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(54) **Title:** A METHOD OF TREATING LIVER FIBROSIS

(57) **Abstract:** The present invention relates to a method of treating hepatitis C and/or liver fibrosis with 3-cycloalkylaminopyrrolidine derivatives of the present invention.



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A Method of Treating Liver Fibrosis

FIELD OF THE INVENTION

The instant invention is directed to chemokine receptor modulators, e.g., antagonists, and their use as medicinal agents. The present invention further relates to novel compounds and medical methods of treatment of hepatitis C and liver fibrosis. More particularly, the present invention relates to the treatment of liver fibrosis associated with chronic HCV infection. The present invention also relates to 3-cycloalkylaminopyrrolidine derivatives and their use as modulators of chemokine receptors.

BACKGROUND OF THE INVENTION

The migration and transport of leukocytes from blood vessels into diseased tissues appears to be a critical component to the initiation of normal disease-fighting inflammatory responses. The process, also known as leukocyte recruitment, is also related to the onset and progression of life-threatening inflammatory, as well as debilitating autoimmune diseases. The resulting pathology of these diseases derives from the attack of the body's immune system defenses on normal tissues. Accordingly, preventing and blocking leukocyte recruitment to target tissues in inflammatory and autoimmune disease would be a highly effective approach to therapeutic intervention.

The different classes of leukocyte cells that are involved in cellular immune responses include monocytes, lymphocytes, neutrophils, eosinophils and basophils. In most cases, lymphocytes are the leukocyte class that initiates, coordinates, and maintains chronic inflammatory responses, and thus are generally the most important class of cells to block from entering inflammatory sites. Lymphocytes attract monocytes to the tissue sites, which, collectively with lymphocytes, are responsible for most of the actual tissue damage that occurs in inflammatory disease. Infiltration of the lymphocytes and/or monocytes is known to lead to a wide range of chronic, autoimmune diseases, and also organ transplant rejection. These diseases include, but are not limited to, rheumatoid arthritis, chronic contact dermatitis, inflammatory bowel disease, lupus, systemic lupus erythematosus, multiple sclerosis, atherosclerosis, psoriasis, sarcoidosis, idiopathic pulmonary fibrosis, dermatomyositis, skin pemphigoid and related diseases, (e.g., pemphigus vulgaris, p. foliaceous, p. erythematosus), glomerulonephritides, vasculitides, hepatitis, diabetes, allograft rejection, and graft-versus-host disease.

The process, by which leukocytes leave the bloodstream and accumulate at inflammatory sites, and start a disease, has at least three steps which have been described

as (1) rolling, (2) activation/firm adhesion and (3) transendothelial migration [Springer, T. A., *Nature* 346:425-433 (1990); Lawrence and Springer, *Cell* 65:859-873 (1991); Butcher, E. C., *Cell* 67:1033-1036 (1991)]. The second step is mediated at the molecular level by chemoattractant receptors. Chemoattractant receptors on the surface of leukocytes then bind chemoattractant cytokines which are secreted by cells at the site of damage or infection. Receptor binding activates leukocytes, increases the adhesiveness of the adhesion molecules that mediate transendothelial migration, and promotes directed migration of the cells toward the source of the chemoattractant cytokine.

Chemotactic cytokines (leukocyte chemoattractant/activating factors) also known as chemokines, also known as intercrines and SIS cytokines are a group of inflammatory/immunomodulatory polypeptide factors, of molecular weight 6-15 kDa, that are released by a wide variety of cells such as macrophages, monocytes, eosinophils, neutrophils, fibroblasts, vascular endothelial cells, smooth muscle cells, and mast cells, at inflammatory sites (reviewed in Luster, *New Eng. J Med.*, 338, 436-445 (1998) and Rollins, *Blood*, 90, 909-928 (1997)). Also, chemokines has been described in Oppenheim, J. J. et al., *Annu. Rev. Immunol.*, 9:617-648 (1991); Schall and Bacon, *Curr. Opin. Immunol.*, 6:865-873 (1994); Baggiolini, M., et al., and *Adv. Immunol.*, 55:97-179 (1994). Chemokines have the ability to stimulate directed cell migration, a process known as chemotaxis. Each chemokine contains four cysteine residues (C) and two internal disulfide bonds. Chemokines can be grouped into two subfamilies, based on whether the two amino terminal cysteine residues are immediately adjacent (CC family) or separated by one amino acid (CXC family). These differences correlate with the organization of the two subfamilies into separate gene clusters. Within each gene cluster, the chemokines typically show sequence similarities between 25 to 60%. The CXC chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils and T lymphocytes, whereas the CC chemokines, such as RANTES, MIP-1 α , MIP-1 β , the monocyte chemotactic proteins (MCP-1, MCP-2, MCP-3, MCP-4, and MCP-5) and the eotaxins (-1 and -2) are chemotactic for, among other cell types, macrophages, T lymphocytes, eosinophils, dendritic cells, and basophils. There also exist the chemokines lymphotactin-1, lymphotactin-2 (both C chemokines), and fractalkine (a CXXXXC chemokine) that do not fall into either of the major chemokine subfamilies.

MCP-1 (also known as MCAF (abbreviation for macrophage chemotactic and activating factor) or JE) is a CC chemokine produced by monocytes/macrophages, smooth muscle cells, fibroblasts, and vascular endothelial cells and causes cell migration and cell adhesion of monocytes (see for example Valente, A. J., et al., *Biochemistry*, 1988, 27, 4162; Matsushima, K., et al., *J. Exp. Med.*, 1989, 169, 1485; Yoshimura, T., et al., *J. Immunol.*,

1989, 142, 1956; Rollins, B. J., et al., *Proc. Natl. Acad. Sci. USA*, 1988, 85, 3738; Rollins, B. J., et al., *Blood*, 1991, 78, 1112; Jiang, Y., et al., *J. Immunol.*, 1992, 148, 2423; Vaddi, K., et al., *J. Immunol.*, 1994, 153, 4721), memory T lymphocytes (see for example Carr, M. W., et al., *Proc. Natl. Acad. Sci. USA*, 1994, 91, 3652), T lymphocytes (see for example Loetscher, P., et al., *FASEB J.*, 1994, 8, 1055) and natural killer cells (see for example Loetscher, P., et al., *J. Immunol.*, 1996, 156, 322; Allavena, P., et al., *Eur. J. Immunol.*, 1994, 24, 3233), as well as mediating histamine release by basophils (see for example Alam, R., et al., *J. Clin. Invest.*, 1992, 89, 723; Bischoff, S. C., et al., *J. Exp. Med.*, 1992, 175, 1271; Kuna, P., et al., *J. Exp. Med.*, 1992, 175, 489). In addition, high expression of MCP-1 has been reported in diseases where accumulation of monocyte/macrophage and/or T cells is thought to be important in the initiation or progression of diseases, such as atherosclerosis (see for example Hayes, I. M., et al., *Arterioscler. Thromb. Vasc. Biol.*, 1998, 18, 397; Takeya, M., et al., *Hum. Pathol.*, 1993, 24, 534; Yla-Herttuala, S., et al., *Proc. Natl. Acad. Sci. USA*, 1991, 88, 5252; Nelken, N. A., *J. Clin. Invest.*, 1991, 88, 1121), rheumatoid arthritis (see for example Koch, A. E., et al., *J. Clin. Invest.*, 1992, 90, 772; Akahoshi, T., et al., *Arthritis Rheum.*, 1993, 36, 762; Robinson, E., et al., *Clin. Exp. Immunol.*, 101, 398), nephritis (see for example Noris, M., et al., *Lab. Invest.*, 1995, 73, 804; Wada, T., et al., *Kidney Int.*, 1996, 49, 761; Gesualdo, L., et al., *Kidney Int.*, 1997, 51, 155), nephropathy (see for example Saitoh, A., et al., *J. Clin. Lab. Anal.*, 1998, 12, 1; Yokoyama, H., et al., *J. Leukoc. Biol.*, 1998, 63, 493), pulmonary fibrosis, pulmonary sarcoidosis (see for example Sugiyama, Y., et al., *Internal Medicine*, 1997, 36, 856), asthma (see for example Karina, M., et al., *J. Invest. Allergol. Clin. Immunol.*, 1997, 7, 254; Stephane, T. H., *Am. J. Respir. Crit. Care Med.*, 1997, 156, 1377; Sousa, A. R., et al., *Am. J. Respir. Cell Mol. Biol.*, 1994, 10, 142), multiple sclerosis (see for example McManus, C., et al., *J. Neuroimmunol.*, 1998, 86, 20), psoriasis (see for example Gillitzer, R., et al., *J. Invest. Dermatol.*, 1993, 101, 127), inflammatory bowel disease (see for example Grimm, M. C., et al., *J. Leukoc. Biol.*, 1996, 59, 804; Reinecker, H. C., et al., *Gastroenterology*, 1995, 106, 40), myocarditis (see for example Seino, Y., et al., *Cytokine*, 1995, 7, 301), endometriosis (see for example Jolicoeur, C., et al., *Am. J. Pathol.*, 1998, 152, 125), intraperitoneal adhesion (see for example Zeyneloglu, H. B., et al., *Human Reproduction*, 1998, 13, 1194), congestive heart failure (see for example Aurust, P., et al., *Circulation*, 1998, 97, 1136), chronic liver disease (see for example Marra, F., et al., *Am. J. Pathol.*, 1998, 152, 423), viral meningitis (see for example Lahrtz, F., et al., *Eur. J. Immunol.*, 1997, 27, 2484), Kawasaki disease (see for example Wong, M.; et al., *J. Rheumatol.*, 1997, 24, 1179) and sepsis (see for example Salkowski, C. A.; et al., *Infect. Immun.*, 1998, 66, 3569). Furthermore, anti-MCP-1 antibody has been reported to show an inhibitory effect or a therapeutic effect in animal models of rheumatoid arthritis (see for example Schimmer, R. C., et al., *J. Immunol.*, 1998, 160, 1466; Schrier, D. J., *J. Leukoc.*

Biol., 1998, 63, 359; Ogata, H., et al., J. Pathol., 1997, 182, 106), multiple sclerosis (see for example Karpus, W. J., et al., J. Leukoc. Biol., 1997, 62, 681), nephritis (see for example Lloyd, C. M., et al., J. Exp. Med., 1997, 185, 1371; Wada, T., et al., FASEB J., 1996, 10, 1418), Asthma (see for example Gonzalo, J.-A., et al., J. Exp. Med., 1998, 188, 157; Lukacs, N. W., J. Immunol., 1997, 158, 4398), atherosclerosis (see for example Guzman, L. A., et al., Circulation, 1993, 88 (suppl.), I-371), delayed type hypersensitivity (see for example Rand, M. L., et al., Am. J. Pathol., 1996, 148, 855), pulmonary hypertension (see for example Kimura, H., et al., Lab. Invest., 1998, 78, 571), and intraperitoneal adhesion (see for example Zeyneloglu, H. B., et al., Am. J. Obstet. Gynecol., 1998, 179, 438). A peptide antagonist of MCP-1, MCP-1(9-76), has been also reported to inhibit arthritis in the mouse model (see Gong, J.-H., J. Exp. Med., 1997, 186, 131), as well as studies in MCP-1-deficient mice have shown that MCP-1 is essential for monocyte recruitment in vivo (see Lu, B., et al., J. Exp. Med., 1998, 187, 601; Gu, L., et al., Moll. Cell, 1998, 2, 275).

The published literature indicate that chemokines such as MCP-1 and MIP-1 α attract monocytes and lymphocytes to disease sites and mediate their activation and thus are thought to be intimately involved in the initiation, progression and maintenance of diseases deeply involving monocytes and lymphocytes, such as atherosclerosis, restenosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, and sepsis (see for example Rovin, B. H., et al., Am. J. Kidney. Dis., 1998, 31, 1065; Lloyd, C., et al., Curr. Opin. Nephrol. Hypertens., 1998, 7, 281; Conti, P., et al., Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R. M., et al., Trends Neurosci., 1998, 21, 154; MacDermott, R. P., et al., Inflammatory Bowel Diseases, 1998, 4, 54).

The chemokines bind to specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal through the associated trimeric G proteins, resulting in, among other responses, a rapid increase in intracellular calcium concentration, changes in cell shape, increased expression of cellular adhesion molecules, degranulation, and promotion of cell migration.

Genes encoding receptors of specific chemokines have been cloned, and it is now known that these receptors are G protein-coupled seven-transmembrane receptors present on various leukocyte populations. So far, at least five CXC chemokine receptors (CXCR1-CXCR5) and eight CC chemokine receptors (CCR1-CCR8) have been identified. For

example IL-8 is a ligand for CXCR1 and CXCR2, MIP-1 α is that for CCR1 and CCR5, and MCP-1 is that for CCR2A and CCR2B (for reference, see for example, Holmes, W. E., et al., Science 1991, 253, 1278-1280; Murphy P. M., et al., Science, 253, 1280-1283; Neote, K. et al, Cell, 1993, 72, 415-425; Charo, I. F., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 2752-2756; Yamagami, S., et al., Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C., et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494, Power, C. A., et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M., et al., Biochemistry, 1996, 35, 3362-3367; Murphy, P. M., Annual Review of Immunology, 1994, 12, 592-633). It has been reported that lung inflammation and granuloma formation are suppressed in CCR1-deficient mice (see Gao, J.-L., et al., J. Exp. Med., 1997, 185, 1959; Gerard, C., et al., J. Clin. Invest., 1997, 100, 2022), and that recruitment of macrophages and formation of atherosclerotic lesion decreased in CCR2-deficient mice (see Boring, L., et al., Nature, 1998, 394, 894; Kuziel, W. A., et al., Proc. Natl. Acad. Sci., USA, 1997, 94, 12053; Kurihara, T., et al., J. Exp. Med., 1997, 186, 1757; Boring, L., et al., J. Clin. Invest., 1997, 100, 2552).

Accordingly, drugs which inhibit the binding of chemokines such as MCP-1 and/or MIP-1 α to these receptors, e.g., chemokine receptor antagonists, may be useful as pharmaceutical agents which inhibit the action of chemokines such as MCP-1 and/or MIP-1 α on the target cells, but the prior art is silent regarding 3-cycloalkylaminopyrrolidine derivatives having such pharmacological effects. The identification of compounds that modulate the function of CCR2 and/or CCR5 represents an excellent drug design approach to the development of pharmacological agents for the treatment of inflammatory conditions and diseases associated with CCR2 and/or CCR5 activation, such as rheumatoid arthritis, lupus and other inflammatory diseases.

The 3-cycloalkylaminopyrrolidine derivatives of the present invention are also being developed specifically for the treatment of liver fibrosis associated with chronic HCV infection, which results in increased rates of hepatic lobular inflammation and hepatocyte apoptosis. Chronic tissue injury, e.g., due to viral infection, can result in liver disease if the organ is unable to repair itself. Sustained inflammatory responses play a significant role in the development of liver fibrosis that results in scar formation, loss of tissue architecture and liver function (Henderson & Iredale et al 2007). Recruitment and activation of a variety of cell types of the innate and adaptive immune system is a hallmark of disease. Resident and newly recruited monocytic cells, e.g., Kupffer cells and macrophages, are essential regulators of the process. Depletion of monocytes or inhibition of their function has been shown to provide efficacy in preclinical animal model of liver fibrosis (Ide et al 2005; Duffield et al 2005; Imamura et al 2005).

Chemokines and their receptors are critical regulators of migration of hematopoietic cells. Both, CCR2 and its ligand CCL2 (MCP-1), are upregulated in the liver (Asselah et al 2005; Marra 2002) and can regulate the recruitment of monocytes to the liver during acute and chronic liver disease (Karlmark et al 2008). Furthermore, a polymorphism in the CCL2 gene is associated with liver fibrosis (Mühlbauer et al 2003). Patients with the disease-associated allele have increased MCP-1 mRNA levels in the liver and their hepatic stellate cells respond to cytokine stimulation with increased MCP-1 secretion compared to controls.

CCR2 deficiency and transgenic over-expression of dominant negative CCL2 that inhibits receptor stimulation result in reduced diseases in pre-clinical animal models of pulmonary and hepatic fibrosis (Moore et al 2001; Imamura et al 2005).

The present invention provides a long felt need in the field of chemokine receptor modulators and antagonists.

OBJECTS OF THE INVENTION

With the foregoing in mind, it is an important object of the present invention to provide chemokine receptor antagonists and chemokine receptor modulators for treating hepatitis C and liver fibrosis.

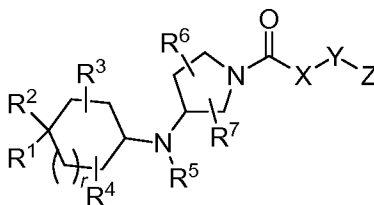
Another main object of the invention is to provide chemokine receptor antagonists and their use as medicinal agents.

A further object of the present invention to provide a treatment for hepatitis C and liver fibrosis by administration of a therapeutically effective amount of N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

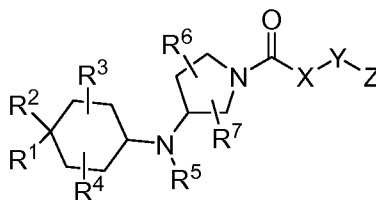
Other objects and embodiments of the present invention will be discussed below. However, it is important to note that many additional embodiments of the present invention not described in this specification may nevertheless fall within the spirit and scope of the present invention and/or the claims.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of the formula I and II:



I



II

its enantiomers, diastereomers, enantiomerically enriched mixtures, racemic mixtures thereof, prodrugs, crystalline forms, non-crystalline forms, amorphous forms thereof, solvates thereof, metabolites thereof, and pharmaceutically acceptable salts, wherein:

X is selected from the group consisting of a bond, aryl, mono or poly substituted aryl, heterocycle, mono or poly substituted heterocycle, heteroaryl, mono or poly substituted heteroaryl, carbocycle, mono or poly substituted carbocycle, $(CR^8R^9)_n$ wherein $n=0-5$;

Y is a bond, or is selected from the group consisting of oxygen, sulfur, nitrogen, amide bond, thioamide bond, sulfonamide, ketone, $-CHOH-$, $-CHO-$ alkyl-, oxime, or a urea;

Z is selected from the group consisting of carbocycle, aryl, heterocycle or heteroaryl with 0-3 R^{10} substituents wherein R^{10} is independently selected from the group consisting of: halogen, alkyl, alkenyl, alkynyl, alkoxy, cyclic alkoxy, heterocyclic alkoxy, alkoxyalkyl, cyclic alkoxyalkyl, heterocyclic alkoxyalkyl, alkylthioalkyl, cyclic alkylthioalkyl, heterocyclic alkylthioalkyl, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, mono- or di-substituted amino, mono- or di-substituted aminoalkyl, carboxyl, esterified carboxyl, carboxamido, mono- or di-substituted carboxamido, carbamate, mono- or di-substituted carbamate, sulfonamide, mono- or di-substituted sulfonamide, alkylsulfonyl, cyclic alkylsulfonyl, heterocyclic alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, cyclic alkylcarbonyl, heterocyclic alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, thiocarboxamido, cyano, and R^{10a} -carbocycle, R^{10a} -heterocycle, R^{10a} -aryl or R^{10a} -heteroaryl wherein R^{10a} is H, halogen, OH, amino, mono- or di-substituted amino, mono-, di- or tri-haloalkyl, alkoxy, mono-, di- or tri-haloalkoxy, carboxamide, sulfonamide, carbamate, urea or cyano;

R^1 is independently selected from the group consisting of: carbocycle, heterocycle, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, arylalkynyl, heteroarylalkynyl, arylaminocarbonyl, heteroarylaminocarbonyl, arylcarboxamido, heteroarylcarboxamido, arylureido, heteroarylureido, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, arylamino or heteroarylamino and wherein said carbocycle, heterocycle, aryl or heteroaryl may be substituted with 0-3 R^{1a} substituents wherein R^{1a} is independently selected from the group consisting of: halogen, alkyl, alkenyl, alkynyl, alkoxy, cyclic alkoxy, heterocyclic alkoxy, alkoxyalkyl, cyclic alkoxyalkyl, heterocyclic alkoxyalkyl, alkylthioalkyl, cyclic alkylthioalkyl, heterocyclic alkylthioalkyl, hydroxyalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, mono- or di-substituted amino, mono- or di-

substituted aminoalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, cyclic aminocarbonyl, heterocyclic aminocarbonyl, aminosulfonyl, mono- or di-substituted aminosulfonyl, cyclic aminosulfonyl, heterocyclic aminosulfonyl, alkylcarbonyl, cyclic alkylcarbonyl, heterocyclic alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkylsulfonyl, cyclic alkylsulfonyl, heterocyclic alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, carboxylic acid, esterified carboxylic acid, alkylcarbonylamino, cyclic alkylcarbonylamino, heterocyclic alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, cyano, arylalkyl, heteroarylalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, carbamate, mono- or di-substituted carbamate, R^{1b} -carbocycle, R^{1b} -heterocycle, R^{1b} -aryl or R^{1b} -heteroaryl wherein R^{1b} is H, halogen, OH, amino, mono- or di-substituted amino, mono-, di- or tri-haloalkyl, alkoxy, mono-, di- or tri-haloalkoxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, carboxamide, sulfonamide, carbamate, urea or cyano;

R^2 is independently selected from the group consisting of: H, amino, mono- or di-substituted amino, OH, carboxyl, esterified carboxyl, carboxamide, N-monosubstituted carboxamide, and N,N-disubstituted carboxamide, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, thioalkyl, mono-, di- or trihaloalkyl, halogen, aryl or heteroaryl;

optionally R^1 and R^2 can be bonded to each other to form a spirocycle;

R^3 and R^4 , are independently selected from the group consisting of: H, amino, OH, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy and thioalkyl;

optionally R^3 and R^4 can occupy multiple positions in the cycloalkyl ring;

optionally R^1 and R^3 can be cyclized to form a carbocycle or heterocycle having 0-3 R^a substituents wherein R^a is selected from the group consisting of halogen, alkyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, carboxyl, esterified carboxyl, carboxamido, thiocarboxamido, cyano, mono, disubstituted, or polysubstituted aryl and heterocycle optionally containing 0-3 R^b wherein R^b is selected from the group consisting of halogen, alkyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, carboxyl, esterified carboxyl, carboxamido, thiocarboxamido and cyano;

optionally R^3 and R^4 can be cyclized to form a bridged bicyclic system having a methylene group or an ethylene group or a heteroatom selected from the group consisting of N, O and S;

optionally R^3 and R^4 can be cyclized to form a spirocycle;

R^5 is independently selected from the group consisting of hydrogen, alkyl, formyl and when R^5 is alkyl the nitrogen may optionally be in the N-oxide form;

R^6 and R^7 are each independently selected from the group consisting of H, C_1 - C_{10} alkyl, optionally C_1 - C_{10} alkyl can be interrupted by oxygen, nitrogen or sulfur, carbocycle,

heterocycle, alkoxy, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, cycloalkoxy, heterocycloalkoxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, aryloxyalkyl, heteroaryloxyalkyl, arylalkoxyalkyl, heteroarylalkoxyalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyloxyalkyl, heterocycloalkyloxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, arylaminoalkyl, heteroarylaminoalkyl, alkylthioalkyl, cycloalkyl-thioalkyl, heterocycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkylsulfonylalkyl, cycloalkylsulfonylalkyl, heterocycloalkylsulfonylalkyl, arylsulfonylalkyl, heteroaryl-sulfonylalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, aminocarbonylalkyl, mono- or di-substituted aminocarbonylalkyl, alkylcarbonylalkyl, cycloalkylcarbonylalkyl, heterocycloalkylcarbonylalkyl, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl, arylsulfonylaminoalkyl, heteroarylsulfonylaminoalkyl;

optionally, R^6 and R^7 can be cyclized to form a carbocycle or heterocycle, or a spirocycle or spiroheterocycle;

R^8 and R^9 are independently selected from the group consisting of H, OH, amino, alkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, alkoxy, alkenyl, alkynyl, alkoxyalkyl, mono- or di-substituted amino, a carbocycle or a heterocycle;

optionally R^8 and R^9 can be cyclized to form a 3-7 membered carbocycle or heterocycle; and

$r=0-3$.

The instant invention also relates to pharmaceutical compositions which comprise anti-inflammatory and/or immunomodulatory compounds of formula I and II as shown above, that act via antagonism of the CCR2 receptor, (also known as the MCP-1 receptor), therefore inhibiting the Monocyte Chemoattractant Protein-1 (MCP-1).

The instant invention is also directed to pharmaceutical compositions which comprise anti-inflammatory and/or immunomodulatory compounds of formula I and II, as shown above, that act via antagonism of the CCR5 receptor (also known as the MCP-1 receptor), therefore inhibiting the Monocyte Chemoattractant Protein-1 (MCP-1).

The present invention is also directed to compounds of formula I and II which are modulators of CCR2 chemokine receptor function and are useful in the prevention or treatment of inflammatory conditions and diseases such as rheumatoid arthritis, allergic diseases, psoriasis, atopic dermatitis, lupus and asthma.

The present invention also describes compounds of formula I and II which are modulators of CCR5 chemokine receptor function and are useful in the prevention or treatment of inflammatory conditions and diseases such as rheumatoid arthritis, allergic diseases, psoriasis, atopic dermatitis, lupus and asthma.

The invention further relates to a method for modulation of chemokine receptor activity in a mammal comprising the administration of an effective amount of a compound of formula I or II.

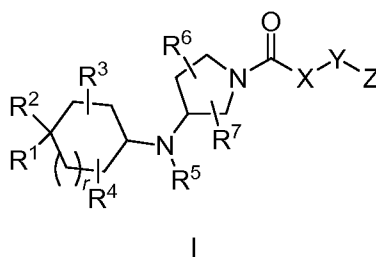
The invention is also provides pharmaceutical compositions comprising compounds selected from the group of formula I and II, and the use of these compounds and compositions in the prevention or treatment of diseases in which CCR2 chemokine receptors are involved.

The invention further provides pharmaceutical compositions comprising compounds selected from the group of formula I and II, and the use of these compounds and compositions in the prevention or treatment of diseases in which CCR5 chemokine receptors are involved.

The invention additionally provides a method for the treatment of liver fibrosis, inflammation, rheumatoid arthritis, lupus, systemic lupus erythematosus, atherosclerosis, restenosis, immune disorders, and transplant rejection in a mammal in need thereof comprising administering to such mammal a therapeutically effective amount of a pharmaceutical composition containing a compound according to formula I and II in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The instant invention is directed to a compound of the formula I:



its enantiomers, diastereomers, enantiomerically enriched mixtures, racemic mixtures thereof, prodrugs, crystalline forms, non-crystalline forms, amorphous forms thereof, solvates thereof, metabolites thereof, and pharmaceutically acceptable salts, wherein:

X is selected from the group consisting of a bond, aryl, mono or poly substituted aryl, heterocycle, mono or poly substituted heterocycle, heteroaryl, mono or poly substituted heteroaryl, carbocycle, mono or poly substituted carbocycle, $(CR^8R^9)_n$ wherein $n=0-5$;

Y is a bond, or is selected from the group consisting of oxygen, sulfur, nitrogen, amide bond, thioamide bond, sulfonamide, ketone, $-CHOH-$, $-CHO-$ alkyl-, oxime, or a urea;

Z is selected from the group consisting of carbocycle, aryl, heterocycle or heteroaryl with 0-3 R^{10} substituents wherein R^{10} is independently selected from the group consisting of: halogen, alkyl, alkenyl, alkynyl, alkoxy, cyclic alkoxy, heterocyclic alkoxy, alkoxyalkyl, cyclic

alkoxyalkyl, heterocyclic alkoxyalkyl, alkylthioalkyl, cyclic alkylthioalkyl, heterocyclic alkylthioalkyl, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, mono- or di-substituted amino, mono- or di-substituted aminoalkyl, carboxyl, esterified carboxyl, carboxamido, mono- or di-substituted carboxamido, carbamate, mono- or di-substituted carbamate, sulfonamide, mono- or di-substituted sulfonamide, alkylsulfonyl, cyclic alkylsulfonyl, heterocyclic alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, cyclic alkylcarbonyl, heterocyclic alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, thiocarboxamido, cyano, and R^{10a} -carbocycle, R^{10a} -heterocycle, R^{10a} -aryl or R^{10a} -heteroaryl wherein R^{10a} is H, halogen, OH, amino, mono- or di-substituted amino, mono-, di- or tri-haloalkyl, alkoxy, mono-, di- or tri-haloalkoxy, carboxamide, sulfonamide, carbamate, urea or cyano;

R^1 is independently selected from the group consisting of: carbocycle, heterocycle, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, arylalkynyl, heteroarylalkynyl, arylaminocarbonyl, heteroarylaminocarbonyl, arylcarboxamido, heteroarylcarboxamido, arylureido, heteroarylureido, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, arylamino or heteroarylamino and wherein said carbocycle, heterocycle, aryl, or heteroaryl may be substituted with 0-3 R^{1a} substituents wherein R^{1a} is independently selected from the group consisting of: halogen, alkyl, alkenyl, alkynyl, alkoxy, cyclic alkoxy, heterocyclic alkoxy, alkoxyalkyl, cyclic alkoxyalkyl, heterocyclic alkoxyalkyl, alkylthioalkyl, cyclic alkylthioalkyl, heterocyclic alkylthioalkyl, hydroxyalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, mono- or di-substituted amino, mono- or di-substituted aminoalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, cyclic aminocarbonyl, heterocyclic aminocarbonyl, aminosulfonyl, mono- or di-substituted aminosulfonyl, cyclic aminosulfonyl, heterocyclic aminosulfonyl, alkylcarbonyl, cyclic alkylcarbonyl, heterocyclic alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkylsulfonyl, cyclic alkylsulfonyl, heterocyclic alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, carboxylic acid, esterified carboxylic acid, alkylcarbonylamino, cyclic alkylcarbonylamino, heterocyclic alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, cyano, arylalkyl, heteroarylalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, carbamate, mono- or di-substituted carbamate, R^{1b} -carbocycle, R^{1b} -heterocycle, R^{1b} -aryl or R^{1b} -heteroaryl wherein R^{1b} is H, halogen, OH, amino, mono- or di-substituted amino, mono-, di- or tri-haloalkyl, alkoxy, mono-, di- or tri-haloalkoxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, carboxamide, sulfonamide, carbamate, urea or cyano;

R^2 is independently selected from the group consisting of: H, amino, mono- or di-substituted amino, OH, carboxyl, esterified carboxyl, carboxamide, N-monosubstituted carboxamide, and N,N-disubstituted carboxamide, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, halogen, aryl or heteroaryl;

optionally R^1 and R^2 can be bonded to each other to form a spirocycle;

R^3 and R^4 , are independently selected from the group consisting of: H, amino, OH, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy and thioalkyl;

optionally R^3 and R^4 can occupy multiple positions in the cycloalkyl ring;

optionally R^1 and R^3 can be cyclized to form a carbocycle or heterocycle having 0-3 R^a substituents wherein R^a is selected from the group consisting of halogen, alkyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, carboxyl, esterified carboxyl, carboxamido, thiocarboxamido, cyano, mono, disubstituted, or polysubstituted aryl and heterocycle optionally containing 0-3 R^b wherein R^b is selected from the group consisting of halogen, alkyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, carboxyl, esterified carboxyl, carboxamido, thiocarboxamido and cyano;

optionally R^3 and R^4 can be cyclized to form a bridged bicyclic system having a methylene group or an ethylene group or a heteroatom selected from the group consisting of N, O and S;

optionally R^3 and R^4 can be cyclized to form a spirocycle;

R^5 is independently selected from the group consisting of hydrogen, alkyl, formyl and when R^5 is alkyl the nitrogen may optionally be in the N-oxide form;

R^6 and R^7 are each independently selected from the group consisting of H, C_1 - C_{10} alkyl, optionally C_1 - C_{10} alkyl can be interrupted by oxygen, nitrogen or sulfur, carbocycle, heterocycle, alkoxy, mono-, di- or trihaloalkyl, mono-, di- or trihaloalkoxy, cycloalkoxy, heterocycloalkoxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, aryloxyalkyl, heteroaryloxyalkyl, arylalkoxyalkyl, heteroarylalkoxyalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyloxyalkyl, heterocycloalkyloxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, arylaminoalkyl, heteroarylaminoalkyl, alkylthioalkyl, cycloalkylthioalkyl, heterocycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkylsulfonylalkyl, cycloalkylsulfonylalkyl, heterocycloalkylsulfonylalkyl, arylsulfonylalkyl, heteroarylsulfonylalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, aminocarbonylalkyl, mono- or di-substituted aminocarbonylalkyl, alkylcarbonylalkyl, cycloalkylcarbonylalkyl, heterocycloalkylcarbonylalkyl, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl, arylsulfonylaminoalkyl, heteroarylsulfonylaminoalkyl;

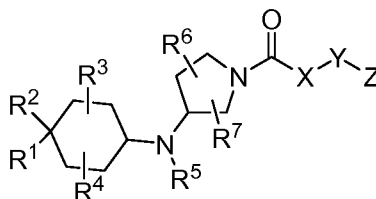
optionally, R^6 and R^7 can be cyclized to form a carbocycle or heterocycle, or a spirocycle or spiroheterocycle;

R^8 and R^9 are independently selected from the group consisting of H, OH, amino, alkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, alkoxy, alkenyl, alkynyl, alkoxyalkyl, mono- or di-substituted amino, a carbocycle or a heterocycle;

optionally R^8 and R^9 can be cyclized to form a 3-7 membered carbocycle or heterocycle; and

$r=0-3$.

In a more preferred embodiment, the invention relates to a compound of the formula II:



II

its enantiomers, diastereomers, enantiomerically enriched mixtures, racemic mixtures thereof, prodrugs, crystalline forms, non-crystalline forms, amorphous forms thereof, solvates thereof, metabolites thereof, and pharmaceutically acceptable salts, wherein:

X is selected from the group consisting of a bond, aryl, mono or poly substituted aryl, heterocycle, mono or poly substituted heterocycle, heteroaryl, mono or poly substituted heteroaryl, carbocycle, mono or poly substituted carbocycle, $(CR^8R^9)_n$ wherein $n=0-5$;

Y is a bond, or is selected from the group consisting of oxygen, sulfur, nitrogen, amide bond, thioamide bond, sulfonamide, ketone, $-CHOH-$, $-CHO-$ alkyl-, oxime, or a urea;

Z is selected from the group consisting of carbocycle, aryl, heterocycle or heteroaryl with 0-3 R^{10} substituents wherein R^{10} is independently selected from the group consisting of: halogen, alkyl, alkenyl, alkynyl, alkoxy, cyclic alkoxy, heterocyclic alkoxy, alkoxyalkyl, cyclic alkoxyalkyl, heterocyclic alkoxyalkyl, alkylthioalkyl, cyclic alkylthioalkyl, heterocyclic alkylthioalkyl, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, mono- or di-substituted amino, mono- or di-substituted aminoalkyl, carboxyl, esterified carboxyl, carboxamido, mono- or di-substituted carboxamido, carbamate, mono- or di-substituted carbamate, sulfonamide, mono- or di-substituted sulfonamide, alkylsulfonyl, cyclic alkylsulfonyl, heterocyclic alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, cyclic alkylcarbonyl, heterocyclic alkylsulfonyl, arylcarbonyl, heteroarylcarbonyl, thiocarboxamido, cyano, and R^{10a} -carbocycle, R^{10a} -heterocycle, R^{10a} -aryl or R^{10a} -heteroaryl wherein R^{10a} is H, halogen, OH, amino, mono- or di-substituted amino, mono-, di- or tri-haloalkyl, alkoxy, mono-, di- or tri-haloalkoxy, carboxamide, sulfonamide, carbamate, urea or cyano;

R^1 is independently selected from the group consisting of: carbocycle, heterocycle, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, arylalkynyl, heteroarylalkynyl, arylaminocarbonyl, heteroarylaminocarbonyl, arylcarboxamido, heteroarylcarboxamido, arylureido, heteroarylureido, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, arylamino or heteroarylamino and wherein said carbocycle, heterocycle,

aryl, or heteroaryl may be substituted with 0-3 R^{1a} substituents wherein R^{1a} is independently selected from the group consisting of: halogen, alkyl, alkenyl, alkynyl, alkoxy, cyclic alkoxy, heterocyclic alkoxy, alkoxyalkyl, cyclic alkoxyalkyl, heterocyclic alkoxyalkyl, alkylthioalkyl, cyclic alkylthioalkyl, heterocyclic alkylthioalkyl, hydroxyalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, mono- or di-substituted amino, mono- or di-substituted aminoalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, cyclic aminocarbonyl, heterocyclic aminocarbonyl, aminosulfonyl, mono- or di-substituted aminosulfonyl, cyclic aminosulfonyl, heterocyclic aminosulfonyl, alkylcarbonyl, cyclic alkylcarbonyl, heterocyclic alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkylsulfonyl, cyclic alkylsulfonyl, heterocyclic alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, carboxylic acid, esterified carboxylic acid, alkylcarbonylamino, cyclic alkylcarbonylamino, heterocyclic alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, cyano, arylalkyl, heteroarylalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, carbamate, mono- or di-substituted carbamate, R^{1b} -carbocycle, R^{1b} -heterocycle, R^{1b} -aryl or R^{1b} -heteroaryl wherein R^{1b} is H, halogen, OH, amino, mono- or di-substituted amino, mono-, di- or tri-haloalkyl, alkoxy, mono-, di- or tri-haloalkoxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, carboxamide, sulfonamide, carbamate, urea or cyano;

R^2 is independently selected from the group consisting of: H, amino, mono- or di-substituted amino, OH, carboxyl, esterified carboxyl, carboxamide, N-monosubstituted carboxamide, and N,N-disubstituted carboxamide, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, halogen, aryl or heteroaryl;

optionally R^1 and R^2 can be bonded to each other to form a spirocycle;

R^3 and R^4 , are independently selected from the group consisting of: H, amino, OH, alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy and thioalkyl;

optionally R^3 and R^4 can occupy multiple positions in the cycloalkyl ring;

optionally R^1 and R^3 can be cyclized to form a carbocycle or heterocycle having 0-3 R^a substituents wherein R^a is selected from the group consisting of halogen, alkyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, carboxyl, esterified carboxyl, carboxamido, thiocarboxamido, cyano, mono, disubstituted, or polysubstituted aryl and heterocycle optionally containing 0-3 R^b wherein R^b is selected from the group consisting of halogen, alkyl, alkoxy, thioalkyl, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, nitro, amino, carboxyl, esterified carboxyl, carboxamido, thiocarboxamido and cyano;

optionally R^3 and R^4 can be cyclized to form a bridged bicyclic system having a methylene group or an ethylene group or a heteroatom selected from the group consisting of N, O and S;

optionally R^3 and R^4 can be cyclized to form a spirocycle;

R^5 is independently selected from the group consisting of hydrogen, alkyl, formyl and when R^5 is alkyl the nitrogen may optionally be in the N-oxide form;

R^6 and R^7 are each independently selected from the group consisting of H, C_1 - C_{10} alkyl, optionally C_1 - C_{10} alkyl can be interrupted by oxygen, nitrogen or sulfur, carbocycle, heterocycle, alkoxy, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, cycloalkoxy, heterocycloalkoxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, aryloxyalkyl, heteroaryloxyalkyl, arylalkoxyalkyl, heteroarylalkoxyalkyl; aryl, heteroaryl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyloxyalkyl, heterocycloalkyloxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, arylaminoalkyl, heteroarylaminoalkyl, alkylthioalkyl, cycloalkylthioalkyl, heterocycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkylsulfonylalkyl, cycloalkylsulfonylalkyl, heterocycloalkylsulfonylalkyl, arylsulfonylalkyl, heteroarylsulfonylalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, aminocarbonylalkyl, mono- or di-substituted aminocarbonylalkyl, alkylcarbonylalkyl, cycloalkylcarbonylalkyl, heterocycloalkylcarbonylalkyl, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl, arylsulfonylaminoalkyl, heteroarylsulfonylaminoalkyl;

optionally, R^6 and R^7 can be cyclized to form a carbocycle or heterocycle, or a spirocycle or spiroheterocycle;

R^8 and R^9 are independently selected from the group consisting of H, OH, amino, alkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, alkoxy, alkenyl, alkynyl, alkoxyalkyl, mono- or di-substituted amino, a carbocycle or a heterocycle; and

optionally R^8 and R^9 can be cyclized to form a 3-7 membered carbocycle or heterocycle.

As defined above, with respect to compounds of the formula I and II, X is selected from the group consisting of aryl, mono or poly substituted aryl, heterocycle, heteroaryl, mono or poly substituted heteroaryl, carbocycle, mono or poly substituted carbocycle $(CR^8R^9)_n$ wherein $n=0-5$. The term aryl groups is intended to include aromatic carbocyclic groups such as phenyl, biphenyl, indenyl, naphthyl and fused aromatic to heterocyclic such as benzothienyl, benzofuranyl, indolyl, quinolyl, benzothiazole, benzoxazole, benzimidazole, isoquinolyl, isoindolyl, benzotriazole, indazole, and acridinyl. The term heteroaryl is intended to include aromatic rings containing from 3 to 20, preferably from 4 to 10 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur, phosphorus or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinoxalyl, benzthiazolyl, benzoxazolyl, benzothienyl or benzofuryl. Heterocycles are non-aromatic carbocyclic rings which include one or more

heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered. Examples include tetrahydrofuranyl, tetrahydrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, pyrane, dioxane and thiazolidinyl. In the instances where X and Z have the same meaning, then the identical definitions apply to their definitions. Additionally, when the heteroaryl or heterocyclic groups are nitrogen containing heterocycles, the nitrogen may be modified to exist in the form of the $N \rightarrow O^+$ (N oxides) and such oxides are intended to be included within the scope of the instant invention. In the cases of sulfur containing heterocycles, the sulfur oxides are also intended to be included within the scope of the present invention.

The substituents in the aryl groups, arylalkyl groups, heteroaryl groups, heteroarylalkyl groups and heterocyclic groups of the invention are selected from the group consisting of halogen, alkyl, alkoxy, monohaloalkoxy, dihaloalkoxy, trihaloalkoxy, thioalkyl and monohaloalkyl, dihaloalkyl, trihaloalkyl, nitro, amino, carboxyl, esterified carboxyl, carboxamide, thiocarboxamido and cyano. More in particular the substituents can also be selected from the group consisting of trifluoromethyl, C_{1-4} alkyl, halo, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-5} alkoxy, C_{1-5} alkanoyl, C_{1-5} alkanoyloxy, C_{1-5} alkylamino, di(C_{1-5} alkyl)-amino, C_{1-5} alkanoylamino, nitro, carboxy, carbamoyl, C_{1-5} alkoxycarbonyl, thiol, C_{1-5} , sulphon-amido, carbamoyl C_{1-5} alkyl, N-(C_{1-5} alkyl)carbamoyl C_{1-5} alkyl, N-(C_{1-5} alkyl)₂ carbamoyl- C_{1-5} alkyl, hydroxy C_{1-5} alkyl or C_{1-5} alkoxy C_{1-4} alkyl. The terms halo or halogen, by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Similarly, terms such as haloalkyl, are meant to include monohaloalkyl and polyhaloalkyl. For example, the term halo(C_1 - C_4)alkyl is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term alkyl when used either alone or as a suffix includes straight chain and branched structures such as primary alkyl groups, secondary alkyl groups and tertiary alkyl groups. These groups may contain up to 15, preferably up to 8 and more preferably up to 4 carbon atoms. Similarly the terms alkenyl and alkynyl refer to unsaturated straight or branched structures containing for example from 2 to 12, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. In the present application, cycloalkyl is also intended to include adamantyl groups and other bridge

compounds. The terms alkoxy, alkylamino and alkylthio (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Therefore, terms such as alkoxy and thioalkyl comprise alkyl moieties as defined above, attached to the appropriate functionality.

Other suitable substituents which can be used in the many carbon rings of the present invention such as cycloaliphatic, aromatic, non-aromatic heterocyclic ring or benzyl group include, for example, -OH, halogen (-Br, -Cl, -I and -F) -O(aliphatic, substituted aliphatic, benzyl, substituted benzyl, phenyl, substituted phenyl, aromatic or substituted aromatic group), -CN, -NO₂, -COOH, -NH₂, -NH(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, phenyl, substituted phenyl, aromatic or substituted aromatic group), -N(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, phenyl, substituted phenyl, aromatic or substituted aromatic group)₂, -COO(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, phenyl, substituted phenyl, aromatic or substituted aromatic group), -CONH₂, -CONH(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, phenyl, substituted phenyl, aromatic or substituted aromatic group)), -SH, -S(aliphatic, substituted aliphatic, benzyl, substituted benzyl, phenyl, substituted phenyl, aromatic or substituted aromatic group) and -NH—C(=NH)—NH₂. A substituted non-aromatic heterocyclic ring, benzylic group or aromatic group can also have an aliphatic or substituted aliphatic group as a substituent. A substituted alkyl or aliphatic group can also have a non-aromatic heterocyclic ring, benzyl, substituted benzyl, aromatic or substituted aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent.

The carbocycle substituent as defined by R₁ is intended to include cycloalkyl of 3-10 carbon atoms, and bicyclic and multicyclic bridge systems such as norbornanyl, adamantyl and bicyclo[2.2.2]octyl. The carbocycle substituent as defined in R¹ may also be further substituted with a heterocycle or heteroaryl ring such as pyridyl, pyrrolidinyl, and all those defined under X above.

Specific examples of R¹ substituents includes phenyl, pyridin-2-yl, 4-methylphenyl, 3-methyl-phenyl, 2-methylphenyl, 4-bromophenyl, 3-bromophenyl, 4-chlorophenyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 3-pyridyl, 4-pyridyl, 2-methoxy-5-pyridyl, 2-ethoxy-5-pyridyl, 3,4-methylenedioxyphenyl, 4-fluorophenyl, 3-trifluoromethyl-1H-pyrazol-1-yl, 3-fluorophenyl, 4-methoxyphenyl, 3-methoxyphenyl, pyridin-4-yl, pyridin-3-yl, 5-methylpyridin-2-yl, 6-methylpyridin-2-yl, quinolin-4-yl, 3-methyl-1H-pyrazol-1-yl, 3,5-dimethyl-1H-pyrazol-1-yl, 4-

trifluoromethylphenyl, 3-trifluoromethylphenyl, 3,4-methylene-dioxyphenyl, 4-cyanophenyl, 4-(methylaminocarbonyl)phenyl, 1-oxidopyridin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 4-methylpyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methylpyridin-2-yl, 6-methoxypyridin-2-yl, 6-methoxypyridin-3-yl, 6-methylpyridin-3-yl, 6-ethylpyridin-3-yl, 6-isopropylpyridin-3-yl, 6-cyclopropylpyridin-3-yl, 1-oxidopyridin-3-yl, 1-oxidopyridin-2-yl, 3-cyanophenyl, 3-(methylaminocarbonyl)-phenyl, 4-(morpholin-4-ylcarbonyl)-phenyl, 5-(morpholin-4-ylcarbonyl)pyridin-2-yl, 6-(morpholin-4-ylcarbonyl)pyridin-3-yl, 4-(4-methylpiperazin-1-ylcarbonyl)phenyl, 6-(azetin-1-yl)pyridin-3-yl, 5-cyanopyridin-2-yl, 6-cyanopyridin-3-yl, 5-(methoxy-methyl)pyridin-2-yl, 5-(1-hydroxy-1-methylethyl)pyridin-2-yl, 5-dimethylaminomethyl, 4-ethylaminocarbonylphenyl, 4-isopropylaminocarbonylphenyl, 4-*tert*-butylamino-carbonylphenyl, 4-dimethylaminocarbonyl-phenyl, 4-(azetidin-1-yl)carbonylphenyl, 4-(pyrrolidin-1-yl)carbonylphenyl, 4-(morpholin-4-yl)carbonylphenyl, 4-(dimethyl-aminocarbonyl)-2-methylphenyl, 2-methyl-4-(methylamino-carbonyl)phenyl, 3-methyl-4-(methylaminocarbonyl)phenyl, 4-(dimethylaminocarbonyl)-3-methylphenyl, 3-methyl-4-(pyrrolidin-1-ylcarbonyl)phenyl, 4-(dimethylaminocarbonyl)-3-fluorophenyl, 4-[(2,2,2-trifluoroethyl)aminocarbonyl]phenyl, 3-fluoro-4-methylaminocarbonyl-phenyl, 4-ethylaminocarbonyl-3-fluorophenyl, 3-methylaminocarbonylphenyl, 3-dimethylaminocarbonylphenyl, 5-dimethylaminocarbonyl-2-methoxyphenyl, 2-methoxy-5-methylaminocarbonylphenyl, 3-(methylaminocarbonylamino)phenyl, 6-(morpholin-4-yl)-pyridin-3-yl, 6-dimethylaminopyridin-3-yl, 6-isopropylaminopyrid-3-yl, 6-(pyrrolidin-1-yl)pyridin-3-yl, 6-cyclopropylaminopyridin-3-yl, 6-ethoxypyridin-3-yl, 6-(2-fluoroethoxy)pyridin-3-yl, 6-(2,2-difluoroethoxy)pyridin-3-yl, 6-(2,2,2-trifluoroethoxy)-pyridin-3-yl, 4-iodophenyl, 5-(pyrrolidin-1-ylcarbonyl)-2-pyridyl, 5-(morpholin-4-yl-carbonyl)-2-pyridyl, 5-dimethylaminocarbonyl-2-pyridyl, 4-methylaminocarbonyl-aminophenyl, 6-(1-hydroxy-1-methylethyl)pyridin-3-yl, 4-(1-hydroxy-1-methylethyl)-phenyl, 4-(methoxymethyl)phenyl, 3-fluoro-4-(methoxymethyl)phenyl, 4-(dimethyl-amino)phenyl, 4-(dimethylamino)-3-fluorophenyl, 1H-indazol-5-yl, 1-methyl-1H-indazol-5-yl, 2-methyl-1H-indazol-5-yl, 1,3-thiazol-2-yl, 5-ethyl-1,3-thiazol-2-yl, 5-(methylaminocarbonyl)-1,3-thiazol-2-yl, 1,3-thiazole-5-yl, 2-(methoxycarbonylamino)-1,3-thiazol-5-yl, 2-isopropyl-1,3-thiazol-5-yl, 5-(pyridin-3-yl)-1,3-thiazol-2-yl, 5-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl, 5-aminocarbonyl-1,3-thiazol-2-yl, 5-dimethylaminocarbonyl-1,3-thiazol-2-yl, 5-(pyrrolidin-1-ylcarbonyl)-1,3-thiazol-2-yl, 5-allyl-1,3-thiazol-2-yl, 5-propyl-1,3-thiazol-2-yl, 5-ethylaminocarbonyl-1,3-thiazol-2-yl, 5-phenyl-1,3-thiazol-2-yl, 5-methyl-1,3-thiazol-2-yl, 5-hydroxymethyl-1,3-thiazol-2-yl, 5-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl, 5-methoxymethyl-1,3-thiazol-2-yl, 5-(2-pyridyl)-1,3-thiazol-2-yl, 2-(pyrrolidin-1-yl)-1,3-thiazol-4-yl, 2-(morpholin-4-yl)-1,3-thiazol-4-yl, 2-methyl-1,3-thiazol-5-yl, 2-(1-hydroxy-1-methylethyl)-1,3-thiazol-5-yl, 2-(pyrrolidin-1-yl)-1,3-thiazol-5-yl, 2-ethoxy-1,3-thiazol-5-yl, 2-ethyl-1,3-thiazol-5-yl, 2-(pyrrolidin-1-ylmethyl)-1,3-thiazol-5-yl, 2-(morpholin-4-yl)-1,3-thiazol-5-yl, 2-methoxy-

methyl-1,3-thiazol-5-yl, 2-isobutyl-1,3-thiazol-5-yl, 2-ethylaminocarbonyl-1,3-thiazol-5-yl, 2-(pyrrolidin-1-ylcarbonyl)-1,3-thiazol-5-yl, 2-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl, 2-(3-pyridyl)-1,3-thiazol-5-yl, 2-(2-pyridyl)-1,3-thiazol-5-yl, 4-methyl-1,3-thiazol-2-yl, 1,3-benzothiazol-2-yl, pyrimidin-5-yl, pyrimidin-2-yl, pyridazin-4-yl, pyridazin-3-yl, pyrazin-2-yl, 2-methoxypyrimidin-5-yl, 2-ethoxypyrimidin-5-yl, 2-(2-fluoroethoxy)pyrimidin-5-yl, 2-methylpyrimidin-5-yl, 2-ethylpyrimidin-5-yl, 2-isopropylpyrimidin-5-yl, 2-cyclopropylpyrimidin-5-yl, pyrimidin-4-yl, 4-(pyrimidin-5-yl)phenyl, 4-(1,3-oxazol-2-yl)phenyl, 4-(1H-imidazol-1-yl)phenyl, 4-(morpholin-4-yl)phenyl, 5-(pyrazin-2-yl)pyridin-2-yl, 4-(1-methyl-1H-imidazol-5-yl)phenyl, 4-(4,6-dimethylpyrimidin-5-yl)phenyl, 6-bromopyridin-3-yl, 5-bromopyridin-2-yl, 4'-(methylsulfonyl)biphenyl-4-yl, 3'-(methylsulfonyl)biphenyl-4-yl, 3'-(methoxy-carbonyl)-biphenyl-4-yl, 4-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl, 4'-(dimethyl-amino)-biphenyl-4-yl, 4-(pyridin-3-yl)phenyl, 4-(1H-pyrazol-4-yl)phenyl, 4-(3,3'-bipyridin-6-yl, 4-(3,4'-bipyridin-6-yl, 5-(3-acetylphenyl)pyridin-2-yl, 5-[3-(dimethyl-amino)phenyl]pyridin-2-yl, 5-[3-(trifluoromethyl)phenyl]pyridin-2-yl, 5-[4-(methyl-sulfonyl)phenyl]pyridin-2-yl, 5-(4-methoxy-phenyl)pyridin-2-yl, 5-(3-methoxy-phenyl)-pyridin-2-yl, 5-[3-(aminocarbonyl)-phenyl]pyridin-2-yl, 5-(4-fluoro-phenyl)pyridin-2-yl, 5-(3,4-difluorophenyl)pyridin-2-yl, 5-(3,5-dimethylisoxazol-4-yl)pyridin-2-yl, 5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 5-(1H-pyrazol-4-yl)pyridin-2-yl, 5-(1-benzofuran-2-yl)pyridin-2-yl, 5-(1,3-benzodioxol-5-yl)pyridin-2-yl, 5-(2-formyl-phenyl)pyridin-2-yl, 4-(2'-formylbiphenyl-4-yl, 5-(1,3-oxazol-2-yl)pyridin-2-yl, 6-(1,3-oxazol-2-yl)pyridin-3-yl, 4-(1,3-thiazol-2-yl)phenyl, 5-(1,3-thiazol-2-yl)pyridin-2-yl, 6-(1,3-thiazol-2-yl)pyridin-3-yl, 6-(1H-imidazol-1-yl)pyridin-3-yl, 5-(1H-imidazol-1-yl)pyridin-2-yl, 6-phenylpyridin-3-yl, 5-(pyrimidin-5-yl)pyridin-2-yl, 5-(pyrimidin-2-yl)pyridin-2-yl, 5-(3-aminocarbonylphenyl)pyridin-2-yl, 4-(1-methyl-1H-imidazol-4-yl)phenyl, 4-(1H-imidazol-4-yl)phenyl, 5-[2-(hydroxymethyl)phenyl]pyridin-2-yl, 2'-(hydroxymethyl)biphenyl-4-yl, 5-{2-[(dimethylamino)methyl]phenyl}pyridin-2-yl, 2'-[(dimethylamino)methyl]biphenyl-4-yl, 5-fluoromethylpyrazin-2-yl, 5-difluoro-methyl-pyrazin-2-yl, 5-methylpyrazin-2-yl, 2-methylpyrimidin-5-yl, 2-fluoromethyl-pyrimidin-5-yl, 2-difluoromethylpyrimidin-5-yl, 2-trifluoromethylpyrimidin-5-yl, 2-cyclopropylpyrimidin-5-yl, isothiazol-5-yl, 3-methylisothiazol-5-yl, 3-fluoromethyl-isothiazol-5-yl, 4-(dimethylamino-carbonyl)phenyl, 4-(methylaminocarbonyl)-phenyl, 4-(morpholin-4-ylcarbonyl)phenyl, 4-(piperidin-1-ylcarbonyl)phenyl, 3-fluoro-4-(pyrrolidin-1-ylcarbonyl)phenyl, 5-(pyrrolidin-1-yl-carbonyl)pyridin-2-yl, 5-(dimethylaminocarbonyl)pyridin-2-yl, 5-(morpholin-4-yl-carbonyl)-pyridin-2-yl, quinolin-4-yl, 6-methoxypyridin-3-yl, 6-(morpholin-4-yl)pyridin-3-yl, 4-(dimethyl-aminomethyl)phenyl, 5-(dimethylaminomethyl)pyridin-2-yl, 5-(dimethyl-aminocarbonyl)-pyridin-2-yl, 4-[hydroxyl-(pyridin-3-yl)methyl]phenyl, 6-[(hydroxy-(pyridin-3-yl)methyl]pyridin-3-yl, 6-(dimethylaminocarbonyl)pyridin-3-yl, 4-(4-hydroxypiperidin-1-ylcarbonyl)phenyl, 4-(4-methoxy-piperidin-1-ylcarbonyl)phenyl, 5-(4-methoxypiperidin-1-ylcarbonyl)-pyridin-2-yl, 6-(4-

methoxy-piperidin-1-ylcarbonyl)pyridin-3-yl, phenoxy, benzyloxy, 2-thienyl, 5-(methoxymethyl)-1,3-thiazol-2-yl, 5-(morpholin-4-ylcarbonyl)-1,3-thiazol-2-yl, 2-isopropyl-1,3-thiazol-5-yl, 2-(methoxymethyl)-1,3-thiazol-5-yl, 5-(methoxymethyl)-1,3-thiazol-2-yl, 4-(pyrimidin-2-yl)phenyl, 4-(pyrimidin-4-yl)phenyl, and 5-(methoxymethyl)pyridin-2-yl.

The R^2 group is selected from the group consisting of H, amino, mono- or di-substituted amino, OH, carboxyl, esterified carboxyl, carboxamide, $N(C_1-C_5)$ -monosubstituted carboxamide, and $N(C_1-C_5), N(C_1-C_5)$ -disubstituted carboxamide, cyano, (C_1-C_8) alkyl, (C_2-C_8) -alkenyl, (C_2-C_8) alkynyl, (C_5-C_7) -cycloalkyl, (C_5-C_7) -cycloalkenyl, alkoxy, alkoxyalkyl, thioalkyl, mono-, di- or trihaloalkyl, halogen, aryl or heteroaryl.

The R^3 and R^4 group substituents are independently selected from the group consisting of: H, amino, OH, (C_1-C_8) alkyl, halo(C_1-C_5)alkyl, dihalo(C_1-C_5)alkyl, trihalo(C_1-C_5)alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, (C_1-C_5) alkoxy and thio(C_1-C_5)alkyl.

The R^5 substituent is independently selected from hydrogen, (C_1-C_8) alkyl, formyl and when R^5 is alkyl, the nitrogen may optionally be in the N-oxide form.

The R^6 and R^7 substituents are each independently selected from the group consisting of H, C_1-C_{10} alkyl, optionally C_1-C_{10} alkyl can be interrupted by oxygen, nitrogen or sulfur, carbocycle, heterocycle, alkoxy, mono-, di- or tri-haloalkyl, mono-, di- or tri-haloalkoxy, cycloalkoxy, heterocycloalkoxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, aryloxyalkyl, heteroaryloxyalkyl, arylalkoxyalkyl or heteroarylalkoxyalkyl; aryl, heteroaryl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyloxyalkyl, heterocycloalkyloxyalkyl, aminoalkyl, mono- or di-substituted aminoalkyl, arylaminoalkyl, heteroarylaminoalkyl, alkylthioalkyl, cycloalkylthioalkyl, heterocycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkylsulfonylalkyl, cycloalkylsulfonylalkyl, heterocycloalkylsulfonylalkyl, arylsulfonylalkyl, heteroarylsulfonylalkyl, aminocarbonyl, mono- or di-substituted aminocarbonyl, aminocarbonylalkyl, mono- or di-substituted aminocarbonylalkyl, alkylcarbonylalkyl, cycloalkylcarbonylalkyl, heterocycloalkylcarbonylalkyl, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl, arylsulfonylaminoalkyl, heteroarylsulfonylaminoalkyl. Specific Examples of R^6 and R^7 substituents are the same such as those defined for R^1 above.

The R^8 and R^9 substituents are independently selected from the group consisting of H, OH, amino, (C_1-C_8) -alkyl, arylalkyl, heteroarylalkyl, aryl, heteroaryl, (C_1-C_8) -alkoxy, (C_2-C_8) -alkenyl, (C_2-C_8) -alkynyl, (C_1-C_8) alkoxyalkyl, mono(C_1-C_8)- or di(C_1-C_8)-substituted amino, a carbocycle or a heterocycle. When R^8 and R^9 are cyclized to form a 3-7 membered carbocycle or heterocycle such groups can be cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl, cyclopentyl, isoxazolyl thiazolyl, dihydrooxazolyl, pyridyl, pyrimidyl, and imidazolyl.

Unless otherwise indicated, the compounds provided in the above formula are meant to include pharmaceutically acceptable salts, prodrugs thereof, enantiomers, diastereomers, racemic mixtures thereof, crystalline forms, non-crystalline forms, amorphous forms thereof and solvates thereof.

The term pharmaceutically acceptable salts is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, phosphoric, partially neutralized phosphoric acids, sulfuric, partially neutralized sulfuric, hydroiodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present invention may contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds of the present invention may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

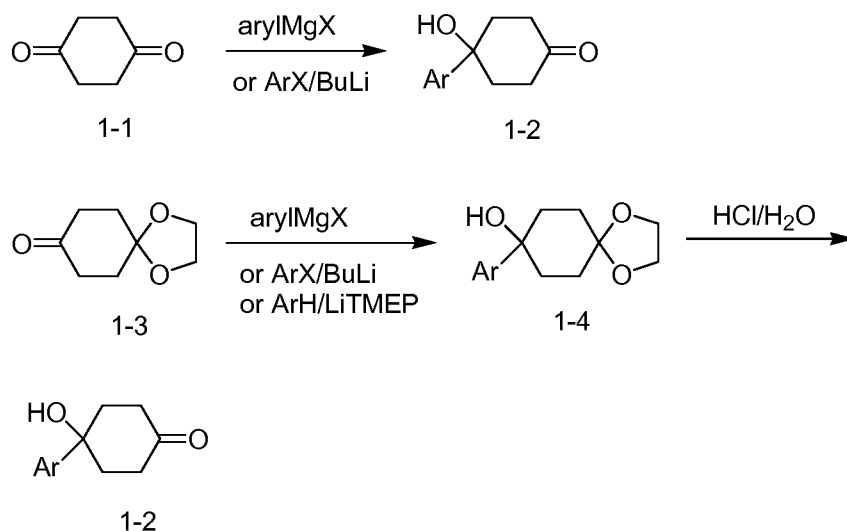
As noted above, some of the compounds of the present invention possess chiral or asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual optical isomers are all intended to be encompassed within the scope of the present invention.

Some of the compounds of formula I or II can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

In addition to salt forms, the present invention provides compounds may be in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex-vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. A variety of 4,4-disubstituted cyclohexanone derivatives can be synthesized using the protocols described in Schemes 1. Compounds of formula **1-2** can be prepared by addition of arylMgX or ArX/BuLi to 1,4-cyclohexanedione **1-1**. Alternatively, compounds of formula **1-2** can be prepared by treatment of 1,4-cyclohexanedione *mono*-ethylene ketal **1-3** with arylMgX, ArX/BuLi or heteroarylH/lithium tetramethylpiperidine followed by converting the ketal in **1-4** to a ketone using an acid such as HCl in aqueous solution.

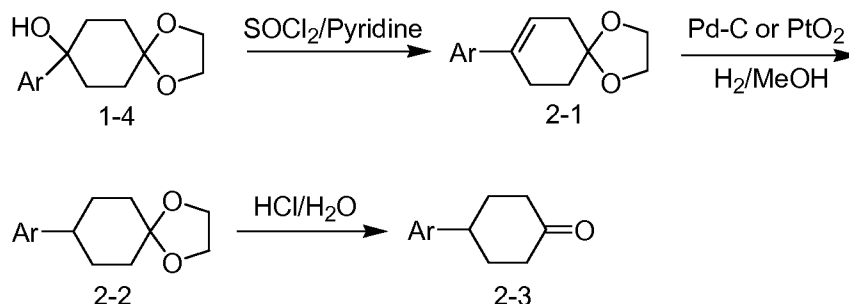
Scheme 1



4-Arylcyclohexanone derivatives of formula **2-3** can be synthesized following the procedures shown in Scheme 2. The intermediate **1-4** is subjected to a treatment with a dehydrating agent such as thionyl chloride/pyridine followed by reduction of the resulting

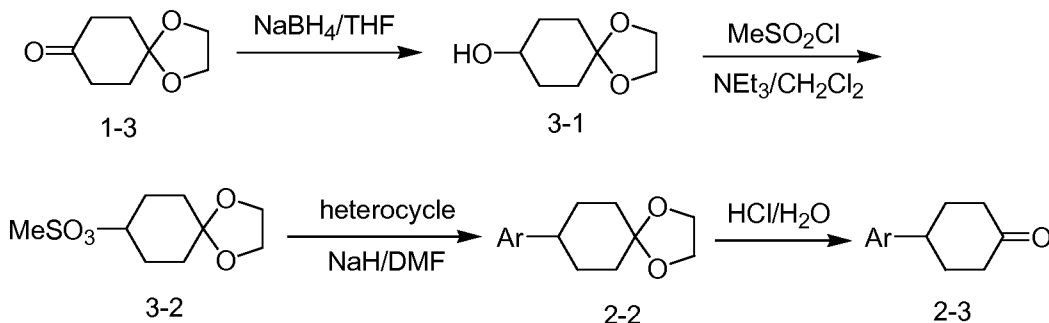
olefin by hydrogenation using a catalyst such as Pd-C or PtO₂. Conversion of the ketal in **2-2** by treatment with an acid provides the ketones of formula **2-3**.

Scheme 2



Alternatively, compounds of formula **2-3** can be synthesized according to Scheme 3. Reduction of ketone **1-3** using a reducing agent such as sodium borohydride produces the alcohol **3-1** which is converted to a mesylate **3-2** by treating with methanesulfonyl chloride. Displacement of the mesylate **3-2** with a heterocycle such as pyrazole, imidazole, triazole or tetrazole provides the intermediate **2-2** which is converted to compounds of formula **2-3** by treatment with an acid such as HCl.

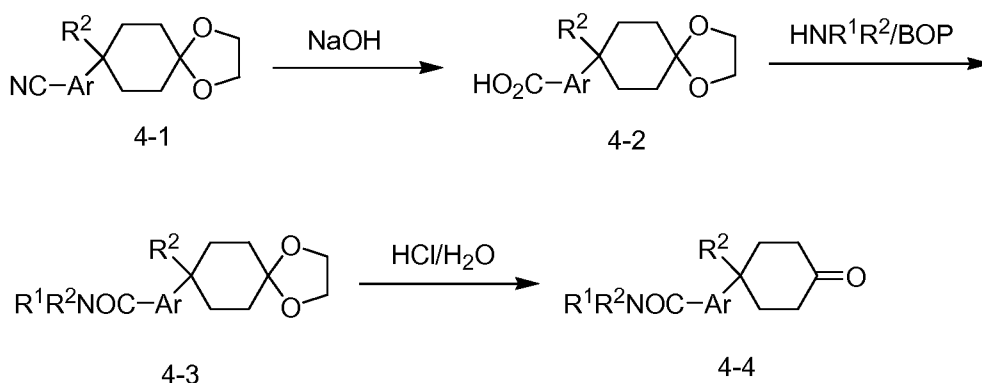
Scheme 3



Ar=substituted pyrazole, imidazole, triazole or tetrazole

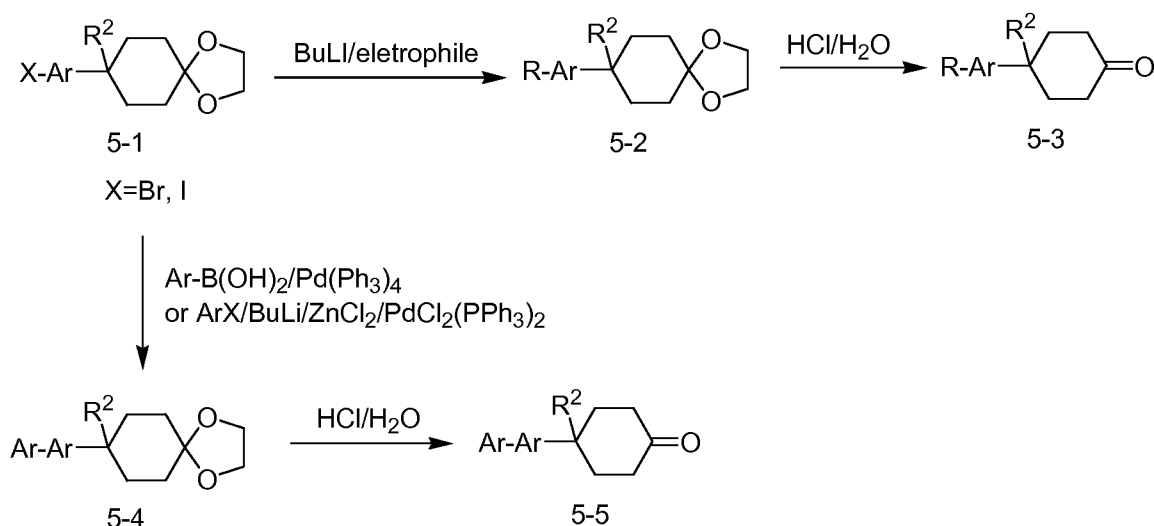
Introduction of a substituent on the aromatic ring in ketones of formula **1-2** or **2-3** can be accomplished starting from the ketal intermediate **1-4** or **2-2** using the methods described in Schemes 4-8. When the aromatic ring in **1-4** or **2-2** bears a cyano group, the ketal **4-1** is subjected to a hydrolysis using a base such as sodium or potassium hydroxide to give the carboxylic acid **4-2**. Coupling of **4-2** with an amine using a coupling agent such as BOP provides the amide **4-3**. Treatment of **4-3** with an acid such as HCl affords the ketones of formula **4-4**.

Scheme 4



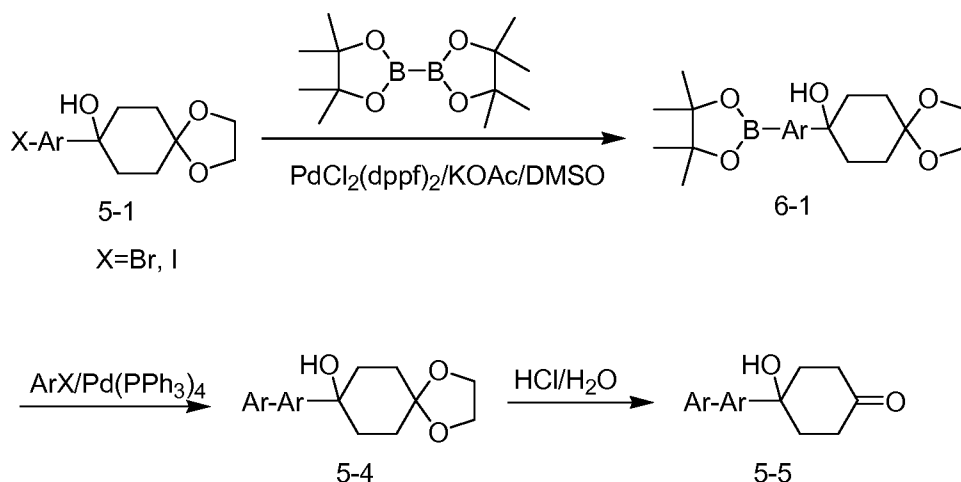
When the aromatic ring in the ketal intermediate **1-4** or **2-2** bears a halide such as bromo or iodo, the halide can be transformed to a substituent using the procedures described in Scheme 5. Treatment of **5-1** with butyl lithium followed by quenching with an electrophile such as alkyl halide, aldehyde, ketone, chloroformate, or carbonate provides the R-substituted ketal **5-2**. Suzuki coupling of **5-1** with a boronic acid $\text{ArB}(\text{OH})_2$ (Ar =aryl or heteroaryl) or coupling of **5-1** with ArZnCl_2 which can be generated in situ by treating ArX ($\text{X}=\text{Br}, \text{I}$) with butyl lithium followed by quenching with zinc chloride provides the Ar-substituted ketal intermediate **5-4**. Treatment of **5-2** and **5-4** with an acid affords their corresponding ketones **5-3** and **5-5**.

Scheme 5



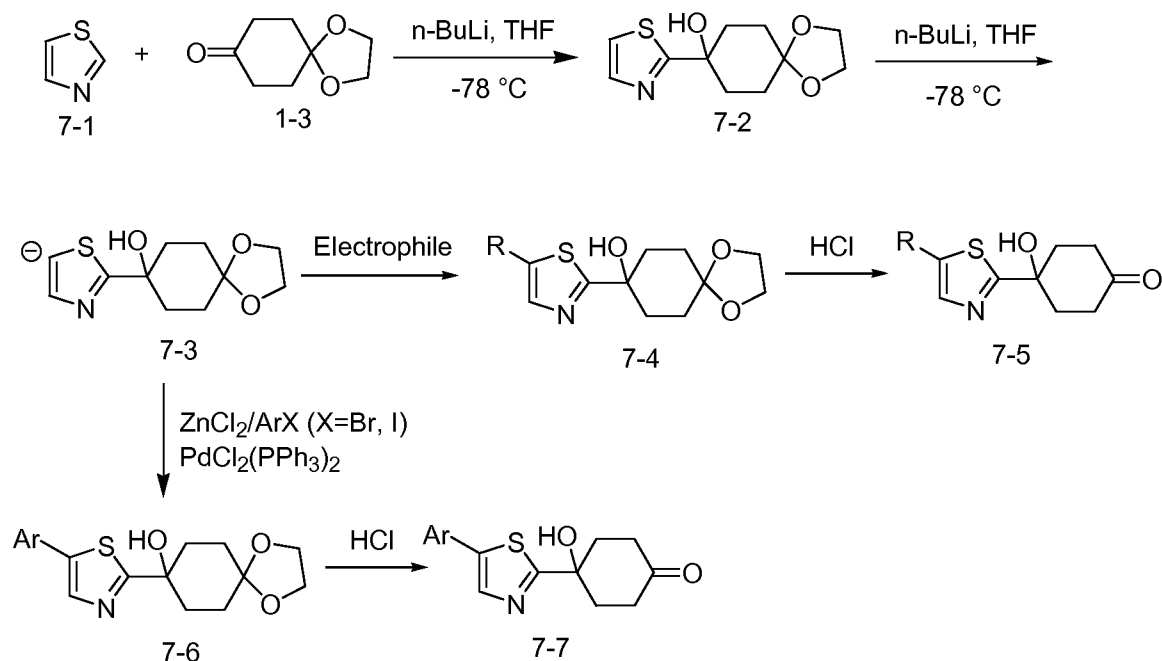
Alternatively, ketones of formula **5-5** can be obtained using the protocol depicted in Scheme 6. Following conversion of **5-1** to a boronic acid ester, the resulting boronic acid ester **6-1** is coupled with ArX ($\text{X}=\text{Br}, \text{I}$) using a palladium catalyst such as $\text{Pd}(\text{PPh}_3)_4$ to give the Ar-substituted ketal **5-4** from which ketones of formula **5-5** are obtained by treatment with an acid such as HCl .

Scheme 6



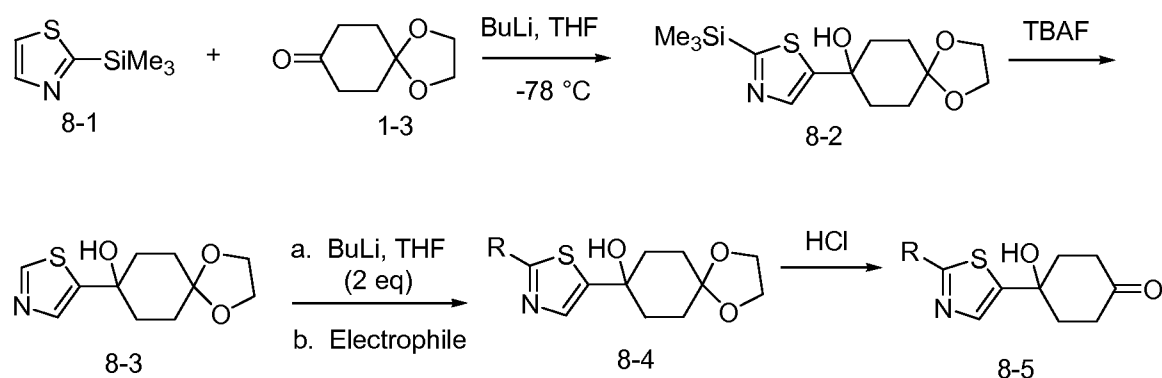
When the Ar group in ketones of formula **1-2** or **2-3** is a 2-thiazole residue, introduction of a substituent at the 5-position on the thiazole can be accomplished using the sequence outlined in Scheme 7. Treatment of thiazole **7-1** with butyl lithium followed by quenching with 1,4-cyclohexanedione *mono*-ethylene ketal **1-3** gives rise to the tertiary alcohol **7-2**. Treatment of **7-2** with butyl lithium followed by quenching the anion **7-3** with an electrophile such as alkyl halide, aldehyde, ketone, chloroformate or carbonate produces the ketal **7-4** with an R substituent at the 5-position on thiazole. Alternatively, the anion **7-3** can be quenched with zinc chloride and the resulting intermediate is coupled with ArX (X=Br, I) using a palladium catalyst such as $\text{PdCl}_2(\text{PPh}_3)_2$ to give the ketal **7-6** with an Ar residue at the 5-position on thiazole. Ketals **7-4** and **7-6** are then converted to their corresponding ketones of formula **7-5** and **7-7** by treatment with an acid such as HCl.

Scheme 7



When the Ar group in ketones of formula **1-2** or **2-3** is a 5-thiazole residue, introduction of a substituent at the 2-position on the thiazole can be accomplished using the sequence outlined in Scheme 7. Lithiation of 2-trimethylsilyl protected thiazole **8-1** followed by quenching with **1-3** gives rise to the intermediate **8-2**. Following removal of the trimethylsilyl group using TBAF, lithiation of **8-3** followed by quenching with an electrophile such as alkylhalide, aldehyde, ketone, isocyanate, chloroformate or carbonate provides the 5-R-substituted thiazole derivative **8-4**. Treatment of **8-4** with an acid such as HCl affords the ketones of formula **8-5**.

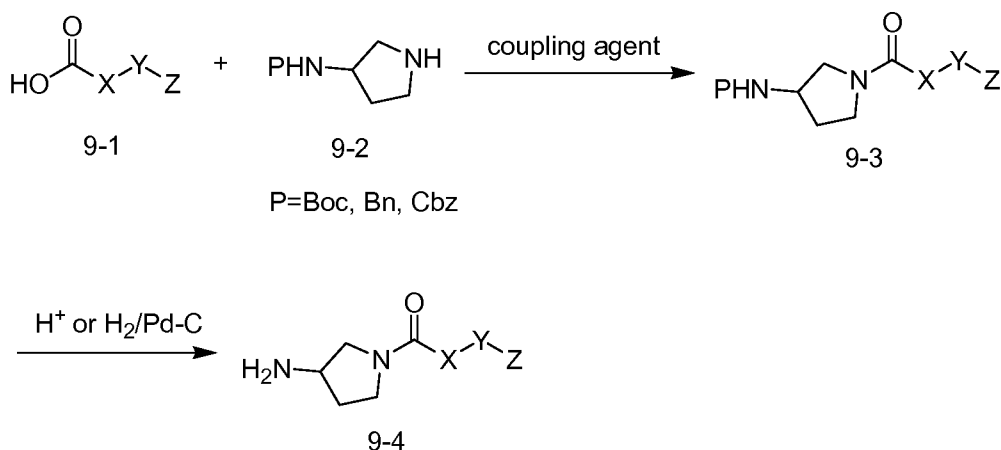
Scheme 8



A variety of 3-aminopyrrolidine intermediates can be prepared as shown in Schemes 6-17. Coupling of a carboxylic acid of formula **9-1** with a commercially available pyrrolidine

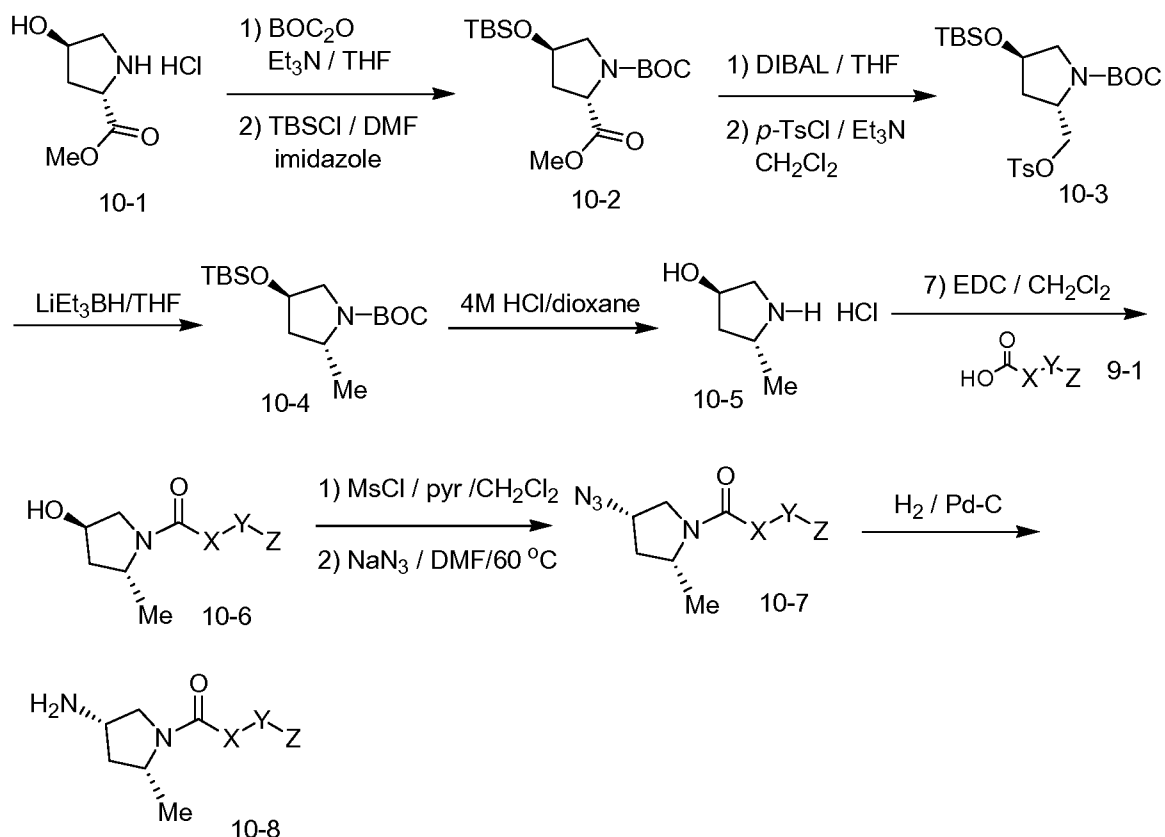
derivative of formula **9-2** using a coupling agent such as BOP gives rise to the amide **9-3**. Removal of the protecting group P (P=Boc, benzyl or Cbz) using an acid such as TFA or HCl or by hydrogenation using a palladium catalyst provides the pyrrolidine intermediates of formula **9-4**.

Scheme 9



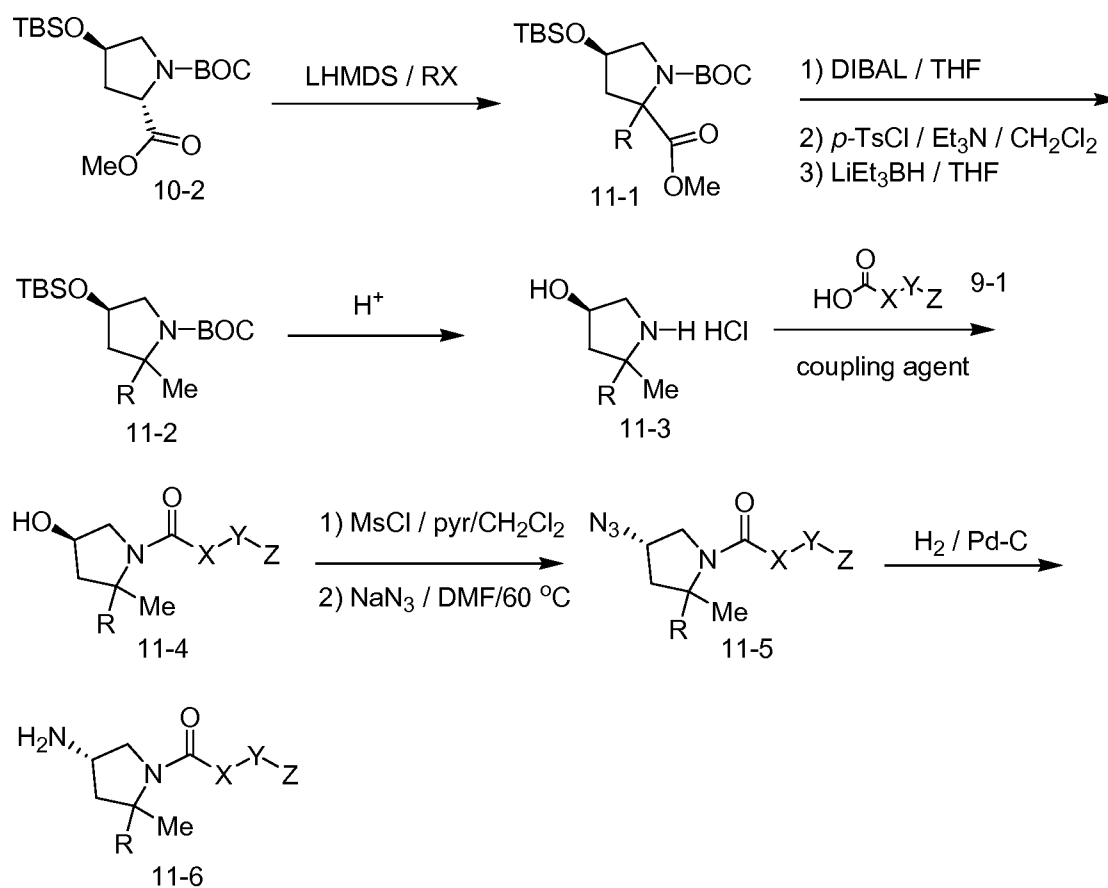
4-Amino-2-methylpyrrolidine derivatives of formula **10-8** can be prepared using the sequence described in Scheme 10. Following Boc protection at the amine and TBS protection at the hydroxyl of *trans*-4-hydroxy-L-proline methyl ester **10-1**, the ester in **10-2** is reduced to an alcohol and the resulting alcohol is converted to a tosylate. Detosylation in **10-3** can be achieved by reduction using lithium triethylborohydride (LiEt_3BH). The resulting intermediate **10-4** is subjected to a deprotection using an acid such as HCl to remove the Boc and the TBS groups. Following coupling of the resulting amine **10-5** with a carboxylic acid of formula **9-1** using a coupling agent such as EDC, conversion of the hydroxyl to a mesylate is followed by displacement with sodium azide. The resulting azido group is then reduced to an amine by hydrogenation to give the pyrrolidine intermediates of formula **10-8**.

Scheme 10



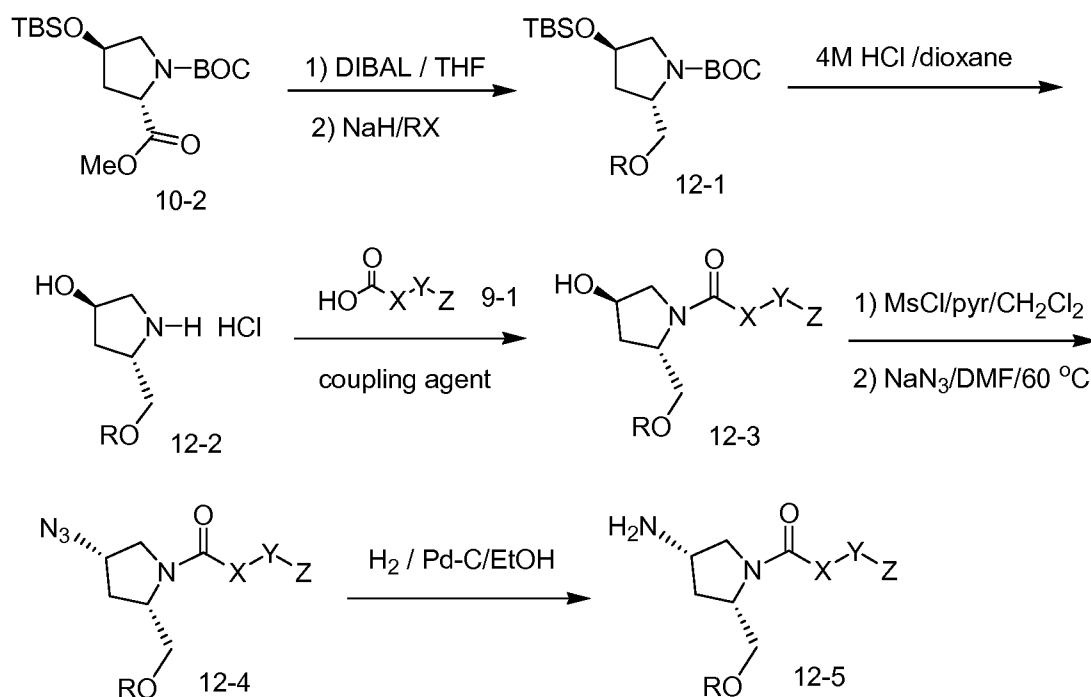
4-Aminopyrrolidine derivatives of formula **11-6** can be prepared according to Scheme 11. Alkylation of the intermediate **10-2** with an alkyl halide (RX) using LHMDS provides the R-substituted intermediate **11-1**. Following reduction of the ester to an alcohol using diisobutylaluminum hydride (DIBAL), the alcohol is converted to a tosylate and the resulting tosylate is reduced using LiEt₃BH to give **11-2**. Intermediate **11-2** is then converted to compounds of formula **11-6** in a manner similar to that described in Scheme 10.

Scheme 11



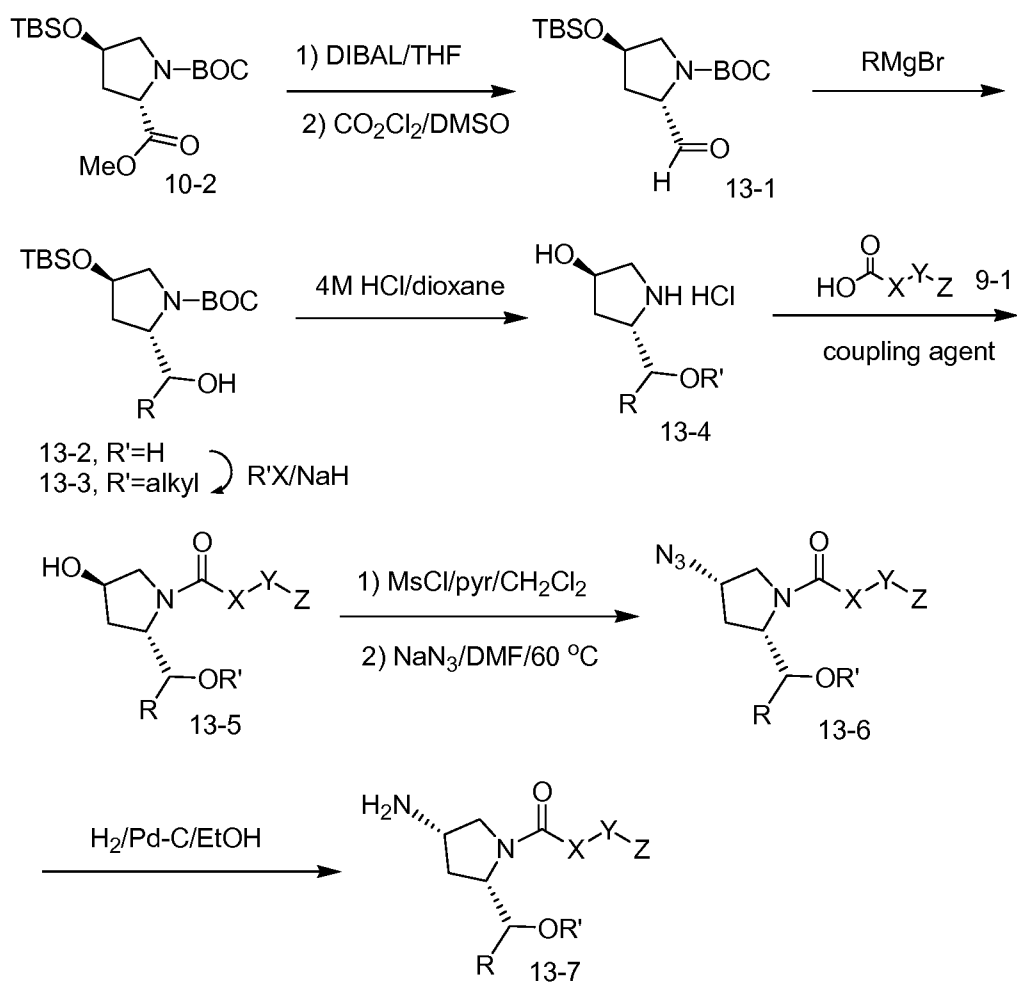
4-Aminopyrrolidine derivatives of formula **12-5** can be synthesized using the method shown in Scheme 12. The intermediate **10-2** is reduced to an alcohol using a reducing agent such as DIBAL and the resulting alcohol is alkylated with an alkyl halide (RX) using sodium hydride to give intermediate **12-1**. Using procedures similar to those described in Scheme 10, compounds of formula **12-5** are obtained from the intermediate **12-1**.

Scheme 12



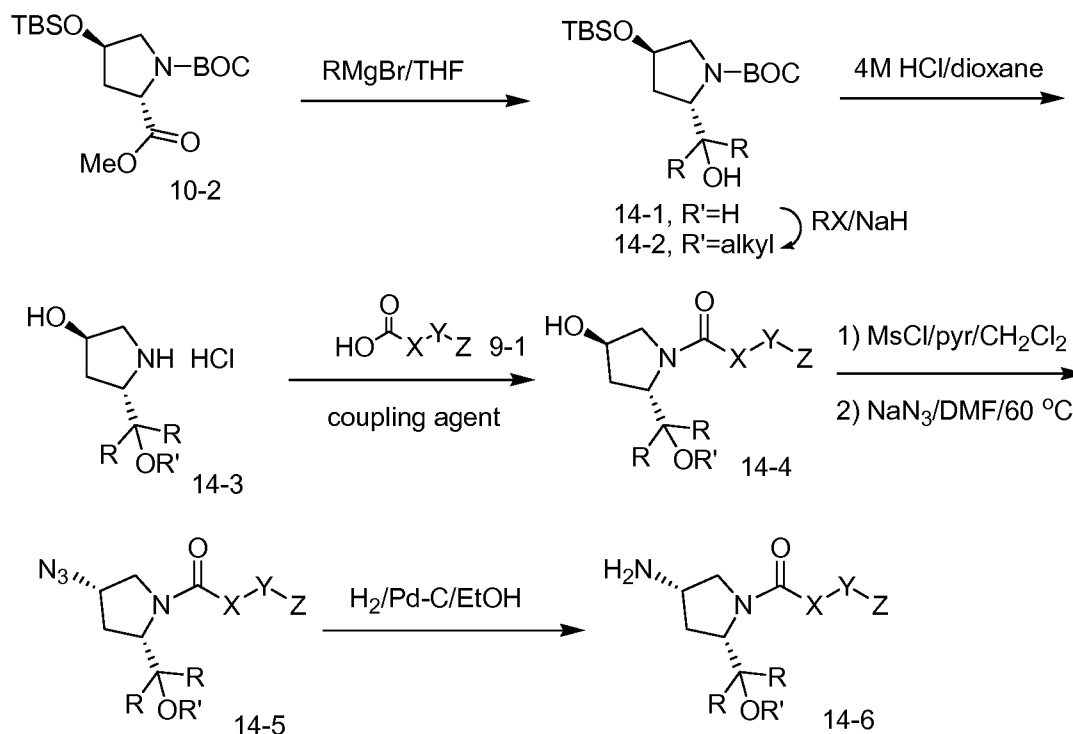
4-Aminopyrrolidine derivatives of formula **13-7** can be generated according to Scheme 13. The intermediate **10-2** is reduced to an alcohol using a reducing agent such as DIBAL and the resulting alcohol is oxidized to an aldehyde using a oxidizing agent such as Swern oxidation. Addition of a Grignard reagent RMgX to the aldehyde **13-1** is followed by alkylation of the resulting alcohol with an alkyl halide (RX) using sodium hydride. After removal of the Boc and TBS protecting groups in **13-2** or **13-3** using an acid such as HCl, the resulting amine **13-4** is condensed with a carboxylic acid of formula **9-1**. Mesylation at the 4-hydroxy on the pyrrolidine followed by displacement of the resulting mesylate with sodium azide and reduction of the azido by hydrogenation provides compounds of formula **13-7**.

Scheme 13



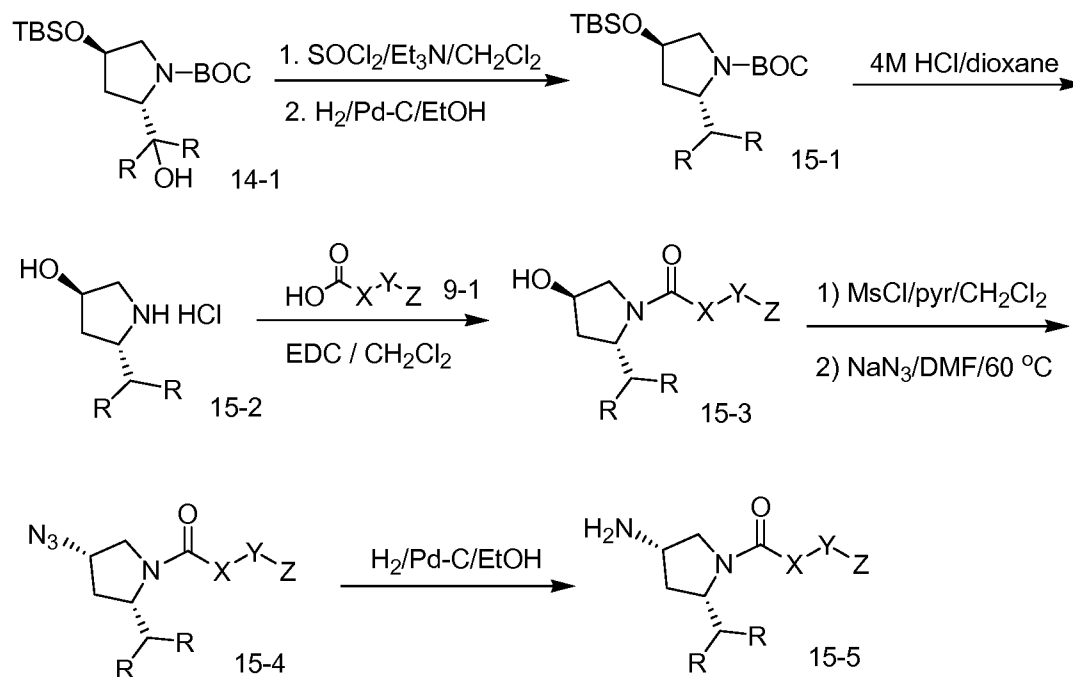
4-Aminopyrrolidine derivatives of formula **14-6** can be synthesized using a protocol depicted in Scheme 14. After double addition of a Grignard reagent RMgX to the intermediate **10-2**, the resulting tertiary alcohol **14-1** is subjected to an alkylation with an alkyl halide (R'X) to give **14-2**. Intermediates **14-1** and **14-2** are then converted to compounds of formula **14-6** in a manner similar to that described in Scheme 13.

Scheme 14



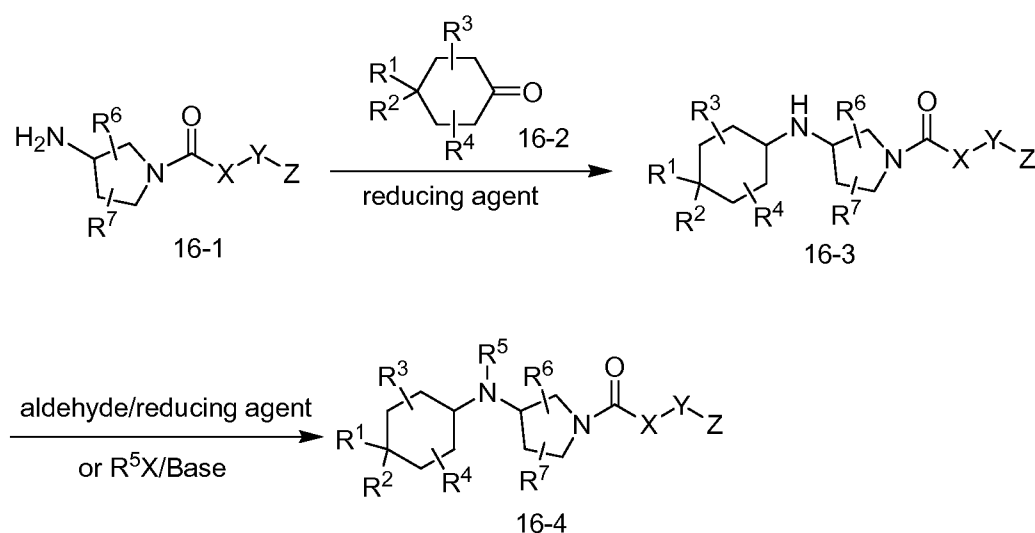
The synthesis of 4-aminopyrrolidine derivatives of formula **15-5** is given in Scheme 15. After dehydration of the intermediate **14-1** followed by reduction of the olefin by hydrogenation, the resulting intermediate **15-1** is converted to compounds of formula **15-5** in a fashion similar to that described in Scheme 10.

Scheme 15



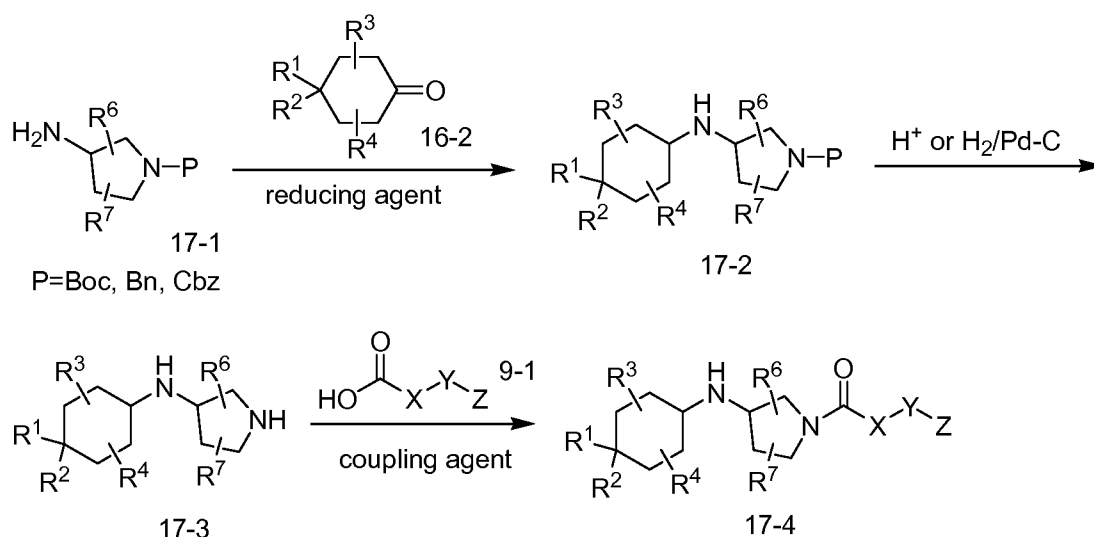
Compounds of formula I can be obtained by assembling the aminopyrrolidine derivatives of formula **16-1** with a ketone of formula **16-2** by reductive amination using a reducing agent such as sodium triacetoxyborohydride or through hydrogenation followed by treating the resulting secondary amine **16-3** via reductive amination with an aldehyde or by alkylation with an alkyl halide (RX).

Scheme 16



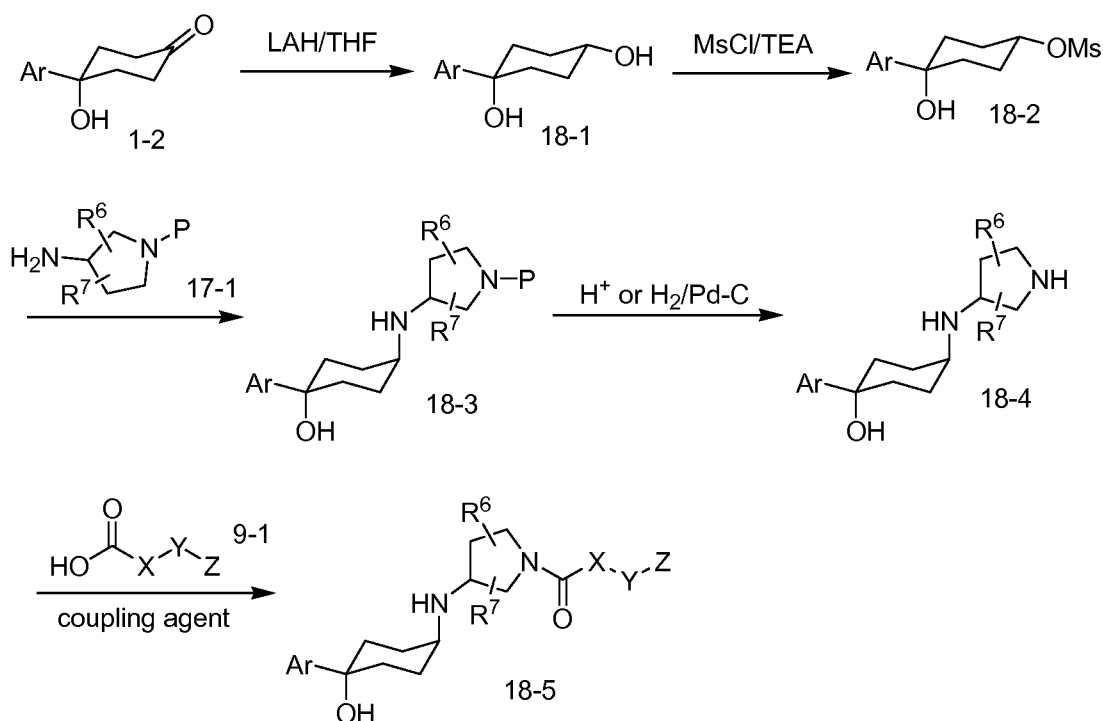
Alternatively, compounds of formula I can be prepared using a sequence outlined in Scheme 17. Reductive amination of the aminopyrrolidine derivatives of formula **17-1** with a ketone of formula **16-2** gives rise to the secondary amine **17-2**. After removal of the protecting group P (P=Boc, benzyl or Cbz) using an acid or through hydrogenation using a catalyst such as Pd-C, the resulting amine **17-3** is condensed with a carboxylic acid of formula **9-1** to provide compounds of formula **17-4**.

Scheme 17



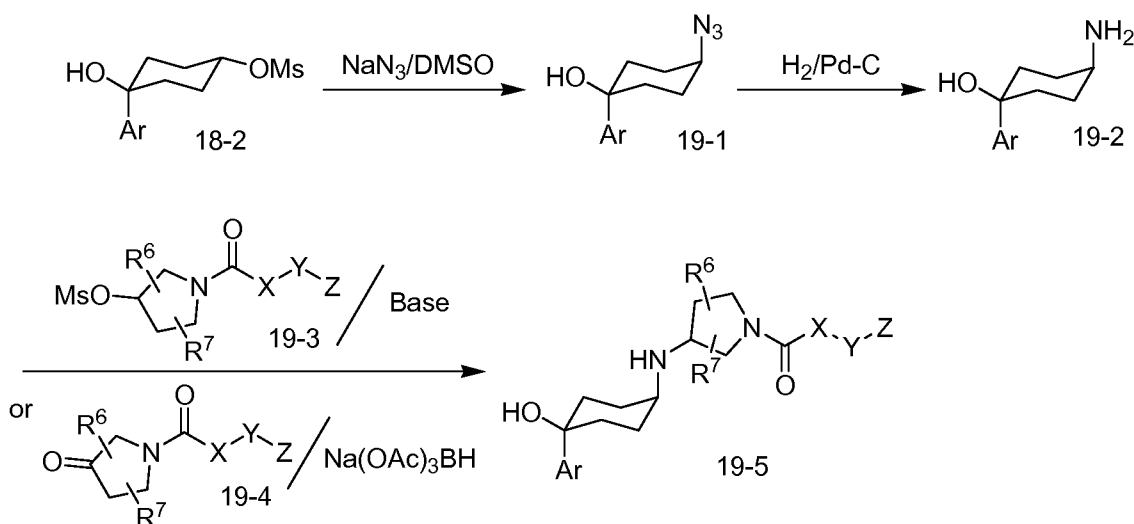
Alternatively, compounds of formula I can be prepared using a sequence outlined in Scheme 18. Reduction of the cyclohexanone **1-2** with a reducing agent such as lithium aluminum hydride produces the *cis* diol **18-1**. After converting the secondary alcohol to a mesylate, the resulting mesylate **18-2** is displaced with an aminopyrrolidine derivative of formula **17-1** to give the *trans* 4-amino-1-cyclohexanol derivative of formula **18-3**. Removal of the protecting group using an acid or through hydrogenation followed by coupling of the resulting amine with a carboxylic acid of formula 9-1 affords compounds of formula **18-5**.

Scheme 18



Alternatively, compounds of formula I can be synthesized according to Scheme 19. Displacement of the mesylate **18-2** with sodium azide gives rise to the azido intermediate **19-1** which is reduced to an amine by hydrogenation using a catalyst such as Pd-C. Displacement of the mesylate of formula **19-3** with the resulting amine **19-2** or reductive amination of **19-2** with a ketone of formula **19-4** affords compounds of formula **19-5**.

Scheme 19



The compounds of the present invention may be MCP-1 receptor modulators, e.g., antagonists, and may be capable of inhibiting the binding of MCP-1 to its receptor. Surprisingly, the compounds block T cell migration in vitro, and have dramatic effects on the recruitment of inflammatory cells in multiple models of inflammatory diseases. Therefore, the compounds of formula I are useful as agents for the treatment of inflammatory disease, especially those associated with lymphocyte and/or monocyte accumulation, such as arthritis, rheumatoid arthritis, multiple sclerosis, neuropathic pain, atherosclerosis and transplant rejection. In addition, these compounds can be used in the treatment of allergic hypersensitivity disorders such as asthma and allergic rhinitis characterized by basophil activation and eosinophil recruitment, as well as for the treatment of restenosis and chronic or acute immune disorders.

Modulation of chemokine receptor activity, as used in the context of the present invention, is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism of the activity associated with a particular chemokine receptor, preferably the CCR2 receptor. The term composition as used herein is intended to include a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By pharmaceutically acceptable it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compounds of formula I of the present invention, and compositions thereof are useful in the modulation of chemokine receptor activity, particularly CCR2. Accordingly, the compounds of the present invention are those which inhibit at least one function or characteristic of a mammalian CCR2 protein, for example, a human CCR2 protein. The

ability of a compound to inhibit such a function can be demonstrated in a binding assay (e.g., ligand binding or promotor binding), a signalling assay (e.g., activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium), and/or cellular response function (e.g., stimulation of chemotaxis, exocytosis or inflammatory mediator release by leukocytes).

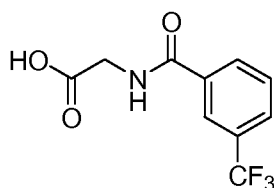
The invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXAMPLES

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wis., USA). Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). In tables, a single m/e value is reported for the M+H (or, as noted, M-H) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases.

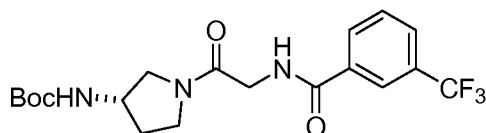
Example 1

Step A



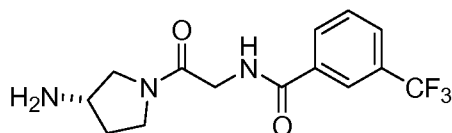
(3-Trifluoromethyl-benzoylamino)acetic acid. To a rapid stirring solution of glycine (15.014 g, 0.20 mol) in MeCN (400 mL) and 2 M NaOH (250 mL) at 0 °C was slowly added a solution of 3-(trifluoromethyl)-benzoyl chloride (41.714 g, 0.20 mol) in 75 mL of MeCN over 30 min. The cloudy yellow solution was stirred at 0 °C for 30 min. The reaction mixture was acidified with 3 M HCl to pH = 3, followed by removal of MeCN on rotary evaporator. The resulting mixture was then extracted with EtOAc (400 mL x 3). The combined organic layers were dried, filtered and concentrated to give a light yellow solid (48.53 g), which was triturated with toluene (500 mL). After filtration, the solid product was washed with cold toluene until the filtrate was colorless. After dried under high vacuum over the weekend, a white powder product: 44.60 g (90%) was afforded. MS (M+H⁺) = 248.1. ¹H NMR (DMSO-d₆) δ 12.70 (br s, 1 H), 9.17 (m, 1H), 8.20 (dd, 2H), 7.94 (dd, 1H), 7.78 (m, 1H), 3.97 (d, 2H).

Step B



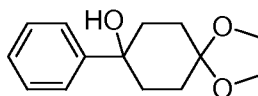
tert-Butyl [(3*S*)-1-({[3-(Trifluoromethyl)benzoyl]amino}acetyl)pyrrolidin-3-yl]carbamate. To a solution of the carboxylic acid (2.7 g, 11 mmol) from step A and *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate (2.0 g, 11 mmol) in DMF (30 mL) cooled in an ice bath was added BOP (5 g, 11 mmol) followed by triethylamine (3 mL, 22 mmol). The mixture was allowed to warm to temperature and stirred overnight. Ethyl acetate (150 mL) was added. The resulting solution was washed with NaHCO₃ and brine each three times, dried over MgSO₄ and concentrated. Chromatography on silica gel eluting with EtOAc provided 4.4 g (96%) of the desired product. MS (M-Boc+H)⁺ 316.

Step C



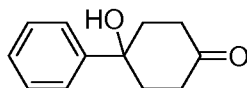
N-{2-[(3*S*)-3-Aminopyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. The above product (4.2 g) was dissolved in 4 N HCl/dioxane (30 mL). After being stirred for 1 hour at room temperature, the solution was concentrated to provide 4.0 g of the title compound. MS (M+H)⁺ 316.

Step D



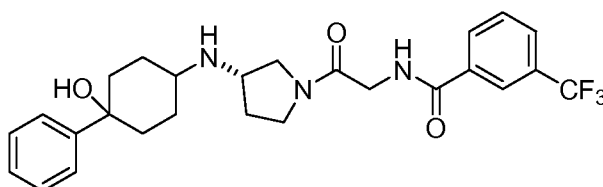
8-Phenyl-1,4-dioxaspiro[4.5]decan-8-ol. To a solution of 1,4-cyclohexanone *mono*-ethylene ketal (8.1 g, 50 mmol) in THF (20 mL) at 10 °C was added a 1 M solution of phenyl magnesium bromide in THF (70 mL, 70 mmol). The resulting mixture was stirred at room temperature for 2 hours before quenching with saturated NH₄Cl solution. The solution was extracted with EtOAc 3 times. The combined organic phase was washed with brine, dried over MgSO₄ and concentrated. Chromatography on silica gel eluting with 40% EtOAc/hexanes provided 9.5 g (81%) of the desired product. MS (M+H)⁺ 234.

Step E



4-Hydroxy-4-phenylcyclohexanone. The above product was dissolved in THF (50 mL). To it was added 10% HCl/H₂O (50 mL). The solution was stirred at room temperature overnight and extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄ and concentrated to give the title compound as a white solid. MS (M+H)⁺ 191.

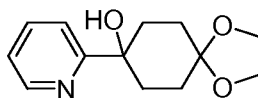
Step F



N-(2-((3S)-3-[(4-Hydroxy-4-phenylcyclohexyl)amino]pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. To a solution of the pyrrolidine intermediate from step C (0.3 g, 0.85 mmol) and the ketone from step E (0.16 g, 0.85 mmol) in THF (5 mL) was added Na(OAc)₃BH (0.35 g, 2.5 mmol) followed by triethylamine (0.2 mL, 1.5 mmol). The reaction was continued at room temperature overnight and quenched by addition of a saturated NaHCO₃ solution. The resulting solution was extracted with EtOAc and the EtOAc layer was dried over MgSO₄ and concentrated. Separation on silica gel eluting with 10% to 30% MeOH/EtOAc provided the *cis* (fast moving spot) and *trans* (slow moving spot) isomers of the title compound. MS (M+H)⁺ 490.0.

Example 2

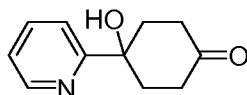
Step A



8-Pyridin-2-yl-1,4-dioxaspiro[4.5]decan-8-ol. To a solution of 2-Bromopyridine (14 g, 88.6 mmol) in anhydrous ether (300 mL) cooled at -78 °C was slowly added a solution of 2.5 M butyl lithium (36 mL). After the addition, stirring was continued at -78 °C for 1 hour. To it was slowly added a solution of 1,4-cyclohexanedione mono-ethylene ketal (15 g, 96 mmol) in anhydrous ether (300 mL). When the addition was complete, the mixture was allowed to

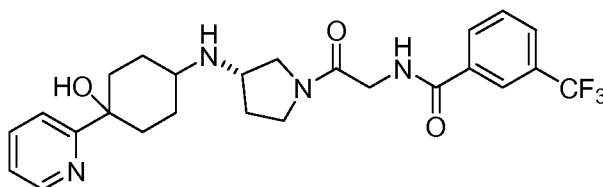
warm to 0 °C and stirring was continued for 1 hour. The reaction was quenched by the addition of an aqueous solution (100 mL) of ammonium chloride (4.5 g). The organic phase was separated and the aqueous phase was extracted with methylene chloride 4 times. The combined organic phases were dried over MgSO_4 and concentrated. Crystallization from EtOAc provided 7 g of the desired product. The mother liquid was purified on silica gel eluting with 10% MeOH/EtOAc to give 3 g of the desired product. MS $(\text{M}+\text{H})^+$ 236.0.

Step B



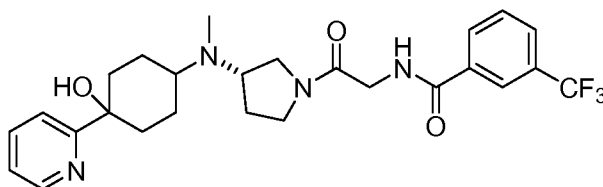
4-Hydroxy-4-(pyridin-2-yl)cyclohexanone. The above product was dissolved in THF (30 mL) and a 3 N solution of HCl in water (30 mL). The mixture was stirred at 50 °C for 3 hours. After cooling to room temperature, NaHCO_3 was added to the solution with stirring until no bubbling occurred. The organic phase was separated and the aqueous layer was extracted with EtOAc three times. The combined organic phase was dried over MgSO_4 and concentrated. The residue was triturated with EtOAc to give 5.5 g of the title compound. MS $(\text{M}+\text{H})^+$ 192.

Step C



N-(2-((3S)-3-((4-Hydroxy-4-(pyridin-2-yl)cyclohexyl)amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared by reductive amination of the ketone obtained above with the pyrrolidine derivative obtained from step C in Example 1 using a procedure analogous to that described in step F, Example 1. MS $(\text{M}+\text{H})^+$ 491.

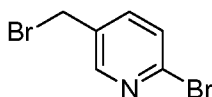
Example 3



N-(2-((3S)-3-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl](methyl)amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. To a solution of N-(2-((3S)-3-[(4-hydroxy-4-pyridin-2-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (49 mg, 0.1 mmol) and formaldehyde (0.3 mL, 37% water solution) in THF (2 mL) was added $\text{Na}(\text{OAc})_3\text{BH}$ (64 mg, 0.3 mmol). After being stirred at room temperature overnight, the reaction was quenched by addition of a saturated NaHCO_3 solution. The resulting solution was extracted with EtOAc and the EtOAc layer was dried (MgSO_4) and concentrated. Purification by prep HPLC provided the title compound as a TFA salt. MS $(\text{M}+\text{H})^+$ 505.

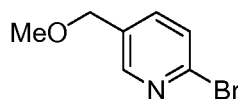
Example 4

Step A



2-Bromo-5-bromomethylpyridine. 2-Bromo-5-methylpyridine (5.00 g, 29.1 mmol) and N-bromosuccinimide (5.22 g, 29.3 mmol) were dissolved in carbon tetrachloride (40 mL) under nitrogen. Benzoyl peroxide (0.35 g, 1.4 mmol) was added and the mixture heated at reflux for four hours. The mixture was cooled to room temperature, filtered, and washed with $\text{NaHCO}_3/\text{H}_2\text{O}$. The mixture was adsorbed onto silica gel and then chromatographed, eluting with a gradient of hexane to 10% ethyl acetate/hexane. Pure fractions were combined and concentrated to provide the desired mono-brominated product as a pale yellow solid, 3.60 g (49%). LC/MS $(\text{M}+\text{H})^+$ m/z = 249.8, 251.8, 253.8.

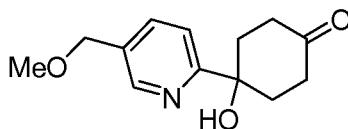
Step B



2-Bromo-5-(methoxymethyl)pyridine. 2-Bromo-5-bromomethylpyridine, 4 (3.58 g, 14.3 mmol) was dissolved in methanol (20 mL) under nitrogen. Sodium methoxide (0.89 g, 15.7 mmol, 95%) was added and the mixture stirred at room temperature. After 3 hours, the methanol was rotovapped off and the residue dissolved in dichloromethane and washed with water. The organic extract was adsorbed onto silica gel and chromatographed. The column was eluted with a gradient of hexane to 20% ethyl acetate/hexane. Pure fractions

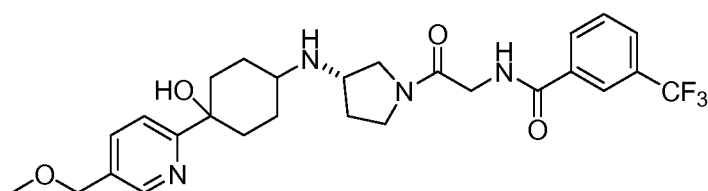
were combined and concentrated to provide the title compound as a colorless oil, 2.62 g (90%). LC/MS (M+H)⁺ m/z = 202.0.

Step C



4-Hydroxy-4-[5-(methoxymethyl)pyridin-2-yl]cyclohexanone. A solution of 2-bromo-5-(methoxymethyl)pyridine (2.61 g, 12.9 mmol) was dissolved in dry THF (40 mL) under nitrogen and cooled to -78 °C. *n*-Butyllithium (6.20 mL, 15.5 mmol, 2.5 M in hexane) was added dropwise over 10 minutes to form a black solution. After 15 minutes, a solution of 1,4-dioxo-spiro[4.5]decan-8-one (2.21 g, 14.1 mmol) in THF was added dropwise over 2 minutes and the mixture was gradually warmed to room temperature over 3 hours. TLC (50% ethyl acetate/hexane) and LC/MS indicated complete conversion. Aqueous HCl (14 mL, 6.0 M) was added and the mixture was stirred for 3 hours at room temperature and then neutralized with NaHCO₃/H₂O. The mixture was extracted 3 times with ethyl acetate and the combined extracts were adsorbed onto silica gel and chromatographed. The column was eluted with a gradient of hexane to 40% ethyl acetate/hexane. Pure fractions were combined and concentrated to provide the title compound as a pale yellow solid, 1.00 g (33%). LC/MS (M+H)⁺ m/z = 236.1.

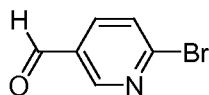
Step D



N-{2-[(3S)-3-({4-Hydroxy-4-[5-(methoxymethyl)pyridin-2-yl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. The title compound was prepared from the ketone of step C using a procedure analogous to that described for Example 1. MS (M+H)⁺ 535.

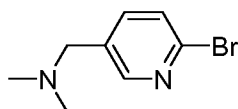
Example 5

Step A



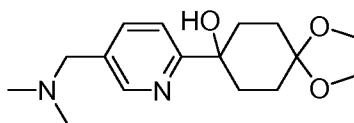
6-Bromo-pyridine-3-carbaldehyde. 2,5-Dibromopyridine 9.48 g (40 mmol) was dissolved in 60 mL of THF and 150 mL of anhydrous ether. After the solution was cooled to -78°C , 16 mL of *n*-butyllithium (2.5 M, 40 mmol) was slowly dropped through a syringe in 30 min. After being stirred at -78°C for 30 minutes, N,N-dimethylformamide (3.5 g, 48 mmol) was added. The reaction mixture was warmed up to room temperature during two hours and then quenched by addition of 10 ml water. The mixture was extracted twice using EtOAc. The combined extracts were dried and concentrated. After flash column using 30-40% EtOAc in hexane, 2.80g white solid was obtained (28% yield), MS: $(\text{M}+\text{H})^{+}$ 186.0, 188.0.

Step B



1-(6-Bromopyridin-3-yl)-N,N-dimethylmethanamine. To a solution of titanium tetrakisopropoxide (6.4g, 22 mmol) and 2.0 M of dimethylamine in methanol (22 mL, 44 mmol), 6-Bromo-pyridine-3-carbaldehyde (2.10 g, 11 mmol) in 20 mL of methanol was added. After being stirred at r. t. for 5 hrs, sodium borohydride (0.43g, 11 mmol) was added and the mixture was stirred overnight. The reaction was quenched by addition of 10 mL of water and extracted twice using EtOAc. The combined extracts were dried and concentrated. After flash column using 20-40% methanol in EtOAc and 0.5% NH_4OH , 1.15g oil was obtained (47% yield), MS: $(\text{M}+\text{H})^{+}$ 214.0, 216.0.

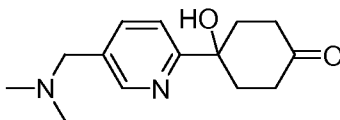
Step C



8-{5-[(Dimethylamino)methyl]pyridin-2-yl}-1,4-dioxaspiro[4,5]decan-8-ol. 1-(6-Bromopyridin-3-yl)-N,N-dimethylmethanamine (1.15 g, 5.4 mmol) was dissolved in 30 mL of THF and 80 mL of anhydrous ether. After the solution was cooled to -78°C , 2.60 mL of *n*-butyllithium (2.5 M, 6.40 mmol) was slowly dropped through a syringe in 10 min. After being

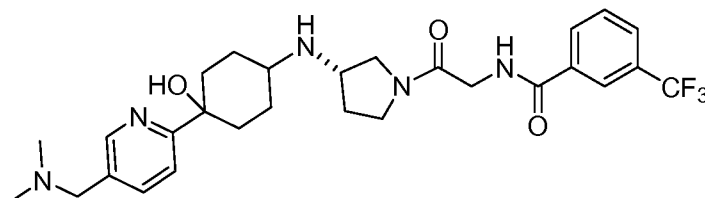
stirred at -78°C for 30 minutes, 1,4-cyclohexanedione *mono*-ethylene ketal (1.01 g, 6.4 mmol) was added. The reaction mixture was allowed to warm up to room temperature during two hours and then quenched by addition of 10 mL of water. The mixture was extracted twice using EtOAc. The combined extracts were dried and concentrated. After flash column using 20-40% methanol in EtOAc and 0.5% NH_4OH , 0.85 g oil was obtained (54% yield), MS: $(\text{M}+\text{H})^+$ 293.2.0.

Step D



4-{5-[(Dimethylamino)methyl]pyridin-2-yl}-4-hydroxycyclohexanone. 8-{5-[(Dimethylamino)methyl]pyridin-2-yl}-1,4-dioxaspiro[4,5]decan-8-ol (0.85 g, 2.9 mmol) was dissolved in 10 mL of THF and 10 mL of 2 N HCl solution was added. After being stirred for two hours, the reaction mixture was neutralized to pH~8-9 by addition of a saturated NaHCO_3 aqueous solution and extracted twice using EtOAc. The combined extracts were dried and concentrated to obtain 0.37 g white solid (51% yield), MS: $(\text{M}+\text{H})^+$ 249.2.

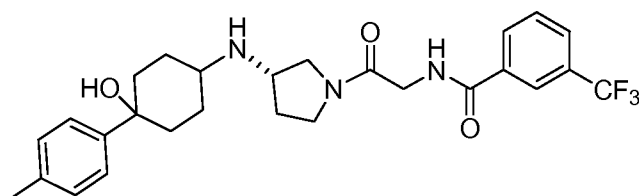
Step E



N-(2-{(3S)-3-[(4-{5-[(Dimethylamino)methyl]pyridin-2-yl}-4-hydroxycyclohexyl)amino]pyrrolidin-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared from the above ketone following the procedure described for Example 1. MS $(\text{M}+\text{H})^+$ 548.

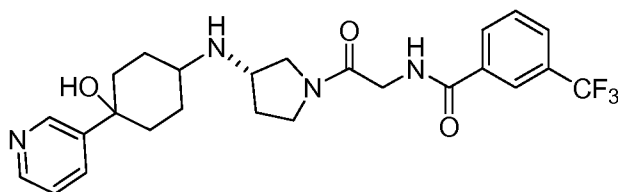
The following Examples were prepared in a similar fashion.

Example 6



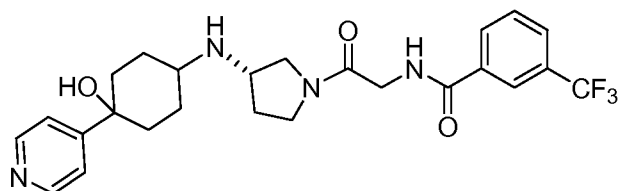
N-[2-((3*S*)-3-[[4-Hydroxy-4-(4-methylphenyl)cyclohexyl]amino]pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 504.

Example 7



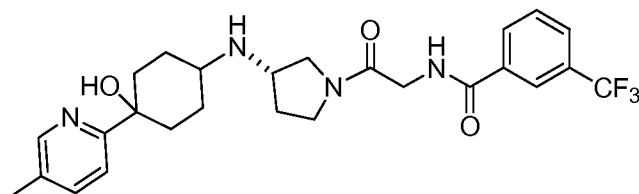
N-(2-((3*S*)-3-[4-hydroxy-4-pyridin-3-ylcyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 491.

Example 8



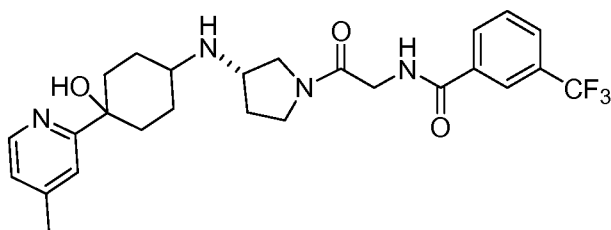
N-(2-((3*S*)-3-[4-hydroxy-4-pyridin-4-ylcyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 491.

Example 9



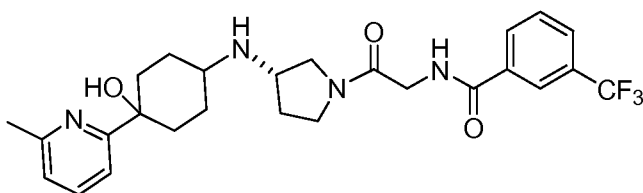
N-[2-((3*S*)-3-{[4-Hydroxy-4-(5-methylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 505.

Example 10



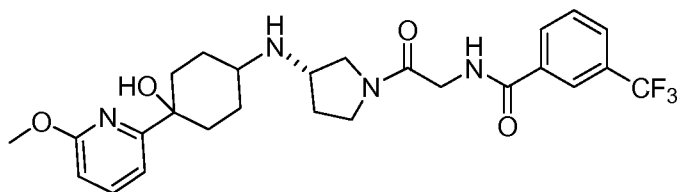
N-[2-((3*S*)-3-{[4-Hydroxy-4-(4-methylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 505.

Example 11



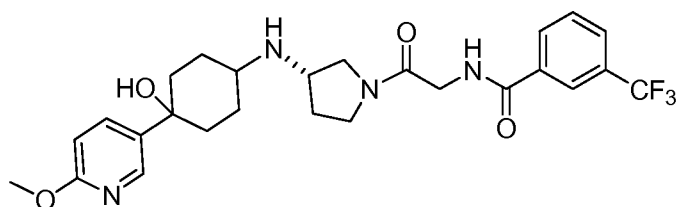
N-[2-((3*S*)-3-{[4-Hydroxy-4-(6-methylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 505.

Example 12



N-[2-((3*S*)-3-{[4-Hydroxy-4-(6-methoxypyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 521.

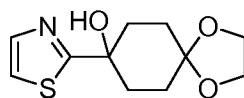
Example 13



N-[2-((3*S*)-3-([4-Hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 521.

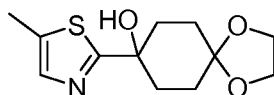
Example 14

Step A



8-(1,3-Thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol. A solution of *n*-butyllithium (8.1 mL of 1.6 M solution in hexane, 12.92 mmol) was added to thiazole (1.0 g, 11.75 mmol) in THF (10 mL) at -78 ° C with stirring under N₂. After being stirred at -78 ° C for 1 h, a solution of 1,4-cyclohexanedione mono-ethylene ketal (1.84 g, 11.75 mmol) in THF (10 mL) was added to the lithiated compound solution via syringe and stirred for 3 h at -78 ° C. Water (5 mL) was added, and the reaction mixture was warmed to room temperature and extracted using EtOAc (3 X). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed to yield 2.531 g of 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol in 89% yield. MS (EI) (M+H)⁺ = 242.2.

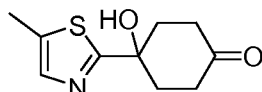
Step B



8-(5-Methyl-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol. A solution of *n*-butyllithium (5.70 mL of 1.6 M solution in hexane, 9.12 mmol) was added to 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.00 g, 4.14 mmol) in THF (10 mL) at -78 ° C with stirring under N₂. After being stirred at -78 ° C for 1 h, methyl iodide (0.71 mL, 9.12 mmol) was added to the lithiated compound solution via syringe at -78 ° C. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight. Water and EtOAc were added. The aqueous layer was extracted with EtOAc (3 ×). The combined organic layers

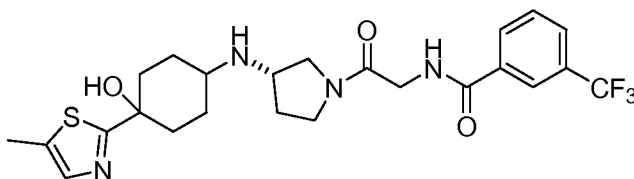
were washed with saturated NaCl, dried (MgSO_4), concentrated and flash chromatographed using 20% EtOAc/hexane to give 0.77 g of the title compound in 71% yield. MS (EI) $(\text{M}+\text{H})^+ = 256.1$.

Step C



4-Hydroxy-4-(5-methyl-1,3-thiazol-2-yl)cyclohexanone. A solution of 8-(5-Methyl-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.0 g, 4.14 mmol) in 20 mL of THF/ 3 N HCl (1:1) was stirred for 1 h at 50 °C. After cooling to room temperature, the mixture was treated with Na_2CO_3 to pH 8 and extracted with EtOAc (3 ×). The combined organic layers were washed saturated NaCl solution, dried (MgSO_4), and concentrated to give 0.82 g of 4-hydroxy-4-(5-methyl-1,3-thiazol-2-yl)cyclohexanone in 99% yield. MS (EI) $(\text{M}+\text{H})^+ = 212.2$.

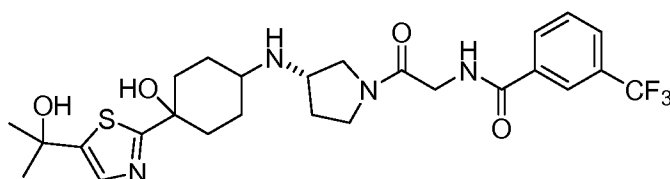
Step D



3-(Trifluoromethyl)-N-[2-((3S)-3-{[4-hydroxy-4-(5-methyl-1,3-thiazol-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]benzamide. The title compound was prepared from the ketone of C using a procedure similar to that described for Example 1. MS (EI): $(\text{M}+\text{H})^+ 511.1$.

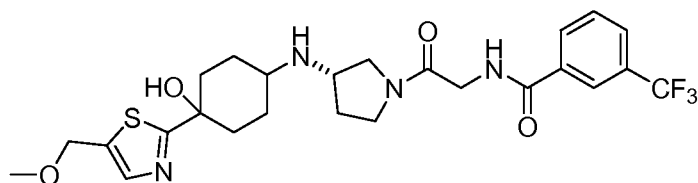
The following Examples were prepared in a similar manner.

Example 15



3-(Trifluoromethyl)-N-[2-[(3S)-3-{[4-hydroxy-4-[5-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]benzamide. MS (EI): $(\text{M}+\text{H})^+ 555.2$.

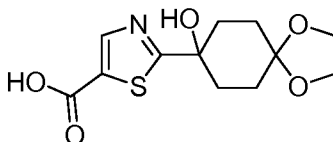
Example 16



3-(Trifluoromethyl)-N-{2-[(3S)-3-({4-hydroxy-4-[5-(methoxymethyl)-1,3-thiazol-2-yl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}benzamide. MS (EI): (M+H)⁺ 541.1.

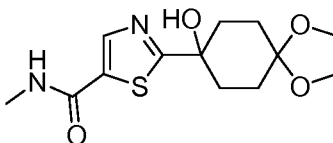
Example 17

Step A



2-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-1,3-thiazole-4-carboxylic acid. A solution of *n*-butyllithium (17.1 mL of 1.6 M solution in hexane, 27.35 mmol) was added to 8-(1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (3.00 g, 12.43 mmol) in THF (50 mL) at -78 ° C with stirring under N₂. After being stirred at -78 ° C for 1 h, dry ice (10 g, 227 mmol) was added to the lithiated compound solution and stirred for 2 h at -78 ° C. Water was added and the solution was warmed to room temperature. The mixture was then treated with 1N HCl to pH 3 to 4 and extracted with EtOAc (3 ×). The combined organic layers were washed saturated NaCl solution, dried (MgSO₄), and concentrated and chromatographed (EtOAc to 1% AcOH/EtOAc) to give 3.23 g of 2-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-1,3-thiazole-4-carboxylic acid. MS (EI) (M+H)⁺ = 286.0.

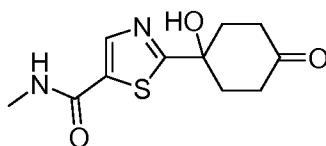
Step B



2-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-N-methyl-1,3-thiazole-4-carboxamide. To a stirred solution of 2-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-1,3-thiazole-4-carboxylic acid (0.30 g, 1.05 mmol) and methylamine (2M in THF, 2 mL, 4 mmol) in CH₂Cl₂ (10 mL) was

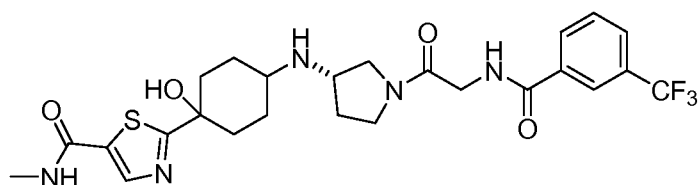
added Et₃N (0.5 mL, 3.6 mmol) followed by EDC (0.242 g, 1.262 mmol) and HOBt (0.193 g, 1.26 mmol). The mixture was stirred at room temperature overnight. Then the reaction mixture was diluted with EtOAc and washed with saturated Na₂CO₃ and brine. The organic layer was dried (MgSO₄), concentrated and flash chromatographed (50% EtOAc EtOAc) to give 0.16 g of the title compound in 50% yield. MS (EI) (M+H)⁺ = 299.0.

Step C



2-(1-Hydroxy-4-oxocyclohexyl)-N-methyl-1,3-thiazole-4-carboxamide. The title compound was prepared by conversion of the ketal of step B to a ketone using a procedure similar to that described in step C of Example 14. MS (EI) (M+H)⁺ = 255.0.

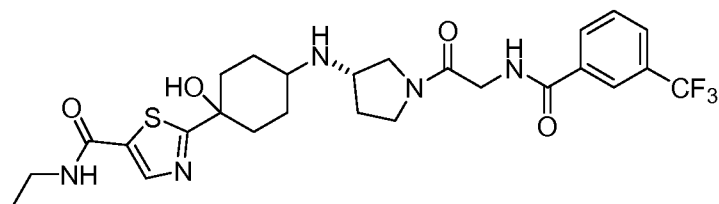
Step D



2-(1-Hydroxy-4-((3S)-1-((3-(trifluoromethyl)benzoyl)amino)acetyl)pyrrolidin-3-yl)amino)cyclohexyl)-N-methyl-1,3-thiazole-5-carboxamide. The title compound was prepared from the ketone of step C using the method described for Example 1. MS (EI): (M+H)⁺ 553.

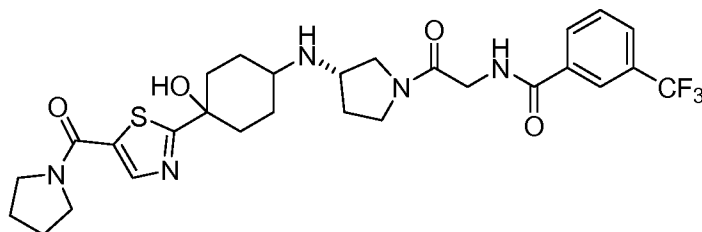
The following Examples were prepared in a similar fashion.

Example 18



N-Ethyl-2-(1-hydroxy-4-([(3S)-1-([3-(trifluoromethyl)benzoyl]amino)acetyl]pyrrolidin-3-yl]amino)cyclohexyl)-1,3-thiazole-5-carboxamide. MS (EI): (M+H)⁺ 567.1.

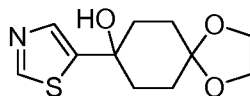
Example 19



N-{2-[(3S)-3-{4-Hydroxy-4-[5-(pyrrolidin-1-ylcarbonyl)-1,3-thiazol-2-yl]cyclohexyl}-amino)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (EI): (M+H)⁺ 594.1.

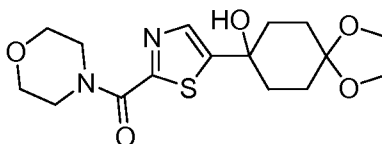
Example 20

Step A



8-(1,3-Thiazol-5-yl)-1,4-dioxaspiro[4,5]decan-8-ol. 2-TMS-thiazole (2.5 g, 15.89 mmol) was added to a solution of *n*-butyllithium (11.9 mL of 1.6 M solution in hexane, 19.07 mmol) in THF (20 mL) at -78 ° C with stirring under N₂. After being stirred at -78 ° C for 0.5 h, a solution of 1,4-cyclohexanedione mono-ethylene ketal (2.48 g, 15.89 mmol) in THF (20 mL) was added to the lithiated compound solution via syringe and stirred for 1 h at -78 ° C. Water (5 mL) and EtOAc were added, and the reaction mixture was warmed to room temperature and extracted using EtOAc (3 X). The combined organic layers were dried (MgSO₄), filtered, and crystallized from EtOAc to yield 3.4 g of 8-(1,3-thiazol-5-yl)-1,4-dioxaspiro[4,5]decan-8-ol in 90% yield. MS (EI) (M+H)⁺ = 242.1.

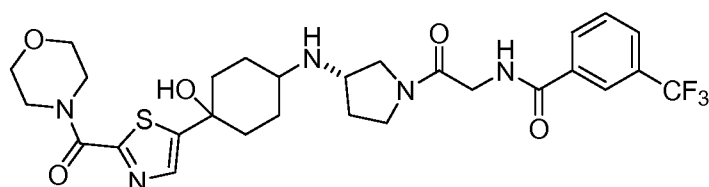
Step B



4-Hydroxy-4-[2-(morpholin-4-ylcarbonyl)-1,3-thiazol-5-yl]cyclohexanone. A solution of *n*-butyllithium (2.90 mL of 1.6 M in hexane, 4.64 mmol) was added to

8-(1,3-thiazol-5-yl)-1,4-dioxaspiro[4,5] decan-8-ol (1.00 g, 4.10 mmol) in THF (20 ml) at -78 °C under N₂. After being stirred at -78 °C for 1h, 4-morpholinecarbonyl chloride (0.93g, 6.15 mmol) was added to the lithiated compound solution via syringe and stirred for 2 h at -78 °C. Water (5 mL) was added, and the reaction mixture was warmed to room temperature. The reaction mixture was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated to give the ketal intermediate. Then this intermediate was treated with 20 mL of THF / 1N HCl (1:1) overnight at room temperature. The reaction solution was justified to pH 10 with Na₂CO₃ and extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (Na₂SO₄), concentrated and flash chromatographed using 20% EtOAc/hexanein to yield 309 mg of the title compound. MS (EI) (M+H)⁺ = 311.0.

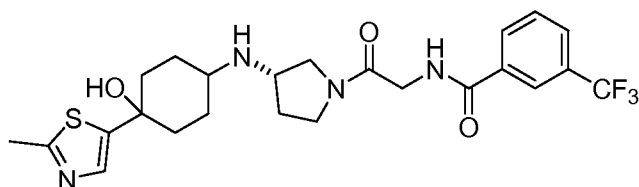
Step C



3-(Trifluoromethyl)-N-{2-[(3S)-3-({4-hydroxy-4-[2-(methoxymethyl)-1,3-thiazol-5-yl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}benzamide. The title compound was prepared from the ketone of step B using procedures similar to that for Example 14. MS (EI): (M+H)⁺ 541.1.

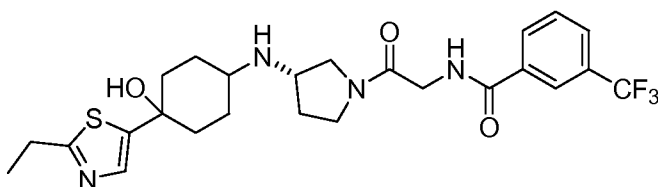
The following Examples were prepared in a similar manner.

Example 21



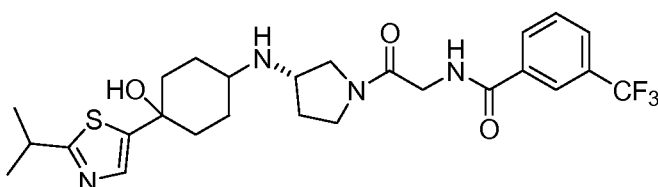
3-(Trifluoromethyl)-N-{2-[(3S)-3-({4-hydroxy-4-(2-methyl-1,3-thiazol-5-yl)cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}benzamide. MS (EI): (M+H)⁺ 511.1.

Example 22



3-(Trifluoromethyl)-N-[2-((3*S*)-3-{[4-(2-ethyl-1,3-thiazol-5-yl)-4-hydroxycyclohexyl]-amino}pyrrolidin-1-yl)-2-oxoethyl]benzamide. MS (EI): (M+H)⁺ 525.2.

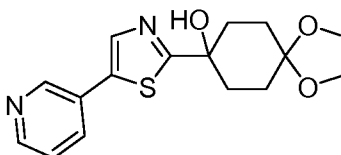
Example 23



N-[2-((3*S*)-3-{[4-Hydroxy-4-(2-isopropyl-1,3-thiazol-5-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (EI): (M+H)⁺ 539.2.

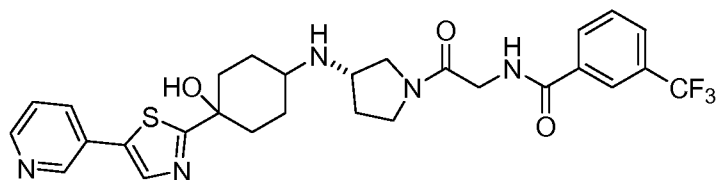
Example 24

Step A



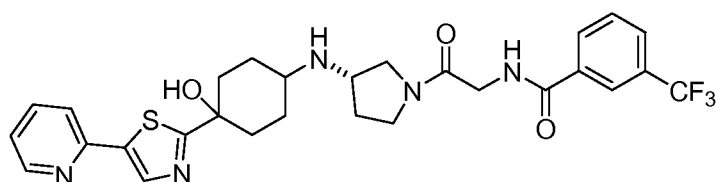
8-(5-Pyridin-3-yl-1,3-thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol. A solution of *n*-butyllithium (7.8 mL of 1.6 M solution in hexane, 12.45 mmol) was added to 8-(1,3-thiazol-5-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.0 g, 4.15 mmol) in THF (20 mL) at -78 °C with stirring under N₂. After being stirred at -78 °C for 0.5 h, 12.5 mL of 0.5 M solution of ZnCl₂ (6.23 mmol) in THF was added. The resulting mixture was stirred at room temperature for 0.5 h and a mixture of 3-bromopyridine (0.40 mL, 4.15 mmol) and PdCl₂(PPh₃)₂ (0.11 g, 0.16 mmol) in 5 mL of THF was added via syringe. After refluxing overnight the reaction was quenched with 10 mL of saturated NH₄Cl solution. The aqueous layer was extracted using EtOAc (3 X). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed to yield 0.68 g of the title compound in 52% yield. MS (EI) calcd: (M+H)⁺ = 319.1; found: 319.1.

Step B



N-[2-(3*S*)-3-([4-Hydroxy-4-(5-pyridin-3-yl-1,3-thiazol-2-yl)cyclohexyl]methyl)-pyrrolidin-1-yl]-2-oxoethyl]-3-(trifluoromethyl)benzamide. The title compound was prepared from the ketal of step A following the procedures described for Example 14. MS (EI): (M+H)⁺ 574.2.

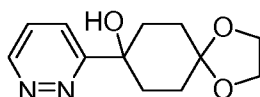
Example 25



N-[2-((3*S*)-1-[4-Hydroxy-4-(5-pyridin-2-yl-1,3-thiazol-2-yl)cyclohexyl]pyrrolidin-3-yl)amino]-2-oxoethyl]-3-(trifluoromethyl)benzamide. The title compound was prepared following the procedures described for Example 24. MS (EI): (M+H)⁺ 574.2.

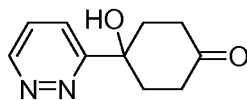
Example 26

Step A



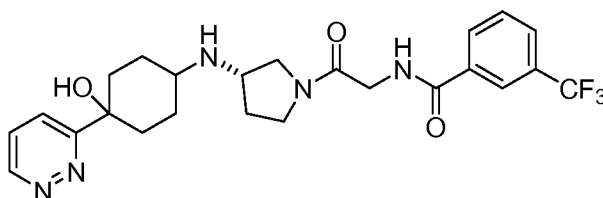
8-Pyridazin-3-yl-1,4-dioxaspiro[4.5]decan-8-ol. To a solution of pyridazine (17.7 mmol, 1.28 mL) in THF (60 mL) was added 2,2,6,6, lithium tetramethylpiperidine (71 mmol, 10 g) at −78 °C. The reaction was then stirred for 6 min and 1,4-dioxaspiro[4.5]decan-8-one (71 mmol, 11 g) was added. The reaction was stirred for 5 h at −78 °C at which point the reaction was quenched using a solution of ethanol, hydrochloric acid and THF (30 mL, 1:1:1). The reaction was allowed to warm to ambient temperature and the reaction was extracted using EtOAc. The organic layers were combined and dried over MgSO₄. The reaction was then purified using flash chromatography to afford the desired alcohol (44%, 1.84 g). MS (M+H)⁺ 237.1.

Step B



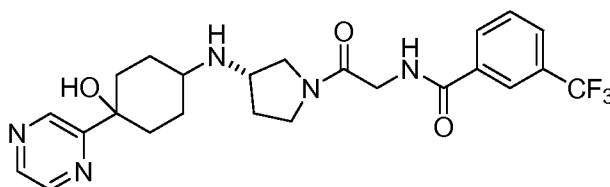
4-Hydroxy-4-pyridazin-3-ylcyclohexanone. To the product from step A (7.79 mmol, 1.84 g) in THF (15 mL) was added HCl (45 mmol, 15 mL). The reaction was stirred overnight and subsequently quenched using Na_2CO_3 . The reaction was then extracted using EtOAc (3 x 100 mL). The organic layers were combined, dried and concentrated in vacuo to afford the desired ketone (780 mg, 52%). MS $(\text{M}+\text{H})^+$ 193.1.

Step C



N-(2-((3S)-3-[(4-hydroxy-4-pyridazin-3-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared from the ketone of step B using a procedure similar to that described for Example 1. MS $(\text{M}+\text{H})^+$ 492.2.

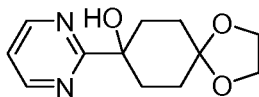
Example 27



N-(2-((3S)-3-[(4-hydroxy-4-pyrazin-2-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared in a manner similar to that for Example 26. MS $(\text{M}+\text{H})^+$ 492.2.

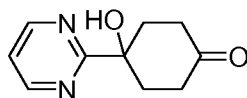
Example 28

Step A



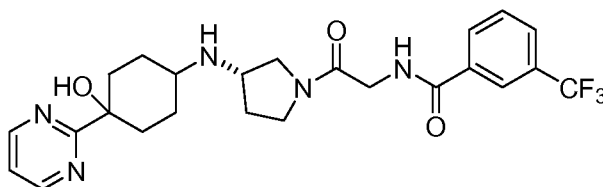
8-Pyrimidin-2-yl-1,4-dioxaspiro[4.5]decan-8-ol (1a). To a solution of 2-bromopyrimidine (0.20 g, 1.258 mmol) in dry methylene chloride (3.0 mL) was dropwise added 1.6 M of *n*-butyllithium in hexane (0.86 mL) at -78 °C. The reaction mixture was stirred for 29 min at -78 °C and 1,4-dioxaspiro[4.5]decan-8-one (0.196 g, 1.26 mmol) in CH₂Cl₂ (3 mL) was added dropwise. The reaction was stirred at -78 °C for 50 min and quenched with an aqueous solution of NH₄Cl. After being warmed to room temperature, the mixture was extracted with CH₂Cl₂ three times. The combined extracts were dried over MgSO₄, filtered and concentrated in vacuo to provide 0.50 g of crude product. Purification by column chromatography on silica gel eluting with 0 → 50% EtOAc in hexanes provided 0.159 g (54%) of desired product as a light brown-yellow solid. MS (M+H)⁺ 237.2.

Step B



4-Hydroxy-4-pyrimidin-2-ylcyclohexanone. To the product from step A (190 mmol, 44 g) in THF (200 mL) was added HCl solution (300 mmol, 100 mL). The reaction was stirred over 2 days after which the reaction was washed using diethyl ether. The aqueous layer was then quenched using NaOH (50%) to obtain a pH of 11. The aqueous layer was extracted using EtOAc (6 x 300 mL). The organic layer was combined and dried over MgSO₄ and concentrated in vacuo. The reaction was purified via flash chromatography to afford the desired ketone (18 g, 49%). MS (M+H)⁺ 193.1.

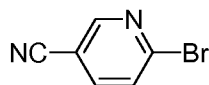
Step C



N-(2-((3S)-3-[(4-Hydroxy-4-pyrimidin-2-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared from the ketone of step B using a procedure similar to that for Example 1. MS (M+H)⁺ 492.2.

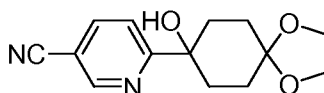
Example 29

Step A



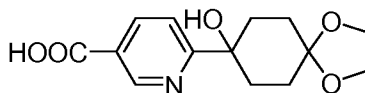
6-Bromonicotinonitrile. 6-Chloronicotinonitrile (13.8 g, 100 mmol) was heated at 145 °C in phosphorus tribromide (150 mL) for 32 h. After cooling, the mixture was concentrated in vacuo. To the residue was added phosphorus tribromide (150 mL), and the mixture was heated at 145 °C for another 32 h. After cooling, the mixture was concentrated in vacuo, and an ice-water mixture (500 mL) was added. Sodium bicarbonate was added to neutralize the mixture, and the product was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was chromatographed (hexanes-ethyl acetate) to give 14.9 g (81%) of 6-bromonicotinonitrile as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 11.0 Hz, 1H), 7.80 (dd, *J* = 3.1, 11.0 Hz, 1H), 8.67 (d, *J* = 3.1 Hz, 1H); MS (M+H)⁺ *m/z*=183.0, 185.0.

Step B



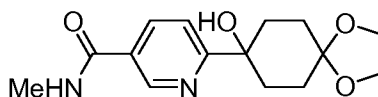
6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)nicotinonitrile. A solution of 6-bromonicotinonitrile (2 g, 11 mmol) in 50 mL of dry THF and 15 mL of dry hexane under argon was cooled to -100 °C in a liquid nitrogen-Et₂O bath. *n*-Butyllithium (7.5 mL, 11 mmol, 1.6 M solution in hexane) was added dropwise so that the internal temperature did not exceed -95 °C. The orange solution was stirred for an additional 10 min at -100 °C to -95 °C and then treated dropwise over 10 min with a solution of 1,4-cyclohexanedione monoethylene ketal (1.8 g, 11 mmol) in 55 mL of dry THF, again carefully maintaining the temperature below -95 °C. The reaction mixture was stirred for 10 min at -100 °C to -95 °C, allowed to warm to 20 °C and poured into ice water (400 mL). The organic layer was separated, and the aqueous layer was extracted twice with Et₂O (200 mL). The combined organic extracts were dried over MgSO₄ and evaporated to give 2.8 g of white crystalline solid. Trituration with Et₂O afforded 1.9 g (67% yield) of white crystals: MS: (M+H)⁺ 261.

Step C



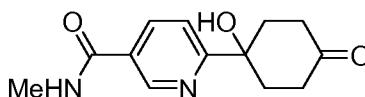
6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)nicotinic acid. A mixture of 6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)nicotinonitrile (1.9g, 7. 3 mmol) in 50 mL of 2-methoxyethanol and 50 mL of 2.5 N NaOH was heated on a steam bath for 15 h. The solution was cooled in an ice bath, adjusted to pH 7-8 with concentrated HCl, and evaporated to driness. Water (375mL) was added, and the pH was adjusted to 2 with HCl. The tan solid was filtered off and washed with water to give 1.92 g (6. 9 mmol, 94% yield) of 6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)nicotinic acid: MS: (M+H)⁺ 280.

Step D



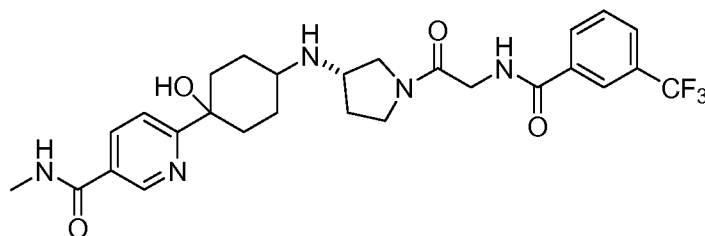
6-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-N-methylnicotinamide. 6-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)nicotinic acid (560 mg, 2 mmol), methylamine (1.2 mL, 2.0 M THF solution), BOP reagent (1.07 g, 2.4 mmol) and 0.8 mL (6 mmol) of triethylamine were dissolved in 15 mL of DMF at room temperature. The reaction mixture was stirred at room temperature overnight. Direct chromatography on silica gel (flash chromatography grade) with 50% ethyl acetate-hexane gave 410 mg (70%) of the desired product, 6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-N-methylnicotinamide: MS: (M+H)⁺ 293.

Step E



6-(1-Hydroxy-4-oxocyclohexyl)-N-methylnicotinamide. 6-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-N-methylnicotinamide (410 mg, 1.4 mmol) was dissolved in the mixture solvent of 7 mL of THF and 7 mL of 1 N HCl aqueous solution at room temperature. The reaction mixture was then stirred at 60 °C for 1h. The solution was cooled down to room temperature, adjusted to pH 7-8 with saturated NaHCO₃ aqueous solution. The organic layer was separated, and the aqueous layer was extracted twice with EA (20 ml X 2). The combined organic extracts were dried over MgSO₄ and evaporated to give an oil residue. Chromatography on silica gel (flash chromatography grade) with 40% ethyl acetate-hexane gave 410 mg (90%) of the desired product, 6-(1-hydroxy-4-oxocyclohexyl)-N-methylnicotinamide: MS: (M+H)⁺ 249.

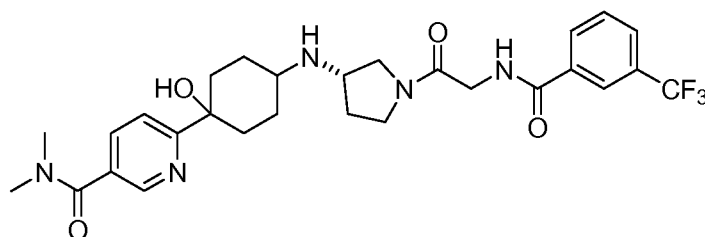
Step F



6-(1-Hydroxy-4-((3*S*)-1-((3-(trifluoromethyl)benzoyl)amino)acetyl)pyrrolidin-3-yl)amino)cyclohexyl)-N-methylnicotinamide. 6-(1-Hydroxy-4-oxocyclohexyl)-N-methylnicotinamide (100 mg, 0.4 mmol) and 126 mg (0.4 mmol) of N-2-[(3*S*)-3-aminopyrrolidin-1-yl]-2-oxoethyl]-3-(trifluoromethyl)benzamide were dissolved in 10.0 mL of methylene chloride. To the solution was added 170 mg (0.8 mmol) of sodium triacetoxymethylborohydride. The reaction mixture was stirred at room temperature for 2 h. Direct chromatography on silica gel gave 48 mg (23%) of the final desired product 48 mg (top spot on TLC and first peak on HPLC). MS: (M+H)⁺ 547.

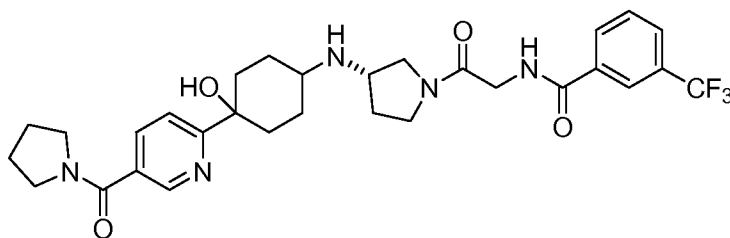
The following Examples were prepared in a similar fashion.

Example 30



6-(1-Hydroxy-4-((3*S*)-1-((3-(trifluoromethyl)benzoyl)amino)acetyl)pyrrolidin-3-yl)amino)cyclohexyl)-N,N-dimethylnicotinamide. MS (M+H)⁺ 562.

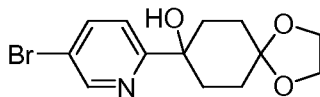
Example 31



N-2-[(3*S*)-3-((4-Hydroxy-4-[5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]cyclohexyl)amino)pyrrolidin-1-yl]-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 588.

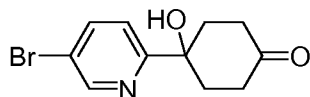
Example 32

Step A



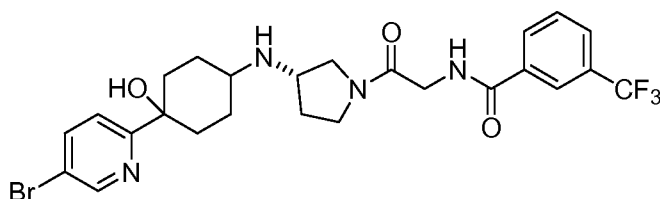
8-(5-Bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol. To a solution of 2,5-dibromopyridine (4.10 g, 17 mmol) in anhydrous toluene (250 mL) at -78°C was dropwise added *n*-BuLi (1.6 M, 12 mL). After stirred at -78°C for 2.5 hours, a solution of 1,4-dioxaspiro[4.5]decan-8-one (2.73 g, 17 mmol) in methylene chloride (25 mL) was added into the reaction mixture, and the resulting mixture was stirred for additional one hour and allowed to warm up to rt slowly. The reaction mixture was poured into aqueous NaHCO_3 (200 mL) and then extracted with EtOAc (2X 50 mL). The organic extracts were combined, washed with saline solution (2X 50 mL), dried over MgSO_4 , concentrated in vacuo. The resulting solid was titrated with ether and the filtrate was collected. The ether was removed and the solid was chromatographed on silica gel, eluting with hexane/ethyl acetate (2 to 1), to give 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (4.27 g) as pale yellow solid. LCMS: 316.10/314.10 ($\text{M}+\text{H}^+$, 100%). ^1H NMR: δ 8.6 (s, 1 H), 7.82 (d, 1 H), 7.38 (d, 1 H), 4.6 (s, 1 H), 4.0 (m, 4 H), 2.2 (m, 4 H), 1.7 (m, 4 H).

Step B



4-(5-Bromopyridin-2-yl)-4-hydroxycyclohexanone. The title compound was prepared by treating the ketal of step A with HCl in water following the procedure described in step B of Example 2. MS ($\text{M}+\text{H}^+$)⁺ 271.

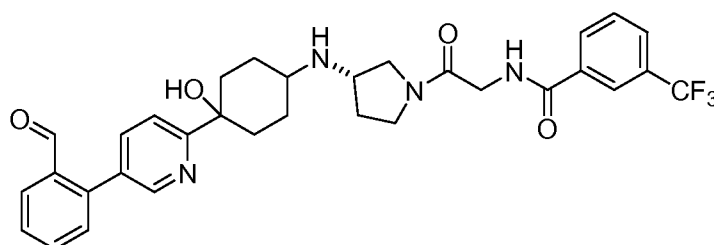
Step C



N-[2-((3S)-3-[4-(5-bromopyridin-2-yl)-4-hydroxycyclohexyl]aminopyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. To a 1-neck round-bottom flask charged with isopropanol (6 mL) was added 4-(5-bromopyridin-2-yl)-4-hydroxycyclohexanone (497.6 mg, 1.85 mmol), N-2-[(3S)-3-aminopyrrolidin-1-yl]-2-oxoethyl-3-(trifluoromethyl)-benzamide

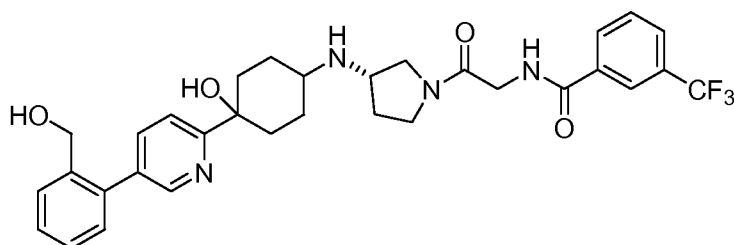
hydrochloride (651 mg, 1.85 mol), and triethylamine (0.851 mL, 6.11 mol). The resulting mixture was stirred for 30 minutes at 25°C. Then to it was added sodium triacetoxyborohydride (619 mg, 2.78 mmol) and the mixture was continued stirring at rt overnight. The reaction mixture was concentrated, and the residue was chromatographed on SiO₂, eluting with acetone/methanol (100% to 90%/10%) to give two fractions, F1 (404 mg) and F2 (368 mg) in total 73% yield. LCMS: (M+H)⁺ 571.1 / 569.1. ¹H NMR (CD₃OD) δ 8.65 (t, 1H), 8.21 (s, 1H), 8.14 (d, 1H), 8.03 (dt, 1H), 7.88 (d, 1H), 7.69 (m, 2H), 4.23 (dd, 1H), 4.16 (s, 1H), 4.10 (m, 2H), 3.90 (m, 2H), 3.70 (m, 2H), 3.60 (dd, 1H), 3.52 (m, 2H), 2.55 (m, 1H), 2.42 (m, 2H), 2.22 (m, 3H), 1.80 (m, 4H).

Example 33



N-{2-[(3S)-3-({4-[5-(2-formylphenyl)pyridin-2-yl]-4-hydroxycyclohexyl}-amino)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. A solution of N-[2-((3S)-3-[4-(5-bromopyridin-2-yl)-4-hydroxycyclohexyl]aminopyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide (30.0 mg, 0.0527 mmol) and (2-formylphenyl)boronic acid (8.6 mg, 0.052 mmol) in DMF (0.60 mL) and aqueous sodium carbonate (2M, 0.198 mL) was degassed with N₂ for 5 minutes. Then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (2.2 mg, 0.0026 mmol) was added in under N₂ flush. The reaction mixture was degassed with N₂ for another 5 minutes and then the tube was sealed. The reaction mixture was heated under microwave at 130°C for 5 minutes. After cooling down, the reaction mixture was filtered through a short pad of silica gel and washed with CH₃CN. The resulting solution was acidified with TFA to pH 1~2, then was subjected to purification on Prep-HPLC. The appropriate fractions were lyophilized to give the product (23 mg, 53%) as a white powder. MS: (M+H)⁺ 595.

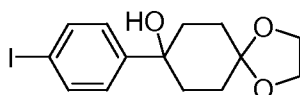
Example 34



N-(2-(3*S*)-3-[(4-Hydroxy-4-5-[2-(hydroxymethyl)phenyl]pyridin-2-yl)cyclohexyl]amino]pyrrolidin-1-yl-2-oxoethyl)-3-(trifluoromethyl)benzamide bis(trifluoroacetate). To a solution of N-2-[(3*S*)-3-(4-[5-(2-formylphenyl)pyridin-2-yl]-4-hydroxycyclohexylamino)pyrrolidin-1-yl]-2-oxoethyl-3-(trifluoromethyl)benzamide bis(trifluoroacetate) (salt) (3.3 mg, 0.004 mmol) in methanol (0.50 mL) at 0°C was added sodium borohydride (0.455 mg, 0.0120 mmol). The reaction mixture was allowed to warm up to room temperature and stirred at rt for 60 minutes and then at 60°C for 60 minutes. The mixture was purified by prep-HPLC to afford the product as a TFA salt (1.1 mg, 33%). LCMS: (M+H)⁺ 597.2.

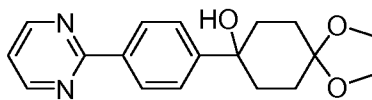
Example 35

Step A



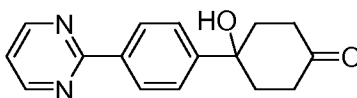
8-(4-Iodo-phenyl)-1,4-dioxaspiro[4.5]decan-8-ol. To a solution of 1,4-diiodobenzene (16.5 g, 50 mmol) in THF (350 mL) at -78°C was added *n*-BuLi (2.5 M, 24 mL) over 1 hour. After stirred additional 30 minutes, a solution of 1,4-dioxaspiro[4.5]decan-8-one (7.8 g, 50 mmol) in THF (30 mL) was added in and the resulting mixture was stirred for 3 hours. To the mixture was added TMSCl (5.4 g, 50 mmol) and the resulting mixture was allowed to warm to rt and stirred at rt for 18 hours. The reaction mixture was neutralized to pH 6.0, and extracted with ethyl acetate (3X 50 mL). The organic extracts were combined, washed with saline solution (2X 50 mL), dried over sodium sulfate, concentrated in vacuo. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (95/5 to 100/0). The appropriate fractions were combined to give 8-(4-Iodo-phenyl)-1,4-dioxaspiro[4.5]decan-8-ol (12 g, 66.6%) with LCMS: 361.2 (M+H⁺, 100%) and {[8-(4-iodophenyl)-1,4-dioxaspiro[4.5]dec-8-yl]oxy}(trimethyl)silane (6 g, 27%) with LCMS: 433.1 (M+H⁺, 100%).

Step B



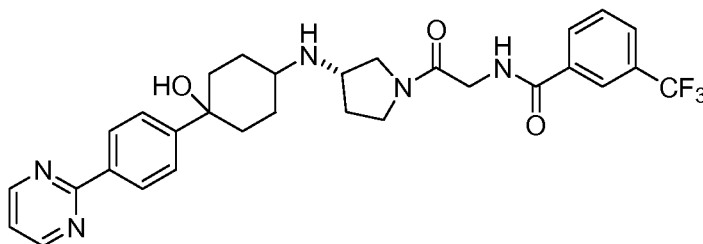
8-(4-pyrimidin-2-ylphenyl)-1,4-dioxaspiro[4.5]decan-8-ol. To a solution of 8-(4-iodophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (450.0 mg, 1.249 mmol) in THF (1.0 mL) at room temperature was added dropwise isopropylmagnesium chloride (2.0 M in THF, 1.37 mL) and the reaction mixture was stirred at room temperature for 30 mins. To another flask charged with nickel acetylacetonate (20 mg, 0.06 mmol) and 1,3-bis(diphenylphosphino)-propane (26 mg, 0.062 mmol) suspended in THF (3 mL) under N₂ was added 2-bromopyrimidine (199 mg, 1.25 mmol). The resulting mixture was stirred at room temperature until it is clear. The second mixture was transferred into the degassed Grignard solution prepared in step 1. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, quenched with water, washed with brine, dried over Na₂SO₄, and concentrated. The residue was columned on silica gel, eluted with hexane/EtOAc (2/1), to gave the desired compound (270 mg, 69%) as white solid. LCMS: 313.1, (M+H, 100%). ¹H NMR (CDCl₃): δ 8.86 (d, 2H), 8.46 (dd, 2H), 7.71 (dd, 2H), 7.24 (t, 1H), 4.05 (d, 4H), 2.30 (dt, 2H), 2.18 (dt, 2H), 1.90 (m, 2H), 1.78 (m, 2H).

Step C



4-Hydroxy-4-(4-pyrimidin-2-ylphenyl)cyclohexanone. The title compound was prepared by treating the ketal of step B with HCl in water following the procedure described in step B of Example 2. MS (M+H)⁺ 269.

Step D

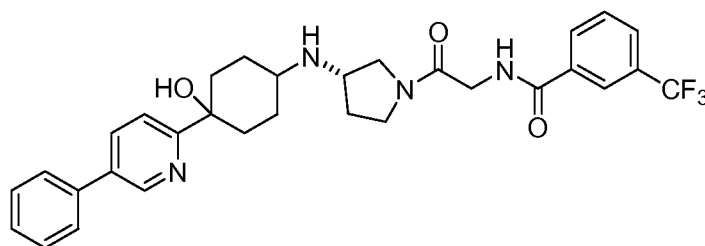


N-[2-((3S)-3-[4-hydroxy-4-(4-pyrimidin-2-ylphenyl)cyclohexyl]aminopyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide bis(trifluoroacetate) (salt). To a 1-neck round-bottom

flask charged with methylene chloride (1 mL) was added 4-hydroxy-4-(4-pyrimidin-2-ylphenyl)cyclohexanone (50.0 mg, 0.186 mmol), N-2-[(3S)-3-aminopyrrolidin-1-yl]-2-oxoethyl-3-(trifluoromethyl)benzamide hydrochloride (65.5 mg, 0.186 mmol), and triethylamine (85.7 μ L, 0.615 mmol). The resulting mixture was stirred at 25°C for 30 minutes, and to it was added sodium triacetoxyborohydride (62.4 mg, 0.28 mmol) in portion. The reaction mixture was stirring at rt overnight. The reaction was concentrated, and the residue was chromatographed on SiO₂, eluted with acetone/methanol (100% to 90%/10%) to give two fractions, which were further purified on prep-LCMS separately to afford F1 (24.2 mg) and F2 (25.9 mg) as white powder in total 34% of the yield. LCMS: 568.2 (M+H, 100%).

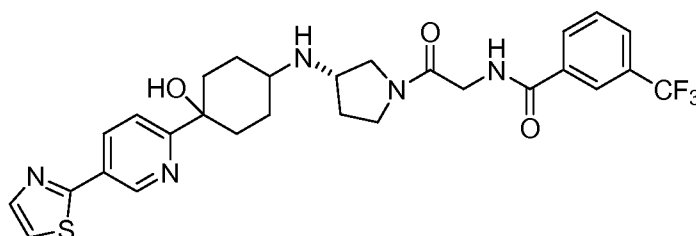
The following Examples were prepared in a manner similar to that for Examples 32-35.

Example 36



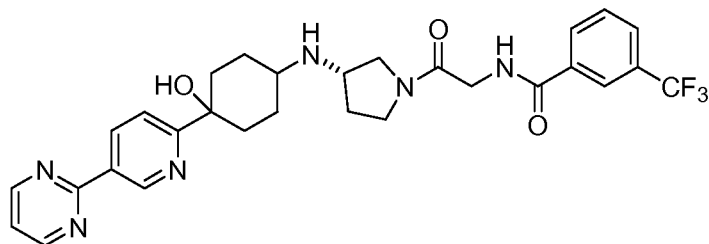
N-[2-((3S)-3-{[4-Hydroxy-4-(5-phenylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 567.

Example 37



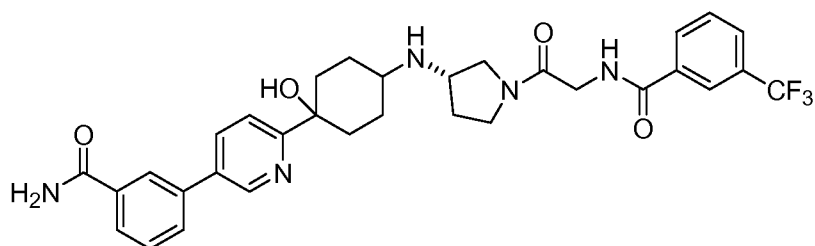
N-{2-[(3S)-3-{[4-Hydroxy-4-[5-(1,3-thiazol-2-yl)pyridin-2-yl]cyclohexyl]amino}pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 574.

Example 38



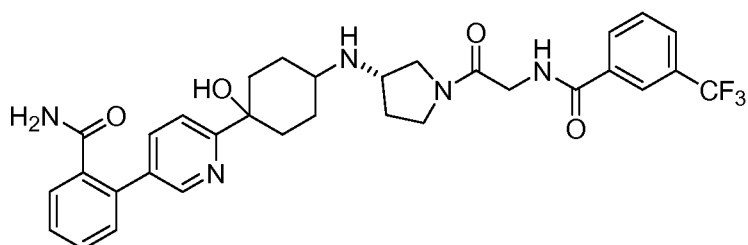
N-[2-((3S)-3-[[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino]pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 569.

Example 39



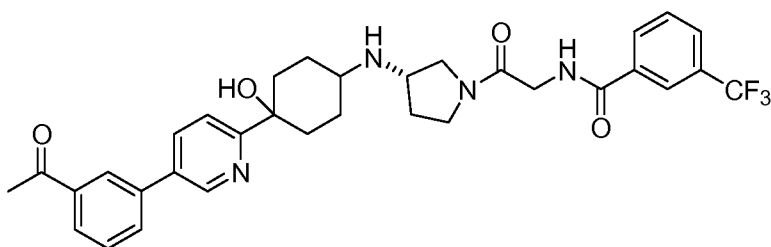
N-(2-((3S)-3-[(4-{5-[3-(Aminocarbonyl)phenyl]pyridin-2-yl}-4-hydroxycyclohexyl)-amino]pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 610.

Example 40



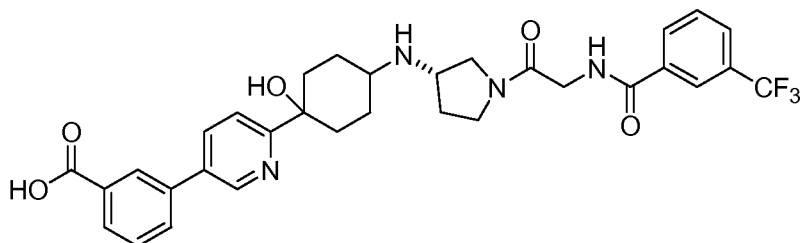
N-(2-((3S)-3-[(4-{5-[2-(Aminocarbonyl)phenyl]pyridin-2-yl}-4-hydroxycyclohexyl)-amino]pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 610.

Example 41



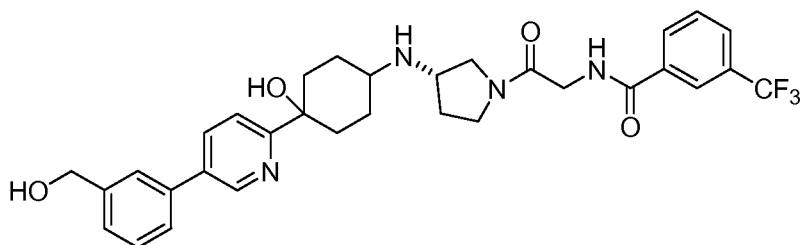
N-{2-[(3S)-3-({4-[5-(3-Acetylphenyl)pyridin-2-yl]-4-hydroxycyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 609.

Example 42



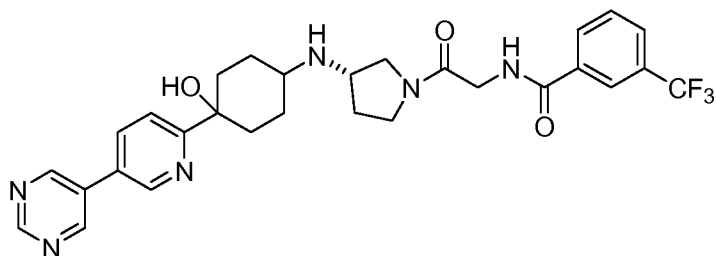
3-[6-(1-Hydroxy-4-[(3S)-1-({3-(trifluoromethyl)benzoyl}amino)acetyl]pyrrolidin-3-yl)amino}cyclohexyl]pyridin-3-yl]benzoic acid. MS (M+H)⁺ 611.

Example 43



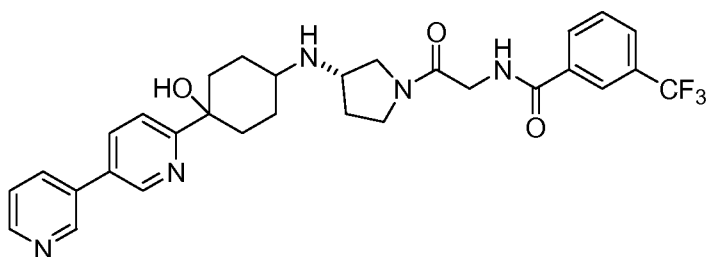
N-(2-[(3S)-3-[(4-Hydroxy-4-[5-[3-(hydroxymethyl)phenyl]pyridin-2-yl]cyclohexyl]amino)pyrrolidin-1-yl]-2-oxoethyl)-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 597.

Example 44



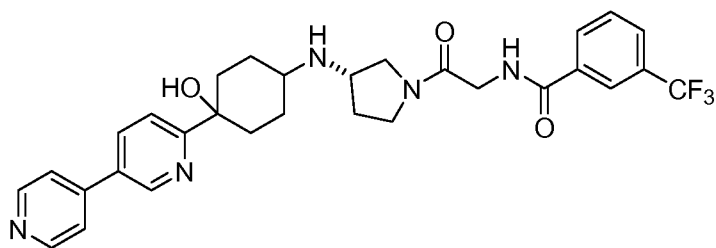
N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-5-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 569.

Example 45



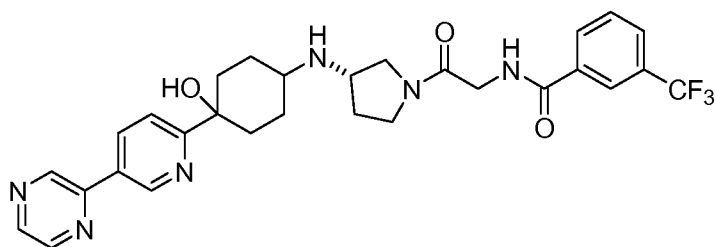
N-[2-((3S)-3-{[4-(3,3'-Bipyridin-6-yl)-4-hydroxycyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 568.

Example 46



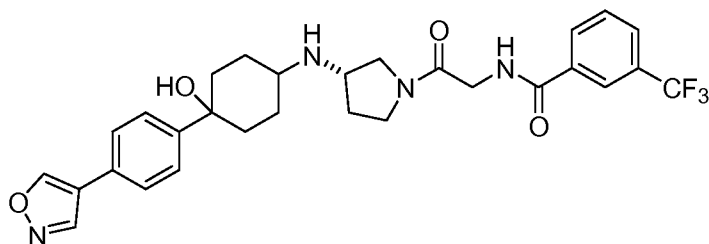
N-[2-((3S)-3-{[4-(3,4'-Bipyridin-6-yl)-4-hydroxycyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 568.

Example 47



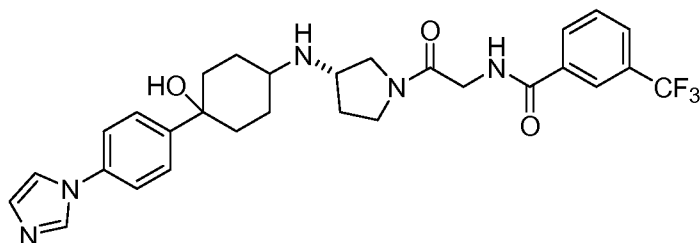
N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrazin-2-yl)pyridin-2-yl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 569.

Example 48



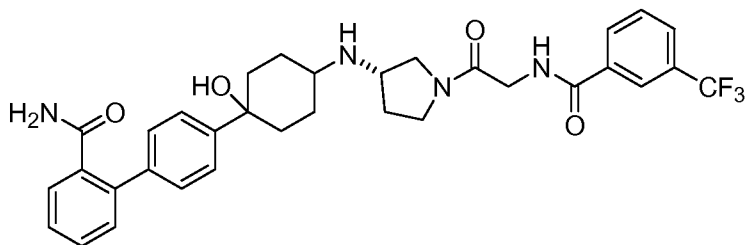
N-[2-((3S)-3-{[4-Hydroxy-4-(4-isoxazol-4-yl)phenyl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 557.

Example 49



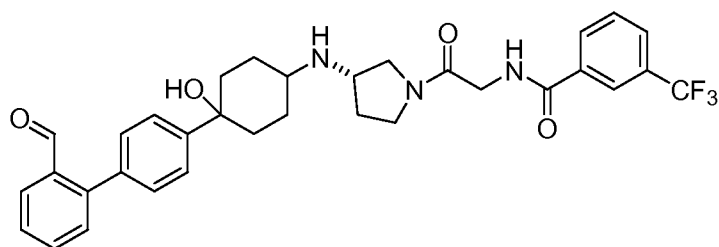
N-[2-((3S)-3-{[4-Hydroxy-4-[4-(1H-imidazol-1-yl)phenyl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 556.

Example 50



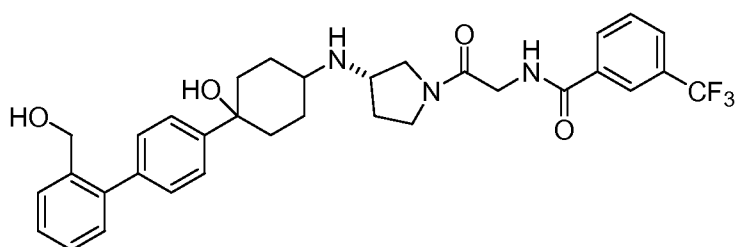
4'-(1-Hydroxy-4-[[3-(trifluoromethyl)benzoyl]amino]acetyl)pyrrolidin-3-yl]amino}cyclohexyl)biphenyl-2-carboxamide. MS (M+H)⁺ 609.

Example 51



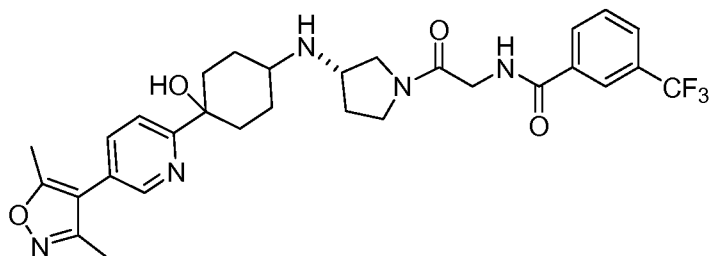
N-[2-((3*S*)-3-([4-(2'-Formylbiphenyl-4-yl)-4-hydroxycyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 594.

Example 52



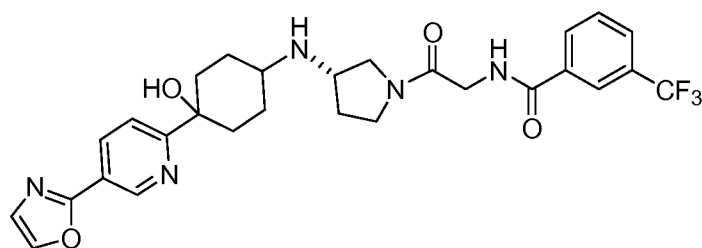
N-{2-[(3*S*)-3-({4-Hydroxy-4-[2'-(hydroxymethyl)biphenyl-4-yl]cyclohexyl}amino)-pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 596.

Example 53



N-{2-[(3*S*)-3-({4-[5-(3,5-Dimethylisoxazol-4-yl)pyridin-2-yl]-4-hydroxycyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 586.

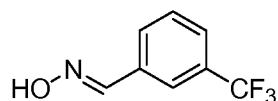
Example 54



N-{2-[(3S)-3-({4-Hydroxy-4-[5-(1,3-oxazol-2-yl)pyridin-2-yl]cyclohexyl}amino)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 574.

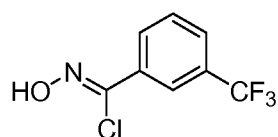
Example 55

Step A



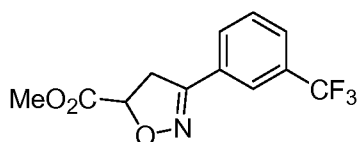
3-(Trifluoromethyl)benzaldehyde oxime. To a flask containing 3-trifluorobenzaldehyde (1.74 g, 10 mmol) and hydroxylamine hydrochloride (0.76 g, 11 mmol) in methanol (25 mL) was added TEA (0.65 g, 11 mmol). The reaction mixture was heated to reflux for 3 h, neutralized to pH 6.0, and extracted with ethyl acetate (3 X 20 mL). The organic extracts were combined, washed with saline solution (20 mL), dried over sodium sulfate, concentrated in vacuo to give the oxime (1.9 g) as a colorless oil. LCMS: (M+H)⁺ 190.2.

Step B



3-(Trifluoromethyl)benzaldehyde oxime. To a dried flask containing 3-(trifluoromethyl)benzaldehyde oxime (1.89 g, 10 mol) in methylene chloride (100 mL) was added N-chlorosuccinimide (1.40 g, 10.5 mmol) slowly at 0 °C. The reaction mixture was warmed to 45 °C for 2 h, poured over ice, diluted with H₂O (20 mL), and extracted with EtOAc (100 mL). The organic phase was washed with H₂O (2X 25 mL) and saline solution (25 mL), dried over sodium sulfate, concentrated in vacuo to give the oxime (2 g, 90%). LCMS: (M+H)⁺ 224.4.

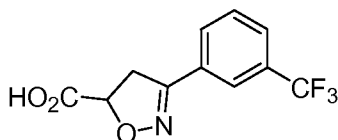
Step C



3-[3-(Trifluoromethyl)phenyl]-4,5-dihydroisoxazole-5-carboxylate. To a flask containing N-hydroxy-3-(trifluoromethyl)benzenecarboximidoyl chloride (2.0 g, 8.9 mmol) and methyl acrylate (0.7 g, 8 mmol) in methylene chloride (100 mL) at 0 °C under an inert

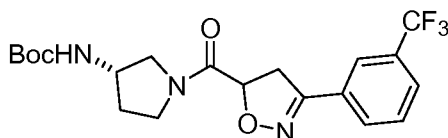
atmosphere was added TEA (0.90 g, 8.8 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 20 h, quenched with water (30 mL), and extracted with methylene chloride (2X 50 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel, eluting with methylene chloride/methanol (100/1 to 95/5). The appropriate fractions were combined and concentrated in vacuo to give the title compound (2.3 g, 100%): LCMS: (M+H)⁺ 274.2. ¹H NMR: (CDCl₃) δ 8.03 (s, 1H), 7.92 (d, 1H), 7.71 (d, 1H), 7.59 (dd, 1H), 5.28 (dd, 1H), 3.86 (s, 3H), 3.71 (dd, 2H).

Step D



3-[3-(Trifluoromethyl)phenyl]-4,5-dihydroisoxazole-5-carboxylic acid. To a solution of methyl 3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole-5-carboxylate (2.3 g, 8.4 mmol) in THF (10 mL) was added 2 M of sodium hydroxide in water (10 mL) at 0 °C. The reaction mixture was slowly warmed to ambient temperature, stirred for 2 h, neutralized with 2 N HCl to pH 7, and extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo. The residue was chromatographed on silica gel, eluting with methylene chloride/methanol (95/5 to 80/20). The appropriate fractions were combined and concentrated in vacuo to give the title compound (2.18 g, 100%) as a white crystalline solid. LCMS: (M-H)⁻ 258.2.

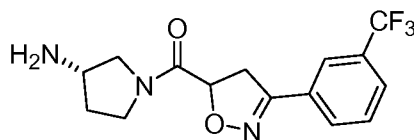
Step E



tert-Butyl [(3*S*)-1-(3-[3-(Trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-yl)pyrrolidin-3-yl]carbamate. To a solution of 3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole-5-carboxylic acid (259 mg, 1 mmol) and *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate (186 mg, 1 mmol) in DMF (0.5 mL) and methylene chloride (5 mL) at 0 °C was added triethylamine (120 mg, 0.0012 mol) and Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (442 mg, 1 mmol). The mixture was allowed to warm to rt over 1 h and stirred at rt for 1 h. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel, eluting with 1% NH₄OH in ethyl acetate to give the

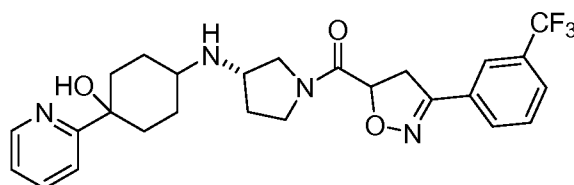
desired coupling intermediate (410 mg) as a white solid. LCMS: $(M+H)^+$ 428.4.

Step F



(3S)-1-(3-[3-(Trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-ylcarbonyl)-pyrrolidin-3-amine hydrochloride. To a solution of the intermediate of step E in methylene chloride (5 mL) was added 4 M HCl in dioxane (5 mL). After stirred at rt for 2 h, the resulting solution was concentrated in vacuo to give the HCl salt (350 mg) of the amine as a white solid. LCMS: $(M+H)^+$ 364.4.

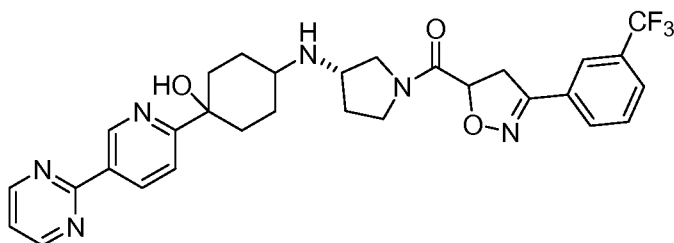
Step G



1-Pyridin-2-yl-4-[(3S)-1-(3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-ylcarbonyl)pyrrolidin-3-yl]aminocyclohexanol. To a solution of (3S)-1-(3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-ylcarbonyl)pyrrolidin-3-amine hydrochloride (178 mg, 0.489 mmol) and 4-hydroxy-4-pyridin-2-yl-cyclohexanone (95.1 mg, 0.498 mmol) in methylene chloride (6 mL) was added triethylamine (50.3 mg, 0.498 mmol) and then $\text{NaBH}(\text{OAc})_3$ (120 mg, 0.54 mmol). After being stirred at rt for 2 h, the reaction mixture was neutralized with 1 N NaOH to pH 7, and extracted with ethyl acetate (2 x 25 mL). The organic extracts were combined, washed with saline solution (20 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel, eluting with 1% NH_4OH in ethyl acetate/methanol (95/5 to 80/20). The appropriate fractions were combined and concentrated in vacuo to give two fractions of the desired compounds: peak 1 (100 mg) and peak 2 (85 mg). Both fractions were further purified by HPLC on a C18 column, eluting with 1% NH_4OH in water / acetonitrile, to give peak 1 (68 mg) and peak 2 (65 mg) as white solids. Both compounds have LCMS: $(M+H)^+$ 503.3. Peak 1 shows two peaks in 1 to 1 ratio in a chiral analytical column. Peak 2 shows two peaks in 1 to 10 ratio in a chiral analytical column.

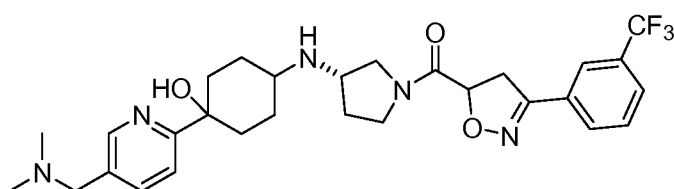
The following Examples were prepared in a similar fashion.

Example 56



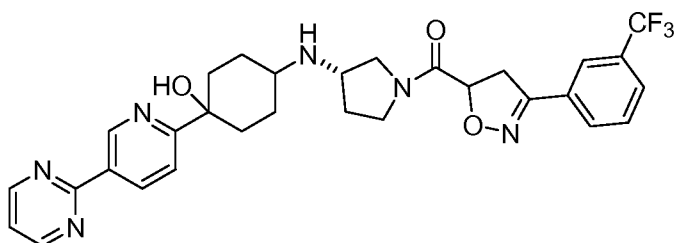
1-(5-Pyrimidin-2-ylpyridin-2-yl)-4-[(3S)-1-({3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-yl}carbonyl)pyrrolidin-3-yl]amino}cyclohexanol. MS (M+H)⁺ 581.

Example 57



1-{5-[(Dimethylamino)methyl]pyridin-2-yl}-4-[(3S)-1-({3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-yl}carbonyl)pyrrolidin-3-yl]amino}cyclohexanol. MS (M+H)⁺ 560.

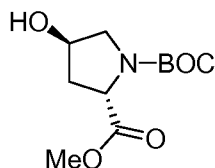
Example 58



1-(5-Pyrimidin-2-ylpyridin-2-yl)-4-[(3S)-1-({3-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazol-5-yl}carbonyl)pyrrolidin-3-yl]amino}cyclohexanol. MS (M+H)⁺ 581.

Example 59

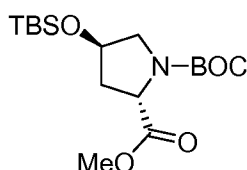
Step A



Methyl (2S,4R)-N-*tert*-Butoxycarbonyl-4-hydroxy-2-pyrrolidinecarboxylate. L-*trans*-4-Hydroxyproline methyl ester hydrochloride (25.00 g, 138.0 mmol) was dissolved in dichloromethane (300 mL) and triethylamine (58.0 mL, 413 mmol). The solution was cooled to 0 °C and then di-*tert*-butyldicarbonate (33.00 g, 151.0 mmol) was added in small portions. After stirring at room temperature overnight, the mixture was concentrated to a thick white

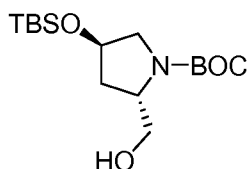
sludge. The residue was dissolved in ethyl acetate and the organic layer was washed successively with $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$, $\text{NaHCO}_3/\text{H}_2\text{O}$ and brine. The organic extracts were dried over MgSO_4 , filtered, and concentrated to give 33.0 g (99%) of desired product as a colorless oil. LC/MS $(\text{M}+\text{Na})^+$ $m/z = 267.9$. ^1H NMR (CDCl_3) δ 4.50 (m, 1H), 4.40 (m, 1H), 3.75 (s, 3H), 3.43-3.68 (m, 2H), 2.30 (m, 1H), 1.95-2.15 (m, 2H), 1.42 and 1.45 (s, 9H).

Step B



1-*tert*-Butyl 2-Methyl (2*S*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]pyrrolidine-1,2-dicarboxylate. Methyl (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxy-2-pyrrolidinecarboxylate (22.1 g, 82.6 mmol) was dissolved in dry DMF (100 mL) under nitrogen. Imidazole (16.8 g, 248 mmol) was added and the mixture cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (13.1 g, 86.7 mmol) was added in small portions and then the mixture was allowed to warm to room temperature. After stirring overnight, the mixture was diluted with 300 mL ethyl acetate and washed with water three times (500 mL, 200 mL, 200 mL). The organic extracts were washed one final time with brine and then dried over MgSO_4 , filtered and concentrated to give 29.5 g (99%) of desired product as a colorless oil. LC/MS $(\text{M}-\text{Boc}+\text{H})^+$ $m/z = 260.2$. ^1H NMR (CDCl_3) δ 4.30-4.47 (m, 2H), 3.73 and 3.75 (s, 3H), 3.60 (m, 1H), 3.28-3.45 (m, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 1.42 and 1.47 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H).

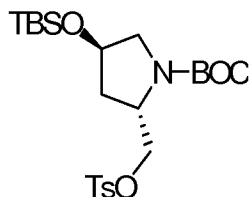
Step C



tert-Butyl (2*S*,4*R*)-4-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(hydroxymethyl)-pyrrolidine-1-carboxylate. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]-oxy]pyrrolidine-1,2-dicarboxylate (5.00 g, 13.91 mmol) was dissolved in dry THF (50 mL) under nitrogen and cooled to -78 °C. Diisobutylaluminum hydride solution (31.0 mL, 31.0 mmol, 1.0 M in toluene) was added dropwise over 30 minutes. After stirring for ten minutes, the mixture was slowly warmed to room temperature at which point TLC indicated complete conversion. The mixture was diluted with ethyl acetate (200 mL) and saturated aqueous sodium potassium tartrate (200 mL). The mixture was stirred vigorously for 30 minutes until two phases were apparent. The aqueous layer was then extracted twice with ethyl acetate and washed with

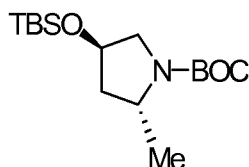
brine. The organic layer was dried over MgSO_4 , filtered and concentrated to give 4.91 g of the crude alcohol as a pale yellow oil. LC/MS ($\text{M-Boc}+\text{H}$)⁺ m/z = 232.2. ^1H NMR (CDCl_3) δ 4.88 (d, 1H), 4.27 (bs, 1H), 4.14 (m, 1H), 3.69 (t, 1H), 3.54 (m, 1H), 3.42 (d, 1H), 3.34 (dd, 1H), 1.96 (m, 1H), 1.58 (m, 1H), 1.47 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H).

Step D



tert-Butyl (2*S*,4*R*)-4-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-([(4-methylphenyl)-sulfonyl]oxy)methylpyrrolidine-1-carboxylate. *tert*-Butyl (2*S*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(hydroxymethyl)pyrrolidine-1-carboxylate (4.91 g) was dissolved in dichloromethane (70 mL) under nitrogen. Triethylamine (5.8 mL, 41.7 mmol) was added followed by *p*-toluenesulfonyl chloride (3.18 g, 16.7 mmol) and the mixture was stirred at room temperature overnight. TLC revealed about half conversion. Pyridine (3.4 mL, 41 mmol) was added to the mixture which turned dark orange after 20 minutes. After two more days, the mixture was diluted with ethyl acetate and the organic layer was washed successively with $\text{NaHCO}_3/\text{H}_2\text{O}$, $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$, water, and brine. The organic extract was dried over MgSO_4 , filtered and concentrated to a red oil which was chromatographed on silica gel (10% to 20% ethyl acetate/hexane). Pure fractions were combined to give the tosylate as a yellow oil, 6.32 g (93%, 2 steps). ^1H NMR (CDCl_3) δ 7.77 (d, 2H), 7.34 (t, 2H), 4.30 (m, 2H), 4.10 (m, 2H), 3.30 (m, 2H), 2.45 (s, 3H), 1.97 (m, 2H), 1.41 and 1.37 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H).

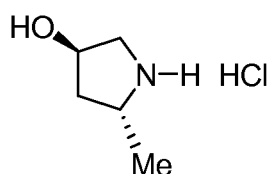
Step E



tert-Butyl (2*R*,4*R*)-4-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-methylpyrrolidine-1-carboxylate. *tert*-Butyl (2*S*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-([(4-methylphenyl)-sulfonyl]oxy)methylpyrrolidine-1-carboxylate (6.32 g, 13.01 mmol) was dissolved in THF (50 mL) under nitrogen and cooled to 0 °C. Lithium triethylborohydride solution (Super Hydride, 14.3 mL, 1.0 M in THF) was added dropwise and the mixture was then slowly warmed to room temperature. After 2 hours, TLC revealed half conversion. More lithium triethylborohydride solution (12.0 mL) was added and the solution stirred at room temperature overnight. Diluted

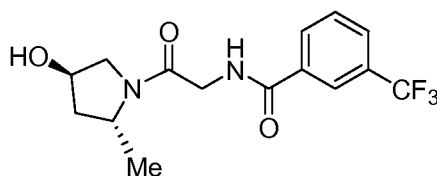
with $\text{NaHCO}_3/\text{H}_2\text{O}$ and extracted twice with ethyl acetate. Washed organic layer with $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ and brine. Dried organic extracts over MgSO_4 , filtered and concentrated to give a colorless oil. Chromatographed on silica gel eluting with 10% ethyl acetate/hexane. Pure fractions were combined to give the desired product as a colorless oil, 3.74 g (91%). LC/MS $(\text{M}+\text{Na})^+$ $m/z = 338.2$. ^1H NMR (CDCl_3) δ 4.34 (m, 1H), 3.95 (m, 1H), 3.35 (m, 2H), 1.98 (m, 1H), 1.65 (m, 1H), 1.47 (s, 9H), 1.20 (bs, 3H), 0.87 (s, 9H), 0.06 (s, 6H).

Step F



(3*R*,5*R*)-5-Methylpyrrolidin-3-ol hydrochloride. *tert*-Butyl (2*R*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-methylpyrrolidine-1-carboxylate (3.74 g, 11.85 mmol) was dissolved in dry THF (20 mL) under nitrogen. Hydrogen chloride solution (40 mL, 4.0 M solution in 1,4-dioxane) was added and the mixture was stirred at room temperature for four hours. Concentrated mixture on the rotovap to an oil, then azeotroped the crude product with toluene and pumped under vacuum to provide the hydrochloride salt as an off white solid, 1.80 g (100%) which was used for the next step without further purification. ^1H NMR (CD_3OD) δ 4.54 (m, 1H), 3.95 (m, 1H), 3.44 (dd, 1H), 3.18 (d, 1H), 2.19 (dd, 1H), 1.76 (m, 1H), 1.44 (d, 3H).

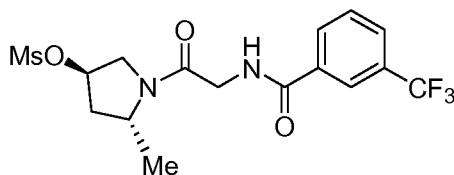
Step G



N-{2-[(2*R*,4*R*)-4-Hydroxy-2-methylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. (3*R*,5*R*)-5-Methylpyrrolidin-3-ol hydrochloride (1.80 g) was dissolved in dichloromethane (50 mL) and diisopropylethylamine (2.1 mL, 12.0 mmol) under nitrogen. (3-Trifluoromethyl-benzoylamino)-acetic acid (2.93 g, 11.85 mmol) was added followed by EDC (3.41 g, 17.8 mmol) and the mixture was stirred at room temperature for four hours. The mixture was diluted with $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ and extracted twice with ethyl acetate. The combined extracts were washed with $\text{NaHCO}_3/\text{H}_2\text{O}$ and brine, dried over MgSO_4 , filtered and concentrated to give a dark orange oil. Chromatography on silica gel eluting with ethyl acetate to 5% methanol/ethyl acetate gave the coupled product as a pale orange solid, 3.19

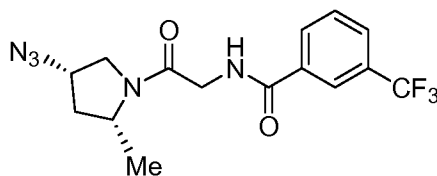
g (81%, 2 steps). LC/MS (M+H)⁺ m/z = 331.1. ¹H NMR (CDCl₃, major rotamer) δ 8.12 (s, 1H), 8.01 (d, 1H), 7.76 (d, 1H), 7.57 (t, 1H), 7.50 (m, 1H), 4.56 (m, 1H), 4.34 (m, 1H), 4.23 (m, 1H), 4.11 (m, 1H), 3.61 (dd, 1H), 3.51 (d, 1H), 2.71 (d, 1H), 2.17 (m, 1H), 1.81 (m, 1H), 1.32 (d, 3H).

Step H



(3*R*,5*R*)-5-Methyl-1-({[3-(trifluoromethyl)benzoyl]amino}acetyl)pyrrolidin-3-yl methanesulfonate. To a solution of N-{2-[(2*R*,4*R*)-4-hydroxy-2-methylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide (1.50 g, 4.54 mmol) in dichloromethane (30 mL) and pyridine (1.83 mL, 22.7 mmol) under nitrogen at 0 °C was added methanesulfonyl chloride (0.42 mL, 5.45 mmoles) dropwise. After being stirred at 0 °C for two hours, the reaction was allowed to slowly warm to room temperature and stirred overnight. The mixture was diluted with NaHCO₃/H₂O and extracted with ethyl acetate. The organic layer was washed with NH₄Cl/H₂O and brine, dried over MgSO₄, filtered and concentrated to give the mesylate as a brown oil, 1.87 g (100%). LC/MS (M+H)⁺ m/z = 409.0. ¹H NMR (CDCl₃, major rotamer) δ 8.12 (s, 1H), 8.01 (d, 1H), 7.78 (d, 1H), 7.59 (t, 1H), 7.29 (bs, 1H), 5.33 (m, 1H), 4.37 (m, 1H), 4.18 (m, 2H), 3.86 (d, 1H), 3.76 (dd, 1H), 3.08 (s, 3H), 2.51 (m, 1H), 1.94 (m, 1H), 1.38 (d, 3H).

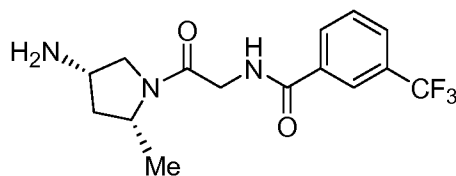
Step I



N-{2-[(2*R*,4*S*)-4-Azido-2-methylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. To a solution of the crude mesylate (1.87 g) in dry DMF (20 mL) was added sodium azide (1.50 g, 22.7 mmol). The mixture was stirred at 60-65 °C for five hours, then 50 °C for twenty hours. Ethyl acetate was added. The organic layer was separated, washed twice with water and then with brine, dried over MgSO₄, filtered and concentrated to an orange oil. Chromatography on silica gel eluting with 80% ethyl acetate/hexane gave the azide as a yellow oil, 1.33 g (82%). LC/MS (M+H)⁺ m/z = 356.1. ¹H

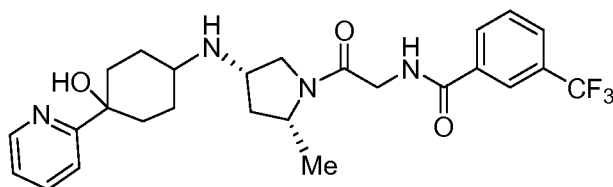
NMR (CDCl₃, major rotamer) δ 8.12 (s, 1H), 8.00 (t, 1H), 7.77 (d, 1H), 7.58 (t, 1H), 7.37 (bs, 1H), 4.35 (m, 2H), 4.17 (m, 2H), 3.73 (dd, 1H), 3.50 (d, 1H), 2.39 (m, 1H), 1.87 (d, 1H), 1.43 (d, 3H).

Step J



N-{2-[(2*R*,4*S*)-4-Amino-2-methylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. N-{2-[(2*R*,4*S*)-4-Azido-2-methylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide (1.33 g, 3.74 mmol) was dissolved in ethanol (50 mL) and then 10% Pd-C (130 mg) was added to the solution. The flask was purged with hydrogen and then stirred under an atmosphere of hydrogen using a balloon for four hours at which point, TLC indicated complete consumption of starting material. The reaction was then flushed with nitrogen and filtered through Celite on a glass frit and washed with methanol. The filtrate was concentrated to give the desired amine as a dark brown oil, 1.21 g (98%). LC/MS (M+H)⁺ *m/z* = 330.1. ¹H NMR (CDCl₃) δ 8.12 (s, 1H), 8.02 (d, 1H), 7.77 (d, 1H), 7.58 (t, 1H), 7.37 (bs, 1H), 4.16 (m, 3H), 3.72 (m, 1H), 3.61 (m, 1H), 3.15 (m, 1H), 2.44 (m, 1H), 1.70-1.20 (m, 3H), 1.43 (d, 3H); ¹⁹F NMR (CDCl₃) -63.12 (s).

Step K

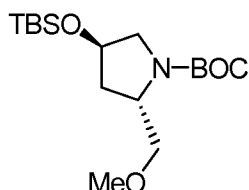


N-(2-{(2*R*,4*S*)-4-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl]amino}-2-methylpyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. N-{2-[(2*R*,4*S*)-4-Amino-2-methylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide (200 mg, 0.607 mmol) and 4-hydroxy-4-pyridin-2-ylcyclohexanone (116 mg, 0.607 mmol) were dissolved in 2-propanol (10 mL). After stirring for 30 minutes, sodium triacetoxyborohydride (257 mg, 1.21 mmol) was added and the mixture was stirred at room temperature overnight. TLC indicated complete conversion to desired products in about a 1:1 ratio of isomers. The reaction mixture was chromatographed on silica gel eluting with dichloromethane to 10% methanol/dichloromethane/0.5% ammonium hydroxide to give 229 mg (75%) as a mixture of isomers. ¹H NMR (CDCl₃,

mixture of isomers) δ 8.53 (m, 1H), 8.13 (bs, 1H), 8.02 (d, 1H), 7.75 (m, 2H), 7.58 (t, 1H), 7.40 (m, 2H), 7.22 (m, 1H), 4.05-4.38 (m, 3H), 3.80 (m, 1H), 3.56 (m, 1H), 3.42 (m, 1H), 3.19 (m, 1H), 3.04 (m, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.16 (m, 2H), 1.40-2.00 (m, 7H), 1.43 (d, 3H). LCMS (M+H)⁺: Higher Rf isomer m/z = 505.2; Lower Rf isomer m/z = 505.2.

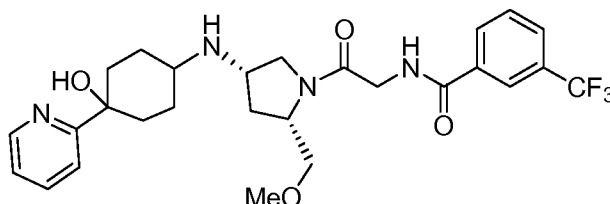
Example 60

Step A



tert-Butyl (2*S*,4*R*)-4-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(methoxymethyl)-pyrrolidine-1-carboxylate. Iodomethane (0.85 mL, 13.6 mmol) was added to a solution of *tert*-Butyl (2*S*,4*R*)-4-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.50 g, 4.52 mmol) in dry DMF (15 mL) under nitrogen. Sodium hydride (0.22 g, 5.42 mmol, 60% dispersion in mineral oil) was added in portions and the mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate. The organic layer was separated, washed twice with water and then brine, dried over MgSO₄, filtered and concentrated to give 1.51 g (96%) of methyl ether as a yellow oil. LC/MS (M-Boc+H)⁺ m/z = 246.2. ¹H NMR (CDCl₃) δ 4.38 (m, 1H), 4.05 (m, 1H), 3.50 (m, 2H), 3.25-3.45 (m, 2H), 3.34 (s, 3H), 1.87-2.06 (m, 2H), 1.47 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H).

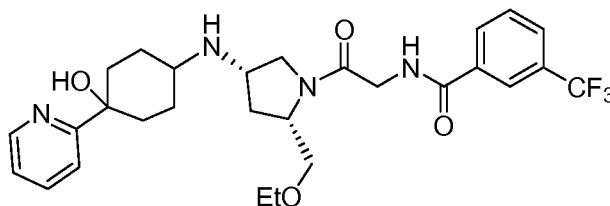
Step B



N-{2-[(2*S*,4*S*)-4-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl]amino]-2-(methoxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. The title compound was prepared from the intermediate of step A following the procedures described for Example 59. Higher Rf isomer: LCMS m/z = 535.2 (M+H); ¹H NMR (CDCl₃) δ 8.53 (d, 1H), 8.12 (s, 1H), 8.03 (d, 1H), 7.77 (m, 1H), 7.72 (m, 1H), 7.58 (t, 1H), 7.47 (m, 1H), 7.34 (m, 1H), 7.21 (m, 1H), 4.90 (m, 1H), 4.12-4.47 (m, 4H), 3.89 (dd, 1H), 3.79 (dd, 1H), 3.54 (m, 2H), 3.38 (s, 3H), 3.03 (m, 1H), 2.40 (m, 1H), 2.18 (m, 3H), 1.90 (m, 1H), 1.75 (m, 1H), 1.60 (m, 2H), 1.50 (m, 2H); ¹⁹F NMR (CDCl₃) δ -63.11 (s). Lower Rf isomer: LCMS (M+H)⁺ m/z

= 535.2; ^1H NMR (CDCl_3) δ 8.53 (d, 1H), 8.12 (s, 1H), 8.02 (d, 1H), 7.78 (m, 1H), 7.72 (m, 1H), 7.58 (t, 1H), 7.42 (m, 1H), 7.34 (m, 1H), 7.21 (m, 1H), 4.12-4.48 (m, 4H), 3.83 (m, 2H), 3.68 (m, 1H), 3.56 (m, 1H), 3.38 (s, 3H), 2.72 (m, 1H), 2.38 (m, 1H), 1.60-2.20 (m, 10H); ^{19}F NMR (CDCl_3) δ -63.12 (s).

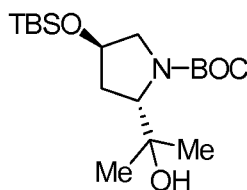
Example 61



N-(2-((2*S*,4*S*)-2-(Ethoxymethyl)-4-[(4-hydroxy-4-pyridin-2-yl)cyclohexyl]-amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared following the procedures described for Example 60. Higher R_f isomer: LCMS ($M+H$) $^+$ m/z = 549.1; ^1H NMR (CDCl_3) δ 8.51 (m, 1H), 8.10 (m, 1H), 7.99 (m, 1H), 7.70 (m, 2H), 7.32-7.60 (m, 3H), 7.18 (m, 1H), 4.03-4.47 (m, 3H), 3.22-3.91 (m, 5H), 3.04 (m, 1H), 1.70-2.47 (m, 7H), 1.51 (m, 4H), 1.21 (m, 4H). Lower R_f isomer: LCMS ($M+H$) $^+$ m/z = 549.1; ^1H NMR (CDCl_3) δ 8.52 (m, 1H), 8.11 (m, 1H), 8.00 (m, 1H), 7.73 (m, 2H), 7.55 (m, 1H), 7.39 (m, 2H), 7.20 (m, 1H), 4.11-4.48 (m, 3H), 3.46-3.88 (m, 5H), 3.21 (m, 1H), 2.63 (m, 1H), 2.38 (m, 1H), 1.55-1.98 (m, 10H), 1.20 (m, 3H).

Example 62

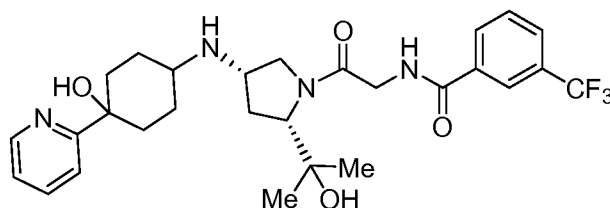
Step A



tert-Butyl (2*S*,4*R*)-4-[[*tert*-Butyl(dimethyl)silyl]oxy]-2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylate. To a solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]pyrrolidine-1,2-dicarboxylate (1.00 g, 2.78 mmol) in dry THF (20 mL) at 0 °C was dropwise added methylmagnesium bromide solution (2.0 mL, 6.0 mmol, 3.0 M in ether) over 5 minutes. After stirring for four hours, the mixture was warmed to room temperature and quenched with $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ and extracted twice with ethyl acetate. The organic extracts were dried over MgSO_4 , filtered and concentrated to give 1.00 g (100%) of

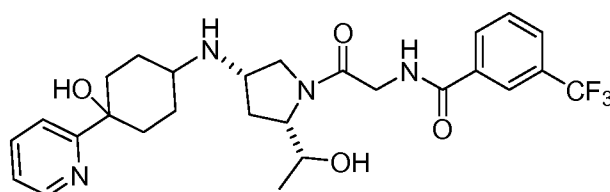
the title compound as a white solid. ^1H NMR (CDCl_3) δ 5.85 (s, 1H), 4.25 (s, 1H), 4.08 (t, 1H), 3.67 (d, 1H), 3.18 (d, 1H), 1.94 (m, 1H), 1.60 (m, 1H), 1.45 (s, 9H), 1.15 (s, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H).

Step B



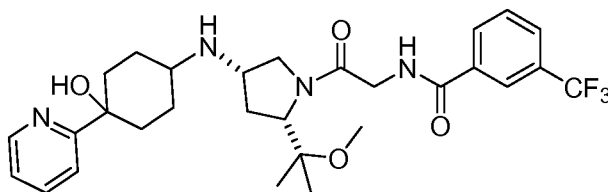
N-(2-((2S,4S)-2-(1-Hydroxy-1-methylethyl)-4-[(trans-4-hydroxy-4-pyridin-2-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared from the alcohol of step A following the procedures described for Example 59. Higher Rf isomer: LCMS ($\text{M}+\text{H}$) $^+$ m/z = 549.3; ^1H NMR (CDCl_3) δ 8.53 (m, 1H), 8.13 (s, 1H), 8.01 (d, 1H), 7.78 (d, 1H), 7.74 (t, 1H), 7.59 (t, 1H), 7.48 (d, 1H), 7.32 (m, 1H), 7.22 (m, 1H), 4.19-4.40 (m, 3H), 3.98 (dd, 1H), 3.49 (m, 2H), 3.29 (m, 1H), 3.08 (m, 1H), 2.10-2.45 (m, 8H), 1.71 (m, 2H), 1.24 (s, 3H), 1.21 (s, 3H); ^{19}F NMR (CDCl_3) δ -63.12 (s). Lower Rf isomer: LCMS ($\text{M}+\text{H}$) $^+$ m/z = 549.3; ^1H NMR (CDCl_3) δ 8.52 (d, 1H), 8.12 (s, 1H), 8.01 (d, 1H), 7.77 (d, 1H), 7.73 (m, 1H), 7.59 (t, 1H), 7.40 (d, 1H), 7.37 (m, 1H), 7.22 (m, 1H), 5.14 (bs, 1H), 4.39 (m, 1H), 4.33 (m, 1H), 4.20 (m, 1H), 3.97 (m, 1H), 3.72 (m, 1H), 3.40 (m, 1H), 2.74 (m, 1H), 1.70-2.35 (m, 12H), 1.24 (s, 3H), 1.21 (s, 3H); ^{19}F NMR (CDCl_3) δ -63.12 (s).

Example 63



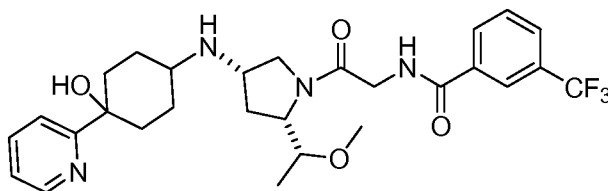
N-(2-((2S,4S)-2-[1-Hydroxyethyl]-4-[(4-hydroxy-4-pyridin-2-yl)cyclohexyl]amino)pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared in a manner similar to that for Example 62. MS ($\text{M}+\text{H}$) $^+$ 535.

Example 64



N-{2-[(2S,4S)-4-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl]amino]-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. The title compound was prepared starting from *tert*-butyl (2S,4R)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylate following the procedures described for Example 60. Higher Rf isomer: LC/MS (M+H)⁺ m/z = 563.3; ¹H NMR (CDCl₃) δ 8.55 (m, 1H), 8.14 (m, 1H), 8.04 (m, 1H), 7.74 (m, 2H), 7.38-7.63 (m, 3H), 7.22 (m, 1H), 5.42-5.80 (bs, 1H), 4.84 (bs, 1H), 4.15-4.43 (m, 3H), 3.96 (m, 1H), 3.42 (m, 1H), 3.22 (m, 4H), 3.02 (m, 1H), 1.89-2.34 (m, 6H), 1.46-1.67 (m, 4H), 1.22 (m, 6H). Lower Rf isomer: LC/MS (M+H)⁺ m/z = 563.3; ¹H NMR (CDCl₃) δ 8.53 (m, 1H), 8.15 (m, 1H), 8.03 (m, 1H), 7.74 (m, 2H), 7.35-7.61 (m, 3H), 7.22 (m, 1H), 3.87-4.43 (m, 4H), 3.50 (m, 1H), 3.21 (m, 4H), 2.64 (m, 1H), 2.27 (m, 1H), 1.67-1.98 (m, 9H), 1.22 (m, 6H).

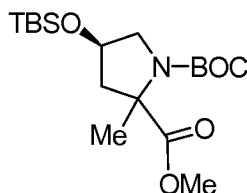
Example 65



N-(2-[(2S,4S)-4-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl]amino]-2-[(1S)-1-methoxyethyl]pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared in a fashion similar to that for Example 64. MS (M+H)⁺ 549.

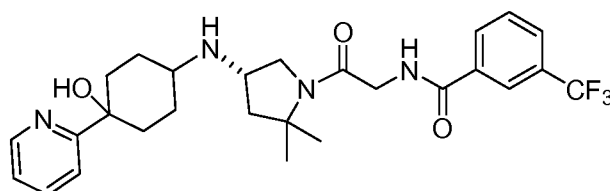
Example 66

Part A



1-*tert*-Butyl 2-Methyl (4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-methylpyrrolidine-1,2-dicarboxylate. To a solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]pyrrolidine-1,2-dicarboxylate (5.11 g, 14.2 mmol) in dry THF (60 mL) at -78 °C was dropwise added lithium bistrimethylsilylamide (17.0 mL, 17.0 mmol, 1.0 M in THF). After being stirred for 30 minutes, iodomethane (1.77 mL, 28.4 mmoles) was then added. The mixture was stirred at -78 °C for one hour, warmed to 0 °C for one hour and finally quenched with NaHCO₃/H₂O. The resulting mixture was extracted twice with ethyl acetate. The combined extracts were dried over MgSO₄, filtered and concentrated. The residue was chromatographed on silica gel eluting with hexane to 5% ethyl acetate/hexane to provide 2.66 g (50%) of a mixture of product isomers as a colorless oil. LC/MS (M-Boc+H)⁺ *m/z* = 274.1. ¹H NMR (CDCl₃) δ 4.38 (m, 1H), 3.71 (m, 4H), 3.36 (m, 1H), 1.84-2.35 (m, 2H), 1.61 (m, 3H), 1.44 (m, 9H), 0.88 (m, 9H), 0.07 (m, 6H).

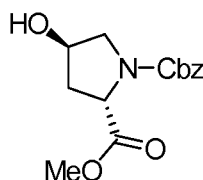
Step B



N-(2-((4*S*)-4-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl]amino)-2,2-dimethyl-pyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared from 1-*tert*-butyl 2-methyl (4*R*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-methylpyrrolidine-1,2-dicarboxylate following the procedures described for Example 59. Higher R_f isomer: LC/MS (M+H)⁺ *m/z* = 519.2; ¹H NMR (CD₃OD, bis-trifluoroacetate salt) δ 8.51 (m, 1H), 8.18 (m, 2H), 7.63-7.90 (m, 4H), 7.27 (m, 1H), 4.15 (dd, 2H), 3.98 (m, 1H), 3.55 (m, 1H), 3.28 (m, 2H), 2.92 (m, 1H), 2.38 (m, 2H), 1.96-2.20 (m, 3H), 1.50-1.79 (m, 7H), 1.42 (s, 3H). Lower R_f isomer: LC/MS (M+H)⁺ *m/z* = 519.2; ¹H NMR (CD₃OD, bis-trifluoroacetate salt) δ 8.49 (m, 1H), 8.21 (m, 1H), 8.14 (m, 1H), 7.65-7.90 (m, 4H), 7.25 (m, 1H), 4.10 (m, 3H), 3.72 (m, 1H), 3.28 (m, 2H), 2.73 (m, 1H), 2.10 (m, 3H), 1.82 (m, 2H), 1.73 (m, 4H), 1.58 (s, 3H), 1.45 (s, 3H).

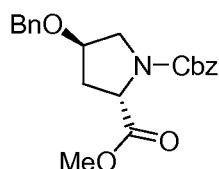
Example 67

Step A



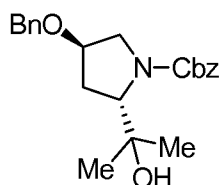
1-Benzyl 2-Methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate. L-*trans*-4-Hydroxyproline methyl ester hydrochloride (9.70 g, 54.0 mmol) was dissolved in dry THF (180 mL) and triethylamine (7.53 mL, 54.0 mmol). N-(Benzyloxycarbonyloxy)succinimide (13.5 g, 54.0 mmoles) dissolved in THF (70 mL) was slowly added to the solution. After stirring at room temperature overnight, the mixture was diluted with ethyl acetate and the organic layer was washed successively with water and brine. The organic extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was chromatographed on silica gel (30% to 70% ethyl acetate/hexane) to provide 12.8 g (85%) of desired product as a colorless oil. LC/MS (M+H)⁺ m/z = 280.0; ¹H NMR (CDCl₃) δ 7.33 (m, 5H), 5.00-5.25 (m, 2H), 4.52 (m, 2H), 3.69 (m, 2H), 3.56 and 3.78 (s, 3H), 2.05-2.40 (m, 2H).

Step B



1-Benzyl 2-Methyl (2*S*,4*R*)-4-(benzyloxy)pyrrolidine-1,2-dicarboxylate. 1-Benzyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (6.60 g, 23.6 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C under nitrogen. Sodium hydride (1.04 g, 26.0 mmol, 60% dispersion in mineral oil) was added in portions and the mixture was stirred for 15 minutes. Tetra-*n*-butylammonium iodide (0.40 g, 1.0 mmol) and benzyl bromide (3.15 mL, 26.0 mmol) were added and the mixture stirred for one hour at 0 °C and then one hour at room temperature. The mixture was diluted with ethyl acetate. The organic layer was washed with water and then brine, dried over MgSO₄, filtered, and concentrated. The residue was chromatographed on silica gel (20% to 50% ethyl acetate/hexane) to give 4.21 g (48%) of benzyl ether. LC/MS (M+H)⁺ m/z = 370.2; ¹H NMR (CDCl₃) δ 7.34 (m, 10H), 5.13 (m, 2H), 4.51 (m, 3H), 4.20 (m, 1H), 3.68 (m, 2H), 3.54 and 3.78 (s, 3H), 2.45 (m, 1H), 2.11 (m, 1H).

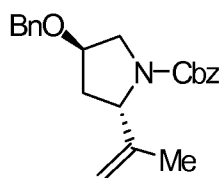
Step C



Benzyl (2*S*,4*R*)-4-(Benzyloxy)-2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylate. 1-Benzyl 2-methyl (2*S*,4*R*)-4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (4.21 g, 11.4 mmol) was dissolved in dry THF (20 mL) under nitrogen and cooled to 0 °C. Methylmagnesium

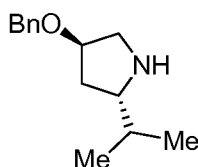
bromide solution (8.4 mL, 25 mmol, 3.0 M in ether) was added dropwise. After stirring for twelve hours at 0 °C, the mixture was warmed to room temperature and quenched with NH₄Cl/H₂O and extracted twice with ethyl acetate. The organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel (20% to 30% ethyl acetate/hexane) to give 2.47 g (59%) of the alcohol as a viscous oil. LC/MS (M+H)⁺ m/z = 370.1; ¹H NMR (CDCl₃) δ 7.33 (m, 10H), 5.55 (bs, 1H), 5.20 (s, 2H), 4.50 (s, 2H), 4.19 (m, 1H), 4.05 (m, 2H), 3.31 (m, 1H), 2.27 (m, 1H), 1.73 (m, 1H), 1.21 (s, 3H), 1.13 (s, 3H).

Step D



Benzyl (2*S*,4*R*)-4-(Benzyloxy)-2-isopropenylpyrrolidine-1-carboxylate. Benzyl (2*S*,4*R*)-4-(benzyloxy)-2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylate (2.22 g, 6.01 mmol) was dissolved in toluene (40 mL) and triethylamine (10.0 mL, 72 mmol) under nitrogen. The mixture was cooled to -50 °C and thionyl chloride (0.44 mL, 6.0 mmol) was added dropwise. After stirring for three hours at -30 °C, the mixture was quenched by addition of water. The resulting mixture was extracted twice with ethyl acetate and the organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel (10% to 20% ethyl acetate/hexane) to give 1.10 g (52%) of the olefin as a pale yellow oil. LC/MS (M+H)⁺ m/z = 352.2; ¹H NMR (CDCl₃) δ 7.35 (m, 10H), 5.16 (m, 2H), 4.84 (m, 2H), 4.52 (m, 3H), 4.16 (m, 1H), 3.87 (m, 1H), 3.58 (m, 1H), 2.29 (m, 1H), 1.94 (m, 1H), 1.69 (m, 3H).

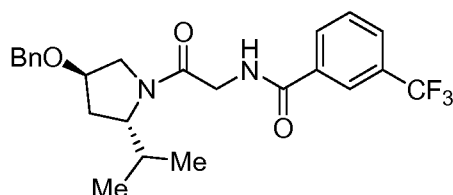
Step E



(2*S*,4*R*)-4-(Benzyloxy)-2-isopropylpyrrolidine. Benzyl (2*S*,4*R*)-4-(benzyloxy)-2-isopropenylpyrrolidine-1-carboxylate (1.00 g, 2.84 mmol) was dissolved in ethanol (40 mL) and then 5% Pd-C (100 mg) was added to the solution. The flask was purged with hydrogen and then shaken on a Parr under 53 psi atmosphere of hydrogen for 17 hours. The reaction was then flushed with nitrogen and filtered through Celite on a glass frit and washed with

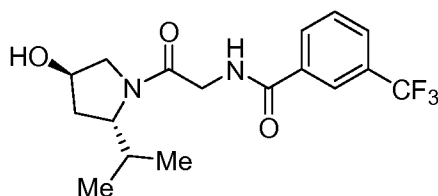
methanol. The filtrate was concentrated and chromatographed on silica gel (1% triethylamine / 10% methanol / 89% ethyl acetate) to furnish the amine as a pale yellow oil, 0.53 g (85%). LC/MS (M+H)⁺ m/z = 220.2; ¹H NMR (CDCl₃) δ 7.33 (m, 5H), 4.49 (m, 2H), 4.12 (m, 1H), 3.19 (dd, 1H), 3.00 (m, 2H), 2.05 (m, 1H), 1.96 (bs, 1H), 1.49 (m, 2H), 1.00 (d, 3H), 0.91 (d, 3H).

Step F



N-{2-[(2*S*,4*R*)-4-Benzyloxy-2-isopropylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. (2*S*,4*R*)-4-(Benzyloxy)-2-isopropylpyrrolidine (0.410 g, 1.90 mmol) was dissolved in dichloromethane (30 mL) under nitrogen. (3-Trifluoromethyl-benzoylamino)-acetic acid (0.462 g, 1.90 mmol) was added followed by EDC (0.394 g, 2.06 mmol) and the mixture was stirred at room temperature overnight. LC/MS revealed the reaction was not yet complete. More (3-Trifluoromethyl-benzoylamino)-acetic acid (0.12 g, 0.48 mmoles) and more EDC (0.30 g, 1.6 mmoles) were added and stirring continued for 3 hours at room temperature, then at reflux for 1.5 hours. The mixture was chromatographed on silica gel eluting with 30% ethyl acetate/hexane to provide 0.66 g (79%) of the coupled product as a colorless oil. LC/MS (M+H)⁺ m/z = 449.2; ¹H NMR (CDCl₃) δ 8.03 (m, 1H), 7.76 (m, 1H), 7.58 (m, 2H), 7.34 (m, 5H), 4.52 (m, 2H), 4.03-4.34 (m, 4H), 3.65 (m, 1H), 3.48 (m, 1H), 2.54 (m, 1H), 2.12 (m, 1H), 1.92 (m, 1H), 0.92 (d, 3H), 0.77 (d, 3H).

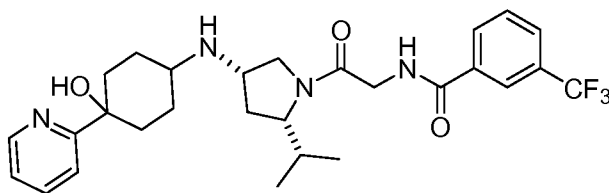
Step G



N-{2-[(2*S*,4*R*)-4-Hydroxy-2-isopropylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. N-{2-[(2*S*,4*R*)-4-Benzyloxy-2-isopropylpyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide (0.630 g, 1.40 mmol) was dissolved in methanol (60 mL) and then palladium hydroxide (90 mg) was added to the solution. The flask was purged with hydrogen and then stirred under an atmosphere of hydrogen using a balloon. After three hours, TLC indicated complete consumption of starting material. The reaction was then flushed with nitrogen and filtered through Celite on a glass frit and washed with methanol.

The filtrate was concentrated to give the desired alcohol as a white solid, 0.52 g (100%). LC/MS (M+H)⁺ m/z = 359.2; ¹H NMR (CDCl₃) δ 8.11 (m, 2H), 7.53-7.82 (m, 3H), 4.04-4.52 (m, 4H), 3.63 (m, 1H), 3.43 (m, 1H), 2.50 (m, 1H), 1.86-2.25 (m, 2H), 0.89 (d, 3H), 0.78 (d, 3H).

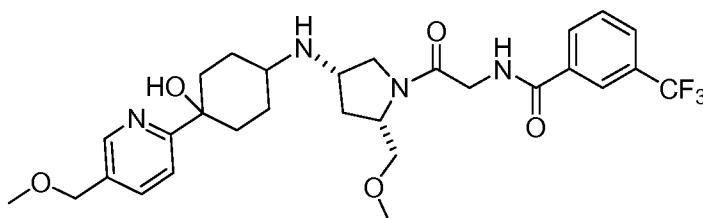
Step H



N-(2-((2S,4S)-4-[(4-Hydroxy-4-pyridin-2-yl)cyclohexyl]amino)-2-isopropylpyrrolidin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide. The title compound was prepared from the above intermediate following the procedures described for Example 59. Higher R_f isomer: LC/MS (M+H)⁺ m/z = 533.3; ¹H NMR (CD₃OD, bis-trifluoroacetate salt) δ 8.66 (m, 1H), 8.20 (m, 3H), 7.94 (m, 2H), 7.74 (m, 1H), 7.59 (m, 1H), 4.36 (m, 2H), 4.06-4.27 (m, 2H), 4.00 (m, 1H), 3.63 (m, 1H), 3.46 (m, 1H), 2.63 (m, 1H), 2.50 (m, 1H), 2.34 (m, 4H), 1.76-2.05 (m, 5H), 0.96 (d, 3H), 0.93 (d, 3H); Lower R_f isomer: LC/MS (M+H)⁺ m/z = 533.2; ¹H NMR (CD₃OD, bis-trifluoroacetate salt) δ 8.66 (m, 1H), 8.24 (m, 3H), 7.96 (m, 2H), 7.72 (m, 2H), 4.00-4.42 (m, 5H), 3.45 (m, 2H), 2.65 (m, 1H), 2.49 (m, 1H), 2.22 (m, 4H), 1.95 (m, 5H), 0.96 (d, 3H), 0.91 (d, 3H).

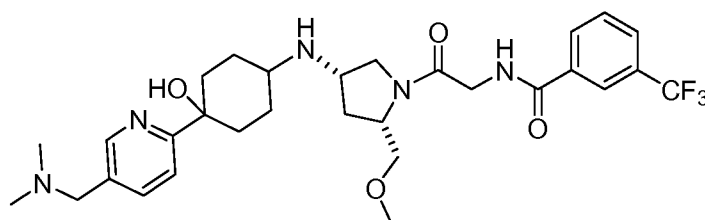
The following Examples were prepared in a similar manner.

Example 68



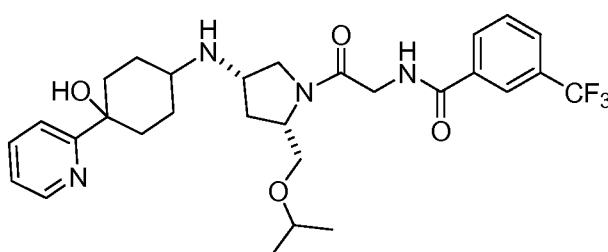
N-{2-[(2S,4S)-4-[(4-Hydroxy-4-[5-(methoxymethyl)pyridin-2-yl]cyclohexyl]-amino)-2-(methoxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 579.

Example 69



N-{2-[(2*S*,4*S*)-4-[(4-{5-[(Dimethylamino)methyl]pyridin-2-yl}-4-hydroxy-cyclohexyl)amino]-2-(methoxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 592.

Example 70



N-{2-[(2*S*,4*S*)-4-(4-Hydroxy-4-pyridin-2-ylcyclohexyl)amino]-2-(isopropoxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide. MS (M+H)⁺ 563.

PHARMACEUTICAL APPLICATIONS OF THE COMPOUNDS OF THE INVENTION

The capacity of the novel compounds of the invention to antagonize CCR2 function can be determined using a suitable screen (e.g., high through-put assay). For example, an agent can be tested in an extracellular acidification assay, calcium flux assay, ligand binding assay or chemotaxis assay (see, for example, Hesselgesser et al., J Biol. Chem. 273(25):15687-15692 (1998); WO 00/05265 and WO 98/02151).

In a practical assay, a CCR2 protein which can be isolated or recombinantly derived is used which has at least one property, activity or functional characteristic of a mammalian CCR2 protein. The specific property can be a binding property (to, for example, a ligand or inhibitor), a signalling activity (e.g., activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium [Ca⁺⁺]_i, cellular response function (e.g., stimulation of chemotaxis or inflammatory mediator release by leukocytes), and the like.

In one embodiment, a composition containing a CCR2 protein or variant thereof is maintained under conditions suitable for binding. The CCR2 receptor is contacted with a compound to be tested, and binding is detected or measured.

In alternate embodiments, the assay is a cell-based assay and cells are used which are stably or transiently transfected with a vector or expression cassette having a nucleic acid sequence which encodes the CCR2 receptor. The cells are maintained under conditions appropriate for expression of the receptor and are contacted with an agent under conditions appropriate for binding to occur. Binding can be detected using standard techniques. For example, the extent of binding can be determined relative to a suitable control. Also, a cellular fraction, such as a membrane fraction, containing the receptor can be used in lieu of whole cells.

Detection of binding or complex formation can be detected directly or indirectly. For example, the agent can be labeled with a suitable label (e.g., fluorescent label, label, isotope label, enzyme label, and the like) and binding can be determined by detection of the label. Specific and/or competitive binding can be assessed by competition or displacement studies, using unlabeled agent or a ligand as a competitor.

The CCR2 antagonist activity of test agents (e.g., the 3-cycloalkylaminopyrrolidine compounds of formula I or II of the invention) can be reported as the inhibitor concentration required for 50% inhibition (IC_{50} values) of specific binding in receptor binding assays using ^{125}I -labeled MCP-1, as ligand, and Peripheral Blood Mononuclear Cells (PBMCs) prepared from normal human whole blood via density gradient centrifugation. Specific binding is preferably defined as the total binding (e.g., total cpm on filters) minus the non-specific binding. Non-specific binding is defined as the amount of cpm still detected in the presence of excess unlabeled competitor (e.g., MCP-1).

The human PBMCs described above can be used in a suitable binding assay. For example, 200,000 to 500,000 cells can be incubated with 0.1 to 0.2 nM ^{125}I -labeled MCP-1, with or without unlabeled competitor (10nM MCP-1) or various concentrations of compounds to be tested. ^{125}I -labeled MCP-1, can be prepared by suitable methods or purchased from commercial vendors (Perkin Elmer, Boston MA). The binding reactions can be performed in 50 to 250 μ l of a binding buffer consisting of 1M HEPES pH 7.2, and 0.1% BSA (bovine serum albumin), for 30 min at room temperature. The binding reactions can be terminated by harvesting the membranes by rapid filtration through glass fiber filters (Perkin Elmer) which can be presoaked in 0.3% polyethyleneimine or Phosphate Buffered Saline (PBS). The filters can be rinsed with approximately 600 μ l of binding buffer containing 0.5 M NaCl or PBS, then dried, and the amount of bound radioactivity can be determined by counting on a Gamma Counter (Perkin Elmer).

The capacity of compounds to antagonize CCR2 function can also be determined in a leukocyte chemotaxis assay using suitable cells. Suitable cells include, for example, cell lines, recombinant cells or isolated cells which express CCR2 and undergo CCR2 ligand-

induced (e.g., MCP-1) chemotaxis. The assay in use, utilizes human peripheral blood mononuclear cells, in a modified Boyden Chamber (Neuro Probe). 500,000 cells in serum free DMEM media (In Vitrogen) are incubated with or without the inhibitors and warmed to 37°C. The chemotaxis chamber (Neuro Probe) is also prewarmed. 400ul of warmed 10nM MCP-1 is added to the bottom chamber in all wells except the negative control which has DMEM added. An 8 micron membrane filter (Neuro Probe) is placed on top and the chamber lid is closed. Cells are then added to the holes in the chamber lid which are associated with the chamber wells below the filter membrane. The whole chamber is incubated at 37°C, 5% CO₂ for 30 minutes. The cells are then aspirated off, the chamber lid opened, and the filter gently removed. The top of the filter is washed 3 times with PBS and the bottom is left untouched. The filter is air dried and stained with Wright Geimsa stain (Sigma). Filters are counted by microscopy. The negative control wells serve as background and are subtracted from all values. Antagonist potency can be determined by comparing the number of cells that migrate to the bottom chamber in wells which contain antagonist, to the number of cells which migrate to the bottom chamber in MCP-1 control wells.

When the binding assay protocol is used, the compounds of the present invention have IC₅₀ in the range of about 0.01 to about 500 (nM). In chemotaxis assays the compounds of the invention have IC₅₀'s in the range of about 1 to about 3000 (nM).

The compounds of the invention are administered to a mammal, such as a human, but can also be other mammals such as an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). The mammal treated in the methods of the invention is a mammal, male or female, in whom modulation of chemokine receptor activity is desired. The term modulation is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism.

In the present specification, the term therapeutically effective amount means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The compounds of the invention are administered in therapeutic effective amounts to treat a disease for example such as hepatitis C and/or liver fibrosis. A therapeutically effective amount of a compound is that amount which results in the inhibition of one or more of the processes mediated by the binding of a chemokine to a receptor such as CCR2 in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Typical examples of such processes include leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium [Ca²⁺]_i and granule release of proinflammatory mediators. Alternatively, a therapeutically effective amount of a

compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

Additional diseases or conditions of human or other species which can be treated with the inhibitors or modulators of chemokine receptor function of the invention, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic cellulitis (e.g., Wells' syndrome), eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), eosinophilic fasciitis (e.g., Shulman's syndrome), delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary and/or liver fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), eosinophilia-myalgia syndrome due to the ingestion of contaminated tryptophan, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinophilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, restenosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

The compounds represented in Formula I or II of the invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the

particular agent and its mode and route of administration; the metabolic stability, rate of excretion, drug combination, and length of action of that compound the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the specific route of administration, the renal and hepatic function of the patient, and the desired effect. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the specific disorder for which treatment is necessary.

Generally, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.0001 to 1000 mg/kg of body weight, preferably between about 0.001 to 100 mg/kg of body weight per day, and most preferably between about 0.1 to 20 mg/kg/day. For intravenous use, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds of the instant invention can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds of the invention are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. For oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Additionally, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include

starch, gelatin, natural sugars such as glucose or β -lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be provided to a patient in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or poly-ethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms for the compounds of the invention suitable for administration may contain from about 0.1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules can also be used as dosage forms and may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

When using liquid dosage forms for oral administration they can contain coloring and flavoring to increase patient acceptance.

Generally, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid,

either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in the field of pharmacology.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

The pharmaceutical compositions and methods of the present invention may further comprise other therapeutically active compounds which are usually applied in the treatment of the above mentioned pathological conditions.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 50 milligrams of powdered active ingredient, 100 milligrams of lactose, 25 milligrams of cellulose, and 3 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 75 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 75 milligrams of active ingredient, 0.15 milligrams of colloidal silicon dioxide, 4 milligrams of magnesium stearate, 250 milligrams of microcrystalline cellulose, 9 milligrams of starch and 75 milligrams of lactose. Appropriate coatings well known to one skilled in the art may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.0% by weight of active ingredient in 8% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 75 mg of finely divided active ingredient, 150 mg of sodium carboxymethyl cellulose, 3.75 mg of sodium benzoate, 0.75 g of sorbitol solution, U.S.P., and 0.015 mL of vanillin.

Example 71

This example describes a procedure to evaluate the efficacy of CCR2 antagonists for treatment of rheumatoid arthritis.

An animal model of rheumatoid arthritis can be induced in rodents by injecting them with type II collagen in selected adjuvants. Three series of rodent groups consisting 15 genetically-susceptible mice or rats per group are injected sub-cutaneously or intra-dermally with type II collagen emulsified in Complete Freund's Adjuvant at days 0 and 21. One series of rodents additionally receives phosphate buffered saline (PBS) and Tween 0.5% i.p. at the initial sensitization, and at different dosing schedules thereafter. A second series consists of groups of rodents receiving different doses of the CCR2 antagonist(s) given either intra-peritoneally, intravenously, sub-cutaneously, intra-muscularly, orally, or via any other mode of administration at the initial sensitization, and at different dosing schedules thereafter. A third series of rodents, serving as positive control, consists of groups treated with either mouse IL-10 i.p., or anti-TNF antibodies i.p. at the initial sensitization, and at different dosing schedules thereafter.

Animals are monitored from weeks 3 til 8 for the development of swollen joints or paws, and graded on a standard disease severity scale. Disease severity is confirmed by histological analysis of joints.

Treatment of Liver Fibrosis

Example 72

The following subsections describe additional non-clinical studies that were performed to support the development of 3-cycloalkylaminopyrrolidine derivatives for the indication of liver fibrosis. These studies were performed in parallel with the clinical program for pain, and were designed to build upon the non-clinical data already available to investigate the rationale for the CCR2 mechanism in liver fibrosis. As such, these additional studies focus on the CCR2 target for inflammatory liver fibrosis, utilising two tool compounds – a CCR2 small molecule and a CCR2 mAb – to fully explore the efficacy potential of CCR2 inhibition in a pre-clinical model of inflammatory liver fibrosis. Additional in vitro cellular pharmacology and in vivopharmacology studies are included.

I. In Vitro Cellular Pharmacology

A. Calcium (Ca²⁺) Mobilization in hCCR2-300.19 Cells

Two tool compounds, a small molecule antagonist (Compound A) and a selective anti-CCR2 mAb (Compound B) were tested for functional antagonism using the hCCR2-300.19 cells, a human pre-B cell line expressing full length human CCR2. In these studies, inhibition of intracellular Ca²⁺ mobilization in response to 50 nM MCP-1 was assessed using an intracellular Ca²⁺-sensitive dye, Fura-2 AM. Concentration-dependent reduction of intracellular Ca²⁺ mobilization by Compound A and Compound B yielding IC₅₀s of 15 nM and 22 nM, respectively, indicates that both antagonists can inhibit signaling by human CCR2.

B. ERK Phosphorylation in Human Monocytes

Stimulation of CCR2 results in activation of downstream signaling events including phosphorylation of ERK (pERK) (Brodmerkel et al, 2005). Therefore, the effect of Compound A and Compound B on MCP-1-induced pERK was tested in freshly isolated human whole blood from healthy volunteers. FACS analysis indicated a high level of pERK in CD14⁺ monocytes 6 minutes after ex vivo addition of 10 nM MCP-1. Compound A and Compound B inhibited MCP-1 induced pERK in whole blood in a concentration-dependent manner with similar IC₅₀ values for Compound A and Compound B at 9.1 nM and 8.5 nM, respectively. These results show that both tool compounds have similar CCR2 antagonist function as N-[2-((3S)-3-[[4-Hydroxy-4-(5-pyrimidin-2-yl)pyridin-2-

yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide. The data also provide support for using pERK as a whole blood biomarker assay for human studies to evaluate pharmacologic CCR2 inhibition by N-[2-((3S)-3-[[4-Hydroxy-4-(5-pyrimidin-2-yl)pyridin-2-yl]cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide, the 3-cycloalkylaminopyrrolidine derivative of Exemplified in Example 38 herein.

II. In Vivo Pharmacology

A. Effect of CCR2 Inhibition in a Pre-Clinical Model of Inflammatory Liver Fibrosis

To test the effects of CCR2 inhibition in a pre-clinical model of inflammatory liver fibrosis, the mouse-reactive CCR2-selective antagonist, Compound A, was utilized as a tool. Efficacy of Compound A was tested in vivo by measuring elevated liver enzymes caused by an acute inflammatory response after a single injection of Concanavalin A (ConA) in Balb/c mice. Emulsified Compound A was administered orally at 25, 50, or 100 mg/kg 30 min before ConA injection to Balb/c mice (n=8). As control, Con-A treated mice were administered vehicle instead of compound in a similar manner (n=8). Twenty-four hours following ConA injection, plasma ALT levels were decreased by Compound A in a dose-dependent manner with significant reductions observed in all dose groups. Dose-dependent attenuation of liver enzyme elevation was also observed upon chronic dosing (oral [p.o.], once daily [q.d.]) of Compound A in animals injected with Con-A once per week for eight weeks.

Further, Compound A attenuated upregulation of collagen 1a1, a key gene in liver fibrosis. Ninety-six hours after ConA injection, quantitative real time RT-PCR analysis revealed significantly reduced hepatic mRNA levels of collagen 1a1 compared to controls at all doses of Compound A. The extent of CCR2 inhibition in vivo in response to Compound A dosing in the mouse was confirmed in a whole blood assay by measuring the ability of exogenous murine MCP-1 to induce pERK. One hundred (100) mg/kg of Compound A completely inhibited pERK of mouse peripheral blood monocytes in vivo, demonstrating potent functional modulation of mouse CCR2 by Compound A.

B. Effects of CCR2 Inhibition on Intrahepatic mRNA Expressions in Chronic ConA Model

To characterize further the effects of inhibition of CCR2-induced inflammation on the development of liver fibrosis, the mRNA expression levels of key genes involved in fibrosis were analyzed after repeated injection of ConA. After four injections of ConA in Balb/c mice,

liver mRNA levels of collagen 1a1 and α -SMA increased significantly (data not shown). Both genes are markers of activation of hepatic stellate cells (HSC), which are the major source of collagen in the fibrotic liver. Administration of Compound A reduced the expression levels of collagen 1a1 in a dose-dependent manner with a statistically significant reduction obtained at a dose of 100 mg/kg. In addition, expression of α -SMA was significantly decreased in all groups treated with the CCR2 inhibitor Compound A. Furthermore, elevated hepatic levels of CD11b mRNA, a marker of activated monocytes/macrophages, were significantly reduced upon administration of Compound A, returning nearly to basal levels at 50 mg/kg. By contrast, upregulation of CCR2 mRNA levels observed after injection within ConA was only partially attenuated by pharmacologic CCR2 inhibition.

After eight weekly injections of ConA into mice, further elevation of the mRNA levels of these targets was observed. Administration of Compound A reduced the expression of collagen 1a1 and α -SMA in a dose-dependent manner with significant reductions obtained at doses of 50 and 100 mg/kg. Similarly, expression levels of both CCR2 and CD11b, as markers of inflammatory responses, were significantly decreased at doses of 50 and 100 mg/kg. These data suggest that pharmacologic inhibition of CCR2 attenuates both HSC activation and infiltration of inflammatory monocytes/macrophages into the liver of ConA-injected mice.

Conclusions

N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide, a 3-cycloalkylaminopyrrolidine derivative Exemplified in Example 38, is a selective antagonist of CCR2. The compound is selective against a panel of chemokine receptors. In human monocytes and whole blood, N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide blocked CCR2 signalling, chemotaxis, and MCP-1 binding at similar concentrations. N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide also reduced pain behaviours with efficacy comparable to clinical comparators in rodent models of inflammatory, OA, and neuropathic pain. Tool compounds with selectivity similar to N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide showed efficacy in pre-clinical models of liver fibrosis, including reduced liver enzyme levels and suppressed transcription of key genes involved in fibrogenesis. Administration of N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide to tumour-bearing mice resulted in reduced MDSC in circulation and the tumour. The results of clinical pharmacology studies demonstrate that N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-

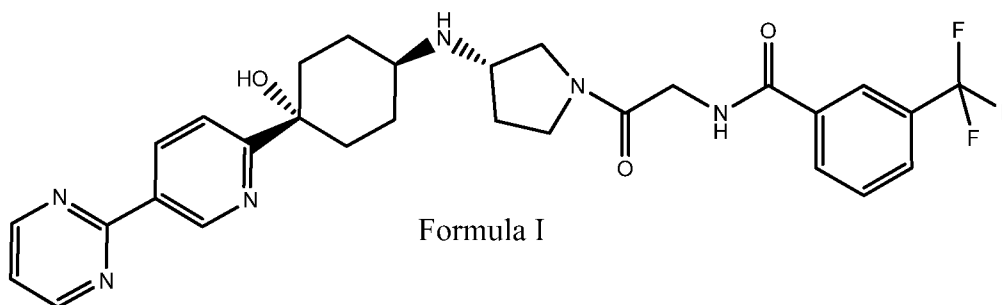
2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide is a selective inhibitor of CCR2 in vitro that exhibits non-clinical efficacy on varying pain states comparable to clinical comparators. Taken together, clinical and pre-clinical studies suggest that N-[2-((3S)-3-{[4-Hydroxy-4-(5-pyrimidin-2-ylpyridin-2-yl)cyclohexyl]amino}pyrrolidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide, which was initially in development for acute and chronic pain, can also be developed further for the treatment of liver fibrosis and oncology indications.

All publications, patents, and patent applications including all cited art and bibliographic references cited herein are hereby incorporated by reference in their entirety for all purposes.

While the many forms of the invention herein disclosed constitute presently preferred embodiments, many others are possible and further details of the preferred embodiments and other possible embodiments are not to be construed as limitations. It is understood that the terms used herein are merely descriptive rather than limiting and that various changes many equivalents may be made without departing from the spirit or scope of the claimed invention.

What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt thereof:

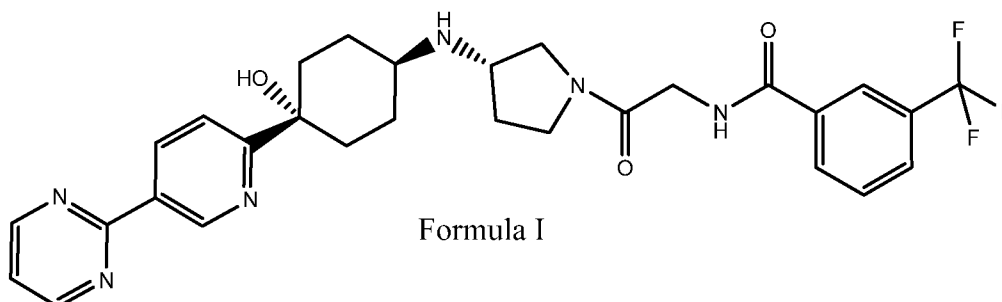


for the treatment of liver fibrosis.

2. The compound of claim 1, wherein said liver fibrosis is associated with hepatitis C.

3. The compound of claim 1, comprising administering a pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

4. A use of a compound of Formula I or a pharmaceutically acceptable salt thereof:



for the manufacture of a medicament for treating liver fibrosis.

5. The use of claim 1, wherein the liver fibrosis is associated with hepatitis C.

6. The use of claim 1, comprising administering a pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2012/050612

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D401/04 A61K31/33
 ADD.

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)
 C07D A61K

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/060665 A2 (INCYTE CORPORATION, USA) 7 July 2005 (2005-07-07) page 1, line 24; claims; example 38 -----	1-6

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 March 2012

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/050612

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