In certain embodiments, the compound has the Formula (I), wherein A is optionally substituted aryl. In additional embodiments, A is optionally substituted phenyl. In further embodiments, A is phenyl substituted with NO_2 and further optionally substituted.

In additional embodiments, the compound has the Formula (I), wherein A is heteroaryl.

In other embodiments, the compound has the Formula (I), wherein A is:



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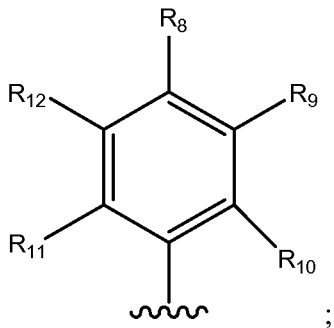
In some embodiments, the compound has the Formula (I) wherein A is:



;

wherein R_8 is selected from the group consisting of optionally substituted optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$; and each of R_9, R_{10}, R_{11} and R_{12} is independently

selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$. In some embodiments, R_8 is selected from the group consisting of halo, haloalkyl, CN, OR_c, NR_cR_c, $NR_cC(O)R_c$, $C(O)OR_c$, $C(O)R_c$, and NO_2. In yet additional embodiments, R_8 is NO_2. In some embodiments, each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_4 alkyl. In yet additional embodiments, each of R_9, R_{10}, R_{11} and R_{12} is hydrogen.

In additional embodiments, the compound has the Formula (I) or is a compound described herein, wherein R_1 and R_2 are selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$. In some embodiments, R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, $C(O)R_c$, $C(O)C(O)R_c$, and $C(O)NR_cR_c$. In yet further embodiments, R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and C(O)R. In some embodiments, R_1 and R_2 are each independently selected from $C(O)OR_c$.

In certain aspects of the invention, the compound has the Formula (I) or is a compound described herein wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 3- to 12-membered heterocyclic, optionally substituted aryl and optionally substituted heteroaryl. In certain embodiments, the fused optionally substituted cyclic group is substituted with an oxo group.

In additional aspects, the compound has the Formula (I) or is a compound described herein, wherein R_2 and R_4 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally

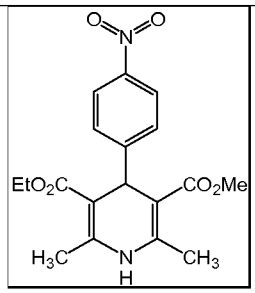
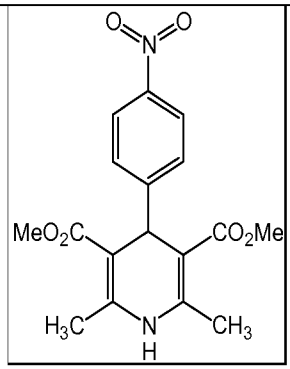
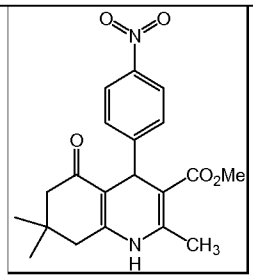
substituted heteroaryl. In certain embodiments, the fused optionally substituted cyclic group is substituted with an oxo group.

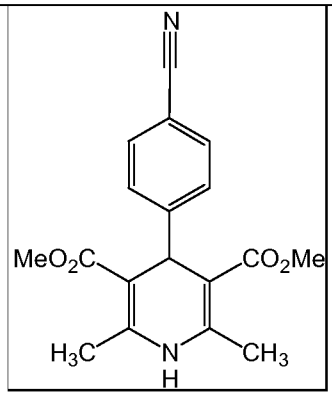
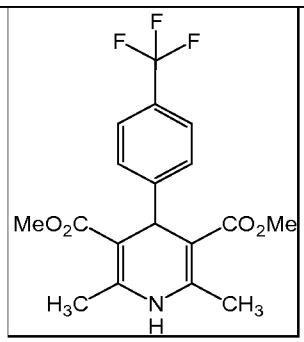
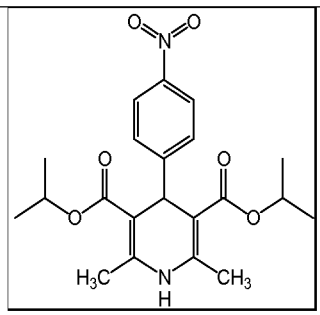
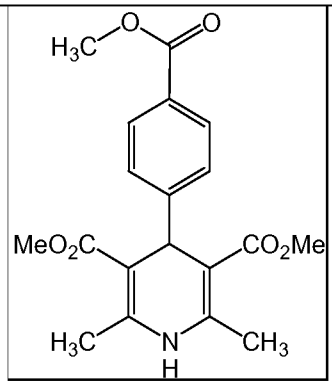
In a further embodiment, the compound has the Formula (I) or is a compound described herein, wherein R_3 and R_4 are each independently optionally substituted C_1-C_{10} alkyl. In some embodiments, R_3 and R_4 are each independently methyl or ethyl.

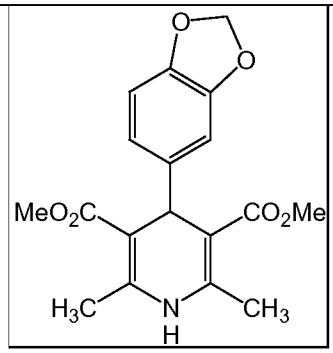
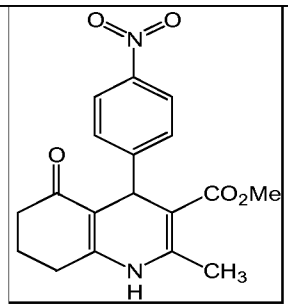
In additional aspects of the invention, the compound has the Formula (I) or is a compound described herein, wherein R_5 is selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl.

Non-limiting examples of compounds that can be utilized in the methods of the invention are shown in Table 1 below:

Table 1

Compound No.	Chemical Structure
1	
2	
3	

4		
5		
6		
7		

8	
9	

It is to be understood that the specific embodiments described herein can be taken in combination with other specific embodiments delineated herein. It will be appreciated that the description of the present invention herein should be construed in congruity with the laws and principals of chemical bonding.

The term "alkyl", as used herein, unless otherwise indicated, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C_1-C_{10} alkyl" denotes alkyl having 1 to 10 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

The term, "alkenyl", as used herein, refers to both straight and branched-chain moieties having the specified number of carbon atoms and having at least one carbon-carbon double bond.

The term, "alkynyl", as used herein, refers to both straight and branched-chain moieties having the specified number or carbon atoms and having at least one carbon-carbon triple bond.

The term "cycloalkyl," as used herein, refers to cyclic alkyl moieties having 3 or more carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl.

The term "cycloalkenyl," as used herein, refers to cyclic alkenyl moieties having 3 or more carbon atoms.

The term "cycloalkynyl," as used herein, refers to cyclic alkynyl moieties having 5 or more carbon atoms.

The term "heterocyclic" encompasses heterocycloalkyl, heterocycloalkenyl, heterobicycloalkyl, heterobicycloalkenyl, heteropolycycloalkyl, heteropolycycloalkenyl and the like. Heterocycloalkyl refers to cycloalkyl groups containing one or more heteroatoms (O, S, or N) within the ring. Heterocycloalkenyl as used herein refers to cycloalkenyl groups containing one or more heteroatoms (O, S or N) within the ring. Heterobicycloalkyl refers to bicycloalkyl groups containing one or more heteroatoms (O, S or N) within a ring. Heterobicycloalkenyl as used herein refers to bicycloalkenyl groups containing one or more heteroatoms (O, S or N) within a ring.

Cycloalkyl, cycloalkenyl, heterocyclic, groups also include groups similar to those described above for each of these respective categories, but which are substituted with one or more oxo moieties.

The term "aryl", as used herein, refers to mono- or polycyclic aromatic carbocyclic ring systems. A polycyclic aryl is a polycyclic ring system that comprises at least one aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof. The term "aryl" embraces aromatic radicals, such as, phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. An aryl group may be substituted or unsubstituted.

The term "heteroaryl", as used herein, refers to aromatic carbocyclic groups containing one or more heteroatoms (O, S, or N) within a ring. A heteroaryl group can be monocyclic or polycyclic. A heteroaryl group may additionally be substituted or unsubstituted. The heteroaryl groups of this invention can also include ring systems substituted with one or more oxo moieties. A polycyclic heteroaryl can comprise fused rings, covalently attached rings or a combination thereof. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, thiazolopyridinyl, oxazolopyridinyl and azaindolyl. The foregoing

heteroaryl groups may be C-attached or heteroatom-attached (where such is possible). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

The term "substituted" refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{15} cycloalkyl, -C_3-C_{15} cycloalkenyl, C_3-C_{15} cycloalkynyl, -heterocyclic, -F, -Cl, -Br, -I, -OH, -NO_2, -N_3, -CN, -NH_2, oxo, thioxo, -NHR_x, -NR_xR_x, dialkylamino, -diarylamino, -diheteroarylamino, -OR_x, -C(O)OR_y, -C(O)R_y, -C(O)C(O)R_y, -OCO_2R_y , -OC(O)R_y, OC(O)C(O)R_y, -NHC(O)R_y, -$NHCO_2R_y$, -NHC(O)C(O)R_y, -$NHC(S)NH_2$, -$NHC(S)NHR_x$, -$NHC(NH)NH_2$, -$NHC(NH)NHR_x$, -$NHC(NH)R_x$, -$C(NH)NHR_x$, -$NR_xC(O)R_x$, -$NR_xCO_2R_y$, -$NR_xC(O)C(O)R_y$, -$NR_xC(S)NH_2$, -$NR_xC(O)NR_xR_x$, -$NR_xS(O)_2NR_xR_x$, -$NR_xC(S)NHR_x$, -$NR_xC(NH)NH_2$, -$NR_xC(NH)NHR_x$, -$NR_xC(NH)R_x$, -$C(NR_x)NHR_x$ -$S(O)_nR_y$, -$NHSO_2R_x$, -CH_2NH_2, -$CH_2SO_2CH_3$, -$(C{=}NR_x)R_x$; -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{15}-cycloalkyl, -polyalkoxyalkyl, -polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-R_x, or -methylthiomethyl, wherein R_x is selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{15} cycloalkyl, -aryl, -heteroaryl and –heterocyclic; -R_y is selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{15} cycloalkyl, -aryl, -heteroaryl, -heterocyclic, -NH_2, -NH-C_1-C_{12} alkyl, -NH-C_2-C_{12} alkenyl, -NH-C_2-C_{12}-alkynyl, -NH-C_3-C_{15} cycloalkyl, -NH-aryl, -NH-heteroaryl and -NH-heterocyclic, and n is 0, 1 or 2. It is understood that the aryls, heteroaryls, alkyls, cycloalkyls, heterocyclics and the like can be further substituted.

The invention encompasses a method of stimulating the migration of an immune cell. In certain embodiments, the immune cell is selected from the group consisting of lymphocytes, monocytes, neutrophils, eosinophils, basophils, peripheral blood mononuclear cells (PBMCs) and mast cells. In a further embodiment, the immune cell is a lymphocyte, neutrophil or a monocyte. In yet other embodiments, the immune cell is a neutrophil or monocyte.

In certain embodiments, the invention is directed to a method of stimulating migration of an immune cell in a patient in need thereof. A patient in need of immune cell migration is a patient suffering from a condition that can be ameliorated (for example, the symptoms for which can be improved or alleviated or for example, the progression of the disease can be delayed, and the like) by migration of an immune cell. Non-limiting examples of such conditions are gout, granuloma, and disseminated intravascular coagulation.

The invention also encompasses a method of stimulating an immune response in a patient in need thereof comprising administering to said patient an effective amount of a compound having the Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof. In some embodiments, the compound is co-administered with a vaccine. In additional embodiments, the patient is suffering from cancer or an infection. In certain aspects, the infection is selected from the group consisting of a viral infection, a bacterial infection, a fungal infection, and a protozoal infection.

Patients in need of immune stimulation include those that are suffering from or are likely to suffer from an infection or from a tumor or cancer. Patients in need of immune stimulation also include patients suffering from conditions associated with immnosuppression, including, but not limited to viral infections (e.g. HIV infection), hepatitis C infection, ataxia-telangiectasia, Chediak-Higashi syndrome, leukocyte adhesion defects, Wiscott-Aldrich syndrome and complement deficiencies. In one embodiment, the invention is a method of stimulating an immune response in a patient comprising administering to said patient an effective amount a compound described herein wherein the patient is suffering from a condition selected from the group consisting of an infection, ataxia-telangiectasia, Chediak-Higashi syndrome, leukocyte adhesion defects, Wiscott-Aldrich syndrome and complement deficiencies.

In another embodiment, the invention is a method of treating cancer in a patient suffering therefrom comprising inducing migration of an immune cell toward a cancer cell, said method comprising administering a compound described herein in an effective amount.

In yet another embodiment, the invention is a method of treating a bacterial infection in a patient suffering therefrom comprising inducing migration of an immune cell toward a bacterial cell or protein, said method comprising administering a compound described herein in an effective amount.

In a further embodiment, the invention is a method of treating a viral infection in a patient suffering therefrom comprising promoting the migration of an immune cell toward a virus or viral protein, said method comprising administering a compound described herein in an effective amount.

In another embodiment, the invention is a method of treating a patient suffering from a condition characterized by decreased cell migration. Disorders characterized by lack of immune cell chemotaxis include, but are not limited to, genetic conditions, infections and therapeutic methods associated with immunosuppression. Exemplary conditions are bacterial infections, granulomatous diseases (e. g., tuberculosis), Gaucher disease (Aker et al. (1993),

Br. J. Haematol., 83(2): 187-91), chronic obstructive pulmonary disease (Yoshikawa et al. (2007), Am J Resp Critical Care Medicine, 175: 473-79) and Crohn's disease (Harbord et al. (2006), Alimentary Pharmacology and Therapeutics 24(4):651-660).

In specific embodiments, the cancer is a solid tumor. In one embodiment, the solid tumor is selected from the group consisting of colon, prostate, breast, lung, skin, liver, bone, pancreas, ovary, testis, bladder, kidney, brain, head and neck cancer.

A bacterial infection includes, but is not limited to, an Actinomyces infection, an anthrax infection, a Bacteriodes infection, a Borrelia infection, a Campylobacter infection, a Citrobacter infection, a Clostridium difficile infection, a Corynebacterium infection, an E. coli infection, an Enterobacter infection, a Gardnerella infection, a Haemophilus infection, an H. pylori infection, a Klebsiella infection, a Legionella infection, a Listeria infection, a Neisseria infection, a Nocardia infection, a Pasteurella infection, a Pneumococcus infection, a Proteus infection, a Pseudomonas infection, a Salmonella infection, a Shigella infection, a Spirillum infection, a Spirochaeta infection, a Staphylococcal infection, a Streptobacillus infection, a Streptococcal infection, and a Treponema infection.

A viral infection includes, but is not limited to, an adenovirus infection, a retrovirus infection, a rotavirus infection, etc. Such infections also include cytomegalovirus infection, an Epstein Barr virus infection, a hepatitis A virus infection, a hepatitis B virus infection, a hepatitis C virus infection, a Herpes simplex virus 1 infection, a Herpes simplex virus 2 infection, an HIV infection, a human papilloma virus infection, an influenza A virus infection, a monkey pox infection, a respiratory syncytial virus infection, a SARS infection a small pox infection, a varicella-zoster virus infection.

The infection can also be a fungal infection. Fungal infections include, but are not limited to, aspergillosis, blastomycosis, candidiasis, chromomycosis, crytococcosis, histoplasmosis, mycetoma infections, paracoccidioidomycosis, pseudallescheriasis, ringworm, and tinea versicolor infection.

Exemplary cancers and tumors that can be treated according to the methods of the invention include, for example, biliary tract cancer; brain cancer including glioblastomas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer, gastric cancer; hematological neoplasms, including acute lymphocytic and myelogenous leukemia; multiple myeloma; AIDS associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms, including Bowen's disease and Paget's disease; liver cancer (hepatocarcinoma); lung cancer; lymphomas, including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer,

including squamous cell carcinoma; ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreas cancer; prostate cancer; rectal cancer; sarcomas, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma and osteosarcoma; skin cancer, including melanoma, Kaposi's sarcoma, basocellular cancer and squamous cell cancer; testicular cancer, including germinal tumors (seminoma, non-seminoma [teratomas, choriocarcinomas]), stromal tumors and germ cell tumors; thyroid cancer, including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor.

In certain embodiments, the compound described herein can be co-administered with a second agent (e.g., an anti-viral drug or a chemotherapeutic agent). Co-administered agents need not be administered at exactly the same time. In certain embodiments, however, the compound is administered substantially simultaneously as the second agent. By "substantially simultaneously," it is meant that the compound is administered before, at the same time, and/or after the administration of the second agent. Second agents include, for example, anti-cancer agents, anti-infective agents, chemoattractants, immunostimulants and other therapeutic compounds. A second agent can be chosen based on the condition or disease to be treated. For example, in a method of treating cancer or a tumor, the compound described herein can be administered with another anti-cancer agent. Similarly, in a method of stimulating an immune response, the compound described herein can be administered with an immunostimulant. The invention also encompasses administering a compound of the invention with an antibiotic, anti-viral or anti-fungal agent.

The compound can be administered in pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient. The excipient can be chosen based on the expected route of administration of the composition in therapeutic applications. The route of administration of the composition depends on the condition to be treated. For example, intravenous injection may be preferred for treatment of a systemic disorder and oral administration may be preferred to treat a gastrointestinal disorder. The route of administration and the dosage of the composition to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

The vaccine can be administered to a person in need of immunostimulation (i.e., a person who would benefit by mounting or increasing an immune response to an antigen, a

tumor cell or a tumor) in order to stimulate an immune response. Examples of vaccines include Hepatitis B Diptheria, Tetanus, Pertussis, Haemoplilus influenzae Type B, Inactivated Polio, Measles, Mumps, Rubella, Varicella, Pneumococcal, Hepatitis A, Influenza, Japanese Encephalitis, Rotavirus, Yellow Fever, Trypanosoma cruzi; and Rabies. If desired, the vaccine can further comprise an adjuvant. As used herein, an "adjuvant" is an immunologic reagent that increases an antigenic response. Examples of adjuvants for use in pharmaceuticals include immunostimulatory oligonucleotides, imidazoquinolines (e.g., imiquimod), monophosphoryl lipid A, and detoxified lipopolysaccharide (LPS), as described, for example, by O'Hagan et al. (Biomol. Eng. 18:69-85, 2001)). An example of an immunostimulatory oligonucleotide is an oligonucleotide having ummethylated CpG sequences.

The invention is additionally directed to a method of increasing immune cell deformability in a patient in need thereof comprising administering to said patient an effective amount of a compound having the Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof. Because the diameter of some capillaries, such as pulmonary capillaries, is smaller than the diameter of neutrophils, neutrophils must have the ability to deform in order to pass through the capillaries (Saito et al. (2005) Journal of Leukocyte Biology 78: 777-784). Inflammation can decrease the deformability of immune cells, such as the deformability of neutrophils. Thus inflammatory diseases are associated with the sequestration of immune cells in the microvasculature of various organs, including, for example, the lungs (Saito et al.). The present invention encompasses a method of increasing the deformability of an immune cell in a patient in need thereof comprising administering an effective amount of a compound described herein. In some embodiments, the patient is suffering from an inflammatory condition. In additional aspects, the patient is suffering from a condition selected from the group consisting of disseminated intravascular coagulation, sepsis, septic shock, adult respiratory distress syndrome, cystic fibrosis, idiopathic pulmonary fibrosis, systemic sclerosis, gout, disseminated intravascular coagulopathy, bacterial pneumonia, and granuloma.

As discussed above, the compound described herein can be co-administered with a second agent. Such second agents include, for example, an anti-infective agent, and an anti-cancer agent.

An anti-infective agent is an agent which reduces the activity of or kills a microorganism and include, but are not limited to: Aztreonam; Chlorhexidine Gluconate; Imidurea; Lycetamine; Nibroxane; Pirazmonam Sodium; Propionic Acid; Pyrithione Sodium;

Sanguinarium Chloride; Tigemonam Dicholine; Acedapsone; Acetosulfone Sodium; Alamecin; Alexidine; Amdinocillin; Amdinocillin Pivoxil; Amicycline; Amifloxacin; Amifloxacin Mesylate; Amikacin; Amikacin Sulfate; Aminosalicylic acid; Aminosalicylate sodium; Amoxicillin; Amphomycin; Ampicillin; Ampicillin Sodium; Apalcillin Sodium; Apramycin; Aspartocin; Astromicin Sulfate; Avilamycin; Avoparcin; Azithromycin; Azlocillin; Azlocillin Sodium; Bacampicillin Hydrochloride; Bacitracin; Bacitracin Methylene Disalicylate; Bacitracin Zinc; Bambermycins; Benzoylpas Calcium; Berythromycin; Betamicin Sulfate; Biapenem; Biniramycin; Biphenamine Hydrochloride; Bispyrithione Magsulfex; Butikacin; Butirosin Sulfate; Capreomycin Sulfate; Carbadox; Carbenicillin Disodium; Carbenicillin Indanyl Sodium; Carbenicillin Phenyl Sodium; Carbenicillin Potassium; Carumonam Sodium; Cefaclor; Cefadroxil; Cefamandole; Cefamandole Nafate; Cefamandole Sodium; Cefaparole; Cefatrizine; Cefazaflur Sodium; Cefazolin; Cefazolin Sodium; Cefbuperazone; Cefdinir; Cefepime; Cefepime Hydrochloride; Cefetecol; Cefixime; Cefinenoxime Hydrochloride; Cefmetazole; Cefmetazole Sodium; Cefonicid Monosodium; Cefonicid Sodium; Cefoperazone Sodium; Ceforanide; Cefotaxime Sodium; Cefotetan; Cefotetan Disodium; Cefotiam Hydrochloride; Cefoxitin; Cefoxitin Sodium; Cefpimizole; Cefpimizole Sodium; Cefpiramide; Cefpiramide Sodium; Cefpirome Sulfate; Cefpodoxime Proxetil; Cefprozil; Cefroxadine; Cefsulodin Sodium; Ceftazidime; Ceftibuten; Ceftizoxime Sodium; Ceftriaxone Sodium; Cefuroxime; Cefuroxime Axetil; Cefuroxime Pivoxetil; Cefuroxime Sodium; Cephacetrile Sodium; Cephalexin; Cephalexin Hydrochloride, Cephaloglycin; Cephaloridine; Cephalothin Sodium; Cephapirin Sodium; Cephradine; Cetocycline Hydrochloride; Cetophenicol; Chloramphenicol; Chloramphenicol Palmitate; Chloramphenicol Pantothenate Complex; Chloramphenicol Sodium Succinate; Chlorhexidine Phosphanilate; Chloroxylenol; Chlortetracycline Bisulfate; Chlortetracycline Hydrochloride; Cinoxacin; Ciprofloxacin; Ciprofloxacin Hydrochloride; Cirolemycin; Clarithromycin; Clinafloxacin Hydrochloride; Clindamycin; Clindamycin Hydrochloride; Clindamycin Palmitate Hydrochloride; Clindamycin Phosphate; Clofazimine; Cloxacillin Benzathine; Cloxacillin Sodium; Cloxyquin; Colistimethate Sodium; Colistin Sulfate; Coumermycin; Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin Sulfate; Dipyrithione; Dirithromycin; Doxycycline; Doxycycline Calcium; Doxycycline Fosfatex; Doxycycline Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Epitetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate;

Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate; Erythromycin Stearate; Ethambutol Hydrochloride; Ethionamide; Fleroxacin; Floxacillin; Fludalanine; Flumequine; Fosfomycin; Fosfomycin Tromethamine; Fumoxicillin; Furazolium Chloride; Furazolium Tartrate; Fusidate Sodium; Fusidic Acid; Gentamicin Sulfate; Gloximonam; Gramicidin; Haloprogin; Hetacillin; Hetacillin Potassium; Hexedine; Ibafloxacin; Imipenem; Isoconazole; Isepamicin; Isoniazid; Josamycin; Kanamycin Sulfate; Kitasamycin; Levofuraltadone; Levopropylcillin Potassium; Lexithromycin; Lincomycin; Lincomycin Hydrochloride; Lomefloxacin; Lomefloxacin Hydrochloride; Lomefloxacin Mesylate; Loracarbef; Mafenide; Meclocycline; Meclocycline Sulfosalicylate; Megalomicin Potassium Phosphate; Mequidox; Meropenem; Methacycline; Methacycline Hydrochloride; Methenamine; Methenamine Hippurate; Methenamine Mandelate; Methicillin Sodium; Metioprim; Metronidazole Hydrochloride; Metronidazole Phosphate; Mezlocillin; Mezlocillin Sodium; Minocycline; Minocycline Hydrochloride; Mirincamycin lydrochloride; Monensin; Monensin Sodium; Nafcillin Sodium; Nalidixate Sodium; Nalidixic Acid; Natamycin; Nebramycin; Neomycin Palmitate; Neomycin Sulfate; Neomycin Undecylenate; Netilmicin Sulfate; Neutramycin; Nifuradene; Nifuraldezone; Nifuratel; Nifuratrone; Nifurdazil; Nifurimide; Nifurpirinol; Nifurquinazol; Nifurthiazole; Nitrocycline; Nitrofurantoin; Nitromide; Norfloxacin; Novobiocin Sodium; Ofloxacin; Ormetoprim; Oxacillin Sodium; Oximonam; Oximonam Sodium; Oxolinic Acid; Oxytetracycline; Oxytetracycline Calcium; Oxytetracycline Hydrochloride; Paldimycin; Parachlorophenol; Paulomycin; Pefloxacin; Pefloxacin Mesylate; Penamecillin; Penicillin G Benzathine; Penicillin G Potassium; Penicillin G Procaine; Penicillin G Sodium; Penicillin V; Penicillin V Benzathine; Penicillin V Hydrabamine; Penicillin V Potassium; Pentizidone Sodium; Phenyl Aminosalicylate; Piperacillin Sodium; Pirbenicillin Sodium; Piridicillin Sodium; Pirlimycin Hydrochloride; Pivampicillin Hydrochloride; Pivampicillin Pamoate; Pivampicillin Probenate; Polymyxin B Sulfate; Porfiromycin; Propikacin; Pyrazinamide; Pyrithione Zinc; Quindecamine Acetate; Quinupristin; Racephenicol; Ramoplanin; Ranimycin; Relomycin; Repromicin; Rifabutin; Rifametane; Rifamexil; Rifamide; Rifampin; Rifapentine; Rifaximin; Rolitetracycline; Rolitetracycline Nitrate; Rosaramicin; Rosaramicin Butyrate; Rosaramicin Propionate; Rosaramicin Sodium Phosphate; Rosaramicin Stearate; Rosoxacil; Roxarsone; Roxithromycin; Sancycline; Sanfetrinem Sodium; Sarmoxicillin; Sarpicillin; Scopafungin; Sisomicin; Sisomicin Sulfate; Sparfloxacin; Spectinomycin Hydrochloride; Spiramycin; Stallimycin Hydrochloride; Steffimycin; Streptomycin Sulfate; Streptonicozid; Sulfabenz: Sulfabenzamide; Sulfacetamide; Sulfacetamide Sodium; Sulfacytine; Sulfadiazine;

Sulfadiazine Sodium; Sulfadoxine; Sulfalene; Sulfamerazine; Sulfameter: Sulfamethazine; Sulfamethizole; Sulfamethoxazole; Sulfamonomethoxine; Sulfamoxole; Sulfanilate Zinc; Sulfanitran; Sulfasalazine; Sulfasomizole; Sulfathiazole; Sulfazamet; Sulfisoxazole; Sulfisoxazole Acetyl; Sulfisoxazole Diolamine; Sulfomyxin; Sulopenem; Sultamicillin; Suncillin Sodium; Talampicillin Hydrochloride; Teicoplanin; Temafloxacin Hydrochloride; Temocillin; Tetracycline; Tetracycline Hydrochloridc; Tetracycline Phosphate Complex; Tetroxoprim; Thiamphenicol; Thiphencillin Potassium; Ticarcillin Cresyl Sodium: Ticarcillin Disodium; Ticarcillin Monosodium; Ticlatone; Tiodonium Chloride; Tobramycin; Tobramycin Sulfate; Tosufloxacin; Trimethoprim; Trimethoprim Sulfate; Trisulfapyrimidines; Troleandomycin; Trospectomycin Sulfate; Tyrothricin; Vancomycin; Vancomycin Hydrochloride; Virginiamycin; Zorbamycin; Difloxacin Hydrochloride; Lauryl Isoquinolinium Bromide; Moxalactam Disodium; Ornidazole; Pentisomicin; and Sarafloxacin Hydrochloride.

Exemplary anti-cancer agents include, but are not limited to, Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexatc; Eflorithine Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta-I a; Interferon Gamma-I b; Iproplatini; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine;

Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Podofilox; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Sulofenur; Talisomycin; Taxotere; Tecogalan Sodium; Tegafur, Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporlin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate Virlrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; and Zorubicin Hydrochloride.

"Treating" or "treatment" includes preventing or delaying the onset of the symptoms, complications, or biochemical indicia of a disease, alleviating or ameliorating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. A "subject' is a mammal in need of treatment. A "patient" refers to a human subject in need of treatment. A "therapeutically effective amount" or an "effective amount" is amount of a compound or composition that, when administered to a subject, for example a human patient, is sufficient to effect treatment, of a disease or condition and/or that is sufficient to achieve the indicated effect (for example, increasing immune cell migration, increasing immune cell deformability). The compounds described herein can be administered in pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient. The excipient can be chosen based on the expected route of administration of the composition in therapeutic applications. The route of administration of the composition depends on the condition to be treated. For example, intravenous injection may be preferred for treatment of a systemic disorder and oral administration may be preferred to treat a gastrointestinal disorder. The route of administration and the dosage of the composition to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard

dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

Pharmaceutical compositions comprising the compounds described herein can be administered by a variety of routes including, but not limited to, parenteral, oral, pulmonary, ophthalmic, nasal, rectal, vaginal, aural, topical, buccal, transdermal, intravenous, intramuscular, subcutaneous, intradermal, intraocular, intracerebral, intralymphatic, intraarticular, intrathecal and intraperitoneal. In some embodiments, the compound is administered using a drug eluting device.

In one embodiment, the pharmaceutical composition can be administered orally. For the purpose of oral therapeutic administration, the pharmaceutical compositions can be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. Tablets, pills, capsules, troches and the like may also contain binders, excipients, disintegrating agent, lubricants, glidants, sweetening agents, and flavoring agents. Some examples of binders include microcrystalline cellulose, gum tragacanth or gelatin. Examples of excipients include starch or lactose. Some examples of disintegrating agents include alginic acid, corn starch and the like. Examples of lubricants include magnesium stearate or potassium stearate. An example of a glidant is colloidal silicon dioxide. Some examples of sweetening agents include sucrose, saccharin and the like. Examples of flavoring agents include peppermint, methyl salicylate, orange flavoring and the like. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used. In another embodiment, the composition is administered as a tablet or a capsule.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor, and the like. For vaginal administration, a pharmaceutical composition may be presented as pessaries, tampons, creams, gels, pastes, foams or spray.

The pharmaceutical composition can also be administered by nasal administration. As used herein, nasally administering or nasal administration includes administering the composition to the mucus membranes of the nasal passage or nasal cavity of the patient. As

used herein, pharmaceutical compositions for nasal administration of a composition include effective amounts of the compounds described herein prepared by well-known methods to be administered, for example, as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. Administration of the composition may also take place using a nasal tampon or nasal sponge.

For topical administration, suitable formulations may include biocompatible oil, wax, gel, powder, polymer, or other liquid or solid carriers. Such formulations may be administered by applying directly to affected tissues, for example, a liquid formulation to treat infection of conjunctival tissue can be administered dropwise to the subject's eye, or a cream formulation can be administered to the skin. The compositions can be administered parenterally such as, for example, by intravenous, intramuscular, intrathecal or subcutaneous injection. Parenteral administration can be accomplished by incorporating a composition into a solution or suspension. Such solutions or suspensions may also include sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents. Parenteral formulations may also include antibacterial agents such as, for example, benzyl alcohol or methyl parabens, antioxidants such as, for example, ascorbic acid or sodium bisulfite and chelating agents such as EDTA. Buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose may also be added. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Compositions comprising a compound described herein can also be administered using a drug-eluting medical device. A "drug eluting medical device" is a device which is capable of being inserted into a human or animal body, internally or subcutaneously, which is intended to remain in said human or animal body for a period of time, and which is capable of eluting one or more pharmaceutical compositions for a portion of the time during which the device resides in the human or animal body. Drug-eluting implantable medical devices include, for example, stents, stent grafts, anastomosis devices, vascular grafts, vascular patches, AV shunts, catheters, guide wires, balloons, and filters. Various drug-eluting coating materials can be applied to the surface of traditional implantable medical devices to impart desired pharmacological effects to the otherwise inert devices, in addition to the basic, mechanical functions performed by the traditional, uncoated devices.

Rectal administration includes administering the pharmaceutical compositions into the rectum or large intestine. This can be accomplished using suppositories or enemas. Suppository formulations can easily be made by methods known in the art. For example,

suppository formulations can be prepared by heating glycerin to about 120°C, dissolving the pharmaceutical composition in the glycerin, mixing the heated glycerin after which purified water may be added, and pouring the hot mixture into a suppository mold.

Transdermal administration includes percutaneous absorption of the composition through the skin. Transdermal formulations include patches, ointments, creams, gels, salves and the like.

In addition to the usual meaning of administering the formulations described herein to any part, tissue or organ whose primary function is gas exchange with the external environment, for purposes of the present invention, "pulmonary" will also mean to include a tissue or cavity that is contingent to the respiratory tract, in particular, the sinuses. For pulmonary administration, an aerosol formulation containing the active agent, a manual pump spray, nebulizer or pressurized metered-dose inhaler as well as dry powder formulations are contemplated. Suitable formulations of this type can also include other agents, such as antistatic agents, to maintain the disclosed compounds as effective aerosols.

A drug delivery device for delivering aerosols comprises a suitable aerosol canister with a metering valve containing a pharmaceutical aerosol formulation as described and an actuator housing adapted to hold the canister and allow for drug delivery. The canister in the drug delivery device has a head space representing greater than about 15% of the total volume of the canister. Often, the compound intended for pulmonary administration is dissolved, suspended or emulsified in a mixture of a solvent, surfactant and propellant. The mixture is maintained under pressure in a canister that has been sealed with a metering valve.

The invention is illustrated by the following examples which are not meant to be limiting in any way.

EXEMPLIFICATION

Example 1

Objective: To identify the chemoattractive, chemorepulsive and chemokinetic properties of a test agent (ligand) with a particular cell type on a single Neuroprobe transmigration plate.

The process described here is a cell migration technique using a modified Boyden chamber to study cell migration. Briefly, cells isolated from whole blood are challenged with an agent via three different assays on one plate. Prior to beginning the assay, the following were prepared:

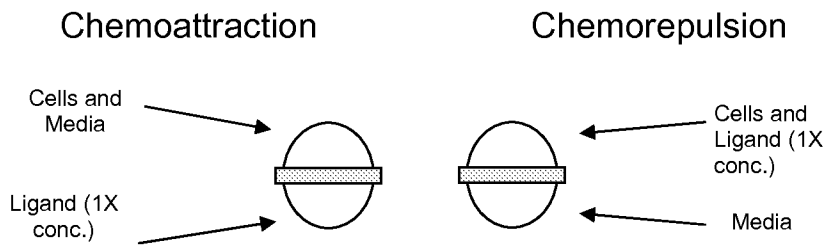
- 0.5% Fetal Calf Serum (FCS) in Iscove's Modified Dulbecco's Medium (IMDM) (Assay Medium).
- Migratory cells at a concentration of $2x10^7$ cells/ml in Assay Medium.
- Four serial (10 or 3-fold) dilutions of the ligand of interest in Assay Medium at 1X concentration as well as 0.5Xconcentration.
- The assay plates are Neuroprobe ChemoTx plates, part number 206-3 (3um pore size) for neutrophils and 206-5 (5um pore size) for PBMCs.
- 31 µl of the following solutions were pipetted into each well:

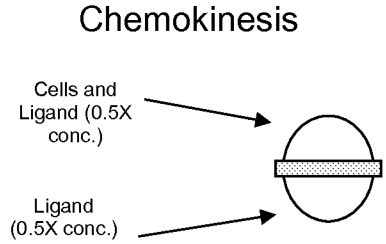
For media controls and for chemorepulsion samples, Assay Medium was used. For chemoattraction samples, appropriate dilution of ligand at 1X concentration was used. For chemokinesis samples, appropriate dilution of ligand at 0.5X concentration was used. The membrane was carefully placed onto the plate, starting at one side and then slowly lowering the other edge onto the plate.

- 29 µl of the following were pipetted onto the top of each circle:

For media controls and chemoattraction samples, use Assay Medium. For chemorepulsion samples, appropriate dilution of ligand at 1X concentration was used. For chemokinesis samples, appropriate dilution if ligand at 0.5X concentration was used.

- 2 µl of cells (40,000 cells) were added to each bubble of liquid.





The plate was covered with the supplied lid and incubated for the desired time at 37°C in 5% CO2. Unless otherwise indicated, the incubation time was 1 hour for neutrophils and 3 hours

for T cells. For monocytes and B cells, the incubation time was 2 hours. After the desired assay time, the liquid was removed from the top of the plate using a Kimwipe. The membrane was carefully removed from the top of the plate and discarded. The plate was examined under a microscope to look for ligand crystallization, contamination and overall migration.

Guava (via cell count for read out) was conducted as follows:

1. U-bottom 96 well plates were preloaded with 50ul assay media and the contents of the Neuroprobe plates were transferred to the U-bottom plate.
2. Equal volumes of Guava viacount reagent was added to each well to stain the cells. The plate was then incubated for 8 minutes in the dark at room temperature.
3. 1% paraformaldehyde was added to fix the cells and they were then sealed with adhesive film and stored at 4°C overnight.
4. The Guava Easy Cyte Plus was used to read the plate and quantify the number of migrated cells.

The extent of cell migration was displayed as a bar graph with thick horizontal line showing the level of spontaneous unstimulated migration (media background).

All compounds were screened at least twice.

The minimum effective dose for stimulating migration of Neutrophil and PBMC for each of the compounds 1-9 is shown in Table 2 below.

Table 2

Compound No.	Minimum effective dose (uM)	Manufacturer
1	0.03	Timtec
2	0.1	Timtec and Sigma
3	1.0	Sigma
4	3.0	Timtec
5	10.0	Timtec
6	30.0	Sigma
7	30.0	Sigma
8	30.0	Timtec
9	30.0	Timtec

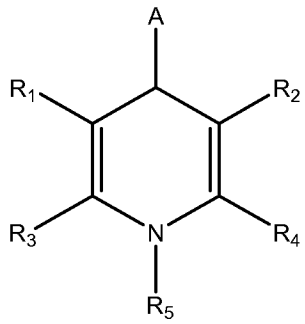
The figure shows the results of transmigration assays measuring the effect of Compound 2 on neutrophils and PBMCs.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of stimulating the migration of an immune cell comprising exposing said immune cell to an effective amount of a compound having the Formula (I):



(I),

or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof; wherein

A is optionally substituted aryl or optionally substituted heteroaryl;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$;

or R_1 and R_3 and R_2 and R_4, are each independently taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

each R_c is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

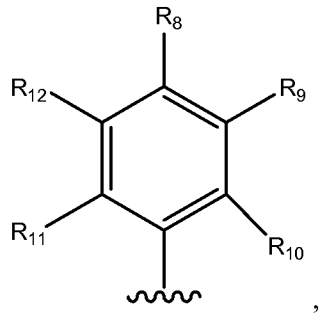
R_5 is selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; and each n is 0, 1 or 2.

2. The method of claim 1, wherein A is optionally substituted aryl.

3. The method of claim 2, wherein A is optionally substituted phenyl.

4. The method of claim 3, wherein A is phenyl substituted with NO_2 and further optionally substituted.

5. The method of any one of claims 1 to 3, wherein A is:



,

wherein R_8 is selected from the group consisting of optionally substituted optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$; and

each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$.

6. The method of claim 5, wherein R_8 is selected from the group consisting of halo, haloalkyl, CN, OR_c, NR_cR_c, $NR_cC(O)R_c$, $C(O)OR_c$, $C(O)R_c$, and NO_2.

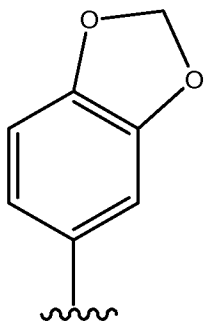
7. The method of claim 6, wherein R_8 is NO_2.

8. The method of any of claims 5 to 7, wherein each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_4 alkyl.

9. The method of claim 8, wherein each of R_9, R_{10}, R_{11} and R_{12} is hydrogen.

10. The method of claim 1, wherein A is heteroaryl.

11. The method of claim 1, wherein A is:



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12. The method of any one of claims 1 to 11, wherein R_1 and R_2 are selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$.

13. The method of claim 12, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, $C(O)R_c$, $C(O)C(O)R_c$, and $C(O)NR_cR_c$.

14. The method of claim 13, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and C(O)R.

15. The method of claim 14, wherein R_1 and R_2 are each independently selected from $C(O)OR_c$.

16. The method of any one of claims 5 to 9, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and $C(O)R_c$.

17. The method of claim 16, wherein R_1 and R_2 are each independently selected from $C(O)OR_c$.

18. The method of any one of claims 1 to 11, wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 3- to 12-membered heterocyclic, optionally substituted aryl and optionally substituted heteroaryl.

19. The method of claim 18, wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, or an optionally substituted C_3-C_{12} cycloalkenyl.

20. The method of any one of claims 1 to 11 and 18 to 19, wherein R_2 and R_4 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl.

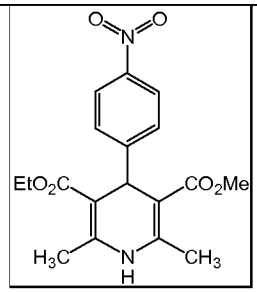
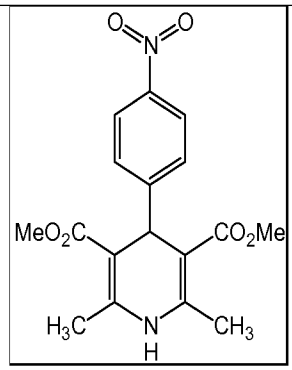
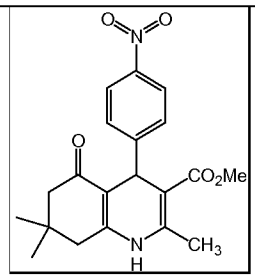
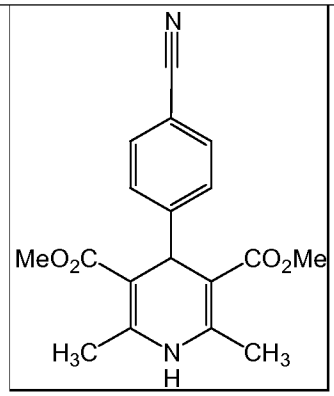
21. The method of any one of claims 1 to 17, wherein R_3 and R_4 are each independently optionally substituted C_1-C_{10} alkyl.

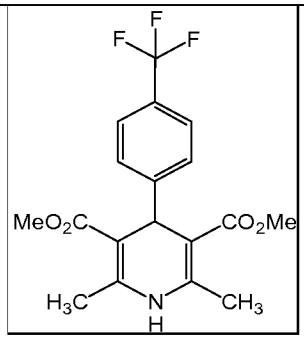
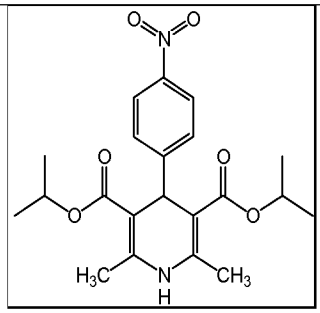
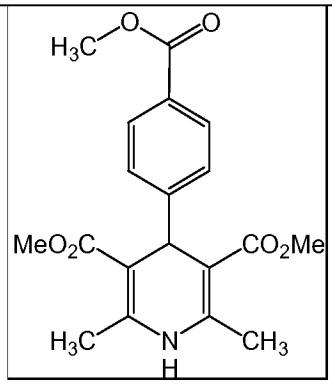
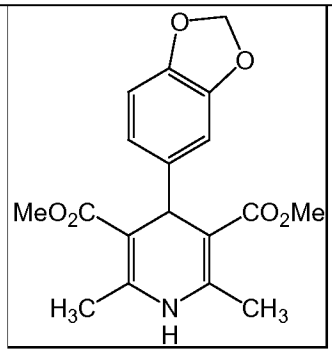
22. The method of any one of claims 18 to 19, wherein R_4 is an optionally substituted C_1-C_{10} alkyl.

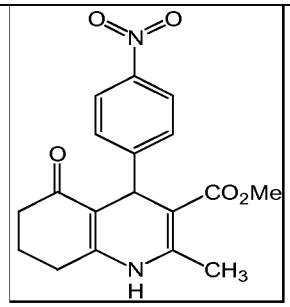
23. The method of claim 21, wherein R_3 and R_4 are each independently methyl or ethyl.

24. The method of any one of claims 1 to 23, wherein R_5 is selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl.

25. The method of claim 1, wherein the compound is selected from the following:

Compound No.	Chemical Structure
1	
2	
3	
4	

5		
6		
7		
8		

9	

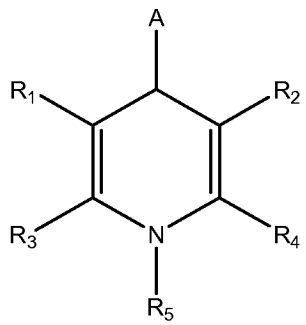
26. The method of any one claims 1 to 25, wherein the immune cell is selected from the group consisting of lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mast cells.

27. The method of claim 26, wherein the immune cell is selected from neutrophils and monocytes.

28. The method of any one of claims 1 to 27, wherein migration of the immune cell is stimulated in a subject in need thereof, wherein the subject is suffering from a condition that can be ameliorated by stimulating the migration of an immune cell.

29. The method of claim 28, wherein the condition is selected from the group consisting of gout, granuloma, and disseminated intravascular coagulation.

30. A method of stimulating an immune response in a patient in need thereof comprising administering to said patient an effective amount of a compound having the Formula (I):



(I),

or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof; wherein

A is optionally substituted aryl or optionally substituted heteroaryl;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally

substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$;

or R_1 and R_3 and R_2 and R_4, are each independently taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

each R_c is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

R_5 is selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; and

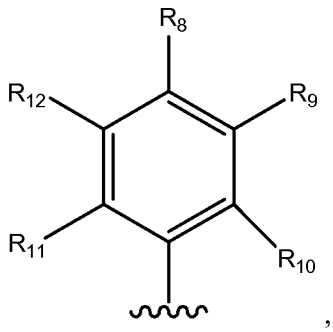
each n is 0, 1 or 2.

31. The method of claim 30, wherein A is optionally substituted aryl.

32. The method of claim 31, wherein A is optionally substituted phenyl.

33. The method of claim 32, wherein A is phenyl substituted with NO_2 and further optionally substituted.

34. The method of any one of claims 30 to 33, wherein A is:



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wherein R_8 is selected from the group consisting of optionally substituted optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$; and

each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$.

35. The method of claim 34, wherein R_8 is selected from the group consisting of halo, haloalkyl, CN, OR_c, NR_cR_c, $NR_cC(O)R_c$, $C(O)OR_c$, $C(O)R_c$, and NO_2.

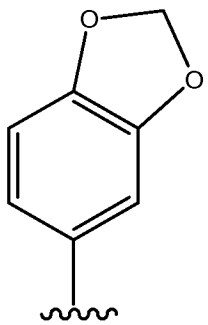
36. The method of claim 35, wherein R_8 is NO_2.

37. The method of any of claims 34 to 36, wherein each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_4 alkyl.

38. The method of claim 37, wherein each of R_9, R_{10}, R_{11} and R_{12} is hydrogen.

39. The method of claim 30, wherein A is heteroaryl.

40. The method of claim 30, wherein A is:



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41. The method of any one of claims 30 to 40, wherein R_1 and R_2 are selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$.

42. The method of claim 41, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, $C(O)R_c$, $C(O)C(O)R_c$, and $C(O)NR_cR_c$.

43. The method of claim 42, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and C(O)R.

44. The method of claim 43, wherein R_1 and R_2 are each independently selected from $C(O)OR_c$.

45. The method of any one of claims 34 to 38, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and C(O)R.

46. The method of claim 45, wherein R_1 and R_2 are each independently selected from $C(O)OR_c$.

47. The method of any one of claims 30 to 40, wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 3- to 12-membered heterocyclic, optionally substituted aryl and optionally substituted heteroaryl.

48. The method of claim 47, wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, or an optionally substituted C_3-C_{12} cycloalkenyl.

49. The method of any one of claims 30 to 40 or 47 to 48, wherein R_2 and R_4 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-

C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl.

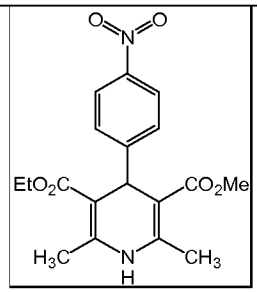
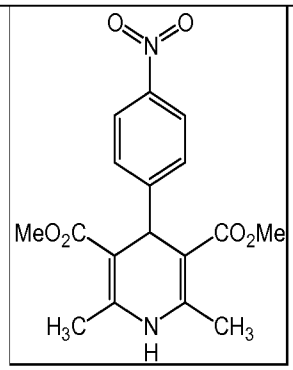
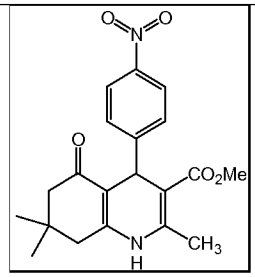
50. The method of any one of claims 30 to 46, wherein R_3 and R_4 are each independently optionally substituted C_1-C_{10} alkyl.

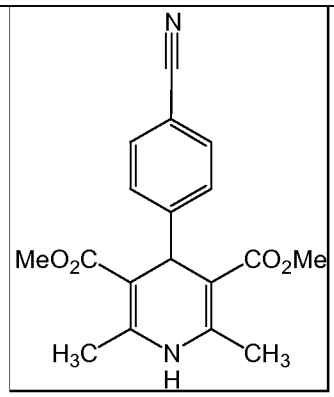
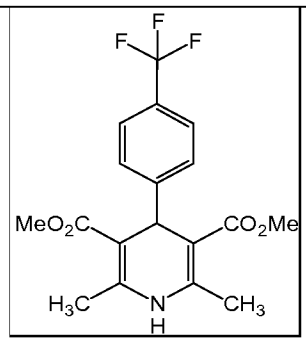
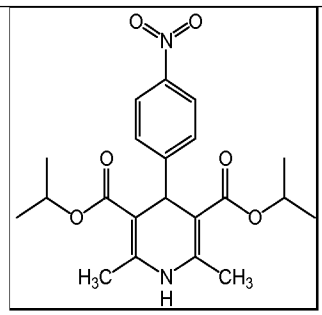
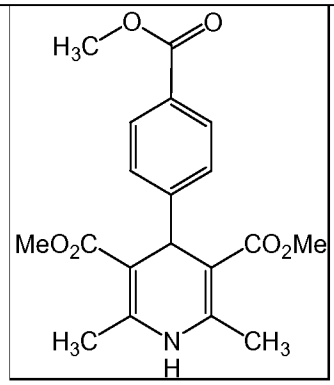
51. The method of any one of claims 47 to 48, wherein R_4 is an optionally substituted C_1-C_{10} alkyl.

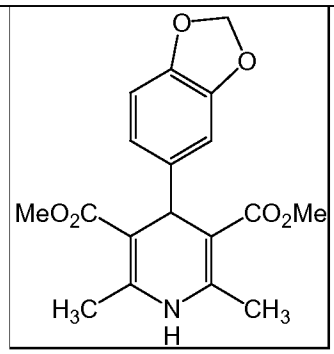
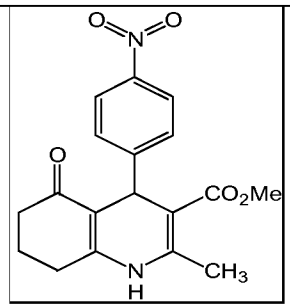
52. The method of claim 50, wherein R_3 and R_4 are each independently methyl or ethyl.

53. The method of any one of claims 30 to 52, wherein R_5 is selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl.

54. The method of claim 30, wherein the compound is selected from the following:

Compound No.	Chemical Structure
1	
2	
3	

4	
5	
6	
7	

8	
9	

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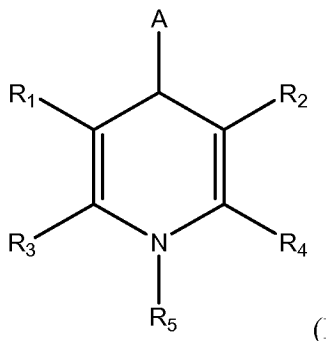
55. The method of claim 30, wherein the compound is co-administered with a vaccine.

56. The method of claim 30, wherein the patient is suffering from cancer.

57. The method of claim 30, wherein the patient is suffering from an infection.

58. The method of claim 57, wherein the infection is selected from the group consisting of a viral infection, a bacterial infection, a fungal infection, and a protozoal infection.

59. A method of increasing immune cell deformability in a patient in need thereof comprising administering to said patient an effective amount of a compound having the Formula (I):



(I),

or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof; wherein A is optionally substituted aryl or optionally substituted heteroaryl;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$;

or R_1 and R_3 and R_2 and R_4, are each independently taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

each R_c is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

R_5 is selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; and

each n is 0, 1 or 2.

60. The method of claim 59, wherein the immune cell is a monocyte or a neutrophil.

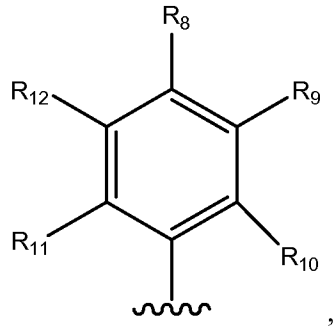
61. The method of claim 60, wherein the immune cell is a neutrophil.

62. The method of claim 59, wherein A is optionally substituted aryl.

63. The method of claim 60, wherein A is optionally substituted phenyl.

64. The method of claim 63, wherein A is phenyl substituted with NO_2 and further optionally substituted.

65. The method of any one of claims 59 to 63, wherein A is:



,

wherein R_8 is selected from the group consisting of optionally substituted optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$; and

each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$.

66. The method of claim 65, wherein R_8 is selected from the group consisting of halo, haloalkyl, CN, OR_c, NR_cR_c, $NR_cC(O)R_c$, $C(O)OR_c$, $C(O)R_c$, and NO_2.

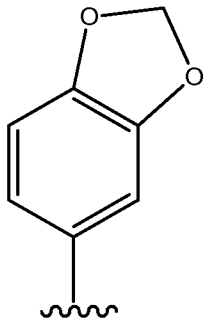
67. The method of claim 66, wherein R_8 is NO_2.

68. The method of any of claims 65 to 67, wherein each of R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_4 alkyl.

69. The method of claim 68, wherein each of R_9, R_{10}, R_{11} and R_{12} is hydrogen.

70. The method of claim 59, wherein A is heteroaryl.

71. The method of claim 59, wherein A is:



72. The method of any one of claims 59 to 71, wherein R_1 and R_2 are selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, halo, cyano, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, OR_c, NO_2, $S(O)_nR_c$, $S(O)_nNR_cR_c$, $C(O)R_c$, $C(O)OR_c$, $C(O)NR_cR_c$, $NR_cC(O)NR_cR_c$, NR_cR_c, and $NR_cC(O)R_c$.

73. The method of claim 72, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, $C(O)R_c$, $C(O)C(O)R_c$, and $C(O)NR_cR_c$.

74. The method of claim 73, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and C(O)R.

75. The method of claim 74, wherein R_1 and R_2 are each independently selected from $C(O)OR_c$.

76. The method of claims 65 to 69, wherein R_1 and R_2 are each independently selected from the group consisting of CN, $C(O)OR_c$, and C(O)R.

77. The method of claim 76, wherein R_1 and R_2 are each independently selected from $C(O)OR_c$.

78. The method of any one of claims 59 to 71, wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl,

optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 3- to 12-membered heterocyclic, optionally substituted aryl and optionally substituted heteroaryl.

79. The method of claim 78, wherein R_1 and R_3 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, or an optionally substituted C_3-C_{12} cycloalkenyl.

80. The method of any one of claims 59 to 72 or 78 to 79, wherein R_2 and R_4 are taken together with the carbon atoms to which they are attached to form a fused optionally substituted cyclic group selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl.

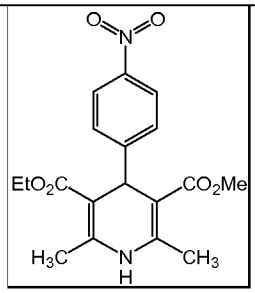
81. The method of any one of claims 61 to 77, wherein R_3 and R_4 are each independently optionally substituted C_1-C_{10} alkyl.

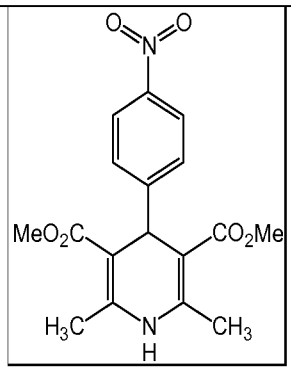
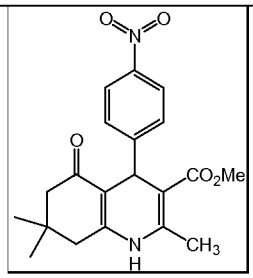
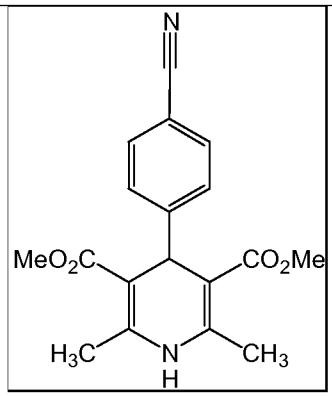
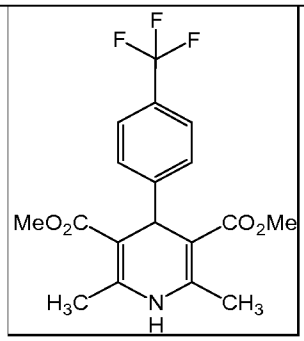
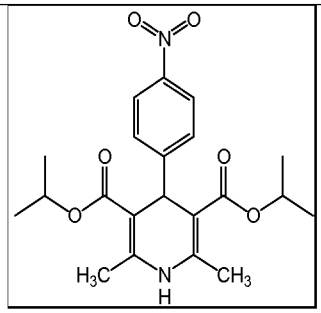
82. The method of any one of claims 78 to 79, wherein R_4 is an optionally substituted C_1-C_{10} alkyl.

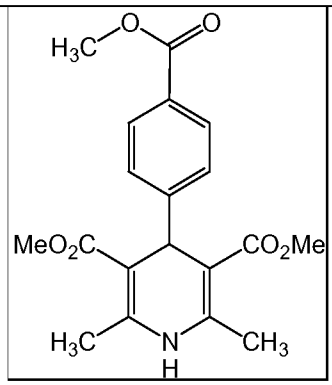
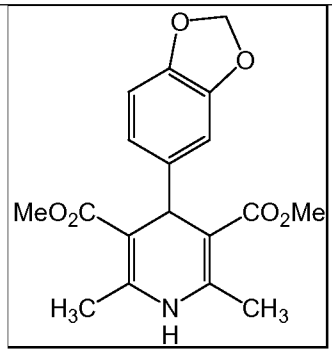
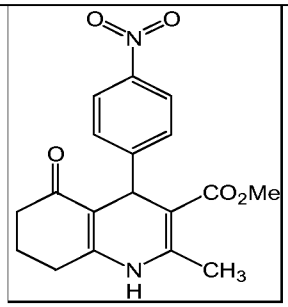
83. The method of claim 81, wherein R_3 and R_4 are each independently methyl or ethyl.

84. The method of any one of claims 59 to 83, wherein R_5 is selected from the group consisting of hydrogen and optionally substituted C_1-C_4 alkyl.

85. The method of claim 59, wherein the compound is selected from the following:

Compound No.	Chemical Structure
1	

2	
3	
4	
5	
6	

7	
8	
9	

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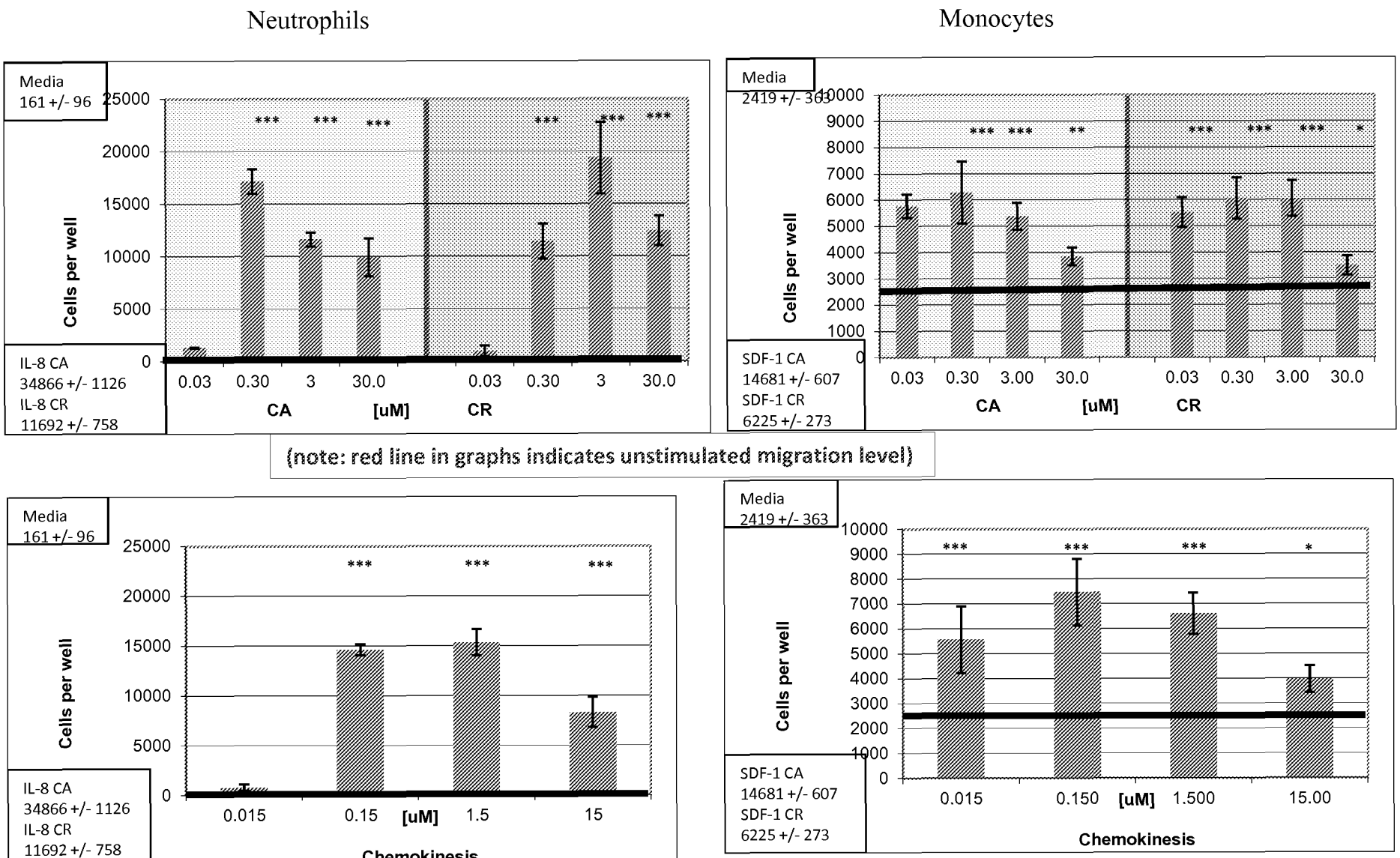
86. The method of claim 59, wherein the patient is suffering from an inflammatory condition.

87. The method of claim 59, wherein the patient is suffering from disseminated intravascular coagulation.

88. The method of claim 59, wherein the patient is suffering from a condition selected from the group consisting of sepsis, septic shock, adult respiratory distress syndrome, cystic fibrosis, idiopathic pulmonary fibrosis, systemic sclerosis, gout, disseminated intravascular coagulopathy, bacterial pneumonia, and granuloma.

Compound 2 Stimulates Migration
of Human Neutrophils and Monocytes (PBMC)



The FIGURE

INTERNATIONAL SEARCH REPORT

PCT/US2014/023120 27.06.2014

International application No.
PCT/US 14/23120

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/44 (2014.01)
USPC - 514/356; 514/277; 514/336; 514/357
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/356
IPC: A61K 31/44 (2014.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/277; 514/336; 514/357 (see search words below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATBASE: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO
Google: Scholar/patents:dihydropyridine nitrophenyl chemoattractant immune cell migration leukocyte cyanophenyl dimethyl chemotaxis vaccine combination ,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5 dicarboxylic acid ethyl methyl ester benzodioxol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 6,545,028 B2 (JENSEN et al.) 08 April 2003 (08.04.2003) Col 3, ln 1-15; Col 11, ln 53-56;Col 5, ln 30-31; Col 13, ln 4-10; Col 13, ln 25-41	30-36;54;56-58 ---------- 1-7;10;11;25;39-40;55;59-67;70;71;85-88
Y	BACON et al. Potent and Specific Inhibition of IL-S, IL-Ia and IL-Ib-induced In Vitro Human Lymphocyte Migration by Calcium Channel Antagonists, Biochemical and Biophysical Research Communications, 1989, Vol 165, pp 349-354. pg 349, abstract; pg 352, Figure 3	1-7;10;11;25
Y	ZHOU et al. New 4-Aryl-1,4-Dihydropyridines and 4-Arylpyridines as P-Glycoprotein Inhibitors in Drug Metabolism and Disposition, 2005, Vol 33, pp 321-328. pg 322, Table I, Compound Io; pg 326, Col 2, para 6 to pg 327, Col 1, para 1	10;11;39;40;70;71
Y	US 2006/0165744 A1 (JAMIL et al.) 27 July 2006 (27.07.2006) para [0005];[0025];[0026];[0031];[0032];[0049]	55
Y	SHWAB. Function and spatial distribution of ion channels and transporters in cell migration, Am J Physiol Renal Physiol., 2001, Vol 280, pp F739-F747. pg F741, Col 1, para 2 to pg F742, Col 2, para 1	59-67;70;71;85-88

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2014 (30.05.2014)	27 JUN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT PCT/US2014/023120 27.06.2014

International application No.
PCT/US 14/23120

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-9, 12-24, 26-29, 37-38, 41-53, 68-69 and 72-84
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.