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(54) Title: COMBINATION THERAPY

(57) Abstract: Methods to mobilize progenitor and/or stem cells from the bone marrow to the bloodstream by administering a combination of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF are described. The combinations may also be used to increase the effectiveness of chemotherapy and radiation therapies for hematopoietic malignancies.

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COMBINATION THERAPY

Related Application

This application claims benefit of U.S. provisional application Serial No. 60/836,409 filed 7 August 2006 which is incorporated herein by reference in its entirety.

Technical Field

The invention is in the field of therapeutics and medicinal chemistry. More particularly, the invention concerns methods to rapidly mobilize progenitor/stem cells, including pre-cancerous progenitor and/or stem cells into the blood stream using combination therapy.

Background Art

Peripheral Blood Stem Cell Transplant (PBSCT) is a new technique in which progenitor and/or stem cells are obtained from a patient's blood and used to restore the immune system of patients (including, in some instances, the donor) who have had chemotherapy and/or radiation therapy. To obtain the stem cells, these cells must be mobilized or moved into the peripheral blood. The strongest predictor of success in such transplantation, measured by the rapid and durable recovery of a patient's immune system, is the number of stem cells available for transplantation. Stem cell transplantation can be characterized as either allogeneic, where cells are transplanted from a healthy donor, usually a sibling, or as autologous, where cells are collected from the patient and reinfused after chemotherapy.

The current strategies of mobilizing bone marrow progenitor and/or stem cells into the blood stream employ growth factors such G-CSF (Neupogen®). *See, e.g.*, U.S. Patent No. 5,582,823. G-CSF can be used alone combined with chemotherapeutic drugs such as Cytoxan®. In both cases, mobilization for progenitor and/or stem cells requires approximately 5-10 days of G-CSF treatment and is associated with significant side-effects such as bone pain or febrile neutropenia.

Stem cell collection, a process called apheresis, can take up to 4 to 5 hours. Using intravenous tubes the patient's blood is continually circulated through an apheresis machine and back into the patient. The apheresis machine separates different types of blood and immune cells. A patient may require multiple apheresis sessions before a sufficient amount of stem cells

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are collected for a stem cell transplant. When G-CSF is used to mobilize, administration of G-CSF is continued on apheresis days. Once the target number of stem cells has been collected, they are stored until used for transplantation.

In some embodiments, the donor/patient receives chemotherapy to treat cancer. This treatment not only destroys the cancer but also seriously damages the immune system. Following chemotherapy, and once the patient has been stabilized, the stored stem cells can be transplanted back into the patient, through an intravenous infusion. Patients are given antibiotics and blood transfusions to prevent infection while their immune systems are recovering. Once in the bloodstream the stem cells migrate back into the bone marrow. Over a period of 11-30 days, these stem cells will increase in number and develop into different types of cells including platelets and immune cells such as neutrophils.

While the majority of patients who serve as stem cell donors provide an adequate quantity of cells, a significant number of patients fail to collect the minimum number of stem cells in order to proceed to transplantation. It has been found that between 60 – 75% of patients do not receive an optimal number of cells upon transplant (Center for International Blood and Marrow Transplant Research (CIBMTR) Registry Data 1998-2002). As a result, these patients have to go through additional stem cell collection sessions to achieve a sufficient number of stem cells. Many of these patients are at a greater risk for serious infections that require antibiotic treatments, blood transfusions and extended hospitalization. In the worst case, some patient's immune systems do not recover and they die of infection.

Factors or agents that increase circulating white blood cells and progenitor cells may provide additional cells for patients requiring transplanation. Such factors or agents reported to increase circuling white blood cells in human and animal subjects include AMD3100, granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-1 (IL-1), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, stem cell factor (SCF), thrombopoietin, flt3, myelopoietin, anti-VLA-4 antibody, anti-VCAM-1 and growth related oncogene (GRO). These may be used as single agents or in combination (Dale, D., *et al.*, *Am. J. of Hematol.* (1998) 57:7-15; Rosenfeld, C., *et al.*, *Bone Marrow Transplantation* (1997) 17:179-183; Pruijt, J., *et al.*, *Cur. Op. in Hematol.* (1999) 6:152-158; Broxmeyer, H., *et al.*, *Exp. Hematol.* (1995) 23:335-340; Broxmeyer, *et al.*, *Blood Cells, Molecules and Diseases* (1998) 24:14-30; Glaspy, J., *et al.*, *Cancer Chemother. Pharmacol.* (1996) 38(suppl):S53-S57; Vadhan-Raj, S., *et al., Ann. Intern. Med.* (1997) 126:673-681; King, A., *et al., Blood* (2001) 97:1534-1542;

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Glaspy, J., *et al.*, *Blood* (1997) 90:2939-2951; and Papayannopoulou, T., *et al.*, *Proc. Natl. Acad. Sci. USA* (1995) 92:9647-9651).

The chemokine receptor CXCR4 and its natural ligand stromal cell derived factor-1 (SDF-1) appear to be important in the process of development and maturation of blood cells wherein mature blood cells are derived from hematopoietic precursor cells (progenitor) cells and stem cells present in specific hematopoietic tissues including bone marrow (for reviews see Maekawa, T., *et al.*, *Internal Med.* (2000) 39:90-100; Nagasawa, T., *et al.*, *Int. J. Hematol.* (2000) 72:408-411). This is demonstrated by reports that CXCR4 or SDF-1 knock-out mice exhibit hematopoietic defects (Ma, Q., *et al.*, *Proc. Natl. Acad. Sci USA* (1998) 95:9448-9453; Tachibana, K., *et al.*, *Nature* (1998) 393:591-594; Zou, Y-R., *et al.*, *Nature* (1998) 393:595-599). It is also known that CD34+ progenitor cells express CXCR4 and require SDF-1 produced by bone marrow stromal cells for chemoattraction and engraftment (Peled, A., *et al.*, *Science* (1999) 283:845-848) and that *in vitro*, SDF-1 is chemotactic for both CD34+ cells (Aiuti, A., *et al.*, *J. Exp. Med.* (1997) 185:111-120; Viardot, A., *et al.*, *Ann. Hematol.* (1998) 77:194-197) and for progenitor/stem cells (Jo, D-Y., *et al.*, *J. Clin. Invest.* (2000) 105:101-111). SDF-1 is also an important chemoattractant, signaling via the CXCR4 receptor, for several other more committed progenitors and mature blood cells including T-lymphocytes and monocytes (Bleul, C., *et al.*, *J. Exp. Med.* (1996) 184:1101-1109), pro-and pre-B lymphocytes (Fedyk, E. R., *et al.*, *J. Leukoc. Biol.* (1999) 66:667-673; Ma, Q., *et al.*, *Immunity* (1999) 10:463-471) and megakaryocytes (Hodohara, K., *et al.*, *Blood* (2000) 95:769-775; Riviere, C., *et al.*, *Blood* (1999) 95:1511-1523; Majka, M., *et al.*, *Blood* (2000) 96:4142-4151; Gear, A., *et al.*, *Blood* (2001) 97:937-945; Abi-Younes, S., *et al.*, *Circ. Res.* (2000) 86:131-138).

CXCR2 receptor, another chemokine receptor, plays a role in mediating hematopoietic cell mobilization (Pelus, L.M., *et al.*, *Crit. Rev. Oncol. Hematol.* (2002) 43:257-75). King, *et al.* (King, A., *et al., Blood* (2001) 97:1534-1542) reported that a recombinant N-terminal 4-amino acid truncated form of the human chemokine GROβ (also known as SB-251353 or Garnocestim) can mobilize progenitor cells after administration of SB-251353 in combination with G-CSF where neutrophils and platelets were mobilized during the studies. Chemokines such as the SB-251353, GROα, GROβ, and GROγ are further discussed in WO 94/29341; WO 97/15594; WO 97/15595; WO 99/26645; WO 02/02132; U.S. Patent 6,080,398; U.S. Patent 6,399,053; and U.S. Patent 6,447,766, all incorporated herein by reference.

Specific CXCR2 receptor agonists include a variety of different molecules. One example is SB-251353, a basic, heparin-binding protein with a molecular mass of approximately

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7500 Da (King, A., *et al., J. Immunol.* (2000) 164: 3774-3782, Hepburn, T., *et al., Journal of Pharmacology and Experimental Therapeutics*, (2001) 298: 886-893). Other chemokines, in addition to GROβ, acting via the CXCR2 receptor include GROα, GROγ, GCP-2 (granulocyte chemo-attractant protein 2), IL-8, NAP-2 (neutrophil activating peptide 2), ENA-78 (epithelial-cell derived neutrophil activating protein 78), and MGSA (melanoma growth stimulating activity).

The CD34+ population is the component thought to be primarily responsible for the improved recovery time after chemotherapy and the cells most likely responsible for long-term engraftment and restoration of hematopoiesis (Croop, J. M., *et al.*, *Bone Marrow Transplantation* (2000) 26:1271-1279). The mechanism by which CD34+ cells re-engraft may be due to the chemotactic effects of SDF-1 on CXCR4 expressing cells (Voermans, C., *Blood* (2001) 97:799-804; Ponomaryov, T., *et al.*, *J. Clin. Invest.* (2000) 106:1331-1339). Furthermore, studies also show that adult hematopoietic stem cells are capable of restoring damaged cardiac tissue in mice (Jackson, K., *et al.*, *J. Clin. Invest.* (2001) 107:1395-1402; Kocher, A., *et al.*, *Nature Med.* (2001) 7:430-436). It was found that 60% of subjects transplanted during the first remission or with low risk myelodysplastic syndrome (MDS) achieved a long-term disease free survival. However, subjects with relapsed leukemia had a poorer outcome where only 10-20% of these subjects achieved long-term disease free survival. Therefore, relapse of the malignancy remains the major cause of treatment failure. Failure to eliminate leukemia completely is likely since leukemic cells originates from their normal counterparts which resides within the bone marrow microenvironment.

Within the microenvironment of the bone marrow, SDF-1 acts as a potent chemoattractant for immature and mature hematopoietic cells, and thus expression of CXCR4 on leukemic progenitor cells may contribute to homing them to the bone marrow microenvironment. Elevated CXCR4 levels are detected on leukemic cells from patients with B chronic lymphocytic leukemia (B-CLL). Mohle, R., *et al.*, *Leukemia* (1999) 13:1954-1959. However, enhanced levels are not detected on leukemic cells from patients with T-ALL or leukemic cells from patients with AML. Mohle, *et al.*, *supra*; Voermans, C., *et al.*, *Leukemia* (2002) 16:650-657; Bradstock, K.F., *et al.*, *Leukemia* (2000) 14:882-888; Dialynas, D.P., *et al.*, *Stem Cells* (2001) 19:443-452; Shen, W., *et al.*, *Exp. Hematol.* (2001) 29:1439-1447. It further appears that autocrine secretion of SDF-1 by blood-derived adherent nurse-like cells in chronic lymphocytic leukemia (CLL) protects leukemic B cells from spontaneous apoptosis (Burger, J.A., *et al.*, *Blood* (2000) 96:2655-2663. Expression levels of CXCR4 vary among various types

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of AML as reported by Rombouts, E.J., *et al.*, *Blood* (2004) 104:550-557; Fukuda, S., *et al.*, *Blood* (2005) 105:3117-3126. CXCR4 is also reported to mediate homing and engraftment of pre-B-ALL and AML cells to bone marrow, although other factors may be involved (Shen, *et al.*, *supra*; Tavor, S., *et al.*, *Cancer Res.* (2004) 64:2817-2824.). These studies suggests that SDF1/CXCR4 interactions are involved in the microenvironmental regulation of leukemic cells where such interaction may play a role in the resistance of residual, post-chemotherapy AML exposure to additional chemotherapeutic agents. Combinations of G-CSF with GROβ/CXCL2 and $GRO\beta_t/CXCL2_{\delta 4}$ as mobilizing hematopoietic stem and progenitor cells is described by Pelus, L. M., *et al., Blood* (2004) 103:110-119.

A common approach to hematopoietic-related cancers, such as myeloid leukemias and lymphoid leukemias, is a session of chemotherapy to destroy the malignant cells combined with transplantation of hematopoietic progenitor cells either of autogeneic or allogeneic origin. It is believed that the lack of success often experienced with this treatment regimen is due to failure of the chemotherapy to completely eliminate the malignant hematopoietic cells or their precursors.

Thus, the role of the CXCR4 receptor in managing cell positioning and differentiation has assumed considerable significance for normal, pre-malignant and malignant cells. The compound AMD3100, which is 1,1[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane, is a known CXCR4 antagonist which itself mobilizes progenitor cells (see, for example, Hubel, K., *et al., Supportive Cancer Therapy* (2004) 1:165-172, citing De Clercq, E., *et al., Nat. Rev. Drug Discov.* (2003) 2:581-587). In addition, PCT publication WO 00/45814 discloses that various cyclic polyamine compounds, including AMD3100 elevate white blood cell counts. WO 03/011277 further shows that such compounds, including AMD3100, mobilize progenitor/stem cells to permit their harvest and to rebuild damaged cardiac tissue. A combination of AMD3100 with various other factors, including GM-CSF, IL-1, IL-3, IL-8, PIXY-321 macrophage inflammatory protein, skin cell factor, thrombopoietin, growth-related oncogene or chemotherapy, or additional active ingredients generally, such as antibiotics, vitamins, herbal extracts, anti-inflammatories, glucose, anti-pyretics, analgesics is also mentioned. AMD3100 was shown to have protective effects in collagen-induced arthritis models in mice (Matthys, P., *et al.*, *J. Immunol.* (2001) 167:4686-4692). WO 06/020891 describes the use of the combination of CXCR4 antagonist with a GROβ protein for stem cell mobilization.

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It was recently shown, in an *in vitro* context, that AMD 3100 blocked SDF-1 induced chemotaxis of pre-B-ALL cells into bone marrow stroma layers, and enhanced the cytotoxic and antiproliferative effects of vincristine and dexamethasone (Juarez, J., *et al.*, *Leukemia* (2003) 17:1294-1300).

There remains a continued need for more efficient and reliable mobilization of cells from bone marrow. Greater efficiency may eliminate or significantly curtail the need for aphersisis, a difficult and expensive procedure. Moreover, effective mobilization is also relevant in the context of chemotherapy directed to hematopoietic-based malignancies. In particular, chemotherapy or radiation therapy of leukemia may be less effective if the leukemic or pre-leukemic cells are retained in or attracted to the bone marrow rather than remaining available in the circulation where they are more susceptible to treatment. Thus, ways to mobilize these malignant cells or their precursors may increase the effectiveness of standard dose chemotherapies while simultaneously decreasing the likelihood of relapse. The methods provided herein seek to address these problems.

Multiple myeloma (MM) is a B-cell malignancy characterized by the accumulation of plasma cells in the bone marrow and accompanying osteoclastic bone destruction with severe pain. SDF-1 has also been implicated in the recruitment and activation of osteoclast precursors to sites within the bone marrow in subjects with MM. MM plasma cells are reported to produce significant levels of SDF-1 and MM patients exhibit elevated levels of plasma SDF-1 compared to age-matched subjects. The CXCR4 antagonist T-140 blocked osteoclast formation *in vitro* and therefore disruption of SDF-1/CXCR4 was suggested as a potential treatment for MM-induced osteolysis (Zannettino, A. C., *et al., Cancer Res.* (2005) 65:1700-1709).

Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein.

Disclosure of the Invention

Provided herein are methods of using combinations of a CXCR4 inhibitor, a CXCR2 agonist, and G-CSF to synergistically mobilize large numbers of stem and/or progenitor cells. Thus, in one aspect, provided herein are methods of treating animal subjects, in particular,

veterinary and human subjects, to enhance the number of progenitor cells and/or stem cells available for harvest. The progenitor and/or stem cells may then be harvested and used in cell transplantation. The methods of the invention employ inhibitors of the CXCR4 receptor such as certain polyamines described below in combination with one or more CXCR2 agonists and G-CSF. The methods are useful in the context of stem cell transplantation, tissue repair, and in situations where direct *in vivo* stimulation of hematopoiesis is desirable.

In one aspect, therefore, provided herein is a method to elevate the number of circulating progenitor cells and/or stem cells, in a subject, which method comprises administering to said subject an effective amount of a combination comprising at least one compound that inhibits the CXCR4 receptor, such as that of formula (1) shown below, at least one CXCR2 agonist, and G-CSF. In a specific embodiment, the combination administered to mobilize progenitor and/or stem cells is AMD3100, GROβ and G-CSF. Surprisingly, the combination of a CXCR4 antagonist, a CXCR2 agonist, and G-CSF, synergistically acts to induce rapid mobilization of progenitor and stem cells.

This is particularly advantageous in the context of providing progenitor and/or stem cells for harvest for various applications. The combination of the invention may be used to treat subject that may or may not require transplantation, and for those requiring transplantation may be used in an allogeneic or autologous or tandem transplantation. In one embodiment, the harvested cells are used in allogeneic or autologous transplantations. The mobilized stem cells may also be circulated to tissues in need of repair in the subject administered the combination. Thus, repair of myocardial tissue may be enhanced in a subject by administration of this combination. In this embodiment, progenitor/stem cells are mobilized from the bone marrow and circulated *in vivo* for myocardial repair.

Further provided herein are methods of mobilizing pre-cancerous or cancerous cells out from the bone marrow and into the peripheral blood system using the combinations provided to potentiate the effects of standard chemotherapeutic and/or radiation agents. In one aspect, provided herein are methods to treat a subject afflicted with or at risk of a hematopoietic malignancy by mobilizing the malignant cells from the bone marrow into the circulation using a combination of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-SCF. The combination may be administered prior to, during, or subsequent to receiving chemotherapy and/or radiation treatments. In a specific embodiment, the combination administered to mobilize progenitor and/or stem cells is AMD3100, GROβ and G-CSF.

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In additional aspects, provided herein are pharmaceutical compositions containing at least one CXCR4 inhibitor, such as a compound of formula (1), at least one CXCR2 agonist, and G-CSF for use in effecting an elevation of progenitor cells and/or stem cells in the circulation of animal subjects, for use in enhancing sensitivity to chemotherapy and/or radiation therapy, and for use in treating hematopoietic cancers, for example, multiple myeloma. In a specific embodiment, the combination administered to mobilize progenitor and/or stem cells is AMD3100, GROβ and G-CSF.

Provided herein are uses of a combination of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF in the manufacture of a medicament to rapidly mobilize stem cells and/or progenitor cells. In another aspect, provided herein are uses of a combination of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF in an amount effective to mobilize pre-cancerous or cancerous cells out from the bone marrow and into the peripheral blood system to potentiate the effects of standard chemotherapeutic and/or radiation agents.

Modes of Carrying Out the Invention

In one aspect, provided herein is a method to mobilize progenitor and/or stem cells into the bloodstream of a subject, which method comprises administering to a subject in need of such mobilization, an effective amount of at least one CXCR4 antagonist, one CXCR2 agonist, and G-CSF. The combination acts suprasynergistically to accomplish this stimulation in more effective than any component alone or in previously disclosed combinations. Specifically, the progenitor/stem cells are mobilized more quickly, in higher numbers and over a more prolonged period than when any single agent is administered alone or some other combination. In another aspect, the mobilization is so effective that the aphersis process is not required to harvest a sufficient number of progenitor and/or stem cells for use in a transplanation. For example, the progenitor and/or stem cells are at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5% or more of the total marrow CFU-GM without aphresis. Mobilization of stem cells and/or progenitor cells is useful in a number of contexts, as further described below.

The same combination is also used to mobilize pre-malignant or malignant cells from the bone marrow into the circulation to expose them more effectively to chemotherapy or radiotherapy.

As used herein, the term "progenitor cells" refers to cells that, in response to certain stimuli, can form differentiated hematopoietic or myeloid cells. The presence of progenitor cells

can be assessed by the ability of the cells in a sample to form colony-forming units of various types, including, for example, CFU-GM (colony-forming units, granulocyte-macrophage); CFU-GEMM (colony-forming units, multipotential); BFU-E (burst-forming units, erythroid); HPP-CFC (high proliferative potential colony-forming cells); or other types of differentiated colonies which can be obtained in culture using known protocols.

As used herein, "stem" cells are less differentiated forms of progenitor cells. Typically, such cells are often positive for CD34. Some stem cells do not contain this marker, however. CD34+ cells can be assayed using fluorescence activated cell sorting (FACS) and thus their presence can be assessed in a sample using this technique. In general, CD34+ cells are present only in low levels in the blood, but are present in large numbers in bone marrow. While other types of cells such as endothelial cells and mast cells also may exhibit this marker, CD34 is considered an index of stem cell presence.

As used herein, the term "pre-malignant cells" refers to cells that can form malignant hematopoietic or myeloid cells. The malignant hematopoietic or myeloid cells are those which characterize the conditions of myeloma, leukemia, and lymphoma. Particular forms of these diseases include acute myelitic leukemia (AML), acute lymphatic leukemia (ALL), multiple myeloma (MM), chronic myelogenous leukemia (CML), hairy cell leukemia (HCL), acute promyelocytic leukemia (APL), and various lymphomas.

Chemotherapeutic compounds which may be used in the methods whose effectiveness is enhanced by the methods of the invention include carmustine, etoposide, cytarabine, melphalan, cyclophosphamide, busulfan, thiotepa, bleomycin, platinum (cisplatin), cytarabine, cyclophosphamide, buside, cytoxan, daunorubicin, doxorubicin, agent ara-C, cyclosporin; Rituxan®; thalidomide; clofarabine; Velcade®; Antegren®; Ontak®; Revlimid® (thalidomide analog); Prochymal™; Genasense® (oblimersen sodium); Gleevec™; Glivec® (imatinib); tamibarotene; nelarabine; gallium nitrate; PT-100; Bexxar®; Zevalin®; pixantrone; Onco-TCS; and agents that are topoisomerase inhibitors, and many others.

A wide variety of chemotherapeutic methods are available in the art. The invention herein employs these standard methods or variations thereof but, in addition, provides for administration of the combinations described above to enhance the effect of such methods. Preferably, the combinations are administered prior to and/or concomitant with subjecting the subject to such methods.

The combination is administered directly to a subject. Each of the essential elements of the combination may be supplied as a single member of the class or may be supplied as a

mixture or other combination of the members of the class. Each component of the combination (indeed, each member of the sub-combination representing a single class) can be administered independently, at the same time, by the same route, or at the same time by different routes, or at different times by the same or different routes as any other component in the combination. Thus, for example, if two different CXCR4 inhibitor are used, both can be, but need not be, administered at the same time; both can be, but need not be, administered intravenously. Similarly, if two or more CXCR2 agonists are used, these too may be subject to the variable types of administration just described. The same applies to administration of a member of the CXCR4 inhibitor class, a member of the CXCR2 agonist class, and G-CSF. The combination of CXCR4 inhibitor(s), CXCR2 agonist(s) and G-CSF may also be administered according to such variable protocols, independently or in the same composition. In one embodiment, G-CSF is administered first for single or multiple doses followed by adminsitration of one or more CXCR4 inhibitors and CXCR2 agonists.

Compounds Useful in the Invention Method, Formulations and Dosage

CXCR2 agonists include any molecule that activates the CXCR2 receptor. Such molecules include chemokines, cytokines, agonist antibodies or biologically active fragments thereof, or small organic molecules. Chemokines acting via the CXCR2 receptor include, but are not limited to GROβ, GROα, GROγ, GCP-2 (granulocyte chemo-attractant protein 2), IL-8, NAP-2 (neutrophil activating peptide 2), ENA-78 (epithelial-cell derived neutrophil activating protein 78), and MGSA.

In one embodiment, CXCR2 agonists are GROβ and modified forms thereof. King, A., *et al., Blood* (2001) 97:1534-1542 have demonstrated that a recombinant N-terminal 4-amino acid truncated form of the human chemokine GROβ (also known as SB-251353 or garnocestim) can mobilize progenitor cells after administration of SB-251353 in combination with G-CSF where neutrophils and platelets were mobilized during the studies. Chemokines such as the SB-251353, GROα, GROβ, and GROγ are further discussed in WO 94/29341; WO 97/15594; WO 97/15595; WO 99/26645; WO 02/02132; U.S. Patent 6,080,398; U.S. Patent 6,399,053; and U.S. Patent 6,447,766, all incorporated herein by reference.

The "GROβ protein" or "GROβ chemokine" class includes GROβ itself as well as modified forms of GROβ. These modified forms may be truncated, multimerized, contain amino acid substitutions, deletions or insertions, or may comprise combinations of these. "Modified forms of GROβ" includes truncated forms thereof, such as those described in U.S.

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patents 6,447,766; 6,399,053; 6,080,398; PCT publication 99/26645; PCT publication WO 97/15595; PCT publication WO 02/02132; PCT publication WO 97/15594; and PCT publication WO 94/29341. Also included in "modified forms of GROβ" are multimeric forms thereof. Thus "modified forms" include those with truncation of between 2 to about 8 amino acids at the amino terminus of the mature protein, truncation of between about 2 to about 10 amino acids at the carboxy terminus of the mature protein, multimeric forms of the modified and/or truncated proteins, *e.g.*, dimers, trimers, tetramers and other aggregated forms. Truncated forms of GROβ may include SB-251353 which consists of amino acids 5-73 and forms thereof where amino acid 69 is deamidated.

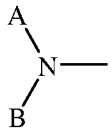
Another specific CXCR2 receptor agonist is SB-251353 is a basic, heparin-binding protein with a molecular mass of approximately 7500 Da (King, A., *et al., J. Immunol.* (2000) 164:3774-3782, Hepburn, T., *et al., Journal of Pharmacology and Experimental Therapeutics*, (2001) 298:886-893).

CXCR4 inhibitors include AMD3100 and AMD3465. One group of CXCR4 inhibitors is exemplified by compounds of the formula:

Z—linker—Z' (1)

wherein Z is an optionally substituted cyclic polyamine containing 9-32 ring members of which 2-8 are nitrogen atoms, said nitrogen atoms separated from each other by at least 2 carbon atoms, and wherein said heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system;

or Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms;

Z' may be embodied in a form as defined by Z above, or alternatively may be of the formula

$$—N(R) — (CR_2)_n—X$$

wherein each R is independently H or straight, branched or cyclic alkyl (1-6C),

n is 1 or 2, and

X is an aromatic ring, including heteroaromatic rings, or is a mercaptan;

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or wherein Z' can be a nitrogen-containing heterocycle, or can be NR_2 where each R is as defined above; and

"linker" represents a bond, alkylene (1-6C) or may comprise aryl, fused aryl, oxygen atoms contained in an alkylene chain, or may contain keto groups or nitrogen or sulfur atoms.

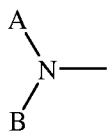
As described in WO 03/011277, the compounds of formula (1) are used to mobilize and harvest CD34+ cells via apheresis with and without combinations with other mobilizing factors. The harvested cells are used in treatments requiring stem cell transplantations.

In some compounds of formula (1), Z and Z' are cyclic polyamine moieties having from 9-24C that include 3-5 nitrogen atoms, as described in U.S. 5,021,409; 6,001,826 and 5,583,131, incorporated herein by reference. Particularly preferred are 1,5,9,13-tetraazacyclohexadecane; 1,5,8,11,14-pentaazacyclohexadecane; 1,4,8,11-tetraazacylotetradecane; 1,5,9-triazacyclododecane; 1,4,7,10-tetraazacyclododecane; and the like, including such cyclic polyamines which are fused to an additional aromatic or heteroaromatic rings and/or containing a heteroatom other than nitrogen incorporated in the ring. These and embodiments wherein the cyclic polyamine contains a fused additional cyclic system or one or more additional heteroatoms are described in U.S. Patent No. 5,698,546 incorporated hereinabove by reference. Also preferred are 3,7,11,17-tetraazabicyclo(13.3.1)heptadeca-1(17),13,15-triene; 4,7,10,17-tetraazabicyclo(13.3.1)heptadeca-1(17),13,15-triene; 1,4,7,10-tetraazacyclotetradecane; 1,4,7-triazacyclotetradecane; and 4,7,10-triazabicyclo(13.3.1)heptadeca-1(17),13,15-triene.

When Z' is other than a cyclic polyamine as defined in Z, its preferred embodiments are set forth in U.S. Patents 5,817,807; 6,756,391; 6,506,770; and 6,667,320, also incorporated herein by reference.

Forms where

Z is of the formula



wherein A comprises a monocyclic or bicyclic fused ring system containing at least one N and B is H or an organic moiety of 1-20 atoms are disclosed in U.S. 6,734,191; 6,750,348; 6,864,265 and 6,835,731, all incorporated herein by reference.

Preferred forms of the linker moiety include those wherein the linker is a bond, or wherein the linker is an alkylene or includes an aromatic moiety flanked by alkylene, preferably

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methylene moieties. Preferred linking groups include the methylene bracketed forms of 1,3-phenylene, 2,6-pyridine, 3,5-pyridine, 2,5-thiophene, 4,4'-(2,2'-bipyrimidine); 2,9-(1,10-phenanthroline) and the like. A particularly preferred linker is 1,4-phenylene-bis-(methylene).

Additional compounds that are CXCR4 antagonists are disclosed in U.S. Patent Publication Nos. U.S. 2004/0209921; U.S. 2005/0059702 and U.S. 2005/0277670, incorporated herein by reference.

Embodiments of the compound of the formula (1) include 2,2'-bicyclam; 6,6'-bicyclam; the embodiments set forth in U.S. Patent Nos. 5,021,409, and 6,001,826, and in particular 1,1'-[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane, set forth in U.S. Patent No. 5,583,131, and designated herein AMD3100. Also preferred are N'-(1H-benzimidazol-2-yl methyl)-N'-(5,6,7,8-tetrahydroquinoline-8-yl)-butane-1,4-diamine as described in U.S. Patent Publication No. 2003/0220341. A list of specific embodiments of Formula (1) is set forth after the Examples section herein as Appendix A.

Methods to synthesize the compounds of Formula (1) useful in the method of the invention are set forth in the U.S. patents and applications above as well as U.S. Patent 6,489,472 and U.S. Patent Publication No. 2005/0209277, incorporated herein by reference. Additional CXCR4 inhibitors are set forth in Appendix B.

Other CXCR4 inhibitors that may be used to practice the methods of the invention include but are not limited to CTCF-0214; CTCF-9908; CP-1221 (linear peptides, cyclic peptides, natural amino-acids, unnatural amino acids, and peptidomimetic compounds); T140 and analogs; 4F-benzoyl-TN24003; KRH-1120; KRH-1636; KRH-2731; polyphemusin analogue; ALX40-4C; or those described in WO 01/85196; WO 99/50461; WO 01/94420; WO 03/090512, each of which is incorporated by reference herein.

Any suitable source of G-CSF may be employed. The G-CSF may be recombinant or purified using known techniques and includes, but is not limited to, Neupogen® filgrastim (Amgen), Neutrogin®/Granocyte® lenograstim (Chugai Pharmaceuticals), and Neulasta® pegylated filgrastim (Amgen). Biologically active fragments, variants, derivatives or fusion proteins can also be employed provided they retain the ability to mobilize progenitor or stem cells.

The CXCR4 inhibitors, the CXCR2 agonists, and G-CSF of the invention may be prepared in the form of prodrugs, *i.e.*, protected forms which release the compounds of the invention after administration to the subject. Typically, the protecting groups are hydrolyzed in

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body fluids such as in the bloodstream thus releasing the active compound or are oxidized or reduced *in vivo* to release the active compound. A discussion of prodrugs is found in Smith and Williams Introduction to the Principles of Drug Design, Smith, H.J.; Wright, 2nd ed., London (1988).

Compounds useful in the invention which are amines, may be administered or prepared in the forms of their acid addition salts or metal complexes thereof. Suitable acid addition salts include salts of inorganic acids that are biocompatible, including HCl, HBr, sulfuric, phosphoric and the like, as well as organic acids such as acetic, propionic, butyric and the like, as well as acids containing more than one carboxyl group, such as oxalic, glutaric, adipic and the like. Typically, at physiological pH, the compounds of the invention will be in the forms of the acid addition salts.

Compounds useful in the invention that are carboxylic acids or otherwise acidic may be administered or prepared in forms of salts formed from inorganic or organic bases that are physiologically compatible. Thus, these compounds may be prepared in the forms of their sodium, potassium, calcium, or magnesium salts as appropriate or may be salts with organic bases such as caffeine or ethylamine. These compounds also may be in the form of metal complexes.

When prepared as purified forms, the compounds may also be crystallized as the hydrates or other solvates. Those forms of the compounds used in the invention that contain chiral centers may be optically pure or may contain a mixture of stereoisomers, including racemic mixtures or mixtures of varying optical purity.

The combinations of the invention may also include additional active ingredients that are therapeutically or nutritionally useful such as antibiotics, vitamins, herbal extracts, anti-inflammatories, glucose, antipyretics, analgesics, cyclophosphamide, recombinant stem cell factor (Stemgen®), granulocyte-macrophage colony stimulating factor (GM-CSF) (such as Leukine®, and Leucomax®), ETRX-101, TLK 199/TILENTRA™, Interleukin-1 (IL-1), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, thrombopoietin, and the like.

Formulations for administration to animal subject use commonly understood formulation techniques well known in the art. Formulations which are suitable for particular modes of administration and for compounds of the type represented by those of formula (1) may be found in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Company, Easton, PA;

similarly, methods for administering polypeptides such as those represented by VLA-4 antagonist thereof are found in this source.

Preferably, the compounds are administered by injection, such as by intravenous injection, but also by subcutaneous or intraperitoneal injection, and the like. Additional parenteral routes of administration include intramuscular and intraarticular injection. For intravenous or parenteral administration, the compounds are formulated in suitable liquid form with excipients as required. The compositions may contain liposomes or other suitable carriers. For injection intravenously, the solution is made isotonic using standard preparations such as Hank's solution.

Besides injection, other routes of administration may also be used. The compounds may be formulated into tablets, capsules, syrups, powders, or other suitable forms for administration orally. By using suitable excipients, these compounds may also be administered through the mucosa using suppositories or intranasal sprays. Transdermal administration can also be effected by using suitable penetrants and controlling the rate of release.

The formulation and route of administration chosen will be tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner.

Suitable dosage ranges for the CXCR4 inhibitor, CXCR2 agonist and G-CSF may vary according to size and weight of patient, condition for which the patient is being treated, and other considerations. In one example, the compounds when administered alone are administered in the range of about 0.1 μg/kg-5 mg/kg of body weight; preferably the range is about 1 μg/kg-300 μg/kg of body weight; more preferably about 10 μg/kg-100 μg/kg of body weight. In some embodiments, the dose is about 240 μg per 1 kg, especially for AMD3100. For a typical 70-kg human subject, thus, the dosage range may be from about 0.7 μg-350 mg. The combination of at least one CXCR4 inhibitor, the at least one CXCR2 agonist, and G-CSF may be administered together in a single formulation, simultaneously in separate formulations by the same or different routes, or at staggered times, again by the same or different routes. Optimization of the protocols for administration to a particular subject is well within ordinary skill. The combination may be administered as a single bolus dose, a dose over time, as in i.v. or transdermal administration, or in multiple dosages. One protocol includes once daily for 2-4 days. In a specific embodiment, AMD3100 is administered at a dose of about 240 μg per 1 kg for 2-4 consecutive days. The dose and days can be varied to further realize the synergistic mobilization mediated by the disclosed combinations. For example, the dose of G-CSF can be

escalated prior to simultaneous administration of a CXCR2 agonist (*e.g.*, GROβ) and a CXCR4 inhibitor (*e.g.*, AMD3100) to futher escalate the progenitor and/or stem cell mobilization. In another example, a reduction in the number of days of G-CSF administration prior to administration of a CXCR2 agonist (*e.g.*, GROβ) and a CXCR4 inhibitor (*e.g.*, AMD3100) may also further synergize mobilization of progenitor and/or stem cells.

Subjects that will respond favorably to the method provided herein include medical and veterinary subjects generally, including human patients. Among other subjects for whom the methods provided herein are useful are cats, dogs, large animals, avians such as chickens, and the like. In general, any subject who would benefit from an elevation of progenitor cells and/or stem cells, or whose progenitor cells and/or stem cells are desirable for stem cell transplantation are appropriate for the method provided herein. Other suitable subjects include subjects with multiple myeloma or other hematopoietic malignancy.

Applications of Combination Treatment

The combination treatment of the invention is useful in a number of contexts. In one embodiment, the combination is able to mobilize stem and/or progenitor cells from bone marrow into the circulation where the mobilized cells may either be harvested or may remain in the subject so as to effect tissue repair, in particular repair of myocardial tissue. The administration of the combination may also result in mobilizing leukemic or other white blood cells into the circulation to make them more accessible to radiation or chemotherapy. Methods to effect this mobilization and treatment are described in detail in WO 2007/022523. The contents of these applications are incorporated herein by reference.

If the cells are harvested, they may be returned to the donor subject (autologous transplant) or may be donated to another subject that is sufficiently compatible to prevent rejection (allogeneic transplant). A common application of autologous transplantation is in combination with radiation or chemotherapy in subjects bearing tumors since the radiotherapeutic or chemotherapeutic methods deplete wanted normal cells. In this application, the subjects cells may be harvested prior to or during the therapeutic treatments, fractionated if necessary, cultured and optionally expanded, and then returned to the subject to restore the damaged immune system depleted by the therapy. Allogeneic recipients may receive the cells for the same purpose, or may have a condition that may be benefited by enhancing their hematopoietic systems.

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In a typical protocol, the mobilized cells are collected from the donor by, for example, apheresis and then stored/cultured/expanded/fractionated as desired. A particular advantage of the methods provided herein is that the time required for harvest of the progenitor and/or stem cells is demonstrably shortened as compared to alternative methods of mobilization. In a specific embodiment, the need for aphersis is eliminated.

In lieu of harvesting the cells from the donor, the mobilization effected by administering the combination may be used internally for tissue repair. Thus, the circulating progenitor cells are allowed to home to a tissue in need of repair, such as a myocardial tissue to restore function.

Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration, and do not limit the invention.

Example 1

Mobilization of Progenitor Cells

Mice were treated with recombinant human Granulocyte-Colony Stimulating Factor (G-CSF) at a dose of 50 μg/kg subcutaneous bid/day for 4 days (total dose of 100 μg/kg/day/mouse). Sixteen hours after the last dose of G-CSF, mice received simultaneous injections of recombinant human GROβ at a dose of 2.5 mg/kg and AMD3100 at a dose of 5.0 mg/kg. Peripheral blood was harvested from mice 15 minuate after administration of GROβ and AMD3100 to quantify mobilization. Injections were scheduled so that control and mobilized mice were evaluated at the same time in every experiment. Mice were killed by CO_2 asphyxiation and blood was obtained by cardiac puncture using syringes coated with EDTA (ethylenediaminetetra acetic acid). PBMC's were obtained by separation of peripheral blood (0.4 mL) on Lympholyte-M (Cedarlane Labs, Hornby, ON, Canada). Complete blood counts (CBC's) were performed on a Hemavet Mascot (CDC Technologies, Oxford, CT). Manual differentials were performed on Wright-Giemsa-stained (Hema-Tek 1000, Bayer, Elkhart, IN) blood smears or spleen and bone marrow cell cytospin preparations (Shandon, Pittsburgh, PA).

CFU-GM Assay

PBMC's were assayed for CFU-GM in McCoy 5A media with 15% heat-inactivated fetal bovine serum (Hyclone Sterile Systems, Logan, UT) and 0.3% agar (Difco Laboratories, Detroit, MI). PBMC's were cultured at 2 x 10^5/mL. CFU-GM were stimulated with 10 ng/mL

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recombinant murine GM-CSF (rmGM-CSF), 10 ng/mL rmIL-1α, and 50 ng/mL stem cell factor (SCF). Triplicate cultures from individual animals were incubated at 37°C, 5% CO_2, 5% O_2 in air for 7 days. Total CFU-GM/mL blood was determined by multiplying CFU frequencies by PBMC/ml blood corrected for white blood cell (WBC) recovery after Lympholyte-M separation.

Results

In mice, the CXCR4 inhibitor AMD3100 and the CXCR2 agonist GROβ rapidly mobilizes short and long term repopulating hematopoietic stem and progenitor cells (HSPC). Synergy in mobilization is observed using GROβ plus G-CSF or AMD plus G-CSF, and recent studies show synergy in rapid mobilization using AMD plus GROβ. In general, a common feature of mobilization is that only a relatively small percentage of HSPC egress from marrow. This study evaluated whether added benefit in HSPC mobilization could be attained by using all three mobilizers in combination. Although this alters the paradigm of rapid mobilization, it addresses shortcomings of poor mobilization response, requirements for multiple aphereses and the need for large numbers of HSPC in transplant and gene therapy applications. BALB/c mice were mobilized with AMD (5 mg/kg SC, 60 min), GROβ (2.5 mg/kg SC, 15 min), G-CSF (100 ug/kg/day, bid, SC x 4 days) or the G-CSF regimen followed by GROβ, AMD or GRO+AMD administered on day 5 and harvest of peripheral blood 15 (GROβ; GROβ+AMD) or 60 (AMD) min later. Significant CFU-GM/mL blood were mobilized by G-CSF (4362±996), GROβ (2562±396) and AMD3100 (991±121) used alone as expected. Single administration of GROβ or AMD to mice mobilized by G-CSF and harvest of blood 15 (GRO) and 60 (AMD) min later, resulted in synergistic mobilization of (12,246±2751) and (12,379±953) CFU-GM, respectively. Rapid mobilization by simultaneous injection of GROβ+AMD was similar in magnitude (10,709±1041) at 15 min post administration to mobilization by GROβ or AMD in combination with a multiday G-CSF regimen. Administration of the combination of GROβ+AMD to mice mobilized by G-CSF resulted in suprasynergistic mobilization of 32,510±3569 CFU-GM/mL after 15 min, representing ~5% of total marrow CFU-GM, with no adverse effects. Fanconi Anemia patients mobilize poorly to G-CSF. FancC -/- mice present a phenotype similar to FancC patients and mobilize poorly to G-CSF, which can be improved by the addition of AMD. Mobilization by GROβ, AMD and G-CSF alone and in combination were evaluated in +/+ C57Bl and FancC -/- mice using the regimens described above. Mobilization by G-CSF was 45% lower in FancC -/- mice (858±21) compared to +/+ controls (1451±80) and AMD+G-CSF

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synergistically mobilized CFU-GM more effectively in FancC -/- mice (5078±597) than controls (2981±267). Similarly, CFU-GM mobilization by GROβ was lower in FancC -/- mice and GROβ+G-CSF synergistically mobilized CFU-GM more effectively in FancC -/- mice. The combination of GROβ+AMD mobilized CFU-GM within 15 min that was similar in magnitude to mobilization by AMD+G-CSF in wild type (2077±541 vs 2511±176) as well as FancC -/- mice (4924±577 vs 5078±1597). Mobilization by addition of the rapid acting combination of GROβ+AMD to mice mobilized by G-CSF was suprasynergistic reaching 44,669±2974 and 41,068±5630 CFU-GM/mL blood in wild type and -/- mice, respectively. In preliminary studies, transduction of mobilized blood cells with FancC and transplant in FancC -/-mice demonstrated durable engraftment. These studies identify highly effective, rapid GRO+AMD mobilization regimens for standalone application in normal donors and combination regimens for potential application in patients who respond poorly to G-CSF or when large quantities of HSPC are required, for example in gene therapy applications.

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Appendix A

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-*N*-methyl-2-(aminomethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-(amino-methyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-3-(amino-methyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-(2-amino-methyl-5-methyl)pyrazine; and

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)pyridine; described in U.S. 6,667,320 referenced above.

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-aminomethyl)pyridine;

7,7'-[1,4-phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo-[13.3.1]heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylenebis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

N-[4-(1,4,7-triazacyclotetra-decane)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

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N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

3,3'-(bis-1,5,9,13-tetraazacyclohexadecane);

3,3'-(bis-1,5,8,11,14-pentaazacyclohexadecane), methylene (or polymethylene) di-1-N-1,4,8,11-tetraazacyclotetradecane;

3,3'-bis-1,5,9,13,-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

3,3'-bis-1,5,9,13-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[3,3'-biphenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,11-tetraazacyclotetradecane;

1,11'-[1,4-phenylene-bis(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,6-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1-[3,5-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,5-thiophene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

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1,1'-[4,4'-(2,2'-bipyridine)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,9-(1,10-phenanthroline)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[5-nitro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,4,5,6-tetrachloro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,3,5,6-tetrafluoro-1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,4-naphthylene-bis-(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylenebis-(methylene)]bis-1,5,9-triazacyclododecane;

1,1'-[1,4-phenylene-bis-(methylene)]-1,5,9-triazacyclododecane;

1,1'-[2,5-dimethyl-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,5-dichloro-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2-bromo-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[6-phenyl-2,4-pyridinebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylene-bis(methylene)]bis[15-chloro-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene];

7,7'-[1,4-phenylene-bis(methylene)]bis[15-methoxy-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene];

7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-13,16-triene-15-one;

7,7'-[1,4-phenylene-bis(methylene)]bis-4,7,10,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene;

8,8'-[1,4-phenylene-bis(methylene)]bis-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-triene;

6,6'-[1,4-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene;

6,6'-[1,3-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene;

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17,17'-[1,4-phenylene-bis(methylene)]bis-3,6,14,17,23,24-hexaazatricyclo[17.3.1.18,12]tetracosa-1(23),8,10,12(24),19,21-hexaene;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)thiophene;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)mercaptan;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-amino-benzylamine;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-amino-benzylamine;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-(amino-ethyl)imidazole;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-benzylamine;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-purine;

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-phenylpiperazine;

N-[4-(1,4,7-Triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[1-(1,4,7-Triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[3-(3,6,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[3-(3,6,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

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N-[4-(4,7,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[6-(3,6,9-Triazabicyclo[11.3.1]pentadeca-1(15),11,13-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,10,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,7-Diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,10-Diazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-Fluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11,11-difluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,4,7-triazacyclotetradecan-2-one)-yl))-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[12-(5-oxa-1,9-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-oxa-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-thia-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-sulfoxo-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-sulfono-1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,4,7-triazacyclotetradecan-3-one)-yl))-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-(6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-2-ylmethyl)amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-2-ylmethyl)amino]ethyl]-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(2-amino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-4-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-quinolinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-(2-naphthoyl)aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(*S*)-(2-acetylamino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-[(*S*)-(2-acetylamino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[3-((2-naphthalenylmethyl)amino)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(*S*)-pyrollidinylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(*R*)-pyrollidinylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[3-pyrazolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-pyrrolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-thiopheneylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine

N-(2-pyridinylmethyl)-N'-[2-thiazolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-furanylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(phenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-3-pyrrolidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine

N-(2-pyridinylmethyl)-N'-4-piperidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(phenyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(6-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-(1-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(7-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;

N-(2-pyridinylmethyl)-N'-(6-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-naphthalenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(isobutylamino)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-furanylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-guanidinoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[bis-[(2-methoxy)phenylmethyl]amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-4-ylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-2-ylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(phenylureido)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[[N"-(n-butyl)carboxamido]methyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxamidomethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(N"-phenyl)carboxamidomethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxymethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(phenylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6-dimethyl-1*H*-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine (hydrobromide salt);

N-(2-pyridinylmethyl)-N'-(5-nitro-1*H*-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(1*H*)-5-azabenzimidazol-2-ylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-(4-phenyl-1*H*-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(2-pyridinyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-benzoxazolyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(*trans*-2-aminocyclohexyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-phenylethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-(3-phenylpropyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(*trans*-2-aminocyclopentyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-glycinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-alaninamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-aspartamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-pyrazinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-prolinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-lysinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-benzamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-picolinamide;

N'-Benzyl-N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N'-phenyl-N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*bacteria*pyridin-9-yl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N-(5,6,7,8-tetrahydro-8-quinolinyl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N,N'-bis(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*bacteria*pyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7-dihydro-5*H*-cyclopenta[*bacteria*pyridin-7-yl)-1,4-benzenedimethanamine;

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N,N'-bis(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-[(5,6,7,8-tetrahydro-8-quinolinyl)methyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'[(6,7-dihydro-5*H*-cyclopenta[*bacteria*pyridin-7-yl)methyl]-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-(2-methoxyethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-[2-(4-methoxyphenyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-1,4-(5,6,7,8-tetrahydro-8-quinolinyl)benzenedimethanamine;

N-[(2,3-dimethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-oyl]-4-piperidinyl]-1,3-benzenedimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-phenoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-carboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

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N-[(4-benzyloxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(thiophene-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[[1-methyl-3-(pyrazol-3-yl)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(phenyl)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-benzyl-3-carboxymethyl-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[[1-methyl-2-(2-tolyl)carboxamido]ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1,5-dimethyl-2-phenyl-3-pyrazolinone-4-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-propoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(1-phenyl-3,5-dimethylpyrazolin-4-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1*H*-imidazol-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

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N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-difluoromethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-difluoromethoxyphenylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,4-benzenedimethanamine;

N-[1-(3-pyridinecarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(cyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(1-phenylcyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-carboxamido]-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(2-thiomethylpyridine-3-carboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2,4-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylpyrrol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[2-(N"-morpholinomethyl)-1-cyclopentyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-piperidinyl)propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimidazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(1-phenyl-3-(N''-morpholino)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(iso-propyl)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(ethoxycarbonyl)-4-piperidinyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-pyrazolyl)propyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-(N'',N''-diethylcarboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-phenylsulfonyl)ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-chloro-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-[N"-(4-chlorophenyl)carboxamido]ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-acetoxyindol-3-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-benzyloxy-4-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

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N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(8-hydroxy)-2-quinolylmethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1H-imidazol-2-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-thiazolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(5-benzyloxy)benzo[b]pyrrol-3-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylpyrazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-methyl)-1H-imidazol-5-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(4-dimethylamino)-1-naphthalenyl]methyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1,5-dimethyl-2-phenyl-3-pyrazolinone-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-[(1-acetyl-2-(R)-prolinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-[2-acetamidobenzoyl-4-piperidinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(2-cyano-2-phenyl)ethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(N"-acetyltryptophanyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

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N-[(N"-benzoylvalinyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-dimethylaminophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimadazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-butyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-benzoyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1-methyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1H-imidazol-4-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-methylbenzimidazol-2-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2-phenyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-methyl-1H-pyrazol-5-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,3-benzenedimethanamine;

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N-(benzyloxyethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxy-1-naphthalenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]guanidine;

N-(2-pyridinylmethyl)-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,4-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]homopiperazine;

1-[[3-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]homopiperazine;

trans and *cis*-1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,5-piperidinediamine;

N,N'-[1,4-Phenylenebis(methylene)]bis-4-(2-pyrimidyl)piperazine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-1-(2-pyridinyl)methylamine;

2-(2-pyridinyl)-5-[[(2-pyridinylmethyl)amino]methyl]-1,2,3,4-tetrahydroisoquinoline;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diaminopyrrolidine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diacetylaminopyrrolidine;

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triaza-3-oxabicyclo[4.3.0]nonane; and

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triazabicyclo[4.3.0]nonane.

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Appendix B

Exemplary CXCR4 antagonists include compounds of formula (1A):

$$V - CR_2 - Ar^1 - CR_2\,NR - (CR_2)_x - Ar^2 \qquad (1A)$$

wherein V is a substituted heterocycle of 9-24 members containing 2-4 optionally substituted amine nitrogen atoms spaced from each other by 2 or more optionally substituted carbon atoms, and which heterocycle may optionally comprise a fused aromatic or heteroaromatic ring, and wherein

(a) said heterocycle contains at least one O or S, said O or S spaced from any adjacent heteroatom by at least 2 carbon atoms, and wherein said S is optionally oxidized or

(b) at least one carbon atom in said ring is substituted by an electron-withdrawing substituent, or

(c) both (a) and (b);

and wherein each R is independently H or a straight chain, branched or cyclic alkyl containing 1-6C;

x is 0-4;

Ar^1 is an unsubstituted or substituted aromatic or heteroaromatic moiety; and

Ar^2 is an unsubstituted or substituted aromatic or heterocyclic group.

In the above Formula (1A), V may contain 2-4 N, preferably 3-4 N if there is no additional heteroatom. Preferable ring sizes for V are 9-18 members, more preferably 12-16 members. V may also include a fused aromatic or heteroaromatic ring, preferably 1,2 or 1,3 or 1,4 phenylene or 2,6 or 2,5 or 2,4 or 2,3 pyridinylene. The fused ring may also be, for example, 2,5 or 2,6 pyrimidinylene or 2,4 or 2,3 pyrrolylene.

In the above Formula 1A, the electron withdrawing substituents present at least one C in ring V may be halogen, nitro, cyano, carboxylic acid, a carboxylic ester formed from an alcohol of 1-6C, an amide formed from an amine of 0-12C, a sulfonic or sulfinic acid, ester or amide, CF_3, and the like. A preferred electron withdrawing substituent is =O, as well as halo. Examples of halogen include fluorine, chlorine, bromine, iodine, with fluorine and chlorine preferred.

In the above Formula (1A), Ar^2 may be an optionally substituted heterocyclic group or aromatic group. Examples of aromatic groups include but are not limited to benzene, naphthalene, dihydronaphthalene and tetrahydronaphthalene. Examples of heterocyclic groups include 5 to 6-membered saturated, partially saturated, or aromatic heterocyclic rings containing

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1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. The heterocycles may be pyridine, quinoline, isoquinoline, imidazole, benzimidazole, azabenzimidazole, benzotriazole, furan, benzofuran, thiazole, benzothiazole, oxazole, benzoxazole, pyrrole, indole, indoline, indazole, pyrrolidine, pyrrolidone, pyrroline, piperidine, piperazine, tetrahydroquinoline, tetrahydroisoquinoline, pyrazole, thiophene, isoxazole, isothiazole, triazole, tetrazole, oxadiazole, thiadiazole, morpholine, thiamorpholine, pyrazolidine, imidazolidine, imidazoline, tetrahydropyran, dihydropyran, benzopyran, dioxane, dithiane, tetrahydrofuran, tetrahydrothiophene, dihydrofuran, dihydrothiophene, and the like. Oxides of the nitrogen and sulfur containing heterocycles are also included.

The optional substituents on Ar^2 include alkyl (1-6C), alkenyl (1-6C), alkynyl (1-6C), halo, nitro, cyano, carboxylic acid, carboxylic ester formed from an alcohol with 1-6C, an amide formed from an amine of 0-12C, a sulfonic or sulfinic acid, ester or amide, OR, SR, NR_2, OCR, OOCR, NRCOR, all wherein R is hydrogen or straight or branched chain alkyl (1-6C), an optionally substituted aromatic or heterocyclic group, CF_3, and the like. Preferred substituents include alkyl, OR, NR_2, and halo. Preferred embodiments of Ar^2 include phenyl, pyridinyl, pyrimidinyl and imidazolyl.

In the above Formula (1A), Ar^1 may be a 5-6 membered aromatic system which is bivalent benzene, pyridine, thiophene, pyrimidine, and the like. Ar^1 may optionally be substituted by alkyl, alkenyl, halo, nitro, cyano, CF_3, COOR, $CONR_2$, OCR, OOCR, NRCOR, OR, NR_2, SR (where R is H or alkyl 1-6C), sulfonic or sulfinic acids, esters or amides and the like. Preferred embodiments of Ar^1 are phenylene, especially 1,3 and 1,4 phenylene and pyridinylene, preferably 2,6 pyridinylene, and 3,5 pyridinylene.

Further, in the compounds of Formula (1A), each R group may be hydrogen or alkyl of 1-2C, preferably hydrogen. The R group may be coupled to a nitrogen is hydrogen or alkyl 1-6C, preferably straight chain alkyl 1-3C, more preferably H or methyl. In one example, 1, 2, 3, 4, or 5 of the R groups are methyl or ethyl and the remaining R groups are hydrogen.

In one embodiment, the CXCR4 antagonist has formula

$$V\text{-}CH_2\text{-}Ar^1\text{-}CH_2NR\text{-}CH_2\text{-}Ar^2$$

wherein V is a heterocycle as defined in formula (1A), and wherein:

(a) said heterocycle is substituted with halo or =O; or

(b) said heterocycle contains O or S; or

(c) both (a) and (b),

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and wherein Ar^1 is unsubstituted 1,3 or 1,4-phenylene, R is H, methyl or ethyl and Ar^2 is unsubstituted phenyl or pyridinyl. Preferred embodiments of x are 0-2 and 1-2.

The heterocycle V may contain 3 N and at least one carbon atom in the heterocycle that is substituted by at least one fluoro substituent. The R moiety may independently be hydrogen or methyl. The number of $(CR_2)_x$ groups may be 0-4, 0-2, or 1-2. The Ar^1 moiety may be 1, 3 or 1,4 -phenylene. The Ar^2 moiety may be phenyl or pyridyl. The heterocycle V may be a 12-16 membered heterocycle, or may contain O or S as a ring member. The heterocycle V may also contain an oxidized sulfur as a ring member. In one example, at least one carbon in the heterocycle V is substituted by =O.

Compounds of formula (1A), and methods of synthesizing such compounds are described in WO 01/44229, incorporated herein by reference. Examples of compounds of Formula (1A), its pharmaceutically acceptable salts or metal complexes thereof, include but are not limited to:

N-[4-(11-fluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine ;

N-[4-(11,11-difluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(1,4,7-triazacyclotetradecan-2-onyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[12-(5-oxa-1,9-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-oxa-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-thia-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-sulfoxo-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-(11-sulfono-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine; or

N-[4-(3-carboxo-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine.

In another aspect, the CXCR4 compound for use in the methods of the present invention is exemplified by compounds having formula (1B):

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$$V\text{-}CR^1R^2\text{-}Ar\text{-}CR^3R^4\text{-}N(R^5)\text{-}(CR^6R^7)_x\text{-}R^8 \qquad (1B)$$

wherein V is an optionally substituted 1,4,8,11-tetraazacyclotetra-decanyl, 4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl, 1,4,7-triazacyclotetra-decanyl, 4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl, 1,7-diazacyclotetradecanyl, or 4,10-diazabicyclo[13.31.1]heptadeca-1(17),13,15-trienyl system;

R^1 to R^7 may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is pyridyl, pyrimidinyl, pyrazinyl, imidazolyl, thiophene-yl, thiophenyl, aminobenzyl, piperidinyl, purine, piperazinyl, phenylpiperazinyl, or mercaptan;

Ar is a phenylene ring optionally substituted at single or multiple positions with alkyl, aryl, amino, alkoxy, hydroxy, halogen, carboxyl and/or carboxamido; and

x is 1 or 2.

In the above formula (1B), the V moiety may be optionally substituted by hydroxyl, alkoxy, thiol, thioalkyl, halogen, nitro, carboxy, amido, sulfonic acid, and/or phosphate.

Compounds of Formula (1B), its pharmaceutically acceptable salts or metal complexes thereof, and methods of synthesizing such compounds are described in WO 00/02870, which is incorporated herein by reference. Examples of compounds having formula (1B) include but are not limited to:

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis-(methylene)]-2-(aminomethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-N-methyl-2-(aminomethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-4-(aminomethyl)pyridine;

N-]1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-3-(aminomethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-(2-aminomethyl-5-methyl)pyrazine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-2-(aminoethyl) pyridine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-2-(aminomethyl)thiophene;

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N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-2-(aminomethyl)mercaptan;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-2-amino benzylamine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-4-amino benzylamine;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-4-(aminoethyl)imidazole;

N-[1,4,8,11-tetraazacyclotetra-decanyl-1,4-phenylenebis(methylene)]-benzylamine;

N-[4-(1,4,7-triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[7-(4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[1-(1,4,7-triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[4-[4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine;

N-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-purine;

1-[1,4,8,11-tetraazacyclotetradecanyl-1,4-phenylenebix(methylene)]-4-phenylpiperazine;

N-[4-(1,7-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine; and

N-[7-(4,10-diazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine.

Other CXCR4 inhibitors are of formula (1C):

$$V^2\text{-}CR_9R_{10}\text{-}Ar^2 \qquad (1C)$$

wherein V^2 is an optionally substituted 1,4,8,11-tetraazacyclotetra-decanyl or 4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl system;

R_9 and R_{10} may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

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Ar_2 is an aromatic or heterocyclic ring each optionally substituted at single or multiple positions with electron-donating or withdrawing groups and/or aromatic and heterocyclic groups and their alkyl derivatives thereof, and the acid addition salts and metal complexes.

In the above Formula (1C), Ar_2 may be optionally substituted with alkyl, aryl, amino, alkoxy, hydroxy, halogen, carboxyl and/or carboxamido. In particular examples, Ar_2 is optionally substituted with alkoxy, alkyl, or halogen.

Compounds having formula (1C), and methods of synthesizing the same, are described in WO 00/02870, incorporated herein by reference. Examples of compounds having formula (1C) include but are not limited to:

1-[2,6-dimethoxypyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1-[2-chloropyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1-[2,6-dimethylpyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1-[2-methylpyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1-[2,6-dichloropyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane;

1-[2-chloropyrid-5-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane; and

7-[4-methylphenyl (methylene)]-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene.

Other CXCR4 antagonists are of formula (1D):

V--R--A--R'--W (1D)

wherein V and W are independently cyclic polyamine moieties having from 9 to 32 ring members and from 3 to 8 amine nitrogens in the ring spaced by 2 or more carbon atoms from each other, and having one or more aromatic or heteroaromatic rings fused thereto,

A is an aromatic or heteroaromatic moiety when V and W have one or more aromatic or heteroaromatic moieties fused thereto, with or without an additional heteroatom other than nitrogen incorporated in the ring, or A is an aromatic or heteroaromatic moiety when V and W contain a heteroatom other than nitrogen incorporated in the ring without having one or more aromatic or heteroaromatic moieties fused thereto,

and R and R' are each a substituted or unsubstituted alkylene chain or heteroatom-containing chain which spaces the cyclic polyamines and the moiety A.

In the above Formula (1D), R and R' may each be methylene. In one example, A is 1,3- or 1,4-phenylene. In another example, each V and W is an unsubstituted or substituted tricyclic or bicyclic ring system containing only carbon and nitrogen atoms in the rings. One of the

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cyclic ring systems may be a 10 to 20 membered polyamine ring system having from 3 to 6 amine nitrogen atoms, and the ring system or systems is a fused benzyl or pyridinyl ring system.

Compounds having formula (1D), and methods of synthesizing such compounds, are described in U.S. patent 5,698,546, incorporated herein by reference. These compounds include but are not limited to:

7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17- tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene;

7,7'-[1,4-phenylene-bis(methylene)]bis[15-chloro-3,7,11,17-tetraazabicyclo [13.3.1]heptadeca-1(17),13,15-triene];

7,7'-[1,4-phenylene-bis(methylene)]bis[15-methoxy-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene];

7,7'-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-13,16-triene-15-one;

7,7'-[1,4-phenylene-bis(methylene)]bis-4,7,10,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene;

8,8'-[1,4-phenylene-bis(methylene)]bis-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-triene;

6,6'-[1,4-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene;

6,6'-[1,3-phenylene-bis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene; and

17,17'-[1,4-phenylene-bis(methylene)]bis-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene.

Other CXCR4 antagonists are of formula (1E):

Z—R—A—R'—Y (1E)

where Z and Y are identical cyclic polyamine moieties having from 10 to 15 ring members and from 3 to 6 amine nitrogens in the ring spaced by 2 or more carbon atoms from each other, said amine nitrogens being the only ring heteroatoms,

A is an aromatic or heteroaromatic moiety other than quinoline,

R and R' are each methylene linked to nitrogen atoms in Z and Y, the amine nitrogen atoms being otherwise unsubstituted.

In the above formula (1E), each moiety Z and Y may have 14 ring members and 4 amine nitrogens in the ring. Compounds having formula (1E), and methods of synthesizing such

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compounds, are described in U.S. patent 5,583,131, incorporated herein by reference. These compounds include but are not limited to:

1,1'-[1,3-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane;

1,1'-[1,4-phenylenebis(methylene)]-bis-1,4,8,11-tetra-azacyclotetradecane (AMD 3100);

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

bis-zinc or bis-copper complex of 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[3,3'-biphenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,11-tetraazacyclotetradecane;

1,11'-[1,4-phenylene-bis-(methylene)]-1,4,8,11-tetraazacyclotetradecane-1, 4,7,11-tetraazacyclotetradecane;

1,1'-[2,6-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1-[3,5-pyridine-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,5-thiophene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[4,4'-(2,2'-bipyridine)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,9-(1,10-phenanthroline)-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,7,10-tetraazacyclotetradecane;

1'-[5-nitro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1'1'-[2,4,5,6-tetrachloro-1,3-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,3,5,6-tetra-fluoro-1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,4-naphthylene-bis-(methylene)]bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[1,3-phenylenebis-(methylene)]bis-1,5,9-triazacyclododecane;

1,1'-[1,4-phenylene-bis-(methylene)]-1,5,9-triazacyclododecane;

1,1'-[2,5-dimethyl-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2,5-dichloro-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane;

1,1'-[2-bromo-1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane; and

1,1'-[6-phenyl-2,4-pyridinebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane.

The CXCR4 antagonist may be of formula (1F):

$$Z—(A)_n—Y \qquad (1F)$$

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where Z and Y are independently cyclic polyamine moieties having from 9 to 32 ring members and from 3 to 8 amine nitrogen atoms in the ring,

A is a linking atom or group, and n is O or an integer from 1 to 6.

In the above formula (1F) each Z and Y moiety may have 10 to 24 ring members, or 12 to 18 ring members. Each Z and Y moiety may also have 4 to 6 amine nitrogen atoms in the ring. In one example, n is 0. In another example, A is methylene.

Compounds having formula (1F), and methods of synthesizing such compounds, are described in U.S. patent 5,021,409, incorporated herein by reference. These compounds include but are not limited to:

2,2'-bicyclam, 6,6'-bicyclam;

3,3'-(bis-1,5,9,13-tetraaza cyclohexadecane);

3,3'-(bis-1,5,8,11,14-pentaazacyclohexadecane);

methylene (or polymethylene) di-1-N-1,4,8,11-tetraaza cyclotetradecane;

3,3'-bis-1,5,9,13-tetraazacyclohexadecane;

3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane;

5,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,5'-bis-1,4,8,11-tetraazacyclotetradecane;

2,6'-bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

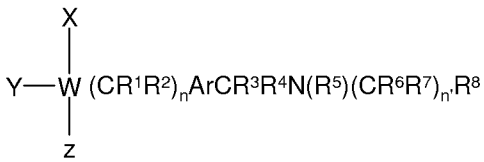
11,11'-(1,2-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane;

11,11'-(1,2-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane; and

11,11'-(1,2-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane.

Other CXCR4 antagonists are of formula (2A):



(2A)

W is a nitrogen atom and Y is void, or W is a carbon atom and Y=H;

R^1 to R^7 may be the same or different and are independently hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is an optionally substituted heterocyclic group or an optionally substituted aromatic group

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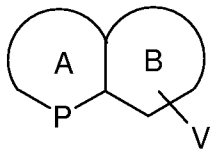
Ar is an aromatic or heteroaromatic ring optionally substituted at single or multiple, non-linking positions with electron-donating or withdrawing groups;

n and n' are independently, 0-2;

X is a group of the formula:



wherein, Ring A is an optionally substituted, saturated or unsaturated 5 or 6-membered ring, and P is an optionally substituted nitrogen atom and wherein any heteroatom in addition to P in ring A is N;

wherein Ring B is an optionally substituted 5 to 7-membered ring;

wherein Ring A or Ring B is bound to group W from any position through group V;

wherein V is a chemical bond or V is a $(CH_2)_{n''}$ group (where n''= 1-2), or V is a C=O group; and

wherein Z is selected from the group consisting of: a hydrogen atom; an optionally substituted C_{1-6} alkyl group; an optionally substituted aromatic or heterocyclic group; an optionally substituted amino group; an optionally substituted C_{1-6} alkylamino or C_{3-7} cycloalkylamino group; and a substituted carbonyl group; or

the pharmaceutically acceptable acid addition salts thereof;

wherein said compound may be in any stereoisomeric form or present as a mixture of stereoisomeric forms thereof;

wherein Ring B is selected from the group consisting of: benzene and a 5 to 7-membered cycloalkyl ring; and the optionally substituted forms thereof.

In the above formula (2A), Ring A may be pyridine; pyrimidine; pyrazine; pyridazine; triazine; piperidine; piperazine; imidazole; pyrazole; or triazole. and the optionally substituted forms thereof. Ring B may be cyclopentyl; cyclohexyl; cycloheptyl; cyclopentenyl; cyclohexenyl; or cycloheptenyl, and the optionally substituted forms thereof. In one embodiment, Ring A and Ring B together are optionally substituted dihydroquinoline or tetrahydroquinoline.

In the above formula (2A), Ring A and Ring B are independently optionally substituted with a substituent selected from the group consisting of: halogen; nitro; cyano; carboxylic acid; an optionally substituted alkyl, alkenyl or cycloalkyl group; an optionally substituted hydroxyl

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group; an optionally substituted thiol group; an optionally substituted amino or acyl group; an optionally substituted carboxylate, carboxamide or sulfonamide group; and an optionally substituted aromatic or heterocyclic group. In one embodiment, the optional substituent in Ring A or Ring B is independently an optionally substituted aralkyl or heterocycloalkyl, wherein said heterocycloalkyl is a 5 or 6 membered ring containing 1-4 heteroatoms. For example, the optionally substituted aralkyl or heterocycloalkyl may be phenylC_{1-4}alkyl; phenylmethyl (benzyl); phenethyl; pyridinylmethyl; or pyridinylethyl.

In the above formula (2A), Z may be an optionally substituted C_{1-6}alkyl group, wherein said C_{1-6}alkyl group is substituted with one or more substituents selected from the group consisting of: halogen; nitro; cyano; carboxylic acid; an optionally substituted alkyl, alkenyl or cycloalkyl group; an optionally substituted hydroxyl group; an optionally substituted thiol group; an optionally substituted amino or acyl group; an optionally substituted carboxylate, carboxamide or sulfonamide group; and an optionally substituted aromatic or heterocyclic group.

In the above formula (2A), Z is an optionally substituted aromatic or heterocyclic group or a C_{1-6}alkyl group optionally substituted with an optionally substituted aromatic or heterocyclic group. In one embodiment, Z is a C_{1-6} alkyl group substituted with an optionally substituted aromatic or heterocyclic group. The optionally substituted aromatic group may be substituted with a substituent selected from the group consisting of: benzene; naphthalene; dihydronaphthalene; and tetrahydronaphthalene; and wherein said optionally substituted heterocyclic group is a 5 to 6-membered saturated, partially saturated, or aromatic heterocyclic ring containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. The heterocyclic group selected from the group consisting of: pyridine, quinoline, isoquinoline, imidazole, benzimidazole, azabenzimidazole, benzotriazole, furan, benzofuran, thiazole, benzothiazole, oxazole, benzoxazole, pyrrole, indole, indoline, indazole, pyrrolidine, pyrrolidone, pyrroline, piperidine, piperazine, tetrahydroquinoline, tetrahydroisoquinoline, pyrazole, thiophene, isoxazole, isothiazole, triazole, tetrazole, oxadiazole, thiadiazole, morpholine, thiamorpholine, pyrazolidine, imidazolidine, imidazoline, tetrahydropyran, dihydropyran, benzopyran, dioxane, dithiane, tetrahydrofuran, tetrahydrothiophene, dihydrofuran, and dihydrothiophene. The heterocyclic group may also contain nitrogen or sulfur heteroatoms; and wherein said nitrogen or sulfur heteroatoms are optionally in the form of oxides.

The CXCR4 antagonists also include compounds of formula (2B):

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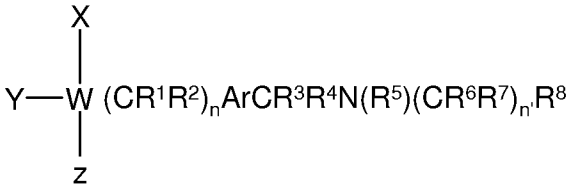


(2B)

wherein, W is a nitrogen atom and Y is void;

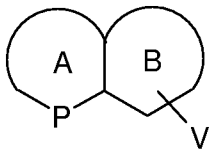
R^1 to R^7 may be the same or different and are independently hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is an optionally substituted heterocyclic group or an optionally substituted aromatic group

Ar is an aromatic or heteroaromatic ring optionally substituted at single or multiple, non-linking positions with electron-donating or withdrawing groups;

n and n' are independently, 0-2;

X is a group of the formula:



wherein, Ring A is an optionally substituted, saturated or unsaturated 5 or 6-membered ring, and P is an optionally substituted nitrogen atom and wherein any heteroatom in ring A or B is N;

wherein Ring B is an optionally substituted 5 to 7-membered ring;

wherein Ring A or Ring B is bound to group W from any position through group V;

wherein V is a chemical bond or V is a $(CH_2)_{n''}$ group (where n''= 1-2), or V is a C=O group; and

wherein Z is selected from the group consisting of: a hydrogen atom; an optionally substituted C_{1-6} alkyl group; an optionally substituted aromatic or heterocyclic group; an optionally substituted amino group; an optionally substituted C_{1-6} alkylamino or C_{3-7} cycloalkylamino group; and a substituted carbonyl group; or the pharmaceutically acceptable acid addition salts thereof;

wherein said compound may be in any stereoisomeric form or present as a mixture of stereoisomeric forms thereof.

In the above formula (2B), Ring A may be pyridine; pyrimidine; pyrazine; pyridazine; triazine; piperidine; piperazine; imidazole; pyrazole; or triazole, and the optionally substituted

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forms thereof. Ring B may be benzene or a 5 to 7–membered cycloalkyl ring; and the optionally substituted forms thereof. For example, Ring B may be cyclopentyl; cyclohexyl; cycloheptyl; cyclopentenyl; cyclohexenyl; or cycloheptenyl. and the optionally substituted forms thereof.

In the above formula (2B), Ring A and Ring B together may be an optionally substituted dihydroquinoline or tetrahydroquinoline. For example, Ring A and Ring B are independently optionally substituted with a substituent selected from the group consisting of: halogen; nitro; cyano; carboxylic acid; an optionally substituted alkyl, alkenyl or cycloalkyl group; an optionally substituted hydroxyl group; an optionally substituted thiol group; an optionally substituted amino or acyl group; an optionally substituted carboxylate, carboxamide or sulfonamide group; and an optionally substituted aromatic or heterocyclic group. In one example, the optional substituent in Ring A or Ring B is independently an optionally substituted aralkyl or heterocycloalkyl, wherein said heterocycloalkyl is a 5 or 6 membered ring containing 1-4 heteroatoms. The optionally substituted aralkyl or heterocycloalkyl is selected from the group consisting of: phenylC_{1-4}alkyl; phenylmethyl (benzyl); phenethyl; pyridinylmethyl; and pyridinylethyl.

In the above formula (2B), Z may be an optionally substituted C_{1-6}alkyl group, wherein said C_{1-6}alkyl group is substituted with one or more substituents selected from the group consisting of: halogen; nitro; cyano; carboxylic acid; an optionally substituted alkyl, alkenyl or cycloalkyl group; an optionally substituted hydroxyl group; an optionally substituted thiol group; an optionally substituted amino or acyl group; an optionally substituted carboxylate, carboxamide or sulfonamide group; and an optionally substituted aromatic or heterocyclic group. In one example, Z is a C_{1-6} alkyl group substituted with an optionally substituted aromatic or heterocyclic group.

In another example, Z is an optionally substituted aromatic or heterocyclic group or a C_{1-6}alkyl group optionally substituted with an optionally substituted aromatic or heterocyclic group. For example, the optionally substituted aromatic group is substituted with a substituent selected from the group consisting of: benzene; naphthalene; dihydronaphthalene; and tetrahydronaphthalene; and wherein said optionally substituted heterocyclic group is a 5 to 6-membered saturated, partially saturated, or aromatic heterocyclic ring containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. The heterocyclic group may be pyridine, quinoline, isoquinoline, imidazole, benzimidazole, azabenzimidazole, benzotriazole, furan, benzofuran, thiazole, benzothiazole, oxazole, benzoxazole, pyrrole, indole, indoline, indazole, pyrrolidine, pyrrolidone, pyrroline, piperidine, piperazine, tetrahydroquinoline,

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tetrahydroisoquinoline, pyrazole, thiophene, isoxazole, isothiazole, triazole, tetrazole, oxadiazole, thiadiazole, morpholine, thiamorpholine, pyrazolidine, imidazolidine, imidazoline, tetrahydropyran, dihydropyran, benzopyran, dioxane, dithiane, tetrahydrofuran, tetrahydrothiophene, dihydrofuran, or dihydrothiophene. In other examples, the heterocyclic group contains nitrogen or sulfur heteroatoms; and wherein said nitrogen or sulfur heteroatoms are optionally in the form of oxides.

In one embodiment, the CXCR4 antagonist is a compound selected from the group consisting of:

N-(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-2-ylmethyl)amino]ethyl]-N'-(1-methyl-1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-2-ylmethyl)amino]ethyl]-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(2-phenyl-5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-5-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-[(2-amino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-4-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-quinolinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-(2-naphthoyl)aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(*S*)-(2-acetylamino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(*S*)-(2-acetylamino-3-phenyl)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[3-((2-naphthalenylmethyl)amino)propyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(*S*)-pyrollidinylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(*R*)-pyrollidinylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[3-pyrazolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-pyrrolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-thiopheneylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine

N-(2-pyridinylmethyl)-N'-[2-thiazolylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-furanylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(phenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-aminoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-3-pyrrolidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine

N-(2-pyridinylmethyl)-N'-4-piperidinyl-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(phenyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(6-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(7-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;

N-(2-pyridinylmethyl)-N'-(6-methoxy-3,4-dihydronaphthalenyl)-1-(aminomethyl)-4-benzamide;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(7-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-imidazol-2-ylmethyl)-N'-(8-Fluoro-1,2,3,4-tetrahydro-2-naphthalenyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1H-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-7-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-naphthalenylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(isobutylamino)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N'-[2-[(2-pyridinylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(2-furanylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-guanidinoethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[bis-[(2-methoxy)phenylmethyl]amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-4-ylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-[(1*H*-imidazol-2-ylmethyl)amino]ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(phenylureido)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[[N"-(n-butyl)carboxamido]methyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxamidomethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(N"-phenyl)carboxamidomethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(carboxymethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(phenylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(1*H*-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(5,6-dimethyl-1*H*-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine (hydrobromide salt);

N-(2-pyridinylmethyl)-N'-(5-nitro-1*H*-benzimidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[(1*H*)-5-azabenzimidazol-2-ylmethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

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N-(2-pyridinylmethyl)-N-(4-phenyl-1*H*-imidazol-2-ylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-[2-(2-pyridinyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-benzoxazolyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(*trans*-2-aminocyclohexyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(2-phenylethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(3-phenylpropyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N'-(*trans*-2-aminocyclopentyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-glycinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-alaninamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-aspartamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-pyrazinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-prolinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-(L)-lysinamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-benzamide;

N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-picolinamide;

N'-Benzyl-N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

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N'-phenyl-N-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-N-(5,6,7,8-tetrahydro-8-quinolinyl)-urea;

N-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*bacteria*pyridin-9-yl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N-(5,6,7,8-tetrahydro-8-quinolinyl)-4-[[(2-pyridinylmethyl)amino]methyl]benzamide;

N,N'-bis(2-pyridinylmethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*bacteria*pyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(6,7-dihydro-5*H*-cyclopenta[*bacteria*pyridin-7-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'-[(5,6,7,8-tetrahydro-8-quinolinyl)methyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N'[(6,7-dihydro-5*H*-cyclopenta[*bacteria*pyridin-7-yl)methyl]-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-(2-methoxyethyl)-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(2-pyridinylmethyl)-N-[2-(4-methoxyphenyl)ethyl]-N'-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-1,4-(5,6,7,8-tetrahydro-8-quinolinyl)benzenedimethanamine;

N-[(2,3-dimethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,3-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-oyl]-4-piperidinyl]-1,3-benzenedimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

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N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-phenoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(1-methyl-2-carboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-benzyloxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[(thiophene-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[bacteriapyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[[1-methyl-3-(pyrazol-3-yl)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(phenyl)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-benzyl-3-carboxymethyl-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3,4-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[[1-methyl-2-(2-tolyl)carboxamido]ethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1,5-dimethyl-2-phenyl-3-pyrazolinone-4-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(4-propoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

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N-(1-phenyl-3,5-dimethylpyrazolin-4-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1*H*-imidazol-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-cyanophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(5-ethylthiophene-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(2,6-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-difluoromethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-difluoromethoxyphenylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[1-(N"-phenyl-N"-methylureido)-4-piperidinyl]-1,4-benzenedimethanamine;

N,N'-bis(2-pyridinylmethyl)-N-[N"-p-toluenesulfonylphenylalanyl)-4-piperidinyl]-1,4-benzenedimethanamine;

N-[1-(3-pyridinecarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(cyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(1-phenylcyclopropylcarboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

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N-(1,4-benzodioxan-6-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-[3-(2-chlorophenyl)-5-methyl-isoxazol-4-carboxamido]-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(2-thiomethylpyridine-3-carboxamido)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(2,4-difluorophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylpyrrol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-hydroxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(3-methoxy-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[2-(N"-morpholinomethyl)-1-cyclopentyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-piperidinyl)propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimidazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(1-phenyl-3-(N''-morpholino)]propyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(iso-propyl)-4-piperidinyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-(ethoxycarbonyl)-4-piperidinyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(1-methyl-3-pyrazolyl)propyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-(N'',N''-diethylcarboxamido)ethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

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N-[(1-methyl-2-phenylsulfonyl)ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(2-chloro-4,5-methylenedioxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[1-methyl-2-[N"-(4-chlorophenyl)carboxamido]ethyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-acetoxyindol-3-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(3-benzyloxy-4-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-[(8-hydroxy)-2-quinolylmethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-acetamidophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1H-imidazol-2-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(3-quinolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(2-thiazolylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(5-benzyloxy)benzo[b]pyrrol-3-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-(1-methylpyrazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(4-methyl)-1H-imidazol-5-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[[(4-dimethylamino)-1-napthalenyl]methyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

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N-[1,5-dimethyl-2-phenyl-3-pyrazolinone-4-ylmethyl]-N,N'-bis(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-[(1-acetyl-2-(R)-prolinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-[2-acetamidobenzoyl-4-piperidinyl]-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(2-cyano-2-phenyl)ethyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[(N"-acetyltryptophanyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(N"-benzoylvalinyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(4-dimethylaminophenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-(4-pyridinylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(1-methylbenzimadazol-2-ylmethyl)-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,4-benzenedimethanamine;

N-[1-butyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-benzoyl-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-3-pyrrolidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[(1-methyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1H-imidazol-4-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,3-benzenedimethanamine;

N-[1-(benzyl)-4-piperidinyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[1-methylbenzimidazol-2-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

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N-[(2-phenyl)benzo[b]pyrrol-3-ylmethyl]-N-[2-(2-pyridinyl)ethyl]-N'-(2-pyridinylmethyl)-1,4-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,4-benzenedimethanamine;

N-(3-methyl-1H-pyrazol-5-ylmethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-methoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxyphenyl)methyl]-N'-(2-pyridinylmethyl)-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-1,3-benzenedimethanamine;

N-(benzyloxyethyl)-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(2-ethoxy-1-naphthalenyl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

N-[(6-methylpyridin-2-yl)methyl]-N'-(2-pyridinylmethyl)-N-(5,6,7,8-tetrahydro-8-quinolinyl)-1,3-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]guanidine;

N-(2-pyridinylmethyl)-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,4-benzenedimethanamine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]homopiperazine;

1-[[3-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]homopiperazine;

trans and *cis*-1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,5-piperidinediamine;

N,N'-[1,4-Phenylenebis(methylene)]bis-4-(2-pyrimidyl)piperazine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-1-(2-pyridinyl)methylamine;

2-(2-pyridinyl)-5-[[(2-pyridinylmethyl)amino]methyl]-1,2,3,4-tetrahydroisoquinoline;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diaminopyrrolidine;

1-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-3,4-diacetylaminopyrrolidine;

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triaza-3-oxabicyclo [4.3.0]nonane; and

8-[[4-[[(2-pyridinylmethyl)amino]methyl]phenyl]methyl]-2,5,8-triazabicyclo[4.3.0] nonane.

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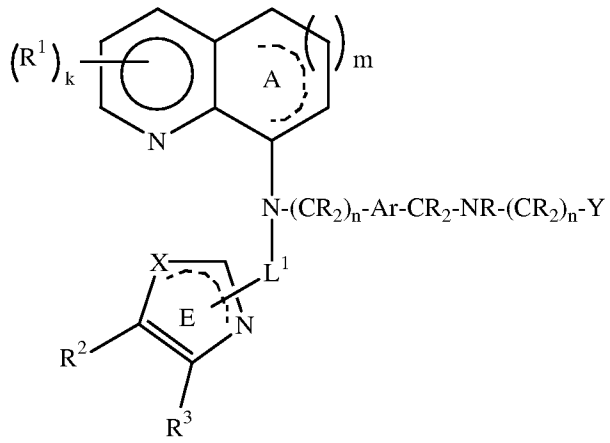
Compounds having formula (2A) and (2B) and methods for synthesizing such compounds are set forth in WO 00/56729, incorporated herein by reference.

Other CXCR4 antagonists are compounds of formula (3):



(3)

or the salts, prodrugs and stereochemical forms thereof, wherein:

Ring A optionally comprises a heteroatom selected from N, O and S;

the dotted lines represent optional unsaturation;

R^1 is halo, nitro, cyano, optionally substituted hydroxy, optionally substituted thiol, optionally substituted amino, carboxylate, carboxamide, sulfonate, sulfonamide, C2-4 alkanoyl, alkylsulfonyl, or aroyl;

R^2 and R^3 are independently H, an optionally halogenated C1-4 alkyl, an optionally substituted aryl or heterocyclic group, or R^2 and R^3 together with ring E may form a substituted or unsubstituted 5-7 membered ring;

k is 0-4;

m is 0-2;

L^1 is a covalent bond of C1-6 alkyl optionally containing N or O;

X is unsubstituted or substituted C, N; or O or S;

Ar is phenylene;

each n is independently 0-2;

each R is independently H or alkyl (1-6C); and

Y is a fused or unfused aromatic or heteroaromatic ring, or a 5-6 membered heterocyclic group.

In the above formula (3), Y may be a substituted or unsubstituted benzene, napthalene, dihydronapthalene , tetrahydronapthalene, pyridine, quinoline, isoquinoline, imidazole, benzimidazole, azabenzimidazole, benzotriazole, furan, benzofuran, thiazole, benzothiazole,

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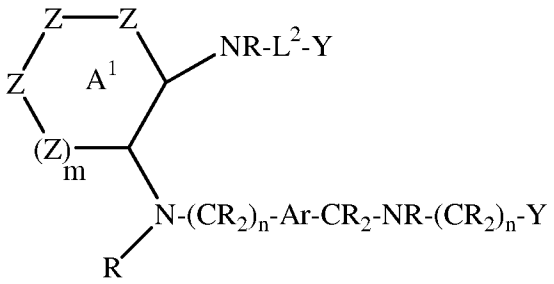
oxazole, benzoxazole, pyrrole, indole, indoline, indazole, pyrrolidine, pyrrolidone, pyrroline, piperidine, piperazine, tetrahydroquinoline, tetrahydroisoquinoline, pyrazole, thiophene, isoxazole, isothiazole, triazole, tetrazole, oxadiazole, thiadiazole, morpholine, thiamorpholine, pyrazolidine, imidazolidine, imidazoline, tetrahydropyran, dihydropyran, benzopyran, dioxane, dithiane, tetrahydrofuran, tetrahydrothiophene, dihydrofuran, or dihydrothiophene.

In the above formula (3), L^1 may be linked to position 2 of ring E. The dotted line in ring E may further represent a double bond between the nitrogen shown and position 2. In one example, R^2 and R^3 are connected so as to form a benzosubstituent to ring E.

In the above formula (3), ring A may be saturated. In some examples, m is 1 and k is 0 or 1.

The CXCR4 antagonists may also have formula (3A):



(3A)

or the salts, prodrugs and stereochemical forms thereof, wherein:

R, m, n, Ar, and each Y are defined as in formula (3);

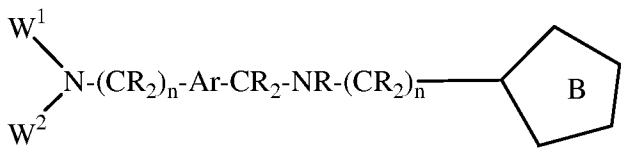
L^2 is a covalent bond or C1-6 alkyl optionally containing N or O;

and each Z is independently CR_2, NR, O or S, with the proviso that only two Z can be other than CR_2.

In the above formula (3A), L^2 may be methylene or ethylene. In one example, m is 1 and all Z embodiments are CR_2, particularly CH_2.

In the above formula (3A), each Y may be pyrimidyl, pyridyl, phenyl, benzimidazole or benzoxazole.

Other CXCR4 antagonists have formula (3B):



(3B)

or the salts, prodrugs and stereochemical forms thereof, wherein:

W^1 is a monocyclic (5-6 membered) or fused bicyclic (8-12 membered) unsubstituted or substituted ring system containing at least one heteroatom selected from N, O and S;

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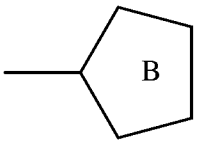
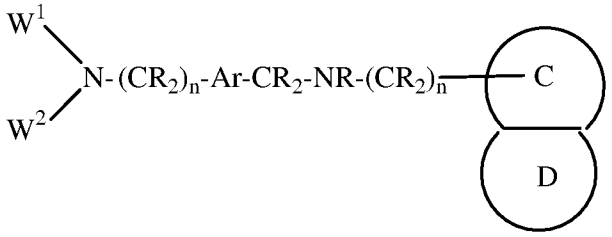
W^2 is H, or is selected from the group consisting of: an optionally substituted C_{1-6} alkyl group; a C_{0-6} alkyl group substituted with an optionally substituted aromatic or heterocyclic group; an optionally substituted C_{0-6} alkylamino or C_{3-7} cycloalkylamino group; and an optionally substituted carbonyl group or sulfonyl;

Ar, R and n are defined as in Formula (3), and



is a saturated or unsaturated 5-membered ring containing 1-2 heteroatoms selected from N, O and S.

Other CXCR4 antagonists have formula (3C):



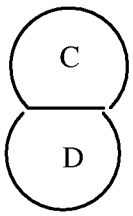
(3C)

or the salts, prodrugs or stereochemical forms thereof, wherein:

W^1 is phenyl, pyridyl, pyridimyl, imidazolyl, thiophenylyl, and a fused ring system optionally having a heteroatom selected from N, O and S;

W^2 is H;

Ar, R and n are defined as in formula (3); and



represents a fused ring system of 10 members, optionally containing 1 or 2 heteroatoms selected from N, O and S.

Compounds having formula (3), and (3A)-(3C) and methods for synthesizing such compounds are set forth in WO 02/22600, which is incorporated herein by reference.

Other CXCR4 antagonists have formula (4):

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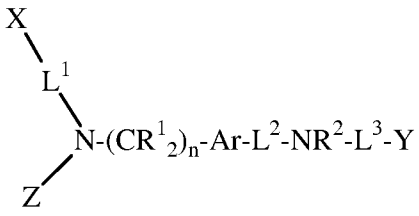

(4)

or the salts, prodrugs and stereochemical forms thereof, wherein:

X is a monocyclic (5-6 membered) or fused bicyclic (9-12 membered) unsubstituted or substituted ring system containing at least one heteroatom selected from N, O and S;

Z is H, or is an optionally substituted 5-6 membered monocyclic or 9-12 membered fused bicyclic ring system containing N, O or S;

Ar is an optionally substituted aromatic or heteroaromatic ring;

each of L^1, L^2 and L^3 is independently a bond, CO, SO_2, or CH_2, wherein at least one of L^2 and L^3 must comprise CO or SO_2; and wherein L^1 can also be alkylene (2-5C) wherein one or two C may optionally be replaced by N and which alkylene may itself optionally be substituted by a bridge alkylene (3-4C); L^2 and L^3 also may be, independently, SO_2NH, CONH, SO_2NHCH_2 or $CONHCH_2$;

n is 0, 1 or 2;

each R^1 and R^2 is independently H or straight or branched chain or cyclic alkyl (1-6C) which may optionally be substituted, and wherein R^2 may be alkylene coupled to Y; and

Y comprises at least one aromatic or heteroaromatic or other heterocyclic substituted or unsubstituted ring coupled directly to L^3.

In the above formula (4), X may be dihydroquinoline, tetrahydroquinoline, pyranopyridine, dihydropyranopyridine, thiapyranopyridine, dihydrothiapyranopyridine, dihydronaphthyridine, tetrahydronaphthyridine, imidazolyl, oxazolyl, thiazolyl, benzimidazolyl, benzothiazolyl, or benzoxazolyl.

In the above formula (4), L^1 may be alkylene (2-5C) wherein one C may optionally be replaced by N and which may optionally be substituted by a bridging alkylene (3-4C). For example, L^1 may be alkylene, CO or SO_2, and X is an optionally substituted imidazole, oxazole, thiazole, benzimidazole, benzothiazole, or benzoxazole. Alternatively, L^1 may be a bond, and X is substituted or unsubstituted dihydroquinoline, tetrahydroquinoline, pyranopyridine, dihydropyranopyridine, thiapyranopyridine, dihydrothiapyranopyridine, dihydronaphthyridine, or tetrahydronaphthyridine.

In the above formula (4), Z may be hydrogen.

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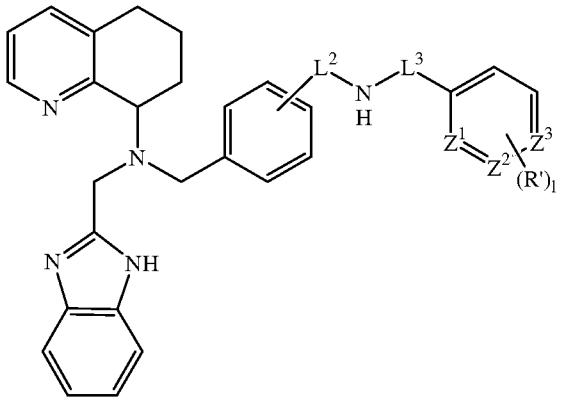
In the above formula (4), Y may be an optionally substituted imidazole, benzimidazole, pyridine, pyridine, pyrimidine, or phenyl, wherein the ring nitrogen may optionally be oxidized. For example, Y may be substituted with halogen, nitrile, alkyl, -OR, -SR, -NR_2, -NRCOR, -OOCR, -COR, -$CONR_2$, -COOR, -NO_2, -NOH, -CF_3, where R is H or alkyl (1-6C).

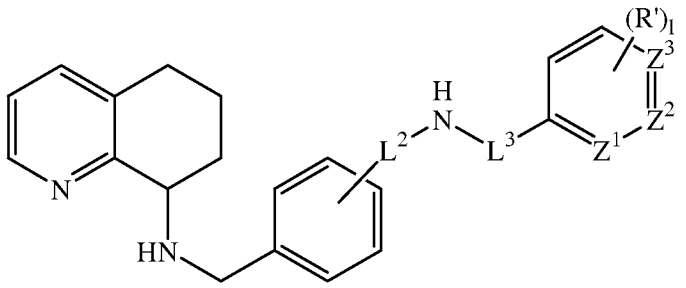
In the above formula (4), each X or Z may optionally be substituted by halo, nitro, cyano, carboxy, C1-10 alkyl, C2-10 alkenyl, C3-10 cycloalkyl, hydroxy, thiol, amino, acyl, carboxylate, carbamate, carboxamide, sulfonamide, a carbonyl or sulfonyl binding to a hydrogen, or substituted with a C1-10-alkyl, C2-10 alkenyl, C3-7 cycloalkyl or a 5-6 membered monocyclic aromatic group; or X or Z may optionally be substituted by a 5-6 membered monocyclic aromatic group, naphthyl or a 5-6 membered heterocyclic ring;

Other CXCR4 antagonists have formula (4A):



(4A)

or formula (4B):



(4B)

wherein l is 0-3, and R′ is OH, MeO, SH SMe, CN, CO_2Me, F, Cl, Br, NO_2, CH_3CO, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_3CONH, CH_3SO_2NH, $CONH_2$, SO_2NH_2, CF_3, or Me;

each of Z^1, Z^2 and Z^3 is independently CH, CR′ or N, wherein only two of said Z^1, Z^2 and Z^3 can be N;

and L^2 and L^3 are as defined in formula (4).

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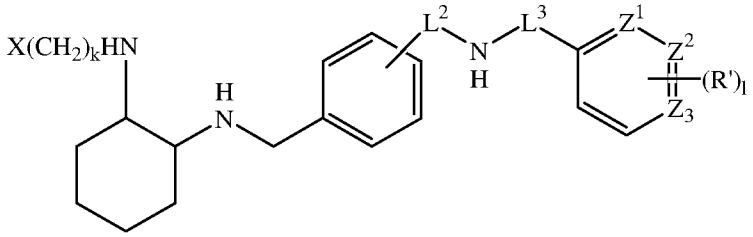
In the above formula (4A) or (4B), all of Z^1, Z^2 and Z^3 may be CH or CR′. In one example, Z^3 is N and L^3 is CO. Furthermore, one of L^2 and L^3 may be SO_2 and the other is a bond or CH_2. Alternatively, one of L^2 and L^3 is CO and the other is a bond or CH_2.

In another embodiment, the compound for use in the methods of the present invention has formula (4C):



(4C)

wherein l is 0-3, and R′ is OH, MeO, SH SMe, CN, CO_2Me, F, Cl, Br, NO_2, CH_3CO, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_3CONH, CH_3SO_2NH, $CONH_2$, SO_2NH_2, CF_3, or Me;

k is 0-2;

each of Z^1, Z^2 and Z^3 is independently CH, CR′ or N, wherein only two of said Z^1, Z^2 and Z^3 can be N;

and X, L^2 and L^3 are as defined in formula (4).

In the above formula (4C), all of Z^1, Z^2 and Z^3 may be CH or CR′. In one example, Z^3 is N and L^3 is CO. Furthermore, one of L^2 and L^3 may be SO_2 and the other is a bond or CH_2. Alternatively, one of L^2 and L^3 may be CO and the other is a bond or CH_2.

Compounds having formula (4), and (4A)-(4C) and methods of synthesizing such compounds are set forth in WO 02/22599, which is incorporated herein by reference.

Other CXCR4 antagonists have formula (5):

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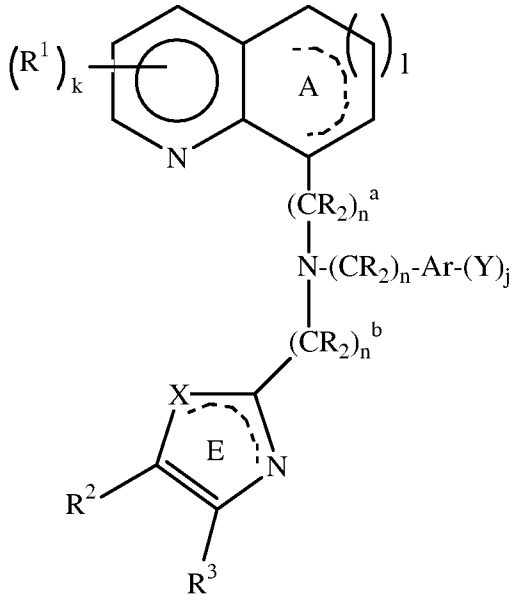

(5)

or the salts, prodrugs and stereoisomeric forms thereof;

Ring A optionally comprises a heteroatom selected from N, O and S;

the dotted lines represent optional unsaturation;

R^1, R^2 and R^3 are independently H, halo, substituted or unsubstituted alkyl, hydroxyl, amino, thiol, or acyl; or R^2 and R^3 may together form a benzo ring;

k is 0-4;

l is 0, 1, or 2;

X is unsubstituted or substituted C or N; or is O or S;

Ar is the residue of an aromatic or heteroaromatic moiety;

each n is independently 0-2;

each R is independently H or alkyl (1-6C);

j is 0-3; and

each Y is independently selected from the group consisting of halo, OR; SH; SO; SO_2; optionally substituted phenyl;

- $(CR_2)_mOR$;
- $(CR_2)_mCOR$;
- $(CR_2)_mCOOR$;
- $(CR_2)_mN{=}CH{-}NR_2$;
- $(CR_2)_mCONHNHR$;
- $(CR_2)_mCN$;
- $(CR_2)_mNR^5{}_2$;

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- $(CR_2)_mNR(CR_2)_mNRR^4$;
- $(CR_2)_mNR(CR_2)_mNR(CR_2)_mNR^5{}_2$;
- $(CR_2)_mCO(CR_2)_mNR^5{}_2$;
- $(CR_2)_mCO(CR_2)_mNR(CR_2)_mNRR^4$;
- $(CR_2)_mCO(CR_2)_mNR(CR_2)_mNR(CR_2)_mNR^5{}_2$;
- $(CR_2)_mNRCO(CR_2)_mNRR^4$;
- $(CR_2)_mNRCO(CR_2)_mNR(CR_2)_mNR^5{}_2$;
- $(CR_2)_mNRCO(CR_2)_mNR(CR_2)_mNR(CR_2)_mNR(CR_2)_mNR^5{}_2$;
- $(CR_2)_mNROH$;
- $(CR_2)_mCONROH$;
- $(CR_2)_mCR{=}NOH$;
- NHNHR;
- CH=N—Z; and
- guanidino or amidino, each of which may be linked to Y through a $(CR_2)_m$ moiety;

wherein R is H or alkyl (1-6C), each m is independently 0-4, and each R^4 and each R^5 is independently H, alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), or acyl (1-6C), each optionally substituted by one or more nonaromatic, nonheterocyclic substituent(s), wherein two R^5 may be connected to form a cyclic amine optionally containing one or more additional heteroatoms selected from N, O and S;

a indicates the linker between Ring A and N;

b indicates the linker between ring E and the N; and

wherein Z is an aromatic or heteroaromatic moiety containing 5-12 ring members.

In the above formula (5), Ar may be a 5-6 membered monocyclic ring or a 9-12 membered fused ring system. For example, Ar may be benzene, naphthalene, dihydronaphthalene, tetrahydronaphthalene, pyridine, pyrimidine, quinoline, isoquinoline, imidazole, benzimidazole, azabenzimidazole, benzotriazole, furan, benzofuran, thiazole, benzothiazole, oxazole, benzoxazole, pyrrole, indole, imidazole, tetrahydroquinoline, tetrahydroisoquinoline, pyrazole, thiophene, isoxazole, isothiazole, triazole, tetrazole, oxadiazole, thiadiazole, imidazoline, and benzopyran. In particular examples, Ar is benzene, benzimidazole, benzothiazole, imidazole, oxazole, benztriazole, thiazole, pyridine, or pyrimidine. In one embodiment, at least one Y is $-(CR_2)_mNR^5{}_2$.

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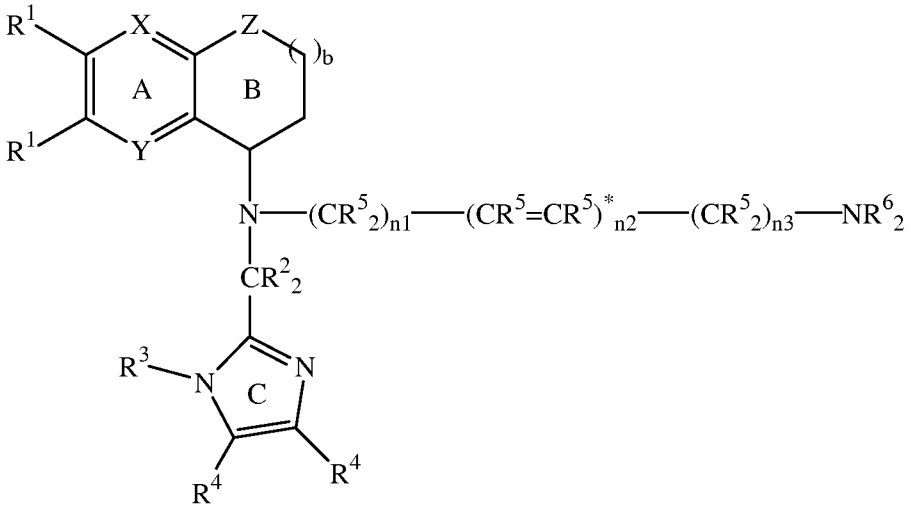
In the above formula (5), R^2 and R^3 taken together may form a benzo substituent. In one embodiment, X is N and ring E comprises a pi bond coupled to one N. In one embodiment, ring E is coupled to the remainder of the molecule at position 2.

In the above formula (5), ring A may be saturated and l is 1. In one example, k is 0-1. In other examples, the ring system which includes A is tetrahydroquinoline or a substituted form thereof.

In the above formula (5), one of $(CR_2)^a_n$ and $(CR_2)^b_n$ may be CH_2 and the other is a bond. For example, $(CR_2)^a_n$ may be a bond and $(CR_2)^b_n$ is CH_2.

Compounds having formula (5) and methods for synthesizing such compounds are set forth in WO 02/34745, which is incorporated herein by reference.

Other CXCR4 antagonists have formula (6):



(6)

or the salts, prodrugs and stereoisomeric forms thereof,

wherein X and Y are independently N or CR^1;

Z is S, O, NR^1 or CR^1_2;

each R^1-R^6 is independently H, halo, O(C=O)R, NR(C=O)R, OR, SR, NR_2, COOR, $CONR_2$, where R is H or optionally substituted alkyl, alkenyl, alkynyl or aryl; or

each R^1-R^6 is alkyl (C_{1-10}), alkenyl (C_{2-10}), alkynyl (C_{2-10}), aryl (C_{5-12}), arylalkyl, arylalkenyl, or arylalkynyl, each optionally containing substituted and optionally containing O, S, or N; or an optionally substituted acyl, arylacyl, alkyl- alkenyl-, alkynyl- or arylsulfonyl wherein each alkyl, alkenyl, alkynyl or aryl moiety may contain O, O or N;

n1 is 0-4;

n2 is 0-1, wherein the * signifies C≡ C may be substituted for CR^5=CR^5;

n3 is 0-4;

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wherein n1+n2+n3 is greater than or equal to 2;

b is 0-2;

wherein the following combinations of R groups may be coupled to generate a ring, which ring may be saturated or unsaturated:

R^2+R^2

one R^2+R^3

R^3+ one R^4,

R^4+R^4,

one R^5+ another R^5,

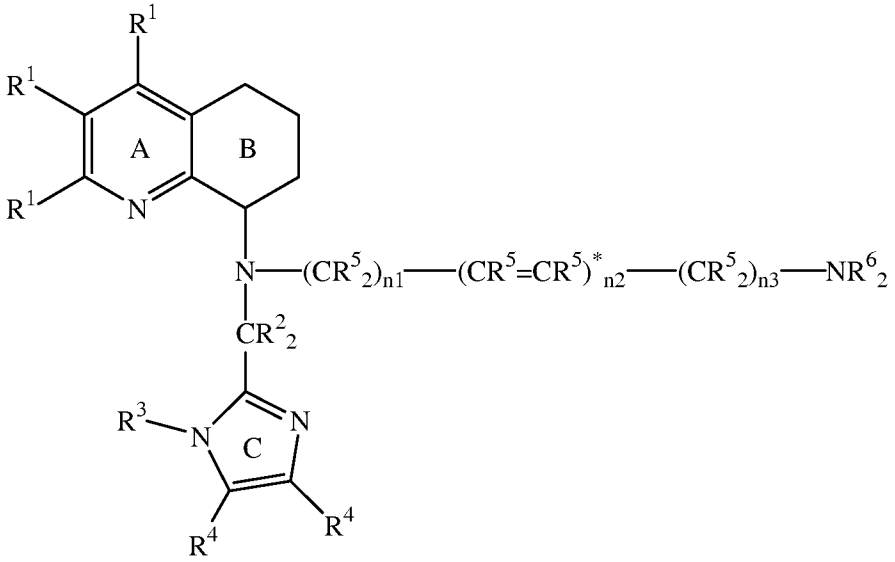
one R^5+ one R^6, and

R^6+R^6;

wherein the ring may not be aromatic when the participants in ring formation are two R^5; and

wherein when n2 is 1, neither n1 nor n3 can be 0.

Other CXCR4 antagonists have formula (6A):



(6A)

or the salts, prodrugs and stereoisomeric forms thereof,

wherein R^1-R^6 and n1-n3 are as defined in formula (6).

Other antagonists have formula (6B) or formula (6C):

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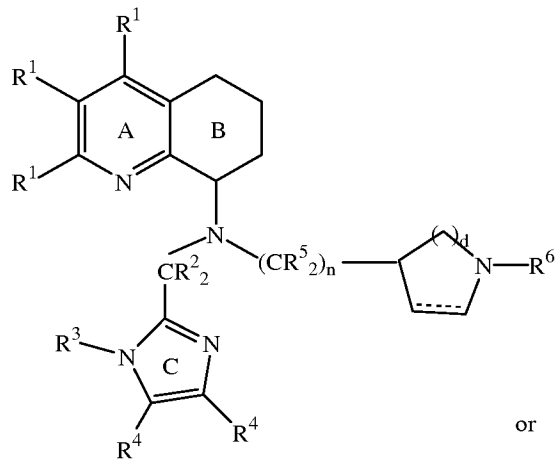
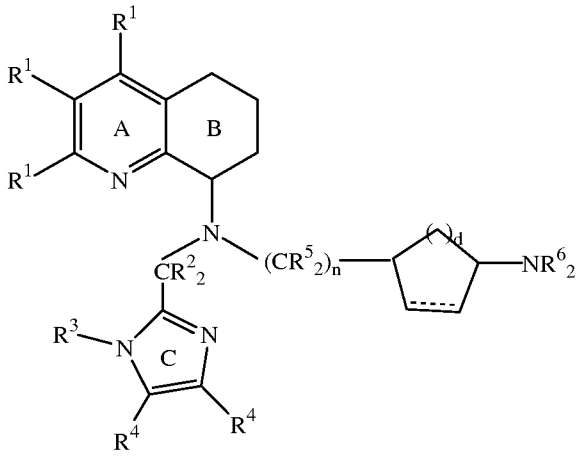


or



(6B) (6C)

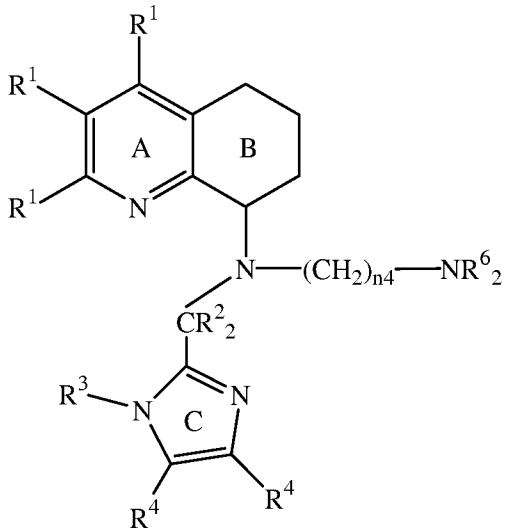
or the salts, prodrugs and stereoisomeric forms thereof,

wherein n is 0-1;

d is 0-3; the dotted line is an optional π bond; and

R^1-R^6 are defined as in formula (6).

In yet another embodiment, the compounds for use in the methods of the present invention have formula (6D):



(6D)

or the salts, prodrugs and stereoisomeric forms thereof,

wherein R^1-R^6 are defined as in formula (6), and n4 is 2-6.

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In the above formula (6) or (6A)-(6D), each R^1 may be H, halo, alkyl, alkoxy, or CF_3. In one embodiment, each R^2 is H or alkyl. In another embodiment, each R^3 is H, alkyl, alkenyl, arylalkyl, or aryl.

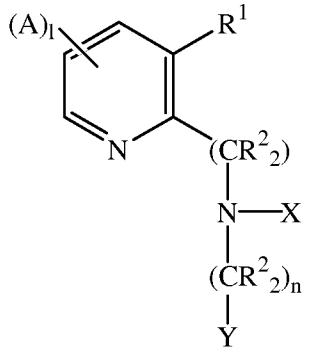
In the above formula (6) or (6A)-(6D), each R^4 may be H, alkyl or aryl. Alternatively, two R^4 may form an optionally substituted aromatic or heteroaromatic ring. For example, two R^4 may form a phenyl or pyridyl ring, which may be substituted with halo, alkyl, halogenated alkyl, hydroxy, or alkoxy.

In the above formula (6) or (6A)-(6D), each R^5 may be H, alkyl, or alkenyl, wherein said alkyl or alkenyl may optionally be substituted. In one embodiment, the alkyl or alkenyl substituents on a single carbon, or on nonadjacent or adjacent carbons, form a saturated or unsaturated ring. In one example, the substituents form a nonaromatic ring. In another embodiment, one R^5 is an oxime, an alkylated oxime, alkylated hydroxylamine, hydroxylamine or halo.

In the above formula (6) or (6A)-(6D), each R^6 may independently H, or an arylalkyl or arylsulfonyl, wherein the aryl moiety may comprise a heteroatom; or two R^6 may comprise a guanidyl, carbonyl, or carbamino group. In one embodiment, two R^6 together, or one R^5 and one R^6 together may form a saturated, unsaturated or aromatic ring, wherein each ring may optionally contain N, S or O.

Compounds having formula (6) and methods for synthesizing such compounds are set forth in WO 03/055876, which is incorporated herein by reference.

The CXCR4 antagonist may have formula (7):



(7)

or the salts, prodrugs and stereoisomeric forms thereof,

wherein X is $(CR^3_2)_o - (CR^3 = CR^3)_p - (CR^3_2)_q - NR^5_2$; $(CR^3_2)_r - R^4$; or an optionally substituted benzyl, or a monocyclic or bicyclic ring optionally containing N, O or S;

Y is an optionally substituted 5-12 membered heterocyclic ring containing a nitrogen atom, said heterocyclic ring may be monocyclic or fused, and is aromatic or partially aromatic;

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A and R^1 are independently halo, CF_3, cyano, nitro, OR, SR, NR_2, COOR, $CONR_2$, NSO_2R, OSO_2R, or OSO_2NR, where each R is H, alkyl, alkenyl, alkynyl or aryl; or A and R^1 are independently an optionally substituted alkoxy (C_{1-10}), alkyl (C_{1-10}), alkenyl (C_{2-10}), alkynyl (C_{2-10}), aryl (5-12 members), arylalkyl, arylalkenyl, or arylalkynyl, each of which may optionally contain O, S, or N;

R^2 and R^3 are independently H or an optionally substituted alkyl;

R^4 is an optionally substituted heterocyclic ring or heteroaryl; or R^4 comprises a urea, hydroxyurea, sulfamide, acetamide, guanidine, cyanamide, hydroxylamine, cyanamide, imidazolidine-2-one, or a nicotinamide moiety, each of which may be substituted with a heterocyclic ring;

R^5 is H or alkyl;

l and n are independently 0-4;

p is 0-1;

o and q are independently 1-4; and

r is 1-6.

In the above formula (7), at least one of R^1 and R^2 may not be H, and may be connected to form an additional ring such as an aryl or heteroaryl. In one example, two As may not form an additional ring. In another example, X is $(CR^3{}_2)_r - R^4$, r is at least two, and R^4 is 2-pyridinyl, quinolinyl, imidazolyl or furan.

In the above formula (7), X may be $(CR^3{}_2)_o - (CR^3 = CR^3)_p - (CR^3{}_2)_q - NR^5{}_2$, wherein each R^3 and R^5 are independently H and p may be zero. In particular embodiments, o and q together are 2-6. Alternatively, X may be $(CR^3{}_2)_r - R^4$, wherein R^4 is a heterocyclic ring or heteroaryl, each of which contains a nitrogen atom. For example, R^4 may be azetidine, pyrrolidinyl, pyridinyl, thiophenyl, imidazolyl, or benzimidazolyl. Alternatively, X may be a monocyclic or bicyclic ring optionally containing N, O or S, such as cyclohexyl, piperidine, 8-aza-bicyclo[3.2.1]octane or 3-aza-bicyclo[3.2.1]octane. In yet another embodiment, X is an optionally substituted benzyl, particularly a disubstituted benzyl.

In the above formula (7), Y may be a 5-6 membered heterocyclic ring containing a nitrogen atom adjacent to the atom that is attached to the remainder of the molecule. The 5-6 membered heterocyclic ring may be fused to another ring. For example, Y may be pyridine, pyrimidine, pyrazine, indole, benzimidazole, benzothiazole, imidazole, isoquinoline, tetrahydroquinoline, pyridazine, thiazole, or benzoimidazole. In particular examples, Y is

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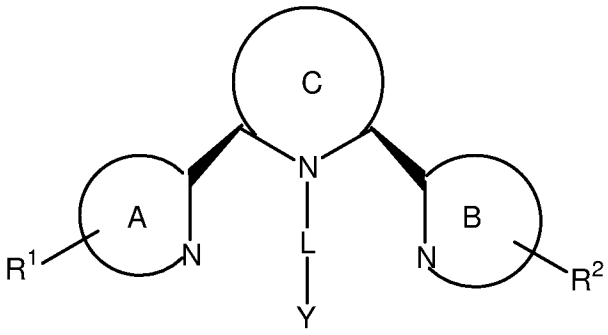
tetrahydroquinoline, particularly a 5,6,7,8 tetrahydroquinoline moiety, attached at position 8 to the remainder of the molecule.

In the above formula (7), each optionally substituted moiety may be substituted with a heteroatom, halo, CF_3, cyano, nitro, hydroxy, alkoxy, carbonyl, carboxy, amino, amido, imino, cyano, sulfonyl; C_{1-6} alkyl or C_{2-6} alkenyl each of which may contain N, O, or S; or substituted with aryl, heteroaryl, carbocyclic or heterocyclic ring, each of which may further be substituted with the same substituents.

Compounds having formula (7) and methods for synthesizing such compounds are set forth in WO 04/091518, which is incorporated herein by reference.

The CXCR4 antagonist may have formula (8)



(8)

or the salts, prodrugs and stereoisomeric forms thereof,

wherein each of rings A and B is independently an optionally substituted 5-6 membered monocyclic heteroaryl;

ring C is an optionally substituted saturated or partially saturated 5-7 membered ring, and may contain a heteroatom in addition to nitrogen, wherein said heteroatom is N, O or S;

Y is H, a C_{1-6} alkyl containing one or more heteroatoms, or a cyclic moiety, each of which is optionally substituted;

R^1 and R^2 are independently H, halo or an optionally substituted alkyl;

L is $(CR^3_2)_l$ or $NR(CR^3_2)_l$ wherein an alkyl bond may be replaced with an alkenyl or alkynyl bond;

l is 1-6; and

each R^3 is H or alkyl.

In the above formula (8), at least one of R^1 and R^2 may not be H when C is piperidinyl or 1,2,3,6-tetrahydropyridinyl and rings A and B are pyridinyl. In other embodiments, R^1 and R^2 are not both naphthalenyl when ring C is piperidinyl and rings A and B are pyridinyl. In yet

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other embodiments, ring C is not 4-oxo-piperidine-3,5-dicarboxylic acid if L-Y is CH_3; and ring C is not 4-hydroxy-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ester if L-Y is benzyl.

In the above formula (8), R^1 and R^2 may be at positions adjacent the bonds to ring C. In one example, R^1 and R^2 are independently unsubstituted alkyl, such as methyl.

In the above formula (8), each of rings A and B may be pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, pyrrole, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiazole, oxazole, isothiazole, isoxazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,2,3-oxadiazole, 1,3,4-oxadiazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, 1,2,3-benzotriazine, 1,2,4-benzotriazine, indole, benzimidazole, 1H-indazole, benzoxazole, benzthiazole, benz[*d*]isoxazole, benz[*d*]isothiazole, or purine. In particular examples, each of rings A and B is pyridine, pyrimidine, imidazole, or benzimidazole, and each of rings A and B may be identical. Each of rings A and B may also contain a single substituent, which may be identical, at the position adjacent to the bond linking the rings to ring C.

In the above formula (8), ring C may be a saturated ring, or may contain a double bond. For example, ring C may be pyrrolidine, piperidine, hexahydro-1*H*-azepine, piperazine, morpholine, thiomorpholine, azepane, azocane, 2,3,4,7-tetrahydro-1*H*-azepine, 2,3,6,7-tetrahydro-1*H*-azepine, 3-pyrroline, 1,2,3,6-tetrahydropyridine, isoindoline, 1,2,3,4-tetrahydroisoquinoline, 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, tetrahydropyran, tetrahydrothiopyran, oxepane, thiepane, oxocane, or thiocane. In particular examples, ring C is pyrrolidine, piperidine, piperazine or hexahydro-1*H*-azapine. Ring C may be substituted with an optionally substituted alkyl, halo, cyano, oxime, OR or C=N-OR, wherein R is an optionally substituted alkyl.

In the above formula (8), Y may be selected from the group consisting of:

$-(CR_2)_m NR_2$,

$-(CR_2)_m NR_2(CR_3)$,

$-(CR_2)_m NR(CR_2)_mNR_2$,

$-(CR_2)_m NR(CR_2)_mNR(CR_2)_mNR_2$,

$-(CR_2)_m OR$,

$-(CR_2)_m CO(CR_2)_mOR$,

$-(CR_2)_m CO(CR_2)_mNR_2$,

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$-(CR_2)_m CO(CR_2)_mNR(CR_2)_mNR_2$,

$-(CR_2)_m NRCO(CR_2)_mNR_2$,

$-(CR_2)_m NR (CR_2)_mCO_2R$,

$-(CR_2)_m NR (CR_2)_mCOR$,

$-(CR_2)_m NR (CR_2)_mSO_2R$,

$-(CR_2)_m NRCO(CR_2)_mNR(CR_2)_mNR_2$,

$-(CR_2)_m NRCO(CR_2)_mNR(CR_2)_mNR(CR_2)_mNR(CR_2)_mNR_2$,

$-(CR_2)_m NR(CR_2)_mOR$,

$-(CR_2)_m CR=NOH$,

$-(CR_2)_m CONR(CR_2)_mOR$,

$-(CR_2)_m N[(CR_2)_mCO_2R]_2$,

$-(CR_2)_m ONRCONR_2$,

$-(CR_2)_m – Z$,

$-(CR_2)_m NR – (CO)_mZ$,

$-(CR_2)_m NR – (CR_2)_mZ$, and

$-(CR_2)_m –CR=N=Z$;

wherein each R is H or an optionally substituted alkyl,

each m is independently 0-4; and

Z is an optionally substituted aromatic or heteroaromatic moiety containing 5-12 ring members.

In particular embodiments, Y is $(CH_2)_lNR_2$ and 1 is 1-10. Alternatively, Y may be a 5-12 membered aromatic, heteroaromatic, or a heterocyclic moiety, each of which may be a monocyclic or fused ring. For example, Y may be phenyl, imidazole, pyridine, thiophene, pyrrolidine, pyrazole, piperidine, azetidine, benzimidazole, benzo[*d*]isoxazole, or thiazole. Furthermore, Y may optionally be substituted with halo; cyano; nitro; alkoxy; halogenated alkyl; substituted carbonyl; a cyclic moiety such as a 5-12 membered aryl or heteroaryl containing N, O or S; or an alkyl, alkenyl, or a heteroalkyl moiety optionally containing one or more N, O, S, each of which is optionally substituted and optionally in the form of oxides. In particular examples, Y is substituted with pyridine, phenyl, piperidine or 2H-tetrazole.

In the above formula (8), each optionally substituted group may be substituted with inorganic moieties such as a heteroatom, halo, nitro, hydroxy, carboxy, amino, amido, cyano, or sulfonyl; or may be substituted with alkyl (C_{1-10}), alkenyl (C_{2-10}), alkynyl (C_{2-10}), aryl (5-12 members), arylalkyl, arylalkenyl, and arylalkynyl, each of which may optionally

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contain a heteroatom such as O, S, or N, and each of which may further be substituted with the same substituents. For example, each optionally substituted alkyl may be substituted with a heteroatom such as N, O, or S, or with a carbocyclic, heterocyclic, aryl or heteroaryl substituent.

Compounds having formula (8) and methods for synthesizing such compounds are set forth in WO 04/093817, and in U.S. patent application serial number 10/977,221, filed 28 October 2004, each of which is incorporated herein by reference.

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Claims

1. Use of an effective amount of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF to mobilize progenitor and/or stem cells into the bloodstream of a subject in need of such mobilization.

2. The use of claim 1, which further comprises harvesting said mobilized cells from the bloodstream.

3. The use of claim 2, which further comprises culturing said harvested cell *ex vivo*.

4. The use of claim 2, which further comprises administering said harvested cells to a recipient subject.

5. The use of claim 4, wherein said recipient subject is the same as the donor subject.

6. The use of claim 1, wherein the CXCR4 inhibitor is AMD3100.

7. The use of claim 1, wherein the CXCR2 agonist is GROβ or a modified form thereof.

8. Use of an effective amount of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF to enhance the effectiveness of a chemotherapeutic treatment or a radiotherapy in a subject afflicted with a hematopoietic or myeloid malignancy.

9. The use of claim 8, wherein the malignancy is a lymphoma, myeloma or leukemia.

10. The use of claim 8, wherein the CXCR4 inhibitor is AMD3100.

11. The use of claim 8, wherein the CXCR2 agonist is GROβ protein or a modified form thereof.

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12. A composition which comprises as active ingredients at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF in a pharmaceutical or veterinary excipient.

13. Use of an effective amount of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF in the manufacture of a medicament to mobilize progenitor and/or stem cells into the bloodstream of a subject.

14. The use of claim 13, wherein the CXCR4 inhibitor is AMD3100.

15. The use of claim 13 or 14, wherein the CXCR2 agonist is GROβ or a modified form thereof.

16. Use of an effective amount of at least one CXCR4 inhibitor, at least one CXCR2 agonist, and G-CSF in the manufacture of a medicament to enhance the effectiveness of a chemotherapeutic treatment or a radiotherapy in a subject afflicted with a hematopoietic or myeloid malignancy.

17. The use of claim 16, wherein the CXCR4 inhibitor is AMD3100.

18. The use of claim 16 or 17, wherein the CXCR2 agonist is GROβ or a modified form thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/75376

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 38/02**(2006.01),**38/18**(2006.01),**38/19**(2006.01);**C07K 14/475**(2006.01),**14/52**(2006.01);**C12P 21/00**(2006.01)

USPC: 424/184.1,198.1;435/4;514/2,12;530/399
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. : 424/184.1, 198.1; 435/4; 514/2, 12; 530/399

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.
Y	US2003/0130250 (BRIDGER et al.) 10 July 2003 (10.07.2003), page 11, [0345]; page 12, [0356]; page 16, [0386]	1-18
Y	KING et al. Rapid Mobilization of Murine Hematopoietic Stem Cells with Enhanced Engraftment Properties and Evaluation of Hematopoietic Progenitor Cell Mobilization in Rhesus Monkeys by a Single Injection of SB-251353, a Specific Truncated Form of the Human CXC Chemokine GRObeta. Blood. March 2001, Vol 97. No. 6, pages 1534-1542, especially page 1534, column 2; page 1536, column 2; page 1537, column 1 and Table 2, Figure 2; page 1539, column 2.	1-18

☐ 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

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"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
31 December 2007 (31.12.2007)

Date of mailing of the international search report
11 JAN 2008

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Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/75376

Continuation of B. FIELDS SEARCHED Item 3:
DIALOG (file biosci); EAST (JPO, EPO, USPAT, DERWENT); US-PGPUB; PALM; MEDLINE
search terms: inventors' names, mobilization, CXCR4 inhibitor, AMD3100, GRObeta, CXCL2, MIP2alpha, G-CSF,