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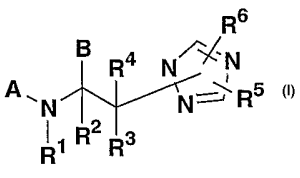
(54) Title: MODULATORS OF THE GLUCOCORTICOID RECEPTOR AND METHOD



(I)

(57) Abstract: Novel non-steroidal compounds are provided which are glucocorticoid receptor modulators which are useful in treating diseases requiring glucocorticoid receptor agonist or antagonist therapy such as obesity, diabetes, inflammatory and immune disorders, and have the structure (I) where A, B, and R^1-R^6 are defined herein.

MODULATORS OF THE GLUCOCORTICOID RECEPTOR AND METHOD

This application claims priority to U.S. Provisional Application 60/477,545 filed June 11, 2003, the entirety of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to new non-steroidal compounds which are glucocorticoid receptor (GR) modulators (that is agonists and antagonists) and thus are useful in treating diseases requiring glucocorticoid receptor agonist or antagonist therapy such as obesity, diabetes and inflammatory or immune associated diseases, and to a method for using such compounds to treat these and related diseases.

BACKGROUND OF THE INVENTION

The nuclear hormone receptor (NHR) family of transcription factors bind low molecular weight ligands and either stimulate or repress transcription. *See, e.g.*,V. LAUDET ET AL., THE NUCLEAR RECEPTOR FACTS BOOK, 345, (2002). NHRs stimulate transcription by binding to DNA and inducing transcription of specific genes. NHRs may also stimulate transcription by not binding to DNA itself, rather they may modulate the activity of other DNA binding proteins. Stocklin, E., et al., *Nature* 383:726-8 (1996). The process of stimulation of transcription is called transactivation. NHRs repress transcription by interacting with other transcription factors or coactivators and inhibiting the ability of these other transcription factors or coactivators from inducing transcription of specific genes. This repression is called transrepression. For a review of this topic, see generally V. Laudet, *supra*, beginning at 42.

The glucocorticoid receptor (GR) is a member of the nuclear hormone receptor family of transcription factors, and a member of the steroid hormone family of transcription factors. Affinity labeling of the glucocorticoid receptor protein allowed the production of antibodies against the receptor which facilitated cloning the glucocorticoid receptors. For results in humans seeWeinberger, et al., *Science* 228, 640-742, (1985); Weinberger, et al., *Nature*, 318, 670-672 (1986) and for results in rats see Miesfeld, R., *Nature*, 312, 779-781, (1985).

Glucocorticoids which interact with GR have been used for over 50 years to treat inflammatory diseases. It has been clearly shown that glucocorticoids exert their anti-inflammatory activity via the inhibition by GR of the transcription factors NF-kappaB and AP-1. This inhibition is termed transrepression. It has been shown that the primary mechanism for inhibition of these transcription factors by GR is via a direct physical interaction. This interaction alters the transcription factor complex and inhibits the ability of NF-kappaB and AP-1 to stimulate transcription. *See* Jonat, C., et al., *Cell*, 62, 1189 (1990); Yang-Yen, H.F., et al,. *Cell*, 62, 1205 (1990); Diamond, M.I. et al., *Science* 249, 1266 (1990); and Caldenhoven, E. et al., *Mol. Endocrinol.*, 9, 401 (1995). Other mechanisms such as sequestration of co-activators by GR have also been proposed. *See* Kamer Y, et al., *Cell*, 85, 403 (1996); and Chakravarti, D. et al., *Nature*, 383, 99 (1996). NF-kappaB and AP-1 play key roles in the initiation and perpetuation of inflammatory and immunological disorders. *See* Baldwin, AS, *Journal of Clin. Investigation,* 107, 3 (2001); Firestein, G.S., and Manning, A.M., *Arthritis and Rheumatism*, 42, 609 (1999); and Peltz, G., *Curr. Opin, in Biotech.* 8, 467 (1997). NF-kappaB and AP-1 are involved in regulating the expression of a number of important inflammatory and immunomodulatory genes including: TNF-alpha, IL-1, IL-2, IL-5, adhesion molecules (such as E-selectin), chemokines (such as Eoxtaxin and Rantes), Cox-2, and others.

In addition to causing transrepression, the interaction of a glucocorticoid with GR can cause GR to induce transcription of certain genes. This induction of transcription is termed transactivation. Transactivation requires dimerization of GR and binding to a glucocorticoid response element (GRE).

Recent studies using a transgenic GR dimerization defective mouse which cannot bind DNA have shown that the transactivation (DNA binding) activities of GR could be separated from the transrepressive (non-DNA binding) effect of GR. These studies also indicate that many of the side effects of glucocorticoid therapy are due to the ability of GR to induce transcription of various genes involved in metabolism, whereas, transrepression, which does not require DNA binding leads to suppression of inflammation. *See* Tuckermann, J. et al., *Cell*, 93, 531 (1998) and Reichardt, HM, *EMBO J.*, 20, 7168 (2001).

The art is in need of modulators of NHRs. A modulator of an NHR may be useful in treating NHR-associated diseases, that is diseases associated with the expression products of genes whose transcription is stimulated or repressed by NHRs. For instance, the art is in need of modulators of NHRs that inhibit AP-1 and NFκB, as such compounds would be useful in the treatment of inflammatory and immune diseases and disorders such as osteoarthritis, rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, transplant rejection and graft vs. host disease.

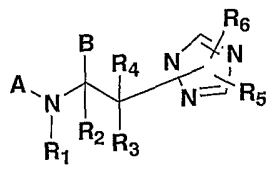
Particularly concerning GR, although glucocorticoids are potent anti-inflammatory agents, their systemic use is limited by side effects. A compound that retained the anti-inflammatory efficacy of glucocorticoids while minimizing the side effects such as diabetes, osteoporosis and glaucoma would be of great benefit to a very large number of patients with inflammatory diseases.

Additionally concerning GR, the art is in need of compounds that antagonize transactivation. Such compounds may be useful in treating metabolic diseases associated with increased levels of glucocorticoid, such as diabetes, osteoporosis and glaucoma.

Additionally concerning GR, the art is in need of compounds that cause transactivation. Such compounds may be useful in treating metabolic diseases associated with a deficiency in glucocorticoid. Such diseases include Addison's disease.

SUMMARY OF THE INVENTION

In accordance with the present invention, a method is provided for preventing or inhibiting the onset of or treating a GR-associated disease which is associated with the expression product of a gene whose transcription is stimulated or repressed by glucocorticoid receptors, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound having formula (I),



(I)

including all stereoisomers, salts, solvates or prodrugs thereof,

wherein:

A and B are independently cycloalkyl, aryl or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$ or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl or heteroaryl, each group of which is optionally substituted where valence allows;

R^5 and R^6 are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^7, NR^7R^8, SR^7, COR^9, CO_2R^9 or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, heteroarylalkyl or arylalkyl, each group of which is optionally substituted;

R^7 and R^8 are independently

(i) hydrogen, COR^9, SO_2R^9 or $S(O)R^9$; or

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, heteroarylalkyl or arylalkyl, each group of which is optionally substituted; and

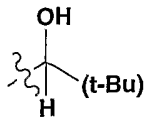
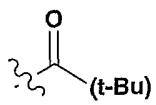
R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, heteroarylalkyl or arylalkyl,

wherein each occurrence of R^7, R^8 and/or R^9 is chosen independently.

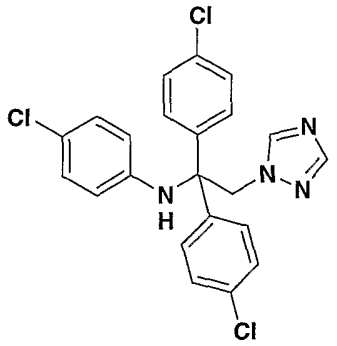
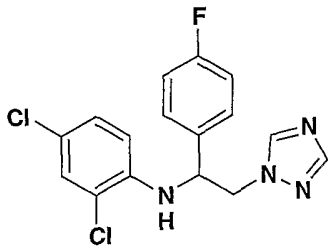
Another aspect of the invention provides compounds within the scope of Formula (I), including all stereoisomers, salts, solvates or prodrugs thereof, wherein:

A and B are independently aryl or heteroaryl, each of which is optionally substituted provided:

(i) A is not benz[c,d]indole;

(ii) R^3 or R^4 is not  or  if the other of R^3 or R^4 is hydrogen; and

(iii) formula (I) is not

 or 

In another aspect of the present invention, there is provided pharmaceutical compositions useful in treating endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, diabetes, obesity, and neoplastic disease, as well as other uses as described herein, which includes a therapeutically effective amount (depending upon use) of a compound of formula (I) of the invention and a pharmaceutically acceptable carrier.

In still another aspect, the present invention provides a method of preventing, inhibiting onset of or treating endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, diabetes, obesity, and neoplastic disease, GR-associated diseases, that is a disease associated with the expression product of a gene whose transcription is stimulated or repressed by GR or a disease associated with GR transactivation, including inflammatory and immune diseases and disorders as described hereinafter, which includes the step of administering a therapeutically effective amount of a compound of formula (I) of the invention to a patient in need of treatment.

Another aspect of the present involves a method for preventing, inhibiting onset of or treating a disease associated with AP-1- and/or NFκB-dependent gene expression, that is a disease associated with the expression of a gene under the regulatory control of AP-1 and/or NFκB such as inflammatory and immune disorders, cancer and tumor disorders, such as solid tumors, lymphomas and leukemia, and fungal infections such as mycosis fungoides.

DETAILED DESCRIPTION

The present invention relates to new non-steroidal compounds which are glucocorticoid receptor (GR) modulators (that is agonists and antagonists) and thus are useful in treating diseases requiring glucocorticoid receptor agonist or antagonist therapy such as obesity, diabetes and inflammatory or immune associated diseases, and to a method for using such compounds to treat these and related diseases.

The term "disease associated with GR transactivation," as used herein, refers to a disease associated with the transcription product of a gene whose transcription is transactivated by a GR. Such diseases include, but are not limited to: osteoporosis, diabetes, glaucoma, muscle loss, facial swelling, personality changes, hypertension, obesity, depression, and AIDS, the condition of wound healing, primary or secondary andrenocortical insufficiency, and Addison's disease.

The term "treat", "treating", or "treatment," in all grammatical forms, as used herein refers to the prevention, reduction, or amelioration, partial or complete alleviation, or cure of a disease, disorder, or condition.

The terms "glucocorticoid receptor" and "GR," as used herein, refer either to a member of the nuclear hormone receptor family of transcription factors which bind glucocorticoids and either stimulate or repress transcription, or to GR-beta. These terms, as used herein, refer to glucocorticoid receptor from any source, including but not limited to: human glucocorticoid receptor as disclosed in Weinberger, et al., *Science* 228, 640-742 (1985) and in Weinberger, et al., *Nature*, 318, 670-672 (1986); rat glucocorticoid receptor as disclosed in Miesfeld, R., *Nature*, 312, 779-781 (1985); mouse glucocortoid receptor as disclosed in Danielson, M. et al., *EMBO J.*, 5, 2513; sheep glucocorticoid receptor as disclosed inYang, K., et al., *J. Mol. Endocrinol.*, 8, 173-180 (1992); marmoset glucocortoid receptor as disclosed in Brandon, D.D., et al,, *J. Mol. Endocrinol.*,. 7, 89-96 (1991); and human GR-beta

as disclosed in Hollenberg, SM. et al., *Nature*, 318, 635 (1985), Bamberger, C.M. et al., *J. Clin Invest.* 95, 2435 (1995).

The term, "disease associated with AP-1-dependent gene expression," as used herein, refers to a disease associated with the expression product of a gene under the regulatory control of AP-1. Such diseases include, but are not limited to: inflammatory and immune diseases and disorders; cancer and tumor disorders, such as solid tumors, lymphomas and leukemia; and fungal infections such as mycosis fungoides.

The term "inflammatory or immune associated diseases or disorders" is used herein to encompass any condition, disease, or disorder that has an inflammatory or immune component, including, but not limited to, each of the following conditions: transplant rejection (e.g., kidney, liver, heart, lung, pancreas (e.g., islet cells), bone marrow, cornea, small bowel, skin allografts, skin homografts (such as employed in burn treatment), heart valve xenografts, serum sickness, and graft vs. host disease, autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Type I and Type II diabetes, juvenile diabetes, obesity, asthma, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), pyoderma gangrenum, lupus (systemic lupus erythematosis), myasthenia gravis, psoriasis, dermatitis, dermatomyositis; eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, atherosclerosis, Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), glomerulonephritis, scleroderma, morphea, lichen planus, viteligo (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, Guillain-Barre syndrome, and alveolitis; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis (including that due to poison ivy), uticaria, skin allergies, respiratory allergies (hayfever, allergic rhinitis) and gluten-sensitive enteropathy (Celiac disease); inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, acute respiratory distress syndrome, Sezary's syndrome and vascular diseases which have an inflammatory and

or a proliferatory component such as restenosis, stenosis and artherosclerosis. Inflammatory or immune associated diseases or disorders also includes, but is not limited to: endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, juvenile rheumatoid arthritis, Ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, epicondylitis, acute rheumatic carditis, pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme, exfoliative dermatitis, seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjunctivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, optic neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, leukemias and lymphomas in adults, acute leukemia of childhood, regional enteritis, autoimmune vasculitis, multiple sclerosis, chronic obstructive pulmonary disease, solid organ transplant rejection, sepsis.

In addition, in accordance with the present invention a method of treating a disease associated with AP-1-induced or NFκB-induced transcription is provided wherein a compound of formula (I) of the invention is administered to a patient in need of treatment in a therapeutically effective amount to induce NHR transrepression of the AP-1-induced or NFκB-induced transcription, thereby treating the disease.

Other therapeutic agents, such as those described hereafter, may be employed with the compounds of the invention in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their

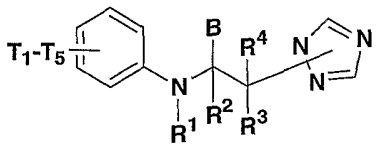
etiology, for example, for the treatment of transplant rejection, rheumatoid arthritis, inflammatory bowel disease, and viral infections.

Preferred compounds include compounds within the scope of formula (I) (above), stereoisomers, salts, solvates or prodrugs thereof, wherein:

A is phenyl preferably substituted by hydrogen, F, Cl, Br, I, NO_2, CN, OR^7, SR^7, C_{1-6}alkyl, or C_{1-6}heteroalkyl; or

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, arylC_{1-6} alkyl, heteroarylC_{1-6} alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein the heteroaryl or aryl component of the arylC_{1-6} alkyl and heteroarylC_{1-6} alkyl groups is optionally substituted

Alternatively preferred compounds are described by formula (II),



(II)

including all stereoisomers, salts, solvates or prodrugs thereof, wherein:

B is aryl or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$ or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, arylC_{1-6} alkyl, heteroarylC_{1-6} alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein the heteroaryl or aryl component of the arylC_{1-6} alkyl and heteroarylC_{1-6} alkyl groups is optionally substituted

R^7 and R^8 are independently

(i) hydrogen, COR^9, SO_2R^9 or $S(O)R^9$

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, allyl, arylalkyl, each group of which is optionally substituted;

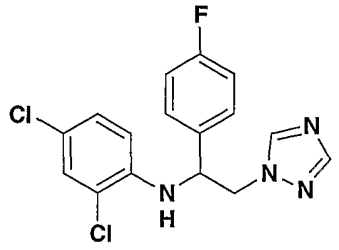
T^1 through T^5 are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^9 or SR^9; or

(ii) C_{1-5}alkyl or C_{1-6}heteroalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl or arylalkyl;

provided that formula (II) is not



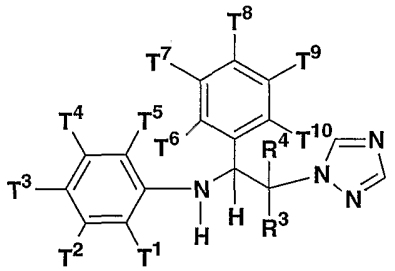
Compounds within the scope of formula (II) that are more preferred are those in which

B is an optionally substituted phenyl ring, (especially a phenyl ring substituted by hydrogen F, Cl, Br, I, NO_2, CN, OR^7, SR^7, C_{1-6}alkyl, or C_{1-6}heteroalkyl); or

R^1 is hydrogen or C_{1-6}alkyl; or

T^1 through T^5 is independently selected from H, F, Cl, Br, I, or -OC_{1-6}alkyl.

Alternatively, preferred compounds are those described by formula (III),



(III)

including all stereoisomers, salts, solvates or prodrugs thereof,

wherein:

R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}arylalkyl, C_{1-6}heteroarylalkyl C_{2-6}alkenyl, C_{2-6}alkynyl or allyl, wherein the heteroaryl or aryl component of the C_{1-6}heteroarylalkyl and C_{1-6}arylalkyl groups is optionally substituted.

T^1 through T^{10} are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^9 or SR^9; or

(ii) C_{1-6}alkyl or C_{1-6}heteroalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl heteroarylalkyl or arylalkyl;

provided that if T^8 is fluoro and T^6, T^7, T^9 and T^{10} are all hydrogen then T^1 and T^3 cannot both be chloro if T^2, T^4, and T^5 are all hydrogen.

Compounds that are more preferred within the scope of formula (III) are those in which

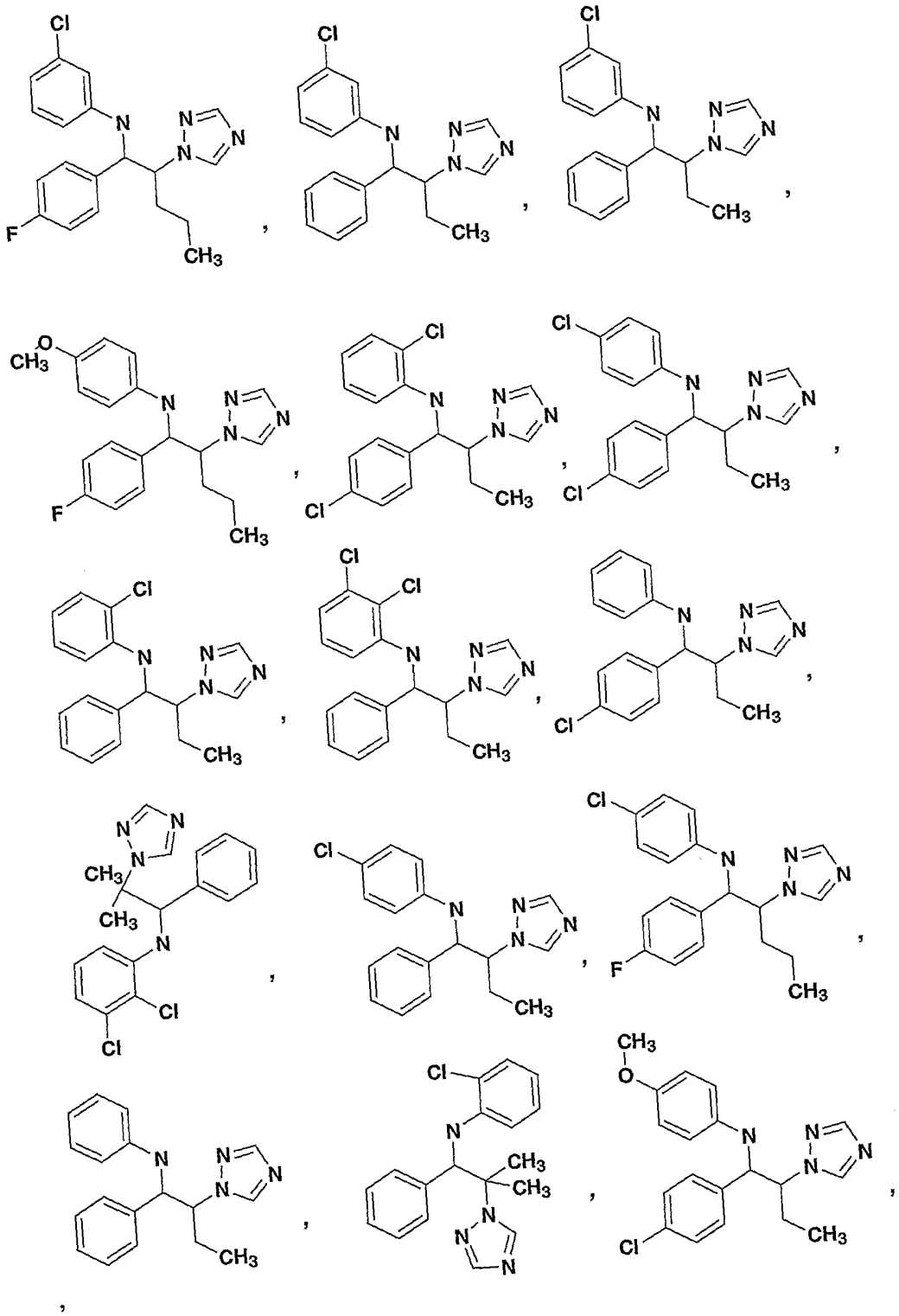
T^1 throughT^{10} are selected independently from hydrogen, F, Cl, Br I., and -OC_{1-6}alkyl; or

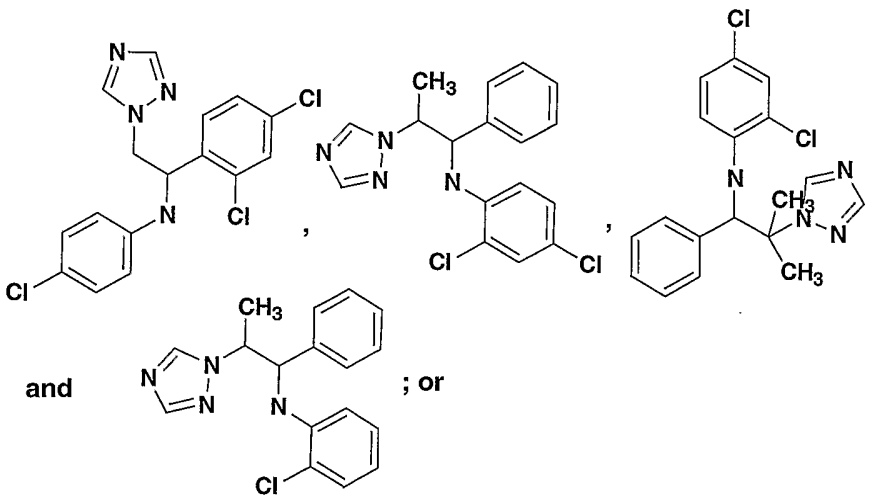
R^3 and R^4 are selected independently from hydrogen and C_{1-6}alkyl.

Especially preferred compounds within the scope of formula (III) are those in which R^3 is hydrogen and R^4 is C_{1-6}alkyl..

Other preferred are compounds selected from the following:

(i)





(iii) or a stereoisomer, salt, solvate or prodrug of (i) thereof.

Pharmaceutical of the present invention are compositions comprising a compound as defined in formulas (I), (II) or (III) as described above.and a pharmaceutically acceptable carrier therefor.

Preferred harmaceutical combinations of the present invention comprise a compound as defined in (I), (II) or (III) as described above and an immunosuppressant, an anticancer agent, an anti-viral agent, an anti-inflammatory agent, an anti-fungal agent, an anti-biotic, an anti-vascular hyperproliferation agent, an anti-depressant agent, a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor and/or an antiosteoporosis agent, wherein

the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide;

the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor or an anorectic agent;

the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor or an ACAT inhibitor; and

the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker or β-adrenergic blocker.

Especially preferred combinations are those wherein

the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A;

the anti-obesity agent is selected from orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol;

the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427;

the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440 or an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan; amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol or clonidine HCl; and

the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban.

Even more preferred combinations are those wherein

the immunosuppressant is a cyclosporin, mycophenolate, interferon-beta, deoxyspergolin, FK-506 or Ant.-IL-2;

the anti-cancer agent is azathiprine, 5-fluorouracel, cyclophosphamide, cisplatin, methotrexate, thiotepa, or carboplatin;

the anti-viral agent is abacavir, aciclovir, ganciclovir, zidanocin, or vidarabine; and

the antiinflammatory drug is ibuprofen, celecoxib, rofecoxib, aspirin, naproxen, ketoprofen, diclofenac sodium, indomethacin, piroxicam, prednisone, dexamethasone, hydrocortisone, or triamcinolone diacetate.

In accordance with the present invention, methods are provided for preventing or inhibiting the onset of or treating a GR-associated disease which is associated with

the expression product of a gene whose transcription is stimulated or repressed by glucocorticoid receptors, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound having formulas (I), (II) or (III) as described above.

Preferred methods are those in whch the GR-associated disease is an inflammatory or immune associated disease or disorder which is an endocrine disorder, rheumatic disorder, collagen disease, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, neoplastic disease and metabolic disease.

Especially preferred are methods wherein the inflammatory or immune associated disease or disorder is transplant rejection of kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts, heart valve xenograft, serum sickness, and graft vs. host disease, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Type I and Type II diabetes, juvenile diabetes, obesity, asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pyoderma gangrenum, systemic lupus erythematosis, myasthenia gravis, psoriasis, dermatitis, dermatomyositis; eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome, pernicious or immunohaemolytic anaemia, atherosclerosis, Addison's disease, idiopathic adrenal insufficiency, autoimmune polyglandular disease, glomerulonephritis, scleroderma, morphea, lichen planus, viteligo, alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, Guillain-Barre syndrome, and alveolitis; contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis, uticaria,skin allergies, respiratory allergies, hayfever, allergic rhinitis and gluten-sensitive enteropathy, osteoarthritis, acute pancreatis, chronic pancreatitis, acute respiratory distress syndrome, Sezary's syndrome, restenosis, stenosis and artherosclerosis, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, juvenile rheumatoid arthritis, Ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteroarthritis, synovitis of osteoarthritis, epicondylitis, acute rheumatic carditis, pemphigus, bullous dermatitis herpetitformis, severe erythema multiforme, exfoliative dermatitis, psoriasis,

seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjuncivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, optic neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, leukemias and lymphomas in adults, acute leukemia of childhood, ulcerative colitis, regional enteritis, Crohn's disease, Sjogren's syndrome, autoimmune vasculitis, multiple sclerosis, myasthenia gravis, sepsis and chronic obstructive pulmonary disease.

Also preferred are methods for preventing or inhibiting the onset of or treating a disease associated with AP-1 and/or NFκB induced transcription comprising administering to a patient in need of treatment a therapeutically effective amount of at least one compound having formulae (I) (II) or (II) as described above.

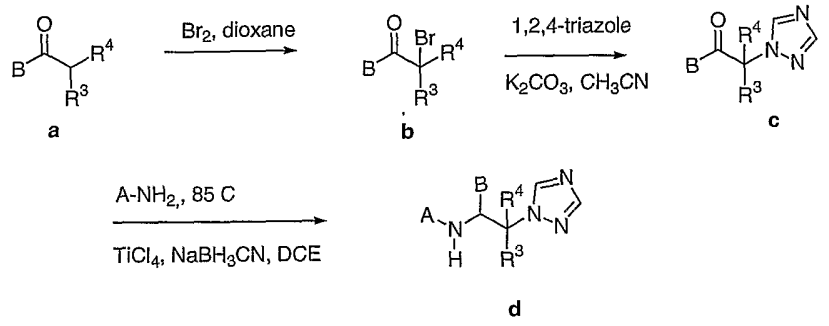
Also preferred are methods for preventing or inhibiting the onset of or treating a disease associated with AP-1 and/or NFκB dependent gene expression, that is a disease associated with the expression of a gene under the regulatory control of AP-1 and/or NFκB comprising administering to a patient in need of treatment a therapeutically effective amount of at least one compound having formulae (I) (II) or (III) as described above.

METHODS OF PREPARATION

The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry. A general synthetic scheme for preparing compounds of the present invention is described below. The scheme is illustrative and is not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds. Examples of compounds of the present invention prepared by methods described in Scheme I are given below.

The intermediate triazol-1-yl-ketones (**c**) are prepared by brominating the appropriately substituted ketone (**a**) with bromine in dioxane. The brominated ketone (**b**) is then stirred with 1,2,4-triazole and K_2CO_3 in acetonitrile to afford the triazol-1-yl ethanones (**c**). Titanium chloride and sodium cyanoborohydride are then used to effect the reductive coupling of (**c**) and the desired amine to give the final product (**d**).

Scheme 1



Definition of Terms

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred. When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, "$C_{1\text{-}6}$alkyl" refers to straight and branched chain alkyl groups with one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, and so forth.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, or three substituents selected from the group consisting of halo (*e.g.*, trifluoromethyl), alkenyl, alkynyl, nitro, cyano, amino, oxo (=O), hydroxy, alkoxy, alkylthio, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, -$NHSO_2$, -N(alkyl)SO_2, -$NHSO_2$(alkyl), -$NHSO_2$(aryl), -N(alkyl)SO_2(alkyl), -N(alkyl)SO_2(aryl), -SO_2(alkyl), -

SO_2(aryl), -SO_2N(aryl)(alkyl), -SO_2N(alkyl)$_2$, -CO_2H, -C(=O)H, -CO_2-alkyl, -C(=O)alkyl, -C(=O)aryl, -C(=O)NH_2, -C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(alkyl)$_2$, -NH-CH_2-CO_2H-NH-CH(alkyl)-CO_2H, -NH-CH_2-CO_2-alkyl, -NH-CH(alkyl)-CO_2-alkyl, =N-OH, =N-O-alkyl, aryl, heteroaryl, heterocyclo, cycloalkyl, and substituted cycloalkyl, including phenyl, benzyl, phenylethyl, phenyloxy, and phenylthio. When a substituted alkyl includes an aryl, heterocyclo, or heteroaryl substituent, said ringed systems are as defined below and thus may have zero, one, two, or three substituents, also as defined below.

When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where one of the substituents is aryl, such as benzyl.

The term heteroalkyl refers to straight or branched chain hydrocarbon groups, having single or double bonds, or combinations thereof, in which one or more skeletal atoms is oxygen, nitrogen, sulfur, or combinations thereof.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6 carbon atoms and having one double bond are preferred.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred.

The term "alkoxy" refers to an alkyl or substituted alkyl group as defined above having one, two or three oxygen atoms (-O-) in the alkyl chain. For example, the term "alkoxy" includes the groups -O-$C_{1\text{-}12}$alkyl, –$C_{1\text{-}6}$alkylene-O-$C_{1\text{-}6}$alkyl, –$C_{1\text{-}4}$alkylene-O-$C_{1\text{-}4}$alkylene-O-$C_{1\text{-}4}$alkyl, O–$C_{1\text{-}4}$alkylene-O-$C_{1\text{-}4}$alkylene-O-$C_{1\text{-}4}$alkyl, and so forth.

The term "thioalkyl" or "alkylthio" refers to an alkyl or substituted alkyl group as defined above bonded through one or more sulfur (-S-) atoms. For example, the

term "thioalkyl" or "alkylthio" includes the groups -S-C_{1-12}alkyl, –S-C_{1-6}alkylene-S-C_{1-6}alkyl, etc.

The term "aminoalkyl" refers to an alkyl or substituted alkyl group as defined above bonded through one or more nitrogen (-NR-) atoms. For example, the term "aminoalkyl" includes the groups -NR-C_{1-12}alkyl, –NR-C_{1-6}alkylene-NR-C_{1-6}alkyl, etc. (where R is preferably hydrogen but may include alkyl or substituted alkyl as defined above.) When a subscript is used with reference to an alkoxy, thioalkyl or aminoalkyl, the subscript refers to the number of carbon atoms that the group may contain in addition to heteroatoms. Thus, for example, monovalent C_{1-2}aminoalkyl includes the groups -CH_2-NH_2, -NH-CH_3, -$(CH_2)_2$-NH_2, -NH-CH_2-CH_3, -CH_2-NH_2-CH_3, and -N-$(CH_2)_2$. A lower aminoalkyl comprises an aminoalkyl having one to four carbon atoms. "Amino" refers to the group NH_2.

The alkoxy, thioalkyl, or aminoalkyl groups may be monovalent or bivalent. By "monovalent" it is meant that the group has a valency (*i.e.*, power to combine with another group), of one, and by "bivalent" it is meant that the group has a valency of two. Thus, for example, a monovalent alkoxy includes groups such as -O-C_{1-12}alkyl, –C_{1-6}alkylene-O-C_{1-6}alkyl, –C_{1-4}alkylene-O-C_{1-4}alkylene-O-C_{1-4}alkyl, whereas a bivalent alkoxy includes groups such as -O-C_{1-12}alkylene-, –C_{1-6}alkylene-O-C_{1-6}alkylene-, –C_{1-4}alkylene-O-C_{1-4}alkylene-O-C_{1-4}alkylene-, and so forth.

The term "acyl" refers to a carbonyl group () linked to an organic radical including an alkyl, alkenyl, alkynyl, aminoalkyl, substituted alkyl, substituted alkenyl, or substituted alkynyl, as defined above. The organic radical to which the carbonyl group is attached may be monovalent (*e.g.*, -C(=O)-alkyl), or bivalent (*e.g.*, -C(=O)alkylene, etc.)

The term "alkoxycarbonyl" refers to a carboxy or ester group () linked to an organic radical including an alkyl, alkenyl, alkynyl, aminoalkyl, substituted alkyl, substituted alkenyl, substituted alkynyl, or substituted aminoalkyl

group, as defined above. The organic radical to which the carboxy group is attached may be monovalent (*e.g.*, -CO_2-alkyl), or bivalent (*e.g.*, -CO_2-alkylene, etc.)

The term "sulfonyl" refers to a sulphoxide group (i.e., –$S(O)_{1-2}$-) linked to an organic radical including an alkyl, alkenyl, alkynyl, aminoalkyl, substituted alkyl, substituted alkenyl, substituted alkynyl, or substituted aminoalkyl group, as defined above. The organic radical to which the sulphoxide group is attached may be monovalent (*e.g.*, -SO_2-alkyl), or bivalent (*e.g.*, -SO_2-alkylene, etc.)

The term "sulfonamide" refers to the group –$S(O)_2NR_aR_b$, wherein R_a and R_b may be hydrogen or alkyl, alkenyl, alkynyl, aminoalkyl, substituted alkyl, substituted alkenyl, substituted alkynyl, or substituted aminoalkyl group, as defined above. R_a and R_b may be monovalent or bivalent (*e.g.*, -SO_2-NH-alkylene, etc.)

The term "cycloalkyl" refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. The term "cycloalkyl" includes such rings having zero, one, two, or three substituents selected from the group consisting of halo, alkyl, substituted alkyl (*e.g.*, trifluoromethyl), alkenyl, alkynyl, nitro, cyano, amino, oxo, hydroxy, alkoxy, alkylthio, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, -$NHSO_2$, -N(alkyl)SO_2 , -$NHSO_2$(alkyl), -$NHSO_2$(aryl), -N(alkyl)SO_2(alkyl), -N(alkyl)SO_2(aryl), -SO_2(alkyl), -SO_2(aryl), -SO_2N(aryl)(alkyl), -SO_2N(alkyl)$_2$, -CO_2H, -C(=O)H, CO_2-alkyl, -C(=O)alkyl, -$C(=O)NH_2$, -C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(alkyl)$_2$, -NH-CH_2-CO_2H, -NH-CH(alkyl)-CO_2H , -NH-CH_2-CO_2-alkyl, -NH-CH(alkyl)-CO_2-alkyl, =N-OH, =N-O-alkyl, aryl, heteroaryl, heterocyclo, and a five or six membered ketal, *e.g.*, 1,3-dioxolane or 1,3-dioxane.

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

The term "aryl" refers to phenyl, biphenyl, 1-naphthyl and 2-naphthyl, with phenyl being preferred. The term "aryl" includes such rings having zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, amino, hydroxy, alkoxy, alkylthio, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, $-NHSO_2$, $-N(alkyl)SO_2$, $-NHSO_2(alkyl)$, $-NHSO_2(aryl)$, $-N(alkyl)SO_2(alkyl)$, $-N(alkyl)SO_2(aryl)$, $-SO_2(alkyl)$, $-SO_2(aryl)$, $-SO_2N(aryl)(alkyl)$, $-SO_2N(alkyl)_2$, $-CO_2H$, -C(=O)H, CO_2-alkyl, -C(=O)alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(alkyl)_2$, $-NH-CH_2-CO_2H$, $-NH-CH(alkyl)-CO_2H$, $-NH-CH_2-CO_2$-alkyl, $-NH-CH(alkyl)-CO_2$-alkyl, phenyl, benzyl, napthyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, and heteroaryl. Addtionally, when reference is made herein to optionally-substituted aryl groups as selections for R^1, R^{4a} R^{4b} and R^{4c}, such aryl groups may in addition to the foregoing substituents contain one or more substituents selected from OR^c, NR^cR^d, CO_2R^c, $C(=O)R^c$, $C(=O)NR^cR^d$, $NR^cC(=O)R^d$, $NR^cC(=O)OR^d$, $S(O)_{0-2}R^c$, $NR^cSO_2R^d$, $SO_2NR^cR^d$, $-NHCH(alkyl)CO_2R^c$, wherein R^c and R^d are (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, substituted alkenyl, alkoxy, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo which in turn may be optionally substituted as set forth below.

The term "heterocyclo" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N). Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring

may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, amino, oxo, hydroxy, alkoxy, alkylthio, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, -$NHSO_2$, -N(alkyl)SO_2, -$NHSO_2$(alkyl), -$NHSO_2$(aryl), -N(alkyl)SO_2(alkyl), -N(alkyl)SO_2(aryl), -SO_2(alkyl), -SO_2(aryl), -SO_2N(aryl)(alkyl), -SO_2N(alkyl)$_2$, - CO_2H, -C(=O)H, CO_2-alkyl, -C(=O)alkyl, -C(=O)aryl, -C(=O)NH_2, -C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(alkyl)$_2$, -NH-CH_2-CO_2H, -NH-CH_2-CO_2-alkyl, -NHCH(C_{1-4}alkyl)-CO_2H, -NHCH(C_{1-4}alkyl)CO_2-alkyl, aryl, heteroaryl, heterocyclo, =N-OH, =N-O-alkyl, and a five or six membered ketal, e.g., 1,3-dioxolane or 1,3-dioxane.

Exemplary monocyclic groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

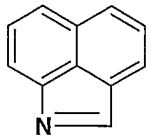
The term "heteroaryl" refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring.

The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, amino, hydroxy, alkoxy, alkylthio, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, -$NHSO_2$, -$N(alkyl)SO_2$, -$NHSO_2$(alkyl), -$NHSO_2$(aryl), -$N(alkyl)SO_2$(alkyl), -$N(alkyl)SO_2$(aryl), -SO_2(alkyl), -SO_2(aryl), -SO_2N(aryl)(alkyl), -$SO_2N(alkyl)_2$, -CO_2H, -C(=O)H, CO_2-alkyl, -C(=O)alkyl, -$C(=O)NH_2$, -C(=O)NH(alkyl), -C(=O)NH(cycloalkyl), -$C(=O)N(alkyl)_2$, -$NH-CH_2-CO_2H$, -NH-CH(alkyl)-CO_2H, -$NH-CH_2-CO_2$-alkyl, -NH-CH(alkyl)-CO_2-alkyl, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, and heteroaryl. Addtionally, when reference is made herein to optionally-substituted heteroaryl groups as selections for R^1, R^{4a} R^{4b} and R^{4c}, such heteroaryl groups may in addition to the foregoing substituents contain one or more substituents selected from OR^c, NR^cR^d, CO_2R^c, $C(=O)R^c$, $C(=O)NR^cR^d$, $NR^cC(=O)R^d$, $NR^cC(=O)OR^d$, $S(O)_{0-2}R^c$, $NR^cSO_2R^d$, $SO_2NR^cR^d$, -$NHCH(alkyl)CO_2R^c$, wherein R^c and R^d are (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, substituted alkenyl, alkoxy, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo which in turn may be optionally substituted as set forth below.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like. One example of a benzindolyl group is benz[c,d]indole which has the following structure



The term "optionally substituted" is intended to be synonymous with substituted or unsubstituted.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

Compounds of formula (I) include salts, prodrugs and solvates. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s) may include zwitterions (inner salts), *e.g.*, when a compound of formula (I) contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of the formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates,

nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. Preferred salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), and/or a salt and/or solvate thereof. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula (I) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, *e.g.*

acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

For further examples of such prodrug derivatives, see:

a) **Design of Prodrugs**, edited by H. Bundgaard, (Elsevier, 1985) and **Methods in Enzymology**, Vol.42, p. 309-396, edited by K. Widder, *et al.* (Acamedic Press, 1985);

b) **A Textbook of Drug Design and Development**, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

c) H. Bundgaard, **Advanced Drug Delivery Reviews**, 8, 1-38 (1992), each of which is incorporated herein by reference.

Compounds of the formula (I), salts and prodrugs thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have *trans* and *cis* isomers and may contain one or more chiral centers, therefore existing in enantiomeric and diastereomeric forms. The invention includes all such isomers, as well as mixtures of *cis* and *trans* isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers). When no specific mention is made of the configuration (*cis, trans* or R or S) of a compound (or of an asymmetric carbon), then any one of the isomers or a mixture of more than one isomer is intended. The processes for preparation can use racemates, enantiomers or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods for example,

chromatographic or fractional crystallization. The inventive compounds may be in the free or hydrate form.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula (I) can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Combinations

Where desired, the compounds of formula (I) may be used in combination with one or more other types of therapeutic agents such as immunosuppressants, anticancer agents, anti-viral agents, anti-inflammatory agents, anti-fungal agents, antibiotics, anti-vascular hyperproliferation agents, anti-depressive agents, hypolipidemic agents or lipid-lowering agents or lipid modulating agents, antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, and/or anti-osteoporosis agents, which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The immunosuppressants which may be optionally employed in combination with compounds of formula (I) of the invention include cyclosporins, for example cyclosporin A, mycophenolate, interferon-beta, deoxyspergolin, FK-506 or Ant.-IL-2.

The anti-cancer agents which may be optionally employed in combination with compounds of formula (I) of the invention include azathiprine, 5-fluorouracil, cyclophosphamide, cisplatin, methotrexate, thiotepa, carboplatin, and the like.

The anti-viral agents which may be optionally employed in combination with compounds of formula (I) of the invention include abacavir, aciclovir, ganciclovir, zidanocin, vidarabine, and the like.

The anti-inflammatory agents which may be optionally employed in combination with compounds of formula (I) of the invention include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, cox-2 inhibitors such as celecoxib, rofecoxib, aspirin, naproxen, ketoprofen, diclofenac sodium, indomethacin, piroxicam, steroids such as prednisone, dexamethasone, hydrocortisone, triamcinolone diacetate, gold compounds, such as gold sodium thiomalate, TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof, infliximab (Remicade® Centocor, Inc.). CTLA-4Ig, LEA29Y, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and CD154 (a.k.a. "gp39"), such as antibodies specific for CD40 and/or CD154, fusion proteins such as etanercept, fusion proteins constructed from CD40 and/or CD154gp39 (e.g. CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG).

The anti-fungal agents which may be optionally employed in combination with compounds of formula (I) of the invention include fluconazole, miconazole, amphotericin B, and the like.

The antibiotics which may be optionally employed in combination with compounds of formula (I) of the invention include penicillin, tetracycline, amoxicillin, ampicillin, erythromycin, doxycycline, vancomycin, minocycline, clindamycin or cefalexin.

The anti-vascular hyperproliferation agents which may be optionally employed with compounds of formula (I) of the invention include methotrexate, leflunomide, FK506 (tacrolimus, Prograf),

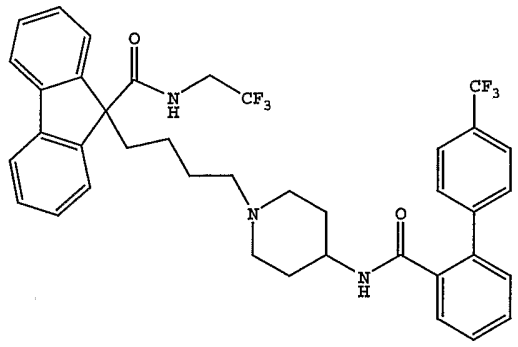
The hypolipidemic agent or lipid-lowering agent or lipid modulating agents which may be optionally employed in combination with the compounds of formula (I) of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl] butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929

and 5,686,104, itavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (ZD-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, *J. Med. Chem.*,V. 31, No. 10, 1869-1871 (1988) including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., et al., *Current Pharmaceutical Design*, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al,, *J. Med. Chem.*, 20, 243-249 (1977), the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, *J. Am. Chem. Soc.*, 98, 1291-1293 (1976), phosphinylphosphonates reported by McClard, R.W., et al., *J.A.C.S.*, 109, 5544 (1987), and cyclopropanes reported by Capson, T.L., PhD dissertation, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary, (June 1987).

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (Avasimibe, 1999); Nicolosi et al, *Atherosclerosis*, (1), 77-85 (1998); Ghiselli and Giancarlo, *Cardiovasc. Drug Rev.*, 16(1), 16-30 (1998); Smith, C., et al, *Bioorg. Med. Chem. Lett.*, 6(1), 47-50 (1996); Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways, 173-98, (CRC, Boca Raton, Fla 1995); Sliskovic et al, *Curr. Med. Chem.* 1(3), 204-25 (1994); Stout et al, *Chemtracts: Org. Chem.*, 8(6), 359-62, (1995); or TS-962 (Taisho Pharmaceutical Co. Ltd).

The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's ezetimibe (SCH58235) and SCH48461 as well as those disclosed in *Atherosclerosis*, 115, 45-63 (1995) and *J. Med. Chem.*, 41, 973 (1998).

The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in *Drugs of the Future*, 24, 425-430 (1999).

The lipid-modulating agent may be a cholesteryl ester transfer protein (CETP) inhibitor such as Pfizer's CP 529,414 (WO/0038722 and EP 818448) and Pharmacia's SC-744 and SC-795.

The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Patent No. 5,447,954.

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, itavastatin and visastatin and ZD-4522.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

The compounds of formula (I) of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the

Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 0.5 to about 80 mg, and more preferably from about 1 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The hypolipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al., *Brit. J. Pharmacology* 120, 1199-1206 (1997), and Cornicelli et al., *Current Pharmaceutical Design*, 5, 11-20 (1999).

The compounds of formula (I) and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin as well as niacin and/or cholestagel.

The other antidiabetic agent which may be optionally employed in combination with the compound of formula (I) may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from the compounds of formula (I) of the invention, which may include

biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, aP2 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1).

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the antidiabetic agent is a biguanide, the compounds of formula (I) will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the □-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

The compounds of formula (I) will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to about 5:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

The compounds of formula (I) will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

The compounds of formula (I) may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S.

Patent No. 5,594,016), Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of formula (I) will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of formula (I).

The compounds of formula (I) may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylin) and LY-315902 (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos.

5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al., *Diabetes*, 47, 1841-1847 (1998).

The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. application Serial No. 09/679,027, filed October 4, 2000 employing dosages as set out therein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be an aP2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. application Serial No. 09/519,079, filed March 6, 2000 employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be a DP4 inhibitor such as disclosed in U.S. application Serial No. 09/788,173 filed February 16, 2001, WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) (preferred) as disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

The meglitinide which may optionally be employed in combination with the compound of formula (I) of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

The compound of formula (I) will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, aP2 inhibitor, DP4 inhibitor or SGLT2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

The other type of therapeutic agent which may be optionally employed with a compound of formula (I) may be 1, 2, 3 or more of an anti-obesity agent including a

beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, an aP2 inhibitor, a thyroid receptor agonist and/or an anorectic agent.

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula (I) may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

The lipase inhibitor which may be optionally employed in combination with a compound of formula (I) may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

The serotonin (and dopoamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula (I) may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

The thyroid receptor agonist which may be optionally employed in combination with a compound of formula (I) may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), GB98/284425 (KaroBio), and U.S. Provisional Application 60/183,223 filed February 17, 2000, with compounds of the KaroBio applications and the above U.S. provisional application being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula (I) may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula (I) or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

The antihypertensive agents which may be employed in combination with the compound of formula (I) of the invention include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers, β-adrenergic blockers and other types of antihypertensive agents including diuretics.

The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline

derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al. mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in *Clin. Exp. Pharmacol. Physiol.* 10:131 (1983); as well as pivopril and YS980.

Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred, phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamidates disclosed in U.S. Pat. No. 4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugai's MC-838 disclosed in C.A. 102:72588v and Jap. *J. Pharmacol.* 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in *Eur. Therap. Res.* 39:671 (1986); 40:543 (1986); ramipril (Hoechsst) disclosed in Euro. Patent No. 79-022 and *Curr. Ther. Res.* 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 34:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in *J. Cardiovasc. Pharmacol.* 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck), indalapril (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (Schering) disclosed in *J. Cardiovasc. Pharmacol.* 5:643, 655 (1983), spirapril (Schering) disclosed in *Acta. Pharmacol. Toxicol.* 59

(Supp. 5):173 (1986); perindopril (Servier) disclosed in *Eur. J. clin. Pharmacol.* 31:519 (1987); quinapril (Warner-Lambert) disclosed in U.S. Pat. No. 4,344,949 and CI925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl)disclosed in *Pharmacologist* 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in *J. Med. Chem.* 26:394 (1983).

Preferred ACE inhibitors are captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril and moexipril.

NEP/ACE inhibitors may also be employed herein in that they possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity. Examples of NEP/ACE inhibitors suitable for use herein include those disclosed in U.S. Pat. No.s. 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 4,749,688, U.S. Patent. No. 5,552,397, U.S. Pat. No. 5,504,080, U.S. Patent No. 5,612,359,U.S. Pat. No. 5,525,723, European Patent Application 0599,444, 0481,522, 0599,444, 0595,610, European Patent Application 0534363A2, 534,396 and 534,492, and European Patent Application 0629627A2.

Preferred are those NEP/ACE inhibitors and dosages thereof which are designated as preferred in the above patents/applications which U.S. patents are incorporated herein by reference; most preferred are omapatrilat, BMS 189,921 ([S-(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat)) and CGS 30440.

The angiotensin II receptor antagonist (also referred to herein as angiotensin II antagonist or AII antagonist) suitable for use herein includes, but is not limited to, irbesartan, losartan, valsartan, candesartan, telmisartan, tasosartan or eprosartan, with irbesartan, losartan or valsartan being preferred.

A preferred oral dosage form, such as tablets or capsules, will contain the ACE inhibitor or AII antagonist in an amount within the range from abut 0.1 to about 500 mg, preferably from about 5 to about 200 mg and more preferably from about 10 to about 150 mg.

For parenteral administration, the ACE inhibitor, angiotensin II antagonist or NEP/ACE inhibitor will be employed in an amount within the range from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg.

Where a drug is to be administered intravenously, it will be formulated in conventional vehicles, such as distilled water, saline, Ringer's solution or other conventional carriers.

It will be appreciated that preferred dosages of ACE inhibitor and AII antagonist as well as other antihypertensives disclosed herein will be as set out in the latest edition of the Physician's Desk Reference (PDR).

Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev®) amlodipine besylate (Norvasc®), prazosin HCl (Minipress®), verapamil, nifedipine, nadolol, diltiazem, felodipine, nisoldipine, isradipine, nicardipine, atenolol, carvedilol, sotalol, terazosin, doxazosin, propranolol, and clonidine HCl (Catapres®).

Diuretics which may be employed in combination with compounds of formula (I) include hydrochlorothiazide, torasemide, furosemide, spironolactono, and indapamide.

Antiplatelet agents which may be employed in combination with compounds of formula (I) of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

The antiplatelet drugs may be employed in amounts as indicated in the PDR. Ifetroban may be employed in amounts as set out in U.S. Patent No. 5,100,889.

Antiosteoporosis agents suitable for use herein in combination with the compounds of formula (I) of the invention include parathyroid hormone or bisphosphonates, such as MK-217 (alendronate) (Fosamax®).

Dosages employed for the above drugs will be as set out in the Physician's Desk Reference.

PHARMACEUTICAL FORMULATIONS

The pharmaceutical composition of the invention includes a pharmaceutically acceptable carrier, adjuvant or vehicle that may be administered to a subject, together with a compound of the present invention, and which does not destroy the pharmacological activity thereof. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of the present invention

include, but are not limited to, the following: ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems ("SEDDS") such as d(-tocopherol polyethyleneglycol 1000 succinate), surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β- and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be used to enhance delivery of the modulators of the present invention.

The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The compounds of the invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The compounds of the invention may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions including the compounds of the invention,

or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The compounds of the invention may also be administered liposomally.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compunds may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the compound(s) of the invention with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (Avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid. The term "parenteral" as used herein includes

subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 500 mg/kg of body weight of active compound per day, or between 5 and 2000 mg per day which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 5 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like.

A typical capsule for oral administration contains compounds of formula (I) (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of formula (I) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

The compounds of formula I of the invention are glucocorticoid receptor modulators as shown either by their ability to bind glucocorticoid receptors in GR binding assays, or by their ability to inhibit AP-1 activity as indicated in cellular

transrespressional assays, and cause none to minimal transactivation as indicated in cellular transscriptional assays.

The cellular transrespressional assay and cellular transcriptional assay employed to determine activity are described in copending provisional application No. 60/396,907, filed July 18, 2002 which is incorporated herein by reference. transactivation as indicated in cellular transscriptional assays.

Glucocorticoid Receptor Binding Assay

In order to measure the binding of compounds to the glucocorticoid receptor a commercially available kit was used (Glucocorticoid receptor competitor assay kit, Panvera Co., Madison, WI). Briefly, a cell lysate containing the glucocorticoid receptor was mixed with a fluorescently labeled glucocorticoid (dexamethasone) plus or minus test molecule. After one hour at room temperature, the fluorescence polarization (FP) of the samples were measured. The FP of a mixture of receptor, fluorescent probe (i.e. fluorescently labeled glucocorticoid) and 1mM dexamethasone represented 100% competition, whereas, the FP of the mixture without dexamethasone was taken to be 100% binding. The percentage competition of test molecules were then compared to the sample with 1mM dexamethasone and expressed as % relative binding activity with dexamethasone being 100% and no competition is 0%. Test molecules were analyzed in the concentration range from 0.1nM to 40 μM.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

The following abbreviations may be employed in the Examples:

H = hydrogen

Ph = phenyl

Bn = benzyl

n-Pr = n-propyl

t-Bu = tertiary butyl

Me = methyl

Et = ethyl

TMS = trimethylsilyl

$TMSN_3$ = trimethylsilyl azide

TBS = tert-butyldimethylsilyl

FMOC = fluorenylmethoxycarbonyl

Boc = tert-butoxycarbonyl

Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl

THF = tetrahydrofuran

Et_2O = diethyl ether

hex = hexanes

EtOAc = ethyl acetate

DMF = dimethyl formamide

MeOH = methanol

EtOH = ethanol

i-PrOH = isopropanol

DMSO = dimethyl sulfoxide

DME = 1,2 dimethoxyethane

DCE = 1,2 dichloroethane

HMPA = hexamethyl phosphoric triamide

HOAc or AcOH = acetic acid

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

i-Pr_2NEt = diisopropylethylamine

Et_3N = triethylamine

NMM = N-methyl morpholine

DMAP = 4-dimethylaminopyridine

$NaBH_4$ = sodium borohydride

$NaBH(OAc)_3$ = sodium triacetoxyborohydride

DIBALH = diisobutyl aluminum hydride

LAH or $LiAlH_4$ = lithium aluminum hydride

n-BuLi = n-butyllithium

LDA = lithium diisopropylamide

Pd/C = palladium on carbon

PtO_2 = platinum oxide

KOH = potassium hydroxide

NaOH = sodium hydroxide

LiOH = lithium hydroxide

K_2CO_3 = potassium carbonate

$NaHCO_3$ = sodium bicarbonate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)

HOBT or HOBT.H_2O = 1-hydroxybenzotriazole hydrate

HOAT = 1-Hydroxy-7-azabenzotriazole

BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate

$NaN(TMS)_2$ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide

Ph_3P = triphenylphosphine

$Pd(OAc)_2$ = Palladium acetate

$(Ph_3P)_4Pd^o$ = tetrakis triphenylphosphine palladium

$TiCl_4$ = titanium (IV) chloride

$NaBH_3CN$ = sodium cyanoborohydride

DEAD = diethyl azodicarboxylate

DIAD = diisopropyl azodicarboxylate

Cbz-Cl = benzyl chloroformate

CAN = ceric ammonium nitrate

SAX = Strong Anion Exchanger

SCX = Strong Cation Exchanger

Ar = argon

N_2 = nitrogen

min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT = room temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet

mp = melting point

Materials.

Reactions requiring air-sensitive manipulations were conducted under N_2 atmosphere. Analytical TLC was performed on 0.20 mm silica gel 60 F254 plates. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Varian Mercury 300MHz spectrometers. Chemical shifts (δ) were measured in parts per million (ppm), and coupling constants (*J* values) are in Hz. High-resolution mass spectra (HR-MS) were recorded on a Micromass Q-TOF spectrometer. All chemicals were purchased from different commercial sources. Most of the reactions were carried out without optimization of the yield.

Representatives Synthetic Procedures:

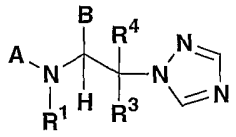
Synthesis of the (1,2,4)-triazolyl ethylamines :

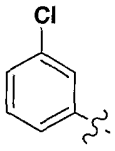
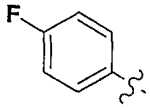
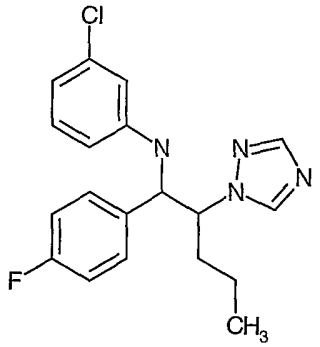
To a stirred solution of 2-chloro-1-(2,4-dichloro-phenyl)-ethanone (3.0 g, 13.4 mmol) in 200 mL of CH_3CN, 1,2,4-triazole (1.39 g, 20.1 mmol) and K_2CO_3 (1.85 g,

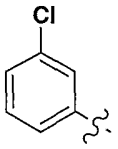
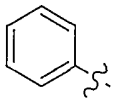
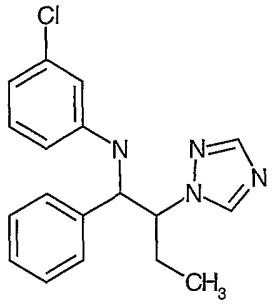
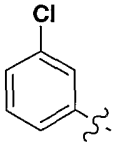
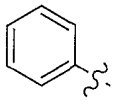
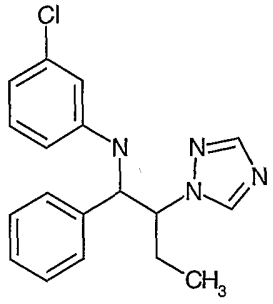
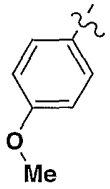
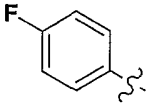
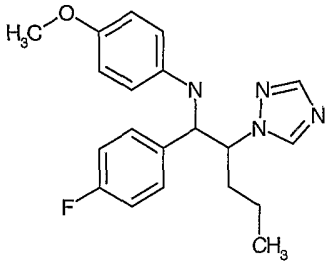
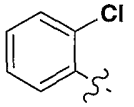
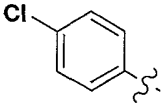
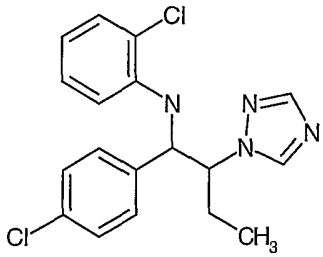
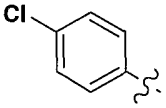
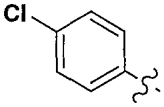
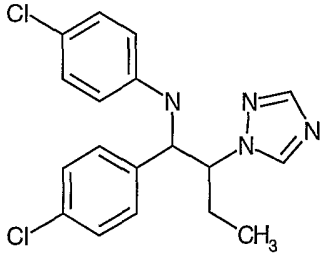
13.4 mmol) was added. The solution was stirred at room temperature overnight. The solvent was removed and the residue was treated with EtOAc and water. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via silica gel chromatography (40-100% EtOAc/hexanes) to give 1.26 g (37%) of the pure ketone intermediate. 300 MHz ^1H NMR ($CDCl_3$) δ: 8.24 (s, 1H), 8.20 (s, 1H), 7.65 (d, *J*= 8.4Hz, 1H), 7.51 (d, *J*= 2.1Hz, 1H), 7.39 (dd, *J*= 8.4, 2.1Hz, 1H), 5.62 (s, 2H); MS (m/e): 256.2.

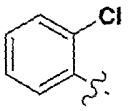
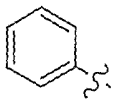
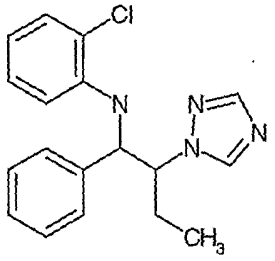
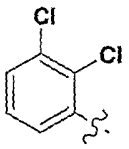
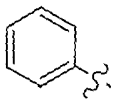
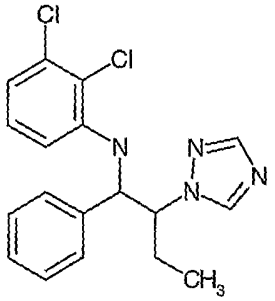
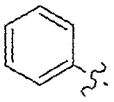
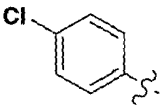
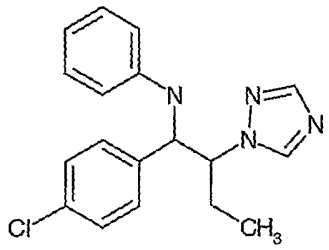
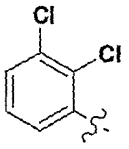
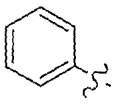
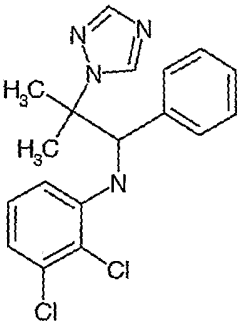
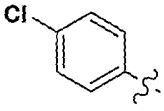
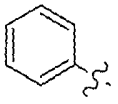
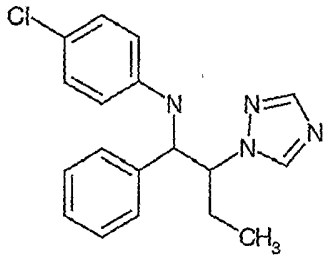
To a solution of the ketone intermediate (0.05 mmol) and the desired amine (0.10 mmol) in 1 mL 1,2-dichloroethane, $TiCl_4$ (0.15 mmol, 1M solution in dichloromethane) and $NaBH_3CN$ (0.10 mmol) were added. The mixture was heated to 85°C for 16h. After cooling to room temperature, the crude mixture was treated with with 1 mL water and 2 mL Et_2O. The ether layer was separated and dried *in vacuo*. The resulting solid was purified via mass triggered RP-HPLC/MS.

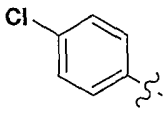
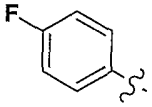
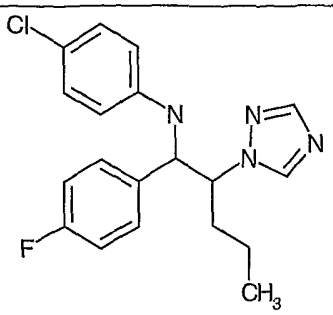
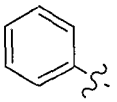
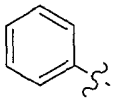
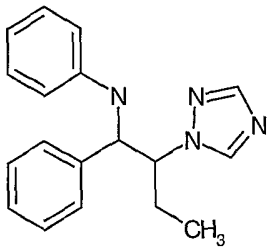
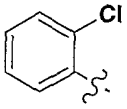
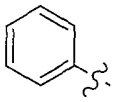
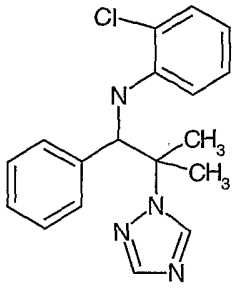
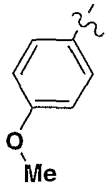
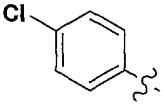
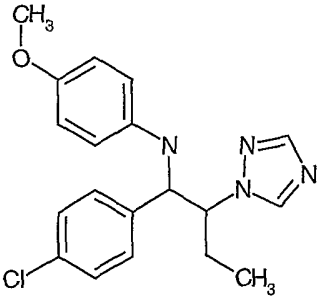
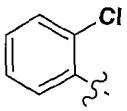
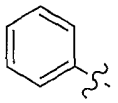
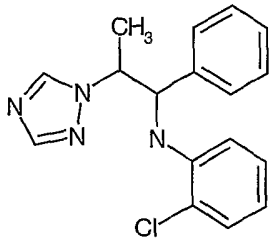
The following compounds were synthesized with the appropriate starting materials using the conditions described above.

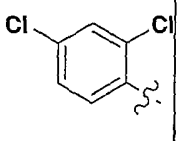
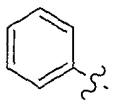
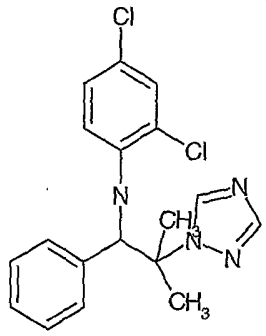
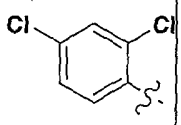
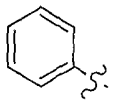
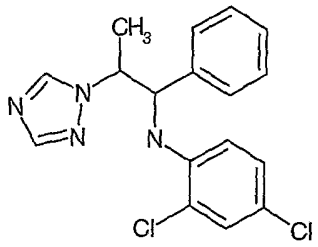
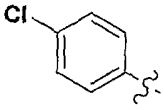
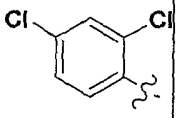
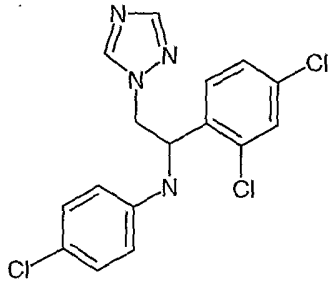


Exp. #	A	B	R^3	R^4	Compound Structure
1			n-Pr	H	

2			Et	H	
3			Et	H	
4			n-Pr	H	
5			Et	H	
			Et	H	

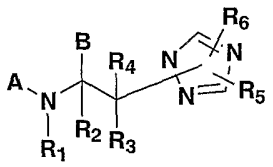
7			Et	H	
8			Et	H	
9			Et	H	
10			Me	Me	
11			Et	H	

12			n-Pr	H	
13			Et	H	
14			Me	Me	
15			Et	H	
16			Me	H	

17			Me	Me	
18			Me	H	
19			H	H	

What is claimed is:

1. A method for preventing or inhibiting the onset of or treating a GR-associated disease which is associated with the expression product of a gene whose transcription is stimulated or repressed by glucocorticoid receptors, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound having formula (I),



(I)

including all stereoisomers, salts, solvates or prodrugs thereof,

wherein:

A and B are independently cycloalkyl, aryl, or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, or heteroaryl, each group of which is optionally substituted where valence allows;

R^5 and R^6 are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^7, NR^7R^8, SR^7, COR^9, CO_2R^9, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl, each group of which is optionally substituted;

R^7 and R^8 are independently

(i) hydrogen, COR^9, SO_2R^9, or $S(O)R^9$; or

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl,

wherein each occurrence of R^7, R^8 and/or R^9 is chosen independently.

2. The method according to Claim 1 wherein:

A and B are independently aryl or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, or heteroaryl, each group of which is optionally substituted where valence allows;

R^5 and R^6 are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^7, NR^7R^8, SR^7, COR^9, CO_2R^9, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl, each group of which is optionally substituted;

R^7 and R^8 are independently

(i) hydrogen, COR^9, SO_2R^9, or $S(O)R^9$; or

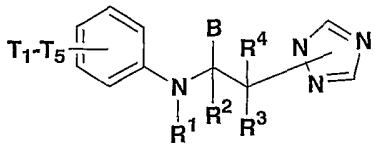
(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl,

wherein each occurrence of R^7, R^8 and/or R^9 is chosen independently,

3. The method according to any one of Claims 1-2 wherein A of formula (I) is an optionally substituted phenyl ring.

4. The method according to any one of Claims 1-3 comprising administering to a patient in need of treatment a therapeutically effective amount of a compound having formula (II),



(II)

including all stereoisomers, salts, solvates or prodrugs thereof, wherein:

B is aryl or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}arylalkyl, C_{1-6}heteroarylalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or allyl, wherein the heteroaryl or aryl component of the C_{1-6}heteroarylalkyl and C_{1-6}arylalkyl groups is optionally substituted;

R^7 and R^8 are independently

(i) hydrogen, COR^9, SO_2R^9, or $S(O)R^9$

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, allyl, or arylalkyl, each group of which is optionally substituted;

T^1 through T^5 are independently

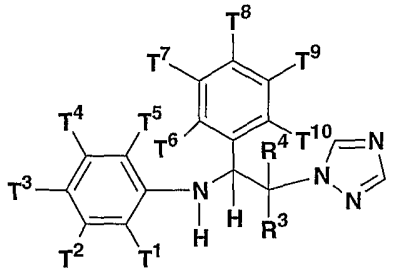
(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^9, or SR^9; or

(ii) C_{1-6}alkyl or C_{1-6}heteroalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, or arylalkyl.

5. The method according to any one of Claims 1-4, wherein B is an optionally substituted phenyl ring.

6. The method according to any one of Claims 1-5 comprising administering to a patient in need of treatment a therapeutically effective amount of a compound having formula (III),



(III)

including all stereoisomers, salts, solvates or prodrugs thereof,

wherein:

R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}arylalkyl, , C_{1-6}heteroarylalkyl C_{2-6}alkenyl, C_{2-6}alkynyl, or allyl, wherein the heteroaryl or aryl component of the C_{1-6}heteroarylalkyl and C_{1-6}arylalkyl groups is optionally substituted.

T^1 through T^{10} are independently

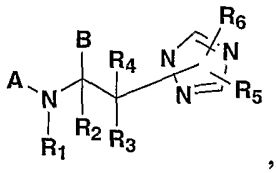
(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^9, or SR^9; or

(ii) C_{1-6}alkyl or C_{1-6}heteroalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl heteroarylalkyl, or arylalkyl,

provided that if T^8 is fluoro and T^6, T^7, T^8 and T^9 are all hydrogen then T^1 and T^3 cannot both be chloro if T^2, T^4, and T^5 are all hydrogen.

7.. A compound having formula (I),



(I)

including all stereoisomers, salts, solvates or prodrugs thereof, wherein:

A and B are independently aryl or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, or heteroaryl, each group of which is optionally substituted where valence allows;

R^5 and R^6 are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^7, NR^7R^8, SR^7, COR^9, CO_2R^9, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl, each group of which is optionally substituted;

R^7 and R^8 are independently at each occurence

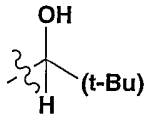
(i) hydrogen, COR^9, SO_2R^9, or $S(O)R^9$; or

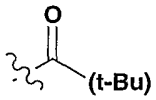
(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl, each group of which is optionally substituted; and

R^9 is, at each occurrence hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, heteroarylalkyl, or arylalkyl;

with the following provisos:

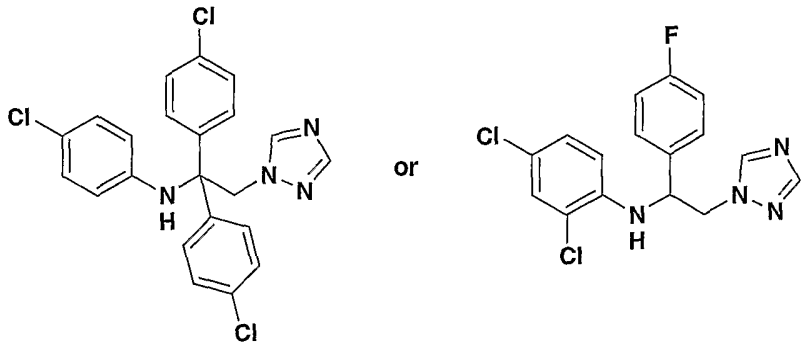
(i) A is not a benz[c,d]indole;

(ii) R^3 or R^4 is not 

or 

if the other of R^3 or R^4 is hydrogen; and

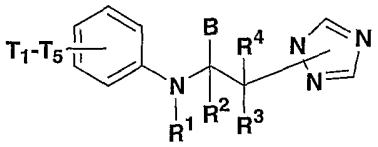
(iii) formula (I) is not



8. A compound of claim 7, including all stereoisomers, salts, solvates or prodrugs thereof, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted phenyl.

9. A compound of claim 8, including all stereoisomers, salts, solvates, or prodrugs thereof, wherein R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6} arylalkyl, C_{1-6} heteroarylalkyl, C_{2-6}alkenyl, or C_{2-6}alkynyl, wherein the heteroaryl or aryl component of the C_{1-6}arylalkyl and C_{1-6}heteroarylalkyl groups is optionally substituted.

10. A compound having formula (II),



(II)

including all stereoisomers, salts, solvates or prodrugs thereof, wherein:

B is aryl or heteroaryl, each of which is optionally substituted;

R^1 is

(i) hydrogen, COR^9, CO_2R^9, SO_2R^9, $S(O)R^9$, or $CONR^7R^8$; or

(ii) C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each group of which is optionally substituted;

R^2, R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}arylalkyl, C_{1-6}heteroarylalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or allyl, wherein the heteroaryl or

aryl component of the C_{1-6}heteroarylalkyl and C_{1-6}arylalkyl groups is optionally substituted.

R^7 and R^8 are independently

(i) hydrogen, COR^9, SO_2R^9, or $S(O)R^9$

(ii) C_{1-6}alkyl, C_{1-6}heteroalkyl C_{1-6}haloalkyl, aryl, heteroaryl, allyl, or arylalkyl, each group of which is optionally substituted;

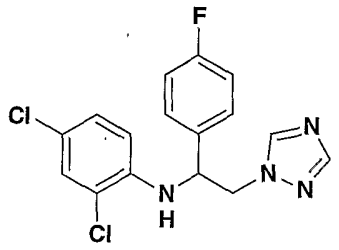
T^1 through T^5 are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^9, or SR^9; or

(ii) C_{1-6}alkyl or C_{1-6}heteroalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, or arylalkyl;

with the following proviso:

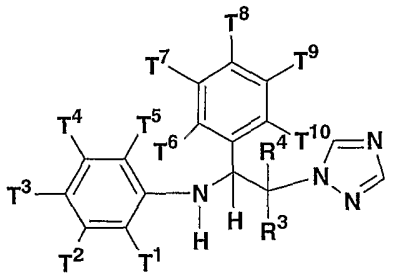


11. A compound of Claim 10, including all stereoisomers, salts, solvates or prodrugs thereof, wherein B is an optionally substituted phenyl ring.

12. A compound according to any one of Claims 10 – 11, including all stereoisomers, salts, solvates or prodrugs thereof, wherein R^1 is hydrogen or C_{1-6}alkyl.

13. A compound according to any one of Claims 10-12, including all stereoisomers, salts, solvates or prodrugs thereof, wherein T^1 through T^5 is independently selected from H, F, Cl, Br, I, and -OC_{1-6}alkyl.

14. A compound having formula (III),



(III)

including all stereoisomers, salts, solvates or prodrugs thereof, wherein:

R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{1-6}arylalkyl, , C_{1-6}heteroarylalkyl C_{2-6}alkenyl, C_{2-6}alkynyl, or allyl, wherein the heteroaryl or aryl component of the C_{1-6}heteroarylalkyl and C_{1-6}arylalkyl groups is optionally substituted.

T^1 through T^{10} are independently

(i) hydrogen, F, Cl, Br, I, NO_2, CN, OR^9, or SR^9; or

(ii) C_{1-6}alkyl or C_{1-6}heteroalkyl, each group of which is optionally substituted; and

R^9 is hydrogen, C_{1-6}alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl heteroarylalkyl, or arylalkyl;

with the proviso that if T^8 is fluoro and T^6, T^7, T^9 and T^{10} are all hydrogen then T^1 and T^3 cannot both be chloro if T^2, T^4, and T^5 are all hydrogen.

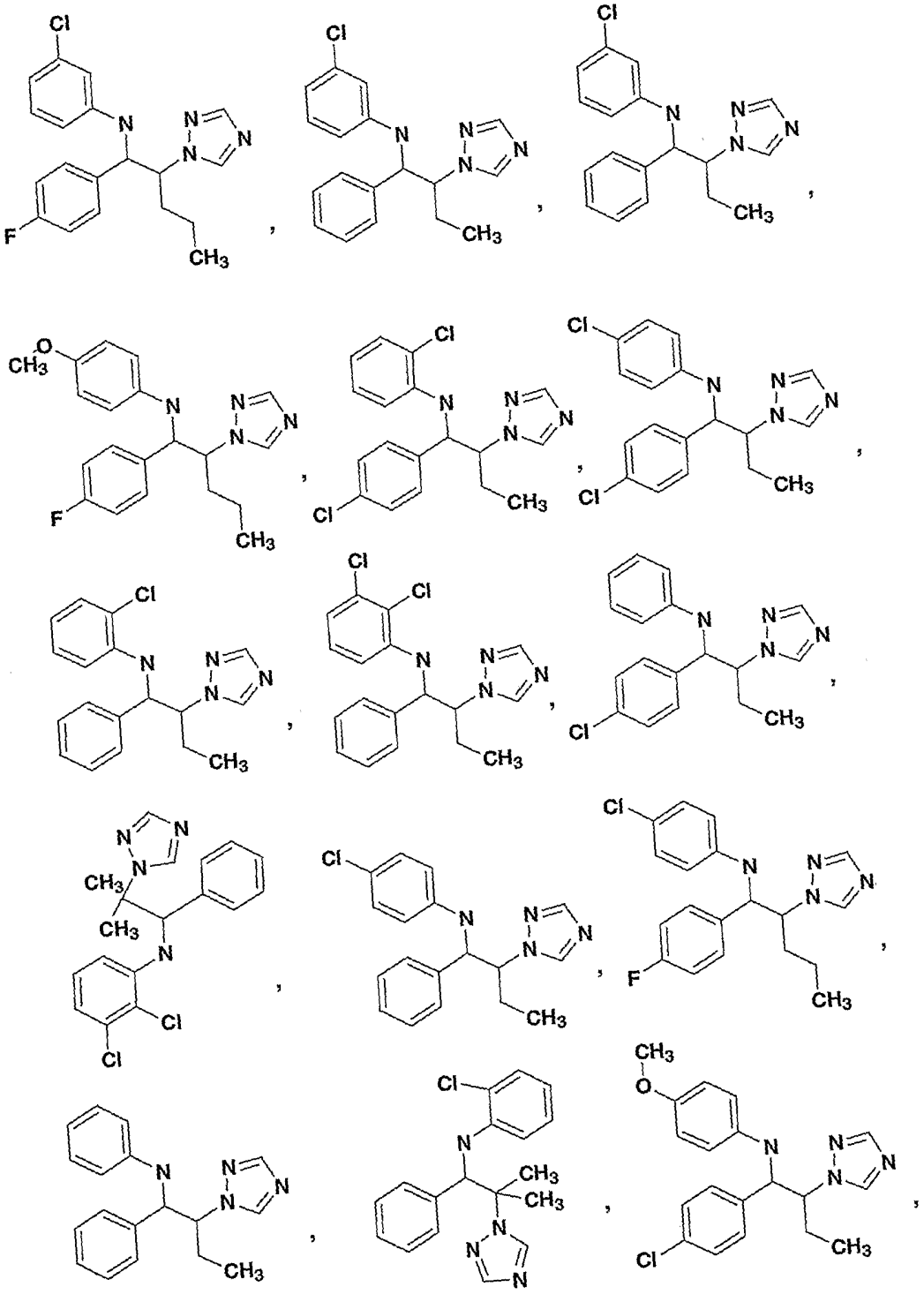
15. A compound according to Claim 14, including all stereoisomers, salts, solvates or prodrugs thereof, wherein T^1 throughT^{10} are selected independently from hydrogen, F, Cl, Br I., and -OC_{1-6}alkyl.

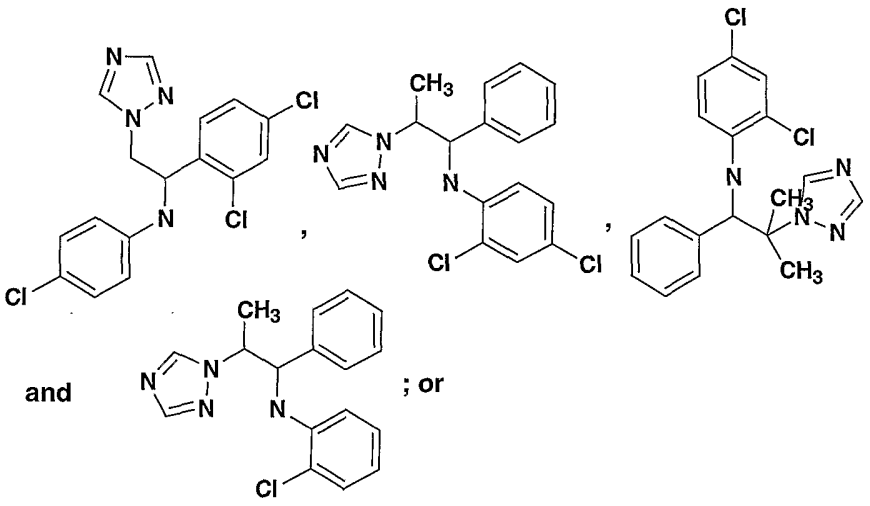
16. A compound of any one of Claims 14-15, including all stereoisomers, salts, solvates or prodrugs thereof, wherein R^3 and R^4 are selected independently from hydrogen and C_{1-6}alkyl.

17. A compound of any one of Claims 14-16, including all stereoisomers, salts, solvates or prodrugs thereof, wherein R^4 is hydrogen and R^3 is C_{1-6}alkyl.

18. A compound selected from:

(i)





and ; or

(ii) a stereoisomer, salt, solvate or prodrug of (i) thereof.

19. A pharmaceutical composition comprising a compound as defined in any one of Claims 1-18 and a pharmaceutically acceptable carrier therefor.

20. A pharmaceutical combination comprising a compound as defined in any one of Claims 1-18 and an immunosuppressant, an anticancer agent, an anti-viral agent, an anti-inflammatory agent, an anti-fungal agent, an anti-biotic, an anti-vascular hyperproliferation agent, an anti-depressant agent, a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor and/or an antiosteoporosis agent, wherein

the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide;

the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor or an anorectic agent;

the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor or an ACAT inhibitor; and

the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker or β-adrenergic blocker.

21. The combination as defined in Claim 20 wherein
the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A;
the anti-obesity agent is selected from orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol;
the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427;
the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440 or an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan; amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol or clonidine HCl; and
the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban.

22. The combination as defined in any one of Claims 20-21 wherein
the immunosuppressant is a cyclosporin, mycophenolate, interferon-beta, deoxyspergolin, FK-506 or Ant.-IL-2;
the anti-cancer agent is azathiprine, 5-fluorouracel, cyclophosphamide, cisplatin, methotrexate, thiotepa, or carboplatin;
the anti-viral agent is abacavir, aciclovir, ganciclovir, zidanocin, or vidarabine; and
the antiinflammatory drug is ibuprofen, celecoxib, rofecoxib, aspirin, naproxen, ketoprofen, diclofenac sodium, indomethacin, piroxicam, prednisone, dexamethasone, hydrocortisone, or triamcinolone diacetate.

23. The method according to any one of claims 1-6 wherein the GR-associated disease is an inflammatory or immune associated disease or disorder which is an endocrine disorder, rheumatic disorder, collagen disease, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, neoplastic disease and metabolic disease.

24. The method as defined in Claim 23 wherein the inflammatory or immune associated disease or disorder is transplant rejection of kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts, heart valve xenograft, serum sickness, and graft vs. host disease, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Type I and Type II diabetes, juvenile diabetes, obesity, asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pyoderma gangrenum, systemic lupus erythematosis, myasthenia gravis, psoriasis, dermatitis, dermatomyositis; eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome, pernicious or immunohaemolytic anaemia, atherosclerosis, Addison's disease, idiopathic adrenal insufficiency, autoimmune polyglandular disease, glomerulonephritis, scleroderma, morphea, lichen planus, viteligo, alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, Guillain-Barre syndrome, and alveolitis; contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis, uticaria,skin allergies, respiratory allergies, hayfever, allergic rhinitis and gluten-sensitive enteropathy, osteoarthritis, acute pancreatis, chronic pancreatitis, acute respiratory distress syndrome, Sezary's syndrome, restenosis, stenosis and artherosclerosis, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, juvenile rheumatoid arthritis, Ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteroarthritis, synovitis of osteoarthritis, epicondylitis, acute rheumatic carditis, pemphigus, bullous dermatitis herpetitformis, severe erythema multiforme, exfoliative dermatitis, psoriasis, seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjuncivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, optic

neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, leukemias and lymphomas in adults, acute leukemia of childhood, ulcerative colitis, regional enteritis, Crohn's disease, Sjogren's syndrome, autoimmune vasculitis, multiple sclerosis, myasthenia gravis, sepsis and chronic obstructive pulmonary disease.

25. A method for preventing or inhibiting the onset of or treating a disease associated with AP-1 induced transcription comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of any one of the claims 1-18.

26. A method for preventing or inhibiting the onset of or treating a disease associated with AP-1- induced transcription dependent gene expression, that is a disease associated with the expression of a gene under the regulatory control of AP-1 comprising administering to a patient in need of treatment a therapeutically effective amount of of a compound of any one of the claims 1-18.

27. A method for preventing or inhibiting the onset of or treating a disease associated with NFκB-induced transcription comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of any one of the claims 1-18.

28. A method for preventing or inhibiting the onset of or treating a disease associated with NFκB-induced transcription dependent gene expression, that is a disease associated with the expression of a gene under the regulatory control of NFκB comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of any one of the claims 1-18.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/18487

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 249/08
US CL : 548/267.2
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)
U.S. : 548/267.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAS ONLINE on STN, Chem. Abstr., Accession No. 1990:158151, SHIMIZU ET AL. 'Alkoxide-induced reaction of 1-[(trimethylsilyl)methyl]azoles with imines and carbonyl compounds'. Synthetic Communications, 1989, 19 (11-12), 2219-27, abstract.	18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* 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 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
08 October 2004 (08.10.2004)	26 OCT 2004
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. (703)305-3230	Authorized officer Rebecca L Anderson Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/18487

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.: 1-17 and 19-25
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:
Please See Continuation Sheet

3. ☒ Claims Nos.: 4-6, 17 and 19-28
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 an additional fee, this Authority did not invite payment of any additional fee.
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.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/18487

Continuation of Box II Reason 2:
The numerous variables, e.g. A, B, R1, R2, R3, R4, R5, R6, R7, R8, R9, T1, T2, T3, T4, T5, T6, T7, T8, T9, T10, etc. and their voluminous complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be carried out on the first discernable invention which is the invention of claim 18.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
STN structure search