TRIAZOLYL PHENYL BENZENESULFONAMIDES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application Serial No. 60/831,042 filed July 14, 2006. The disclosure of this priority application is incorporated herein in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] The present invention described herein was supported at least in part by NIH (U19-AI056690-01). The government may have certain rights in the invention.

BACKGROUND

[0003] The present invention provides compounds, pharmaceutical compositions containing one or more of those compounds or their pharmaceutically acceptable salts, which are effective in inhibiting the binding or function of various chemokines to chemokine receptors. As antagonists or modulators of chemokine receptors, the compounds and compositions have utility in treating various immune disorder conditions and diseases.

[0004] Chemokines, also known as chemotactic cytokines, are a group of small molecular-weight proteins that are released by a wide variety of cells and have a variety of biological activities. Chemokines attract various types of cells of the immune system, such as macrophages, T cells, eosinophils, basophils and neutrophils, and cause them to migrate from the blood to various lymphoid and none-lymphoid tissues. They mediate infiltration of inflammatory cells to sites of inflammation, and are responsible for the initiation and perpetuation of many inflammation diseases (reviewed in Schall, *Cytokine*, 3:165-183 (1991), Schall et al., *Curr. Opin. Immunol.*, 6:865-873 (1994)).

[0005] In addition to stimulating chemotaxis, chemokines can induce other changes in responsive cells, including changes in cell shape, granule exocytosis, integrin up-regulation, formation of bioactive lipids (e.g., leukotrienes), respiratory burst associated with leukocyte activation, cell

proliferation, resistance to induction of apoptosis and angiogenesis. Thus, chemokines are early triggers of the inflammatory response, causing inflammatory mediator release, chemotaxis and extravasation to sites of infection or inflammation. They are also stimulators of a multitude of cellular processes that bear important physiological functions as well as pathological consequences.

[0006] Chemokines exert their effects by activating chemokine receptors expressed by responsive cells. Chemokine receptors are a class of G-protein coupled receptors, also known as seven-transmembrane receptors, found on the surface of a wide variety of cell types such as leukocytes, endothelial cells, smooth muscle cells and tumor cells.

[0007] Chemokines and chemokine receptors are expressed by intrinsic renal cells and infiltrating cells during renal inflammation (Segerer et al., *J. Am. Soc. Nephrol.*, 11:152-76 (2000); Morii et al., *J. Diabetes Complications*, 17:11-5 (2003); Lloyd et al. *J. Exp. Med.*, 185:1371-80 (1997); Gonzalez-Cuadrado et al. *Clin. Exp. Immunol.*, 106:518-22 (1996); Eddy & Giachelli, *Kidney Int.*, 47:1546-57 (1995); Diamond et al., *Am. J. Physiol.*, 266:F926-33 (1994)). In humans, CCR2 and ligand MCP-1 are among the proteins expressed in renal fibrosis, and are correlated with the extent of macrophage infiltration into the interstitium (Yang et al., *Zhonghua Yi Xue Za Zhi*, 81:73-7 (2001); Stephan et al., *J. Urol.*, 167:1497-502 (2002); Amann et al., *Diabetes Care*, 26:2421-5 (2003); Dai et al., *Chin. Med. J. (Engl)*, 114:864-8 (2001)). In animal models of renal fibrosis, blockade of CCR2 or MCP-1 leads to a marked reduction in severity of renal inflammation (Kitagawa et al., *Am. J. Pathol.*, 165:237-46 (2004); Wada et al., *Am. J. Pathol.*, 165:237-46 (2004); Shimizu et al., *J. Am. Soc. Nephrol.*, 14:1496-505 (2003)).

[0008] Rheumatoid arthritis is a chronic disease of the joints characterized by synovial inflammation that leads to the destruction of cartilage and bone. Although the underlying causes of the disease are unknown, it is believed that macrophages and Th-1 type T cells play a key role in the initiation and perpetuation of the chronic inflammatory process (Vervoordeldonk et al., *Curr. Rheumatol. Rep.*, 4:208-17 (2002)).

[0009] MCP-1 is among the several chemokines, including MIP-1α and IL-8, identified in rheumatoid synovium (Villiger et al., *J. Immunol.*, 149:722-7 (1992); Scaife et al., Rheumatology (Oxford), 43:1346-52 (2004); Shadidi et al., Scand. *J. Immunol.*, 57:192-8 (2003); Taylor et al., *Arthritis Rheum.*, 43:38-47 (2000); Tucci et al., *Biomed. Sci. Instrum.*, 34:169-74 (1997)). Chemokine receptors CCR1, CCR2, CCR3 and CCR5 are up-regulated in the joints from arthritic mice (Plater-Zyberk et al., *Immunol. Lett.*, 57:117-20 (1997). Blockade of MCP-1 activity using a CCR2 antagonist or an antibody against MCP-1 have been shown efficacious in reducing joint inflammation in experimental models of rheumatoid arthritis (Gong et al., *J. Exp. Med.*, 186:131-7 (1997); Ogata et al., *J. Pathol.*, 182:106-14 (1997)).

[0010] Chemokine receptor-mediated infiltration of macrophages in the fat tissues may also contribute to the complications arising from obesity, a condition resulting from excessive storage of fat in the body. Obesity predisposes the affected individuals to many disorders, such as non-insulin-dependent diabetes, hypertension, stroke, and coronary artery disease. In obesity, adipose tissues have altered metabolic and endocrine functions that lead to an increased release of fatty acids, hormones, and pro-inflammatory molecules. Adipose tissue macrophages are believed to be a key source of pro-inflammatory cytokines including TNF-alpha, iNOS and IL-6 (Weisberg et al., *J. Clin. Invest.*, 112:1796-808 (2003)). Recruitment of macrophages to the adipose tissue is likely mediated by MCP-1 produced by adipocytes (Christiansen T, et al., *Int. J. Obes.* (Lond). 2005 Jan;29(1):146-50; Sartipy et al., *Proc. Natl. Acad. Sci. U.S.A.*, 100:7265-70 (2003)).

[0011] Elevated MCP-1 may induce adipocyte differentiation and insulin resistance, and contribute to pathologies associated with hyper-insulinemia and obesity. MCP-1 is over-expressed in plasma in obese mice compared to lean controls and white adipose is a major source. MCP-1 has also been shown to accelerate wound healing, and has a direct angiogenic effect on epithelial cells, and may play a direct role in the remodeling of adipose tissue in obesity. (Sartipy P, Loskutoff DJ., *Proc. Natl. Acad. Sci. U.S.A.*,100:7265 (2003)).

[0012] MCP-1 plasma levels are substantially increased in Diet Induce Obesity (DIO) mice, and a strong correlation between plasma MCP-1 levels and body weight has been identified. Furthermore, elevation of MCP-1 induced by high fat diet causes changes in the CD11b positive monocyte population in DIO mice. (Takahashi K, et al., *J. Biol. Chem.*, 46654 (2003)).

[0013] Furthermore, chronic inflammation in fat is thought to play a crucial role in the development of obesity-related insulin resistance (Xu H, et al., *J Clin Invest.* 2003 Dec;112(12):1821-30). It has been proposed that obesity related insulin resistance is, at least in part, a chronic inflammatory disease initiated in adipose tissue. Many inflammation and macrophage specific genes are dramatically upregulated in white adipose tissue in mouse models of genetic and high fat diet-induced obesity (DIO), and this upregulation precedes a dramatic increase in circulating insulin.

[0014] Increased expression levels of monocyte CCR2 and monocyte chemoattractant protein-1 in patients with diabetes mellitus (*Biochemical and Biophysical Research Communications*, 344(3):780-5 (2006)) were found in a study involving diabetic patients. Serum MCP-1 concentrations and surface expression of CCR2 on monocytes in diabetic patients were significantly higher than in non-diabetics, and the serum MCP-1 levels correlated with HbA1c, triglycerides, BMI, hs-CRP. Surface expression levels of CD36 and CD68 on monocytes were significantly increased in diabetic patients and more unregulated by MCP-1 in diabetics, augmenting uptake of ox-LDL, and hence potentially foam cell transformation. Elevated serum MCP-1 and increased monocyte CCR2, CD36, CD68 expression correlated with poor blood glucose control and potentially correlate with increased vessel wall monocyte recruitment.

[0015] MCP-1 is a potential player in negative cross talk between adipose tissue and skeletal muscle (Bianco JJ, et al., *Endocrinology*, 2458 (2006)). MCP-1 can significantly reduce insulin-stimulated glucose uptake, and is a prominent inducer of insulin resistance in human skeletal muscle cell. Adipose tissue is a major secretory and endocrine active organ producing bioactive proteins regulating energy metabolism and insulin sensitivity.

[0016] CCR2 modulates inflammatory and metabolic effects of high-fat feeding (Weisberg SP, et al., *J. Clin. Invest.*, 115 (2006)). Genetic deficiency in CCR2 reduced food intake and attenuated the development of obesity in mice fed a high fat diet. In obese mice matched for adiposity, CCR2 deficiency reduced macrophage content and inflammatory profile of adipose tissue, increased adiponectin expression, and improved glucose homeostatis and insulin sensitivity. In lean animals, no effect of CCR2 genotype on metabolic trait was found. In high-fat diet mice, CCR2 genotype modulated feeding, the development of obesity and adipose tissue inflammation. Once established, short term antagonism was shown to attenuate macrophage accumulation in adipose tissue and insulin resistance.

[0017] Chemokine and chemokine receptors are the key regulators of immune cell trafficking. MCP-1 is a potent chemoattractant of monocytes and T cells; its expression is induced under inflammatory conditions including proinflammatory cytokine stimulations and hypoxia. The interaction between MCP-1 and CCR2 mediates migration of monocytes, macrophage as well as activated T cells and play a key role in the pathogenesis of many inflammatory diseases. Inhibition of CCR2 functions using small molecule antagonists described in this invention represents a new approach for the treatments of inflammatory disorders.

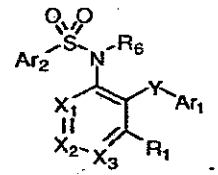
[0018] Psoriasis is a chronic inflammatory disease characterized by hyperproliferation of keratinocytes and pronounced leukocyte infiltration. It is known that keratinocytes from psoriasis lesion express abundant CCR2 ligand MCP-1, particularly when stimulated by proinflammatory cytokines such as TNF-α (Vestergaard et al., *Acta. Derm. Venereol.*, 84(5):353-8 (2004); Gillitzer et al., *J. Invest. Dermatol.*, 101(2):127-31 (1993); Deleuran et al., *J. Dermatol. Sci.*, 13(3):228-36 (1996)). Since MCP-1 can attract migration of both macrophages and dendritic cells expressing CCR2 to the skin, this receptor and ligand pair is believed to be important in regulating the interaction between proliferating keratinocytes and dermal macrophage during the development of psoriasis. A small molecule antagonist may thus be useful in the treatment of psoriasis.

[0019] In addition to inflammatory diseases, chemokines and chemokine receptors have also been implicated in cancers (Broek et al., *Br. J. Cancer*, 88(6):855-62 (2003)). Tumor cells stimulate the formation of stroma that secretes various mediators pivotal for tumor growth, including growth factors, cytokines, and proteases. It is known that the level of MCP-1 is associated significantly with tumor-associated macrophage accumulation, and prognostic analysis reveals that high expression of MCP-1 is a significant indicator of early relapse in breast cancer (Ueno et al., *Clin. Cancer Res.*, 6(8):3282-9 (2001)). A small molecule antagonist of a chemokine may thus be able to reduce the release of growth-stimulating cytokines by blocking accumulation of macrophages at sites of tumor formation.

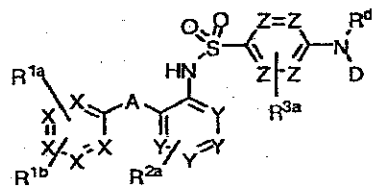
[0020] T lymphocyte (T cell) infiltration into the small intestine and colon has been linked to the pathogenesis of Coeliac diseases, food allergies, rheumatoid arthritis, human inflammatory bowel diseases (IBD) which include Crohn's disease and ulcerative colitis. Blocking trafficking of relevant T cell populations to the intestine can lead to an effective approach to treat human IBD. More recently, chemokine receptor 9 (CCR9) has been noted to be expressed on gut-homing T cells in peripheral blood, elevated in patients with small bowel inflammation such as Crohn's disease and celiac disease. The only CCR9 ligand identified to date, TECK (thymus-expressed chemokine) is expressed in the small intestine and the ligand receptor pair is now thought to play a pivotal role in the development of IBD. In particular, this pair mediates the migration of disease causing T cells to the intestine. See for example, Zaballos et al., *J. Immunol.*, 162(10):5671 5675 (1999); Kunkel et al., J. Exp. Med., 192(5):761-768 (2000); Papadakis et al., *J. Immunol.*, 165(9):5069-5076 (2000); Papadakis et al., *Gastroenterology*, 121(2):246-254 (2001); Campbell et al., *J. Exp. Med.*, 195(1):135-141 (2002); Wurbel et al., *Blood*, 98(9):2626-2632 (2001); and Uehara et al., *J. Immunol.*, 168(6):2811-2819 (2002). Rivera-Nieves, et al., *Gastroenterology*, 2006 Nov;131(5):1518-29; and Kontoyiannis et al., *J. Exp. Med.*, Vol. 196, Number 12, Dec. 16, 2002. In addition CCR9 bearing lymphocytes have been show to mediate the pathology of filariasis (lymphatic filarial disease) and inhibition of CCR9 has been correlated with reduction of the pathology associated with such

conditions. See for example Babu et al., Journal of Infectious Diseases, 191: 1018-26, 2005.

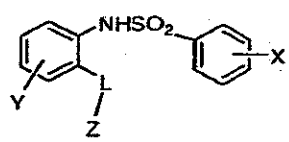
[0021] PCT Published Application WO 2003/099773 (Millennium Pharmaceuticals, Inc.) discloses compounds which can bind to CCR9 receptors of the formula



[0022] PCT Published Application WO 2005/004810 (Merck & Co., Inc.) discloses brandykinin B1 antagonists or inverse agonists of the formula



[0023] US Published Patent Application 2005/137193 A1 (ChemoCentryx, Inc.) discloses CCR9 modulators of the formula



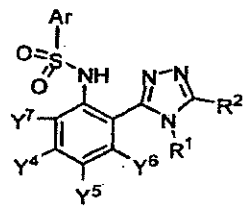
SUMMARY

[0024] The present disclosure is directed to compounds and pharmaceutically acceptable salts thereof, compositions, and methods useful in modulating chemokine activity. The compounds and salts thereof, compositions, and methods described herein are useful in treating or preventing chemokine-mediated conditions or diseases, including certain inflammatory and immunoregulatory disorders and diseases.

[0025] The compounds of the present disclosure have been shown to modulate one or more of CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR3, CXCR4, CXCR5, and CX3CR1. In particular,

various compounds of the present disclosure modulate CCR2 and CCR9 as shown in the examples.

[0025a] In a first aspect, there is provided a compound of the formula (I), or a salt thereof:



(I)

where

Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl;

Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^5C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

R^{15} and R^{16}, R^{16} and R^{17} or R^{15} and R^{17} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

R^1 is selected from the group consisting of $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or

unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^2 is selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, $-NR^7C(O)NR^8R^9$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3-to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3-to 10-membered heterocyclyl;

R^7 and R^8, R^8 and R^9 or R^7 and R^9 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring; and

where R^1 and R^2 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

wherein the substituents for substituted alkyl, substituted alkenyl, and substituted alkynyl are selected from halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R", oxo (=O or -O-), -OR', -OC(O)R', -OC(O)NR'R" $-NO_2$, -NR'C(O)R", -NR'"C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R'"$, -NR'"S(O)NR'R", $-NR'"S(O)_2NR'R"$, -SR',-S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR'", -SiR'R"R'", $-N_3$, unsubstituted C_{6-10} aryl, unsubstituted 5- to 10-membered heteroaryl, and unsubstituted 3- to 10-membered heterocyclyl; and

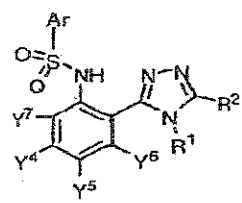
the substituents for substituted aryl, substituted heteroaryl and substituted heterocyclyl are selected from halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R", oxo (=O or -O-), -OR', -OC(O)R', -OC(O)NR'R", $-NO_2$, -NR'C(O)R", -NR'"C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R"$, -NR'"S(O)NR'R", $NR'"S(O)_2NR'R"$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR'", -SiR'R"R'", $-N_3$, unsubstituted C_{1-8} alkyl, unsubstituted C_{2-8} alkenyl, unsubstituted

C_{2-8} alkynyl, unsubstituted C_{6-10} aryl, unsubstituted 5- to 10-membered heteroaryl, and unsubstituted 3- to 10-membered heterocyclyl;
wherein R', R" and R"' each independently is selected from hydrogen, unsubstituted C_{1-8} alkyl, unsubstituted C_{2-8} alkenyl, unsubstituted C_{2-8} alkynyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted heterocyclyl, unsubstituted arylalkyl and unsubstituted aryloxyalkyl,
wherein substituted or unsubstituted C_{1-8} alkyl may be linear, cyclic, or branched or a combination thereof.

[0025b] In a second aspect, there is provided a composition comprising a pharmaceutically acceptable carrier and a compound as defined above.

[0025c] In a third aspect, there is provided a compound as defined above, or a salt thereof, or a composition as defined above, for use in a method of treating a CCR2-mediated condition or disease or a CCR9-mediated condition or disease.

[0026] In one embodiment, the present compound may be represented by formula (I) or salts thereof:



(I)

where Ar, Y^4, Y^5, Y^6, Y^7, R^1 and R^2 are as defined below.

[0027] In another embodiment, the present disclosure provides compositions useful in modulating chemokine activity. In one embodiment, a composition according to the present disclosure comprises a compound according to the invention and a pharmaceutically acceptable carrier or excipient.

[0028] In yet another embodiment, the present disclosure provides a method of modulating chemokine function in a cell, comprising contacting the cell with a therapeutically effective amount of a compound or composition according to the disclosure.

[0029] In still another embodiment, the present disclosure provides a method for modulating chemokine function, comprising contacting a chemokine receptor with a therapeutically effective amount of a compound or composition according to the disclosure.

[0030] In still another embodiment, the present disclosure provides a method for treating a chemokine-mediated condition or disease, comprising administering to a subject a safe and effective amount of a compound or composition according to the disclosure.

[0031] In addition to the compounds provided herein, the present disclosure further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds in therapeutic methods, primarily to treat diseases associated with chemokine signaling activity.

DETAILED DESCRIPTION

[0032] General

[0033] The present invention is directed to compounds and salts thereof, compositions and methods useful in the modulation of chemokine receptor function, particularly CCR2 or CCR9 function. Modulation of chemokine receptor activity, as used herein in its various forms, is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism of the activity associated with a particular chemokine receptor, preferably the CCR2 or CCR9 receptor. Accordingly, the compounds of the present invention are compounds which modulate at least one function or characteristic of mammalian CCR2 or CCR9, for example, a human CCR2 or CCR9 protein. The ability of a compound to modulate the function of CCR2 or CCR9, can be demonstrated in a binding assay (*e.g.*, ligand binding or agonist binding), a migration assay, a signaling 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 assay (*e.g.*, stimulation of chemotaxis, exocytosis or inflammatory mediator release by leukocytes).

[0034] Abbreviations and Definitions

[0035] When describing the compounds, compositions, methods and processes of this invention, the following terms have the following meanings, unless otherwise indicated.

[0036] "Alkyl" by itself or as part of another substituent refers to a hydrocarbon group which may be linear, cyclic, or branched or a combination thereof having the number of carbon atoms designated (i.e., C_{1-8} means one to eight carbon atoms). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, cyclopentyl, (cyclohexyl)methyl, cyclopropylmethyl, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc. Alkyl groups can be substituted or unsubstituted, unless otherwise indicated. Examples of substituted alkyl include haloalkyl, thioalkyl, aminoalkyl, and the like.

[0037] "Alkoxy" refers to –O-alkyl. Examples of an alkoxy group include methoxy, ethoxy, n-propoxy etc.

[0038] "Alkenyl" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. Alkenyl groups with 2-8 carbon atoms are preferred. The alkenyl group may contain 1, 2 or 3 carbon-carbon double bonds. Examples of alkenyl groups include ethenyl, n-propenyl, isopropenyl, n-but-2-enyl, n-hex-3-enyl, cyclohexenyl, cyclopentenyl and the like. Alkenyl groups can be substituted or unsubstituted, unless otherwise indicated.

[0039] "Alkynyl" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. Alkynyl groups with 2-8 carbon atoms are preferred. The alkynyl group may contain 1, 2 or 3 carbon-carbon triple bonds. Examples of alkynyl groups include ethynyl, n-propynyl, n-but-2-ynyl, n-hex-3-ynyl and the like. Alkynyl groups can be substituted or unsubstituted, unless otherwise indicated.

[0040] "Aryl" refers to a polyunsaturated, aromatic hydrocarbon group having a single ring (monocyclic) or multiple rings (bicyclic), which can be fused together or linked covalently. Aryl groups with 6-10 carbon atoms are preferred, where this number of carbon atoms can be designated by C_{6-10}, for example. Examples of aryl groups include phenyl and naphthalene-1-yl, naphthalene-2-yl, biphenyl and the like. Aryl groups can be substituted or unsubstituted, unless otherwise indicated.

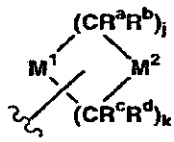
[0041] "Halo" or "halogen", by itself or as part of a substituent refers to a chlorine, bromine, iodine, or fluorine atom.

[0042] "Haloalkyl", as a substituted alkyl group, refers to a monohaloalkyl or polyhaloalkyl group, most typically substituted with from 1-3 halogen atoms. Examples include 1-chloroethyl, 3-bromopropyl, trifluoromethyl and the like.

[0043] "Heterocyclyl" refers to a saturated or unsaturated non-aromatic ring containing at least one heteroatom (typically 1 to 5 heteroatoms) selected from nitrogen, oxygen or sulfur. The heterocyclyl ring may be monocyclic or bicyclic. Preferably, these groups contain 0-5 nitrogen atoms, 0-2 sulfur atoms and 0-2 oxygen atoms. More preferably, these groups contain 0-3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Examples of

heterocycle groups include pyrrolidine, piperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, quinuclidine and the like. Preferred heterocyclic groups are monocyclic, though they may be fused or linked covalently to an aryl or heteroaryl ring system.

[0044] In one preferred embodiment, heterocyclic groups may be represented by formula (AA) below:



AA

[0045] where formula (AA) is attached via a free valence on either M^1 or M^2; M^1 represents O, NR^e, or $S(O)_l$; M^2 represents CR^fR^g, O, $S(O)_l$, or NR^e; l is 0, 1 or 2; j is 1, 2 or 3 and k is 1, 2 or 3, with the proviso that j + k is 3, 4, or 5; and R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, $-COR^h$, $-CO_2R^h$, $-CONR^hR^i$, $-NR^hCOR^i$, $-SO_2R^h$, $-SO_2NR^hR^i$, $-NSO_2R^hR^i$ $-NR^hR^i$, $-OR^h$, $-Q^1COR^h$, $-Q^1CO_2R^h$, $-Q^1CONR^hR^i$, $-Q^1NR^hCOR^i$, $-Q^1SO_2R^{28}$, $-Q^1SO_2NR^hR^i$, $-Q^1NSO_2R^hR^i$, $-Q^1NR^hR^i$, $-Q^1OR^h$, wherein Q^1 is a member selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene and C_{2-4} alkynylene, and R^h and R^i are independently selected from the group consisting of hydrogen and C_{1-8} alkyl, and wherein the aliphatic portions of each of the R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and R^i substituents are optionally substituted with from one to three members selected from the group consisting of halogen, -OH, $-OR^n$, $-OC(O)NHR^n$, $-OC(O)NR^nR^o$, -SH, $-SR^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-SO_2NH_2$, $-S(O)_2NHR^n$, $-S(O)_2NR^nR^o$, $-NHS(O)_2R^n$, $-NR^nS(O)_2R^o$, $-C(O)NH_2$, $-C(O)NHR^n$, $-C(O)NR^nR^o$, $-C(O)R^n$, $-NHC(O)R^o$, $-NR^nC(O)R^o$, $-NHC(O)NH_2$, $-NR^nC(O)NH_2$, $-NR^nC(O)NHR^o$, $-NHC(O)NHR^n$, $-NR^nC(O)NR^oR^p$, $-NHC(O)NR^nR^o$, $-CO_2H$, $-CO_2R^n$, $-NHCO_2R^n$, $-NR^nCO_2R^o$,

-CN, -NO_2, -NH_2, -NHR^n, -NR^nR^o, -$NR^nS(O)NH_2$ and –$NR^nS(O)_2NHR^o$, wherein R^n, R^o and R^p are independently an unsubstituted C_{1-8} alkyl. Additionally, any two of R^a, R^b, R^c, R^d, R^e, R^f and R^g may be combined to form a bridged or spirocyclic ring system.

[0046] In one preferred embodiment, the number of $R^a + R^b + R^c + R^d$ groups that are other than hydrogen is 0, 1 or 2. In a more preferred embodiment, R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, -COR^h, -CO_2R^h, -$CONR^hR^h$, -NR^hCOR^h, -SO_2R^h, -$SO_2NR^hR^i$, -$NSO_2R^hR^i$, -NR^hR^i, and –OR^h, wherein R^h and R^i are independently selected from the group consisting of hydrogen and unsubstituted C_{1-8} alkyl and wherein the aliphatic portions of each of the R^a, R^b, R^c, R^d, R^e, R^f and R^g substituents are optionally substituted with from one to three members selected from the group consisting of halogen, -OH, -OR^n, -$OC(O)NHR^n$, -$OC(O)NR^nR^o$, -SH, -SR^n, -$S(O)R^o$, -$S(O)_2R^n$, -SO_2NH_2, -$S(O)_2NHR^n$, -$S(O)_2NR^nR^o$, -$NHS(O)_2R^n$, -$NR^nS(O)_2R^o$, -$C(O)NH_2$, -$C(O)NHR^n$, -$C(O)NR^nR^o$, -$C(O)R^n$, -$NHC(O)R^n$, -$NR^nC(O)R^o$, -$NHC(O)NH_2$, -$NR^nC(O)NH_2$, -$NR^nC(O)NHR^o$, -$NHC(O)NHR^n$, -$NR^nC(O)NR^oR^p$, -$NHC(O)NR^nR^o$, -CO_2H, -CO_2R^n, -$NHCO_2R^n$, -$NR^nCO_2R^o$, -CN, -NO_2, -NH_2, -NHR^n, -NR^nR^o, -$NR^nS(O)NH_2$ and –$NR^nS(O)_2NHR^o$, wherein R^n, R^o and R^p are independently an unsubstituted C_{1-8} alkyl.

[0047] In a more preferred embodiment, R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently hydrogen or C_{1-4} alkyl. In another preferred embodiment, at least three of R^a, R^b, R^c, R^d, R^e, R^f, and R^g are hydrogen.

[0048] "Heteroaryl" refers to an aromatic group containing at least one heteroatom, where the heteroaryl group may be monocyclic or bicyclic. Examples include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiazolyl, benzofuranyl, benzothienyl, indolyl, azaindolyl, azaindazolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl,

tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl or thienyl. Preferred heteroaryl groups are those having at least one aryl ring nitrogen atom, such as quinolinyl, quinoxalinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl and the like. Preferred 6-ring heteroaryl systems include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl and the like. Preferred 5-ring heteroaryl systems include isothiazolyl, pyrazolyl, imidazolyl, thienyl, furyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, thiazolyl and the like.

[0049] Heterocyclyl and heteroaryl can be attached at any available ring carbon or heteroatom. Each heterocyclyl and heteroaryl may have one or more rings. When multiple rings are present, they can be fused together or linked covalently. Each heterocyclyl and heteroaryl must contain at least one heteroatom (typically 1 to 5 heteroatoms) selected from nitrogen, oxygen or sulfur. Preferably, these groups contain 0-5 nitrogen atoms, 0-2 sulfur atoms and 0-2 oxygen atoms. More preferably, these groups contain 0-3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Heterocyclyl and heteroaryl groups can be substituted or unsubstituted, unless otherwise indicated. For substituted groups, the substitution may be on a carbon or heteroatom. For example, when the substitution is oxo (=O or $-O^-$), the resulting group may have either a carbonyl (-C(O)-) or a N-oxide ($-N^+-O^-$).

[0050] Suitable substituents for substituted alkyl, substituted alkenyl, and substituted alkynyl include halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R", oxo (=O or $-O^-$), $-OR'$, -OC(O)R', -OC(O)NR'R" $-NO_2$, -NR'C(O)R', -NR"'C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R"$, -NR"'S(O)NR'R", $-NR"'S(O)_2NR'R"$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR"', -SiR'R"R"',$-N_3$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl. The number of possible substituents range from zero to (2m'+1), where m' is the total number of carbon atoms in such radical.

[0051] Suitable substituents for substituted aryl, substituted heteroaryl and substituted heterocyclyl include halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R",

oxo (=O or –O⁻), –OR', -OC(O)R', -OC(O)NR'R", $-NO_2$, -NR'C(O)R", -NR"'C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R"$, -NR"'S(O)NR'R", $-NR"'S(O)_2NR'R"$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR"', -SiR'R"R"', $-N_3$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10 membered heterocyclyl. The number of possible substituents range from zero to the total number of open valences on the aromatic ring system.

[0052] As used above, R', R" and R"' each independently refer to a variety of groups including hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryloxyalkyl. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring (for example, -NR'R" includes 1-pyrrolidinyl and 4-morpholinyl). Furthermore, R' and R", R" and R"', or R' and R"' may together with the atom(s) to which they are attached, form a substituted or unsubstituted 5- ,6- or 7-membered ring.

[0053] Two of the substituents on adjacent atoms of an aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently –NR""-, -O-, $-CH_2-$ or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula –A'-$(CH_2)_r$-B'-, wherein A' and B' are independently $-CH_2-$, -O-, -NR""-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2NR""-$ or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR""-, -

S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. R"" in is selected from hydrogen or unsubstituted C_{1-8} alkyl.

[0054] "Heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0055] "Pharmaceutically acceptable" carrier, diluent, or excipient is a carrier, diluent, or excipient compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0056] "Pharmaceutically-acceptable salt" refers to a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids, 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. Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary, tertiary and quaternary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. 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. Salts derived from pharmaceutically-acceptable acids include acetic,

ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, gluconic, glucoronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nicotinic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

[0057] 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 (see, for example, Berge, S.M. et al, "Pharmaceutical Salts", J. Pharmaceutical Science, 1977, 66:1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0058] The neutral forms of the compounds 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.

[0059] "Salt thereof" refers to a compound formed when the hydrogen of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. Preferably, the salt is a pharmaceutically-acceptable salt, although this is not required for salts of intermediate compounds which are not intended for administration to a patient.

[0060] In addition to salt forms, the present invention provides compounds which are 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.

[0061] Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in

routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation, selection, and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

[0062] The compounds of the invention may be present in the form of pharmaceutically acceptable metabolites thereof. The term "metabolite" means a pharmaceutically acceptable form of a metabolic derivative of a compound of the invention (or a salt thereof). In some aspects, the metabolite may be a functional derivative of a compound that is readily convertible in vivo into an active compound. In other aspects, the metabolite may be an active compound.

[0063] "Therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

[0064] "Treating" or "treatment" as used herein refers to the treating or treatment of a disease or medical condition (such as a viral, bacterial or fungal infection or other infectious diseases, as well as autoimmune or inflammatory conditions) in a patient, such as a mammal (particularly a human or a companion animal) which includes ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient; suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or alleviating the symptoms of the disease or medical condition in a patient.

[0065] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, both solvated forms and unsolvated forms 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 (i.e., as polymorphs). 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.

[0066] It will be apparent to one skilled in the art that certain compounds of the present invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention. Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0067] The compounds of the present invention may include a detectable label. A detectable label is a group that is detectable at low concentrations, usually less than micromolar, possibly less than nanomolar, and that can be readily distinguished from other molecules, due to differences in a molecular property (e. g. molecular weight, mass to charge ratio, radioactivity, redox potential, luminescence, fluorescence, electromagnetic properties, binding properties, and the like). Detectable labels may be detected by spectroscopic, photochemical, biochemical, immunochemical, electrical, magnetic, electromagnetic, optical or chemical means and the like.

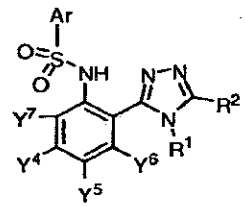
[0068] A wide variety of detectable labels are within the scope of the present invention, including hapten labels (e.g. biotin, or labels used in

conjunction with detectable antibodies such as horse radish peroxidase antibodies); mass tag labels (e.g. stable isotope labels); radioisotopic labels (including ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P); metal chelate labels; luminescent labels including fluorescent labels (such as fluorescein, isothiocyanate, Texas red, rhodamine, green fluorescent protein, and the like), phosphorescent labels, and chemiluminescent labels, typically having quantum yield greater than 0.1; electroactive and electron transfer labels; enzyme modulator labels including coenzymes, organometallic catalysts horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA;photosensitizer labels; magnetic bead labels including Dynabeads; colorimetric labels such as colloidal gold, silver, selenium, or other metals and metal sol labels (see U. S. Patent No. 5,120,643, which is herein incorporated by reference in its entirety for all purposes), or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) bead labels; and carbon black labels. Patents teaching the use of such detectable labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; 4,366,241; 6,312,914; 5,990,479; 6,207,392; 6,423,551; 6,251,303; 6,306,610; 6,322,901; 6,319,426; 6,326,144; and 6,444,143, which are herein incorporated by reference in their entirety for all purposes.

[0069] Detectable labels are commercially available or may be prepared as known to one skilled in the art. Detectable labels may be covalently attached to the compounds using a reactive functional group, which can be located at any appropriate position. Methods for attaching a detectable label are known to one skilled in the art. When the reactive group is attached to an alkyl, or substituted alkyl chain tethered to an aryl nucleus, the reactive group may be located at a terminal position of an alkyl chain.

[0070] **Compounds**

[0071] In one embodiment, the compounds of the present invention are represented by formula (I), or salts thereof:



(I)

[0072] Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl;

[0073] Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

[0074] R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

[0075] R^{15} and R^{16}, R^{16} and R^{17} or R^{15} and R^{17} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

[0076] R^1 is selected from the group consisting of hydrogen, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

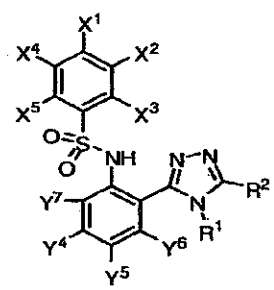
[0077] R^2 is selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, $-NR^7C(O)NR^8R^9$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

[0078] R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

[0079] R^7 and R^8, R^8 and R^9 or R^7 and R^9 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring; and

[0080] where R^1 and R^2 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

[0081] In one embodiment, the compounds of the present invention are represented by formula (II), or salts thereof:



(II)

[0082] where Y^4, Y^5, Y^6, Y^7, R^1 and R^2 are as defined for formula (I);

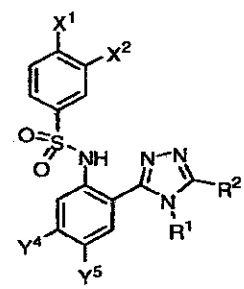
[0083] X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$,

$-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

[0084] R^{18}, R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

[0085] R^{18} and R^{19}, R^{19} and R^{20} or R^{18} and R^{20} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

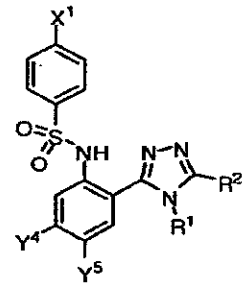
[0086] In another embodiment, the compounds are represented by formula (III), or salts thereof:



(III)

[0087] where Y^4, Y^5, R^1 and R^2 are as defined for formula (I); and X^1 and X^2 are as defined for formula (II); with the proviso that at least one of X^1 and X^2 is other than hydrogen and at least one of Y^4 and Y^5 is other than hydrogen.

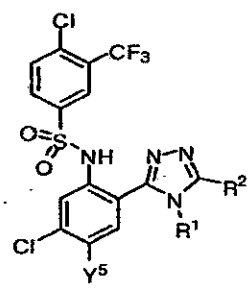
[0088] In another embodiment, the compounds are represented by formula (IV), or salts thereof:



(IV)

[0089] where Y^4, Y^5, R^1 and R^2 are as defined for formula (I); and X^1 is as defined for formula (II), with the proviso that X^1 is other than hydrogen and at least one of Y^4 and Y^5 is other than hydrogen.

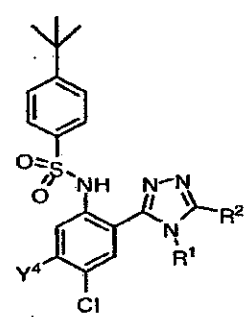
[0090] In another embodiment, the compounds of the present invention are represented by formula (V), or salts thereof:



(V)

[0091] where Y^5 is halogen or hydrogen; and R^1 and R^2 are as defined for formula (I).

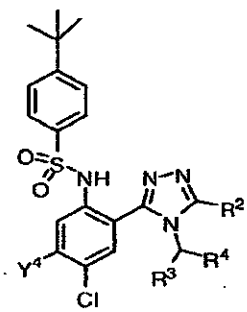
[0092] In another embodiment, the compounds of the present invention are represented by formula (VI), or salts thereof:



(VI)

[0093] where Y^4 is hydrogen or fluoro; R^1 and R^2 is as defined in formula (I).

[0094] In another embodiment, the compounds of the present invention are represented by formula (VIIa), or salts thereof:

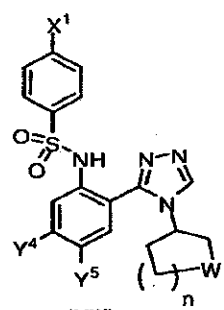


(VIIa)

[0095] where Y^4 is hydrogen or fluoro; R^2 is as defined in formula (I); and

[0096] R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4 -10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

[0097] In another embodiment, the compounds of the present invention are represented by formula (VIII), or salts thereof:



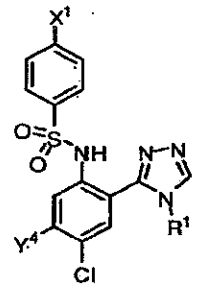
(VIII)

[0098] where Y^4 and Y^5 are as defined for formula (I); X^1 is as defined for formula (II), with the proviso that X^1 and Y^5 are other than hydrogen;

[0099] W is NH or O; and

[00100] n is 0, 1, or 2.

[00101] In another embodiment, the compounds of the present invention are represented by formula (IXa), or salts thereof:

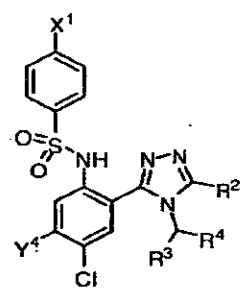


(IXa)

[00102] where Y^4 is hydrogen or fluoro; R^1 is as defined in formula (I); and

[00103] X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00104] In another embodiment, the compounds of the present invention are represented by formula (IXb), or salts thereof:



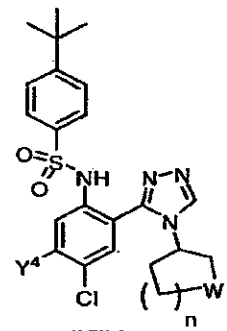
(IXb)

[00105] where Y^4 is hydrogen or fluoro; R^2 is as defined in formula (I);

[00106] X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

[00107] R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4 -10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

[00108] In another embodiment, the compounds of the present invention are represented by formula (VIIb), or salts thereof:



(VIIb)

[00109] Y^4 is hydrogen or fluoro;

[00110] W is NH or O; and

[00111] n is 0, 1, or 2.

[00112] **Compounds that Modulate CCR2 or CCR9 Activity**

[00113] The present invention provides compounds that modulate at least one of CCR2 or CCR9 activity. Chemokine receptors are integral membrane proteins which interact with an extracellular ligand, such as a chemokine, and mediate a cellular response to the ligand, *e.g.*, chemotaxis, increased intracellular calcium ion concentration, etc. Therefore, modulation of a chemokine receptor function, *e.g.*, interference with a chemokine receptor ligand interaction, will modulate a chemokine receptor mediated response, and treat or prevent a chemokine receptor mediated condition or disease. Modulation of a chemokine receptor function includes both inducement and inhibition of the function. The type of modulation accomplished will depend on the characteristics of the compound, i.e., antagonist or full, partial or inverse agonist.

[00114] Without intending to be bound by any particular theory, it is believed that the compounds provided herein interfere with the interaction between a chemokine receptor and one or more cognate ligands. In particular, it is believed that the compounds interfere with the interaction between CCR2 and a CCR2 ligand, such as MCP-1. Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein and salts thereof.

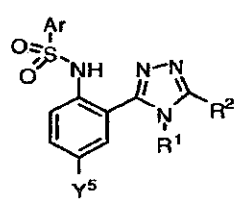
[00115] For example, compounds of this invention act as potent CCR2 antagonists, and this antagonistic activity has been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR2. Accordingly, the compounds provided herein are useful in pharmaceutical compositions, methods for the treatment of CCR2-mediated diseases, and as controls in assays for the identification of competitive CCR2 antagonists.

[00116] The compounds of the invention are thought to interfere with inappropriate T-cell trafficking by specifically modulating or inhibiting a chemokine receptor function. Without intending to be bound by any particular theory, it is believed that the compounds provided herein interfere with the interaction between a chemokine receptor and one or more cognate ligands. In particular, it is believed that the compounds interfere with the interaction between CCR9 and a CCR9 ligand, such as TECK. Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein and salts thereof.

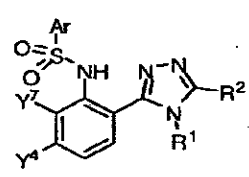
[00117] For example, compounds of this invention act as potent CCR9 antagonists, and this antagonistic activity has been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR9. Accordingly, the compounds provided herein are useful in pharmaceutical compositions, methods for the treatment of CCR9-mediated diseases, and as controls in assays for the identification of competitive CCR9 antagonists.

[00118] **Preferred Compounds**

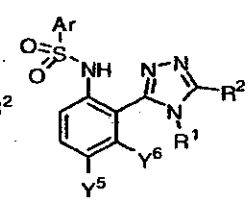
[00119] In several preferred embodiments, the compounds may be represented by the following formulae, or salts thereof:



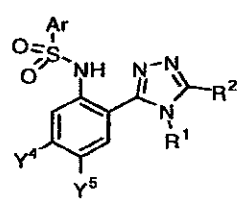
(X)



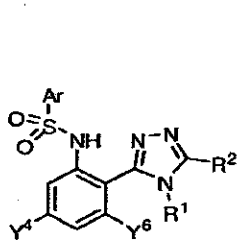
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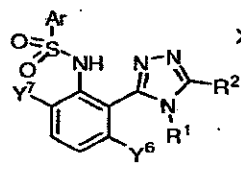
(XII)



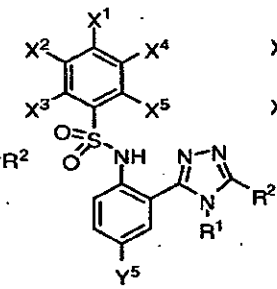
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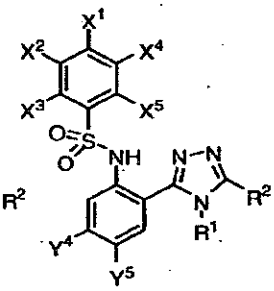
(XIV)



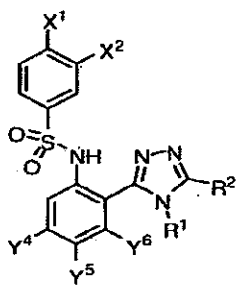
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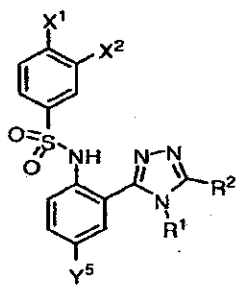
(XVI)



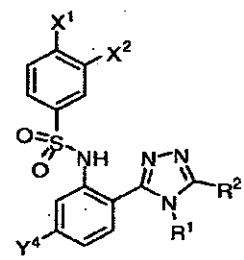
(XVII)



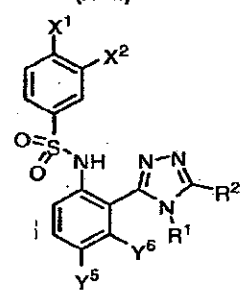
(XVIII)



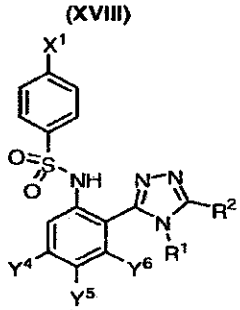
(XIX)



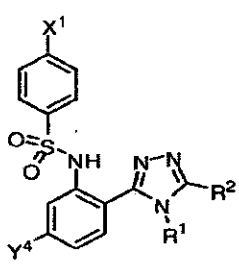
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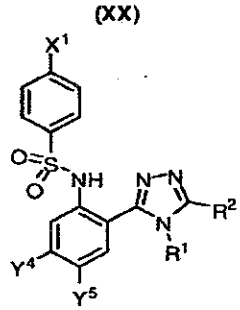
(XXI)



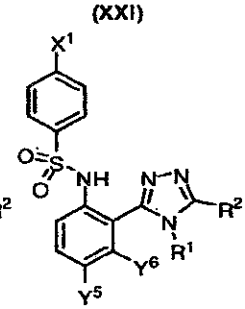
(XXII)



(XXIII)



(XXIV)



(XXV)

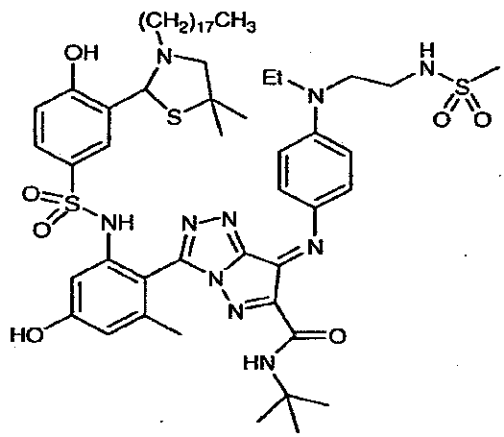
[00120] Formulae X to XXV are examples of Formula I.

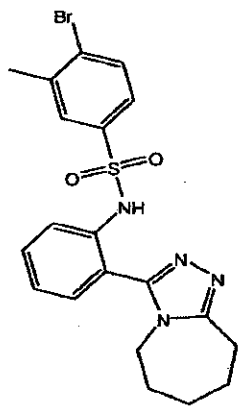
[00121] In the following descriptions and embodiments, references to specific substituents only correspond to formula numbers in which those specific substituents are present or appear.

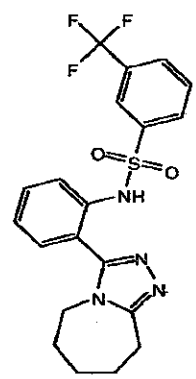
[00122] In each of the formulae (X to XXV); Ar, X^1, X^2, X^3, X^4, X^5, Y^4, Y^5, Y^6, Y^7, R^1 and R^2 are as defined above.

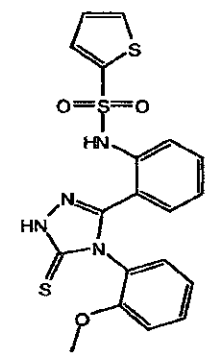
Known Compound

[00123] The compound shown below:









[00124] also referred to as

[00125] N-(1,1-dimethylethyl)-3-[2-[[[3-(5,5-dimethyl-3-octadecyl-2-thiazolidinyl)-4-hydroxyphenyl]sulfonyl]amino]-4-hydroxy-6-methylphenyl]-7-[[4-[ethyl[2-[(methylsulfonyl)amino]ethyl]amino]phenyl]imino]-7H-pyrazolo[5,1-c]-1,2,4-triazole-6-carboxamide;

[00126] Benzenesulfonamide, 4-bromo-3-methyl-N-[2-(6,7,8,9-tetrahydro-5H-1,2,4-triazolo[4,3-a]azepin-3-yl)phenyl];

[00127] Benzenesulfonamide, N-[2-(6,7,8,9-tetrahydro-5H-1,2,4-triazolo[4,3-a]azepin-3-yl)phenyl]-3-(trifluoromethyl); and

[00128] 2-Thiophenesulfonamide, N-[2-[4,5-dihydro-4-(2-methoxyphenyl)-5-thioxo-1H-1,2,4-triazol-3-yl]phenyl];

[00129] are known, but not as CCR9 or CCR2 antagonists

[00130] **Preferred Embodiments**

[00131] In one embodiment of formula (II), X^1 is selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl; Y^7 is hydrogen; Y^4, Y^5, and Y^6 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00132] In one embodiment of formula (III) X^1 is halogen; X^2 is halogen or $-CF_3$; Y^4 is halogen; Y^5 is hydrogen or halogen; R^1 is aryl or heteroaryl; and R^2 is hydrogen or substituted or unsubstituted C_{1-8} alkyl.

[00133] In one embodiment of formula (V), Y^5 is halogen or hydrogen; R^1 is substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is as defined for formula (I).

[00134] In one embodiment of formula (III), X^2 and Y^4 are each independently hydrogen or halogen; X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl; Y^5 is selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00135] In one embodiment of formula (IV), Y^4 is hydrogen or halogen; X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered

heterocyclyl; Y^5 is selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00136] In one embodiment of formula (V), Y^5 is halogen or hydrogen; R^1 is substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is selected from the group consisting of hydrogen, $C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, and substituted or unsubstituted C_{1-8} alkyl.

[00137] In one embodiment of formula (VI), Y^4 is hydrogen or fluoro; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00138] In one embodiment of formula (VII), Y^4 is hydrogen or fluoro; R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4-10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

[00139] In one embodiment of formula (VIII), X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$,

and substituted or unsubstituted 3- to 10-membered heterocyclyl; Y^4 is hydrogen or fluoro; Y^5 is chloro; W is NH or O; and n is 0, 1, or 2.

[00140] In one embodiment of formula (VIII), Y^4 and Y^5 are as defined for formula (I); X^1 is tert-butyl, with the proviso that at least one of Y^4 and Y^5 is other than hydrogen; W is NH or O; and n is 0, 1, or 2.

[00141] In one embodiment of formula (VIII), X^1 is tert-butyl; Y^4 is hydrogen or fluoro; Y^5 is chloro; W is NH or O; and n is 0, 1, or 2.

[00142] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 and Y^5 are halogen; and R^1 and R^2 are as defined for formula (I).

[00143] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 is hydrogen and Y^5 is -CN; and R^1 and R^2 are as defined for formula (I).

[00144] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 is fluoro and Y^5 is chloro; and R^1 and R^2 are as defined for formula (I).

[00145] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 and Y^5 are halogen, and R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl and substituted or unsubstituted 3- to 10-membered heterocyclyl; and R^2 is as defined for formula (I).

[00146] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 and Y^5 are halogen, and R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl and substituted or unsubstituted 3- to 10-membered heterocyclyl; and R^2 is substituted or unsubstituted C_{2-8} alkyl and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00147] In one embodiment of formula (VI), R^1 is heterocyclyl, and R^2 is hydrogen or substituted or unsubstituted C_{1-8} alkyl.

[00148] In one embodiment of formula (XXV), X^1 is t-butyl, Y^5 is chloro, Y^6 is fluoro.

[00149] In one embodiment of formula (XXIV), X^1 is t-butyl, Y^4 is fluoro, and Y^5 is fluoro.

[00150] In one embodiment of formula (XXIV), X^1 is t-butyl, Y^4 is fluoro, and Y^5 is chloro.

[00151] In one embodiment of formulae (IV and XXII-XXV), X^1 is *t*-Bu or –OiPr; X^2, Y^4, Y^5, and Y^6 are each independently hydrogen or halogen,

wherein at least one of Y^4, Y^5, and Y^6 is halogen; and R^1 and R^2 are defined as in formula (I).

[00152] In one embodiment of formulae (IV and XXII-XXV), X^1 is substituted or unsubstituted C_{1-8} alkyl, $-NR^{18}R^{19}$, or $-OR^{18}$; X^2, Y^4, Y^5, and Y^6 are each independently hydrogen or halogen, wherein at least one of Y^4, Y^5, and Y^6 is halogen; and R^1 and R^2 are defined as in formula (I).

[00153] In one embodiment of formulae (IV and XXII-XXV), X^1 is substituted or unsubstituted C_{1-8} alkyl, $-NR^{18}R^{19}$, or $-OR^{18}$; X^2, Y^4, Y^5, and Y^6 are each independently halogen or hydrogen, wherein at least one of Y^4, Y^5, and Y^6 is halogen; R^1 is hydrogen, Me, Et, *i*-Bu, *i*-Pr, cyclopropyl, cyclobutyl, cyclopentyl,
$-CH(CH_3)CH_2OH$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)CH_3$, phenyl, 2-pyridyl, 4-pyridyl, 1H-pyrazol-3-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, azetidin-3-yl, pyrrolidin-3-yl, 1-isopropylpyrrolidin-3-yl, 1-(methylsulfonyl)pyrrolidin-3-yl, 1-(carboxamido)pyrrolidin-3-yl piperidin-3-yl, piperidin-4-yl, 1-carboxamido-piperidin-4-yl, 1-methylsulfonyl-piperidin-4-yl, 1-acetyl-piperidin-4-yl, 1-methyl-piperidin-4-yl, or 3-pyrrolidin-2-only; R^2 is hydrogen, Me, Et, *i*-Pr, $-NH_2$, $-CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH_3$, $-CH_2C(CH_3)_2OH$, $-CH_2C(O)OCH_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2CH_2OCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_3$, $-CH_2NHCH_2CH_3$, $-CH_2NHCH(CH_2CH_2)$, $-CH_2NHCH(CH_3)_2$, $-CH_2SO_2CH_3$, $-CH_2CH_2SO_2CH_3$, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, 2-pyridyl, oxazol-4-yl, 5-methyloxazol-4-yl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydro-4-methyl-2H-pyran-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, morpholinomethyl, piperidin-4-yl, (pyrrolidin-1-yl)methyl, or (azetidin-1-yl)methyl)

[00154] In one embodiment of formulae (III, and XVIII-XXI), X^2, Y^4, Y^5, and Y^6 are halogen, and X^1, R^1 and R^2 are defined as in formula (I).

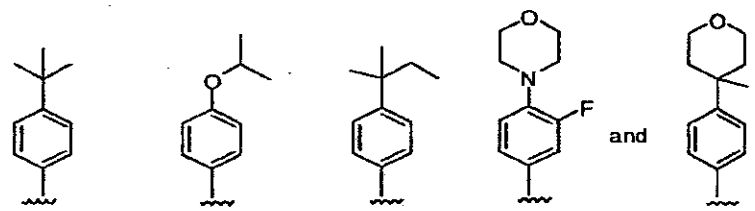
[00155] *Preferred Ar Groups*

[00156] In one embodiment of any the formulae (I and X-XV), Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl.

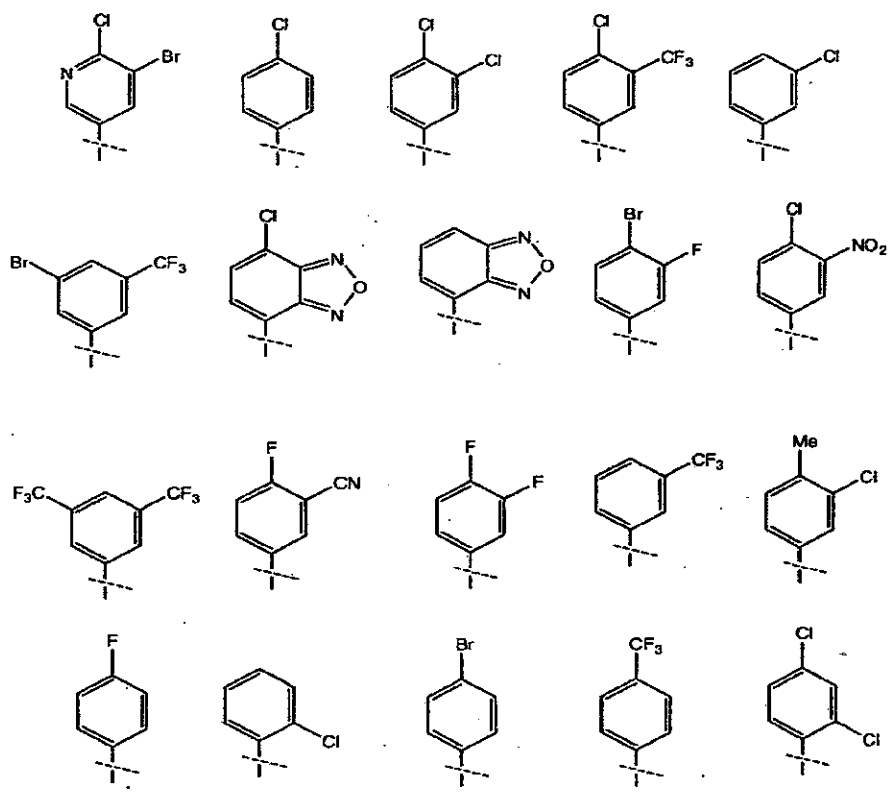
[00157] In one embodiment of any the formulae (I and X-XV), Ar is a C_{6-10} aryl with at least 2 substituents other than hydrogen.

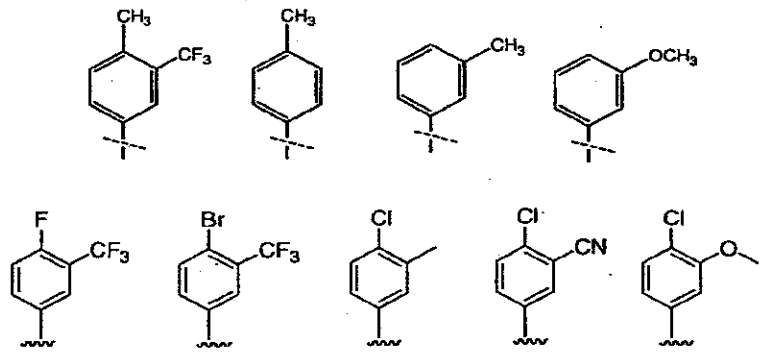
[00158] In one embodiment of any the formulae (I and X-XV), Ar is a substituted or unsubstituted bicyclic aryl or substituted or unsubstituted bicyclic heteroaryl.

[00159] In one embodiment of any the formulae (I and X-XV), Ar is selected from the group consisting of:



[00160] In one embodiment of any the formulae (I and X-XV), Ar is selected from the group consisting of:





[00161] *Preferred X Groups*

[00162] In one embodiment of formulae (II-IV, and XX-XV), at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen;

[00163] In one embodiment of formulae (II, III, XVI-XXI), at least two of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00164] In one embodiment of formula (II, III, XVI-XXI), X^1 and X^2 are other than hydrogen.

[00165] In one embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl.

[00166] In one embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted C_{2-8} alkyl, substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl.

[00167] In another embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl,

unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl; with the proviso that at least two of X^1, X^2, X^3, X^4, and X^5 are other than hydrogen; or with the proviso that at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00168] In another embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl; with the proviso that at least two of X^1, X^2 and X^4 are other than hydrogen; or with the proviso at least one of X^1, X^2 and X^4 is other than hydrogen.

[00169] In a further embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, and $-NR^{18}R^{19}$; with the proviso that at least three of X^1, X^2, X^3, X^4, and X^5 are other than hydrogen; or with the proviso that at least two of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen; or with the proviso that at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00170] In a further embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of: hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl; with the proviso that at least three of X^1, X^2, X^3, X^4, and X^5 are other than hydrogen; or with the proviso that at least two of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen; or with the proviso that at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00171] In one embodiment of formulae (II-IV, VIII, IX and XX-XV), any two occurrences of X^1, X^2, X^3, X^4, and X^5 that are located adjacently to each other, can be joined to form a substituted 5- or 6-membered substituted or unsubstituted heterocyclyl or substituted or unsubstituted heteroaryl.

[00172] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is other than hydrogen.

[00173] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is other than methyl.

[00174] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, -CN, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00175] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, and $-S(O)_2NR^{18}R^{19}$.

[00176] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is $-OR^{18}$.

[00177] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is $-NR^{18}R^{19}$.

[00178] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, and substituted or unsubstituted C_{2-8} alkynyl.

[00179] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted C_{1-8} alkyl or unsubstituted C_{2-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, and substituted or unsubstituted C_{2-8} alkynyl.

[00180] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is an unsubstituted C_{2-8} alkyl.

[00181] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is tert-butyl.

[00182] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is iso-propoxy.

[00183] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is morpholinyl.

[00184] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00185] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted or unsubstituted phenyl, substituted or unsubstituted 5- to 6-membered heteroaryl, and substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00186] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted phenyl.

[00187] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted 5- to 6-membered heteroaryl.

[00188] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00189] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), when X^2, X^3, X^4 and X^5 are hydrogen, X^1 is other than –Cl, $-NO_2$, $-OCH_3$, $-CH_3$, $-NHC(O)CH_3$, or $-CH_2CH_2$-(phenyl).

[00190] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted or unsubstituted 5- or 6- membered heterocyclic ring, and the heterocycle is selected from the group consisting of pyrrolidine, piperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, and tetrahydrothiophene.

[00191] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted or unsubstituted 5- or 6-membered heteroaryl

ring selected from the group consisting of pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, isothiazolyl, pyrazolyl, imidazolyl, thienyl, furyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, and thiazolyl.

[00192] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted heterocyclic group selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,3-dioxalanyl, thiomorpholinyl, thiomorpholinyl-S,S-dioxide, piperazinyl and pyranyl.

[00193] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted C_{1-8} alkyl. Preferably, the substituent is a substituted or unsubstituted heterocyclic group of the formula (AA) as defined in paragraph [0044], [0045] and [0046]. More preferably, the substituent is selected from the group including pyrrolidine, piperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, and tetrahydrothiophene.

[00194] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), a suitable substituent for substituted C_{1-8} alkyl (X^1, X^2, X^3, X^4, or X^5) can be selected from the group consisting of –CN, $-OR^{18}$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-O(CO)R^{18}$, $-SO_2R^{18}$ and halogen. In one embodiment, X^2, X^3, X^4, and X^5 are hydrogen.

[00195] In one embodiment of each of the (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is halogen, particularly chlorine.

[00196] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is an unsubstituted C_{1-8} alkyl.

[00197] In one embodiment of each of the formulae (II-IV, VIII and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is an unsubstituted C_{2-8} alkyl.

[00198] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is t-butyl.

[00199] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is oxazolyl.

[00200] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is trifluoromethoxy.

[00201] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-SO_2R^{18}$. In one particular embodiment, R^{18} is methyl.

[00202] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV, at least one of X^1, X^2, X^3, X^4, or X^5 is $-OR^{18}$. In one particular embodiment, R^{18} is methyl.

[00203] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-SR^{18}$. In one particular embodiment, R^{18} is methyl.

[00204] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is unsubstituted C_{1-6} alkyl (in particular methyl) or C_{1-6} haloalkyl (in particular $-CF_3$).

[00205] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is substituted C_{1-6} alkyl (preferably not C_{1-6} haloalkyl).

[00206] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is isopropyl.

[00207] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is a cyano.

[00208] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is a cyano, halogen or trifluoromethyl group.

[00209] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-C(Me)_2CH_2OH$.

[00210] In one embodiment of each of the formulae ((II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is -C(O)Me.

[00211] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-(CH_2)_2CO_2Me$.

[00212] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is isoamyl.

[00213] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, X^5 is 1,3-dioxalanyl.

[00214] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is furyl.

[00215] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is pyrazolyl.

[00216] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is thienyl.

[00217] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted C_{1-8} alkyl, where suitable substituents are as defined for formula (II). In one preferred embodiment, the substituted C_{1-8} alkyl is substituted with a 5- or 6-membered heteroaryl selected from the group consisting of pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, isothiazolyl, pyrazolyl, imidazolyl, thienyl, furyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, and thiazolyl. More preferably, the substituted C_{1-8} alkyl is substituted with oxazolyl.

[00218] In one embodiment of formula (II-IV, VIII and XVI-XXV), X^1 and X^2 are other than hydrogen.

[00219] In one embodiment of formula (II-IV, VIII and XVI-XXV), X^1 and X^2 are selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, OR^{18}, $-NO_2$, -CN, and $-CO_2R^{18}$.

[00220] In one embodiment of formulae (II, III, XVI-XXI), at least one of X^1 and X^2 is selected from the group consisting of halogen, -CN, and $-CF_3$.

[00221] In one embodiment of formulae (II, III, XVI-XXI), both X^1 and X^2 are selected from the group consisting of halogen, -CN, and $-CF_3$.

[00222] In an additional embodiment of formulae (II, III, XVI-XXI), one of X^1 and X^2 is halogen and one of X^1 and X^2 is selected from the group consisting of halogen, -CN, and $-CF_3$.

[00223] In an additional embodiment of formulae (II, III, XVI-XXI), one of X^1 and X^2 is halogen and one of X^1 and X^2 is selected from the group consisting of halogen, -CN, $-CH_3$ and $-CF_3$.

[00224] In an additional embodiment of formulae (II, III, XVI-XXI), X^1 is selected from the group consisting of halogen and $-CH_3$, and X^2 is selected from the group consisting of halogen, $-CN$, $-CH_3$, $-OCH_3$, $-OCF_3$ and $-CF_3$.

[00225] In one embodiment of formula (II, III, XVI-XXI), X^1 is selected from the group consisting of halogen and $-CH_3$, and X^2 is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-CF_2H$, and CF_2R^{10}, where R^{10} is substituted or unsubstituted C_{1-8} alkyl.

[00226] In one embodiment of formula (II, III, XVI-XXI), X^1 and X^2 are selected from the group consisting of -Cl, -F, -Br, $-CF_3$, $-CONHCH_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-NO_2$, -CN, and $-CO_2H$.

[00227] In one embodiment of formula (II, III, XVI-XXI), X^1 is selected from the group consisting of halogen and $-CH_3$, and X^2 is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$.

[00228] In one embodiment of formula (II, III, XVI-XXI), X^1 is chloro and X^2 is $-CF_3$.

[00229] In one embodiment of formula (II, III, XVI-XXI), X^2 is other than hydrogen.

[00230] In one embodiment of formulae (II, III, XVI-XXI), X^2 is other than hydrogen.

[00231] In one embodiment of formula (II, III, XVI-XXI), X^2 is selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, OR^{18}, $-NO_2$, -CN, and $-CO_2R^{18}$.

[00232] In one embodiment of formula (II, III, XVI-XXI), X^2 is selected from the group consisting of -Cl, -F, -Br, $-CF_3$, $-CONHCH_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-NO_2$, -CN, and $-CO_2H$.

[00233] In one embodiment of formulae (II, III, XVI-XXI), X^2 is fluoro.

[00234] *Preferred Y Groups*

[00235] In one embodiment of any of formula (I-IX and X-XXV), Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-OR^{15}$, and substituted or unsubstituted C_{1-8} alkyl, where 1 to 2 of Y^4, Y^5, Y^6, and Y^7 are other than hydrogen.

[00236] In one embodiment of any of formulae (I-IX and X-XXV), Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, -CN, fluorine, chlorine, and bromine, where 1 to 2 of Y^4, Y^5, Y^6, and Y^7 are other than hydrogen.

[00237] In another embodiment of any of formulae (I-IX and X-XXV), at least one of Y^4, Y^5, Y^6, and Y^7 is other than hydrogen; preferably Y^4 is halogen.

[00238] In another embodiment of any of formula (I-VIII and X-XXV), at least one of Y^4, Y^5, Y^6, and Y^7 is other than hydrogen; preferably Y^5 is halogen.

[00239] In another embodiment of any of formulae (I-VIII and X-XXV)), Y^5 and Y^7 are hydrogen and Y^4 is halogen.

[00240] In another embodiment of any of formulae (I-VIII and X-XXV)), Y^5 and Y^7 are hydrogen and Y^4 is chloro.

[00241] In one embodiment of any of formulae (I, II and X-XXV)), Y^7 and Y^6 are hydrogen, and Y^4 and Y^5 are fluoro.

[00242] In one embodiment of any of formulae (I, II and X-XXV)), Y^7 and Y^6 are hydrogen, and Y^4 is chloro and Y^5 is $-CH_3$.

[00243] In one embodiment of any of formulae (I-IX and X-XXV)), Y^4 and Y^5 are selected from the group consisting of halogen, -CN, $-OR^{15}$, and substituted or unsubstituted C_{1-6} alkyl.

[00244] In one embodiment of any of formulae (I-IX and X-XXV)), Y^4 and Y^5 are selected from the group consisting of –Cl, -Br, -F, $-OCH_3$, $-CH_3$, $-CF_3$, and -CN

[00245] In one embodiment of any of formulae (I-IV, VI-IX and X-XXV)), Y^4 is selected from the group consisting of –Cl, -Br, -F, and $-OCH_3$.

[00246] In one embodiment of any of formulae ((I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 is halogen.

[00247] In one embodiment of any of formulae ((I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 is fluoro.

[00248] In one embodiment of any of formulae ((I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 is chloro.

[00249] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is selected from the group consisting of -Cl, -Br, -F, $-CH_3$, $-CF_3$, and -CN.

[00250] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is halogen.

[00251] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is chloro.

[00252] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is fluoro.

[00253] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is -CN.

[00254] In one embodiment of any of formulae (I, II, XII, XIV, XV, XVIII, XXI, XXII, XXV), Y^6 is fluoro.

[00255] In one embodiment of any of formula (I, II, XII, XVIII, XXI, XXII, XXV), Y^5 is chloro and Y^6 is fluoro.

[00256] In one embodiment of any of formulae(I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 is chloro and Y^4 is fluoro.

[00257] In one embodiment of any of formulae (I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 and Y^4 are fluoro.

[00258] In one embodiment of any of formulae(I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 is -CN and Y^4 is fluoro.

[00259] In one embodiment of any of formulae(I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 is -CN and Y^4 is hydrogen.

[00260] *Preferred R^1 and R^2 Groups*

[00261] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is other than hydrogen.

[00262] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, and $-S(O)_2NR^7R^8$.

[00263] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 and R^2 together with the atoms which they substitute form a carbocyclic or heterocyclic ring.

[00264] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00265] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 5- to 6-membered heterocyclyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5- to 6-membered heteroaryl.

[00266] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted C_{1-8} alkyl.

[00267] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted phenyl.

[00268] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted 5- to 6-membered heteroaryl.

[00269] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00270] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is methyl, ethyl or isopropyl.

[00271] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of unsubstituted or substituted phenyl, unsubstituted or substituted pyridyl, and unsubstituted or substituted pyrazolyl.

[00272] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is methyl, ethyl, isopropyl or isobutyl.

[00273] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is cyclopropyl, cyclobutyl, or cyclopentyl.

[00274] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is heterocyclyl.

[00275] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is hydrogen.

[00276] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is other than hydrogen.

[00277] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of halogen, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, and $-NR^7C(O)NR^8R^9$.

[00278] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00279] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 5- to 6-membered heterocyclyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5- to 6-membered heteroaryl.

[00280] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted C_{1-8} alkyl.

[00281] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted phenyl.

[00282] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00283] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted 5- to-6-membered heteroaryl.

[00284] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is methyl.

[00285] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of methyl, ethyl, isopropyl, and 4-tetrahydro-2H-pyranyl.

[00286] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is methyl, ethyl, or isopropyl.

[00287] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted C_{1-8} alkyl.

[00288] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is $-CH_2OR^7$ or $-CH_2NR^7R^8$.

[00289] In one embodiment of formulae (I-VII and X-XXV), R^1 and R^2 combine to form a 6-membered ring.

[00290] *Preferred R^3 and R^4 Groups*

[00291] In one embodiment of formula (VII and IXb), R^3 and R^4 are each hydrogen.

[00292] In one embodiment of formula (VII and IXb), one of R^3 and R^4 is hydrogen and the other is unsubstituted or substituted C_{1-8} alkyl.

[00293] In one embodiment of formula (VII and IXb), both of R^3 and R^4 are unsubstituted or substituted C_{1-8} alkyl.

[00294] In one embodiment of formula (VII and IXb), R^3 and R^4 together with the carbon which they substitute form a 3-10 member carboxylic ring.

[00295] In one embodiment of formula (VII and IXb), R^3 and R^4 together with the carbon which they substitute form a 4 -10 member heterocyclic ring.

[00296] In one embodiment of formula (VII and IXb), R^3 and R^4 together with the carbon which they substitute form a 5-10 member heteroaryl ring.

[00297] *Preferred W Groups*

[00298] In one embodiment of formula (VIII and VIIb), W is NH.

[00299] In one embodiment of formula (VIII and VIIb), W is O.

[00300] **Exemplary Compounds**

[00301] The following compounds are within the scope of the formula (I):

[00302] 4-tert-butyl-N-(4-chloro-2-(4,5-diisopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00303] 4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00304] 4-tert-butyl-N-(4-chloro-2-(4-cyclopentyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00305] 4-tert-butyl-N-(4-chloro-2-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00306] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00307] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00308] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00309] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00310] 4-tert-butyl-N-(4-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00311] 4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00312] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00313] 4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00314] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00315] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00316] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00317] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00318] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00319] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00320] N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00321] N-(2-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)ethyl)acetamide;

[00322] (R)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00323] (S)-4-tert-butyl-N-(4,5-difluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00324] (S)-4-tert-butyl-N-(4-chloro-2-(4-(1-hydroxypropan-2-yl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00325] (S)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00326] (S)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00327] 4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

[00328] 4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00329] 4-tert-butyl-N-(4,5-difluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00330] 4-tert-butyl-N-(4-chloro-2-(4,5-diethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00331] 4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

[00332] 4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00333] 4-tert-butyl-N-(4-chloro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00334] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

[00335] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00336] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00337] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

[00338] 4-tert-butyl-N-(4-chloro-2-(4-isobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00339] 4-tert-butyl-N-(4-chloro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00340] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00341] 4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00342] 4-tert-butyl-N-(4-chloro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00343] 4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00344] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00345] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00346] 4-tert-butyl-N-(5-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00347] 4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00348] 4-tert-butyl-N-(5-fluoro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00349] N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00350] ethyl 2-(5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)acetate;

[00351] 5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazole-3-carboxamide;

[00352] 5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-N,4-dimethyl-4H-1,2,4-triazole-3-carboxamide;

[00353] (R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00354] (S)-4-tert-butyl-N-(4-chloro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00355] (S)-4-tert-butyl-N-(4-chloro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00356] (S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00357] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00358] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00359] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00360] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00361] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00362] (S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00363] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00364] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00365] 4-tert-butyl-N-(4-chloro-2-(5-((cyclopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00366] 4-tert-butyl-N-(4-chloro-2-(5-((ethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00367] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00368] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00369] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00370] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00371] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00372] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00373] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00374] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(methylsulfonylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00375] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00376] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00377] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00378] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00379] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00380] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00381] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00382] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00383] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxy-2-methylpropyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00384] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxypropan-2-yl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00385] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00386] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(hydroxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00387] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00388] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00389] N-(2-(5-(azetidin-1-ylmethyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

[00390] N-(2-(5-acetyl-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

[00391] (S)-4-tert-butyl-N-(4,5-difluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00392] (S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00393] (S)-4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00394] (S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00395] 4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00396] 4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

[00397] 4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00398] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00399] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00400] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00401] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00402] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00403] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00404] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00405] N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00406] N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00407] (S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00408] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-oxopyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00409] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00410] (S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-(4-methyltetrahydro-2H-pyran-4-yl)benzenesulfonamide;

[00411] 4-tert-butyl-N-(4-chloro-2-(4-cyclobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00412] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00413] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00414] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-methylpiperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00415] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(2-(methylsulfonyl)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00416] N-(2-(4-(1-acetylpiperidin-4-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00417] N-(2-(4-(2-aminoethyl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00418] N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

[00419] (R)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00420] 4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

[00421] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00422] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00423] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00424] 4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00425] 4-tert-butyl-N-(4-chloro-2-(5-(isopropoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00426] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00427] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00428] 4-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)piperidine-1-carboxamide;

[00429] 4-tert-butyl-N-(4-chloro-2-(4-(2-(dimethylamino)ethyl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00430] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00431] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(2-(methylamino)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00432] 4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00433] N-(2-(4-(1-acetylpyrrolidin-3-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00434] N-(2-(5-amino-4-isopropyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00435] (R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00436] (R)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00437] 4-tert-butyl-N-(4-cyano-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00438] 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzamide;

[00439] 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoic acid;

[00440] N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00441] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00442] methyl 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoate;

[00443] N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-3-fluoro-4-morpholinobenzenesulfonamide;

[00444] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00445] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00446] 4-tert-butyl-N-(4-chloro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00447] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00448] (R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00449] (S)-4-tert-butyl-N-(4-chloro-2-(4-(1-isopropylpyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00450] (S)-3-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-4H-1,2,4-triazol-4-yl)pyrrolidine-1-carboxamide;

[00451] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00452] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00453] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperazin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00454] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydrofuran-3-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00455] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(((2-methoxyethyl)(methyl)amino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00456] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00457] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((4-methylpiperazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00458] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00459] (S)-4-tert-butyl-N-(4-chloro-2-(4-(1-(methylsulfonyl)pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00460] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00461] N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chlorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

[00462] 4-chloro-N-(5-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

[00463] 4-chloro-N-(5-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

[00464] N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chloro-4-fluorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

[00465] 5-(4-chloro-2-(4-chloro-3-(trifluoromethyl)phenylsulfonamido)-5-fluorophenyl)-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazole-3-carboxamide; and

[00466] N-(2-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide.

[00467] **Compositions that Modulate Chemokine activity**

[00468] In another aspect, the present invention provides compositions that modulate chemokine activity, specifically CCR2 activity or CCR9 activity. Generally, the compositions for modulating chemokine receptor activity in humans and animals will comprise a pharmaceutically acceptable excipient or diluent and a compound having the formula provided above as formula (I).

[00469] The term "composition" as used herein is intended to encompass 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.

[00470] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory

ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[00471] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self emulsifications as described in U.S. Pat. No. 6,451,339, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated enterically or otherwise by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

[00472] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for

example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[00473] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[00474] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti oxidant such as ascorbic acid.

[00475] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or

more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00476] 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.

[00477] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative. and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[00478] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, axed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00479] 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. Additionally, the compounds can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like.

[00480] For topical use, creams, ointments, jellies, solutions or suspensions 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.

[00481] The pharmaceutical compositions and methods of the present invention may further comprise other therapeutically active compounds as noted herein, such as those applied in the treatment of the above mentioned pathological conditions.

[00482] In one embodiment, the present invention provides a composition consisting of a pharmaceutically acceptable carrier and a compound of the invention.

[00483] **Methods of Treatment**

[00484] Depending on the disease to be treated and the subject's condition, the compounds and compositions of the present invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each rouse of administration. The present invention also contemplates administration of the compounds and compositions of the present invention in a depot formulation.

[00485] In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5, 0.5 to 5.0, or 5.0 to 50 mg/kg per day. 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.

[00486] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, hereditary characteristics, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00487] In still other embodiments, the present methods are directed to the treatment of allergic diseases, wherein a compound or composition of the invention is administered either alone or in combination with a second therapeutic agent, wherein said second therapeutic agent is an antihistamine. When used in combination, the practitioner can administer a combination of the compound or composition of the present invention and a second therapeutic agent. Also, the compound or composition and the second therapeutic agent can be administered sequentially, in any order.

[00488] The compounds and compositions of the present invention can be combined with other compounds and compositions having related utilities

to prevent and treat the condition or disease of interest, such as inflammatory conditions and diseases, including inflammatory bowel disease, allergic diseases, psoriasis, atopic dermatitis and asthma, and those pathologies noted above. Selection of the appropriate agents for use in combination therapies can be made one of ordinary skill in the art. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

[00489] In treating, preventing, ameliorating, controlling or reducing the risk of inflammation, the compounds of the present invention may be used in conjunction with an anti-inflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal anti-inflammatory agent, or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, biological TNF sequestrants, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like.

[00490] Similarly, the compounds of the present invention may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as pseudophedrine; an antitussive such as codeine; a diuretic; a sedating or non-sedating antihistamine; a very late antigen (VLA-4) antagonist; an immunosuppressant such as cyclosporin, tacrolimus, rapamycin, EDG receptor agonists, or other FK-506 type immunosuppressants; a steroid; a non-steroidal anti-asthmatic agent such as a β2-agonist, leukotriene antagonist, or leukotriene biosynthesis inhibitor; an inhibitor of phosphodiesterase type IV (PDE-IV); a cholesterol lowering agent such as a HMG-CoA reductase inhibitor, sequestrant, or cholesterol

absorption inhibitor; and an anti-diabetic agent such as insulin, α-glucosidase inhibitors or glitazones.

[00491] The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00492] Methods of Treating or Preventing CCR2-mediated Conditions or Diseases

[00493] In yet another aspect, the present invention provides methods of treating or preventing a CCR2-mediated condition or disease by administering to a subject having such a condition or disease a therapeutically effective amount of any compound of formula (I) above. Compounds for use in the present methods include those compounds according to formula (I), those provided above as embodiments, those specifically exemplified in the Examples below, and those provided with specific structures herein. The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[00494] As used herein, the phrase "CCR2-mediated condition or disease" and related phrases and terms refer to a condition or disease characterized by inappropriate, i.e., less than or greater than normal, CCR2 functional activity. Inappropriate CCR2 functional activity might arise as the result of CCR2 expression in cells which normally do not express CCR2, increased CCR2 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased CCR2 expression.

Inappropriate CCR2 functional activity might also arise as the result of MCP-1 secretion by cells which normally do not secrete MCP-1, increased MCP-1 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased MCP-1 expression. A CCR2-mediated condition or disease may be completely or partially mediated by inappropriate CCR2 functional activity. However, a CCR2-mediated condition or disease is one in which modulation of CCR2 results in some effect on the underlying condition or disease (e.g., a CCR2 antagonist results in some improvement in patient well being in at least some patients). Furthermore, MCP-2, 3 and 4 are also CCR2 ligands.

[00495] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention.

[00496] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is atherosclerosis.

[00497] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is restenosis.

[00498] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is multiple sclerosis.

[00499] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is selected from the group consisting of inflammatory bowel disease, renal fibrosis, rheumatoid arthritis, obesity and non-insulin-dependent diabetes.

[00500] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is type 2 diabetes.

[00501] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is selected from the group consisting of chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and idiopathic pneumonia syndrome.

[00502] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the administering is oral, parenteral, rectal, transdermal, sublingual, nasal or topical.

[00503] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the compound is administered in combination with an anti-inflammatory or analgesic agent.

[00504] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where an anti-inflammatory or analgesic agent is also administered.

[00505] In one embodiment, the present invention provides a method of modulating CCR2 function in a cell, where the CCR2 function in the cell is modulated by contacting the cell with a CCR2 modulating amount of the compound of the present invention.

[00506] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the disease is selected from the group consisting of

pulmonary fibrosis, transplantation rejection, graft-versus-host disease and cancer.

[00507] In yet other embodiments, the present methods are directed to the treatment of psoriasis wherein a compound or composition of the invention is used alone or in combination with a second therapeutic agent such as a corticosteroid, a lubricant, a keratolytic agent, a vitamin D_3 derivative, PUVA and anthralin.

[00508] In other embodiments, the present methods are directed to the treatment of atopic dermatitis using a compound or composition of the invention either alone or in combination with a second therapeutic agent such as a lubricant and a corticosteroid.

[00509] In further embodiments, the present methods are directed to the treatment of asthma using a compound or composition of the invention either alone or in combination with a second therapeutic agent such as a β2-agonist and a corticosteroid.

[00510] Methods of Treating or Preventing CCR9-mediated Conditions or Diseases

[00511] In yet another aspect, the present invention provides methods of treating or preventing a CCR9-mediated condition or disease by administering to a subject having such a condition or disease a therapeutically effective amount of any compound of formula (I) above. Compounds for use in the present methods include those compounds according to formula (I), those provided above as embodiments, those specifically exemplified in the Examples below, and those provided with specific structures herein. The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[00512] As used herein, the phrase "CCR9-mediated condition or disease" and related phrases and terms refer to a condition or disease characterized by inappropriate, i.e., less than or greater than normal, CCR9 functional activity. Inappropriate CCR9 functional activity might arise as the

result of CCR9 expression in cells which normally do not express CCR9, increased CCR9 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased CCR9 expression. Inappropriate CCR9 functional activity might also arise as the result of TECK secretion by cells which normally do not secrete TECK, increased TECK expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased TECK expression. A CCR9-mediated condition or disease may be completely or partially mediated by inappropriate CCR9 functional activity. However, a CCR9-mediated condition or disease is one in which modulation of CCR9 results in some effect on the underlying condition or disease (e.g., a CCR9 antagonist results in some improvement in patient well being in at least some patients).

[00513] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a cell, tissue, system, or animal, such as a human, that is being sought by the researcher, veterinarian, medical doctor or other treatment provider.

[00514] Diseases and conditions associated with inflammation, immune disorders, infection and cancer can be treated or prevented with the present compounds, compositions, and methods. In one group of embodiments, diseases or conditions, including chronic diseases, of humans or other species can be treated with inhibitors of CCR9 function. These diseases or conditions include: (1) allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as fibromyalagia, scleroderma, ankylosing spondylitis, juvenile RA, Still's disease, polyarticular juvenile RA, pauciarticular juvenile RA, polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polyarticular arthritis, multiple

sclerosis, systemic lupus erythematosus, type I diabetes, type II diabetes, glomerulonephritis, and the like, (10) graft rejection (including allograft rejection), (11) graft-v-host disease (including both acute and chronic), (12) other diseases in which undesired inflammatory responses are to be inhibited, such as atherosclerosis, myositis, neurodegenerative diseases (e.g., Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis, Behcet's syndrome and gout, (13) immune mediated food allergies such as Coeliac (Celiac) disease (14) pulmonary fibrosis and other fibrotic diseases, and (15) irritable bowel syndrome.

[00515] In another group of embodiments, diseases or conditions can be treated with modulators and agonists of CCR9 function. Examples of diseases to be treated by modulating CCR9 function include cancers, cardiovascular diseases, diseases in which angiogenesis or neovascularization play a role (neoplastic diseases, retinopathy and macular degeneration), infectious diseases (viral infections, e.g., HIV infection, and bacterial infections) and immunosuppressive diseases such as organ transplant conditions and skin transplant conditions. The term "organ transplant conditions" is means to include bone marrow transplant conditions and solid organ (e.g., kidney, liver, lung, heart, pancreas or combination thereof) transplant conditions.

[00516] Preferably, the present methods are directed to the treatment of diseases or conditions selected from inflammatory bowel disease including Crohn's disease and Ulcerative Colitis, allergic diseases, psoriasis, atopic dermatitis and asthma, autoimmune disease such as rheumatoid arthritis and immune-mediated food allergies such as Coelaic disease.

[00517] In yet other embodiments, the present methods are directed to the treatment of psoriasis where a compound or composition of the invention is used alone or in combination with a second therapeutic agent such as a corticosteroid, a lubricant, a keratolytic agent, a vitamin D_3 derivative, PUVA and anthralin.

[00518] In other embodiments, the present methods are directed to the treatment of atopic dermatitis using a compound or composition of the

invention either alone or in combination with a second therapeutic agent such as a lubricant and a corticosteroid.

[00519] In further embodiments, the present methods are directed to the treatment of asthma using a compound or composition of the invention either alone or in combination with a second therapeutic agent such as a β2-agonist and a corticosteroid.

[00520] **Preparation of modulators**

[00521] The following examples are offered to illustrate, but not to limit, the claimed invention.

[00522] Additionally, those skilled in the art will recognize that the molecules claimed in this patent may be synthesized using a variety of standard organic chemistry transformations.

[00523] Certain general reaction types employed widely to synthesize target compounds in this invention are summarized in the examples. Specifically, generic procedures for sulfonamide formation, pyridine N-oxide formation and 2-aminophenyl-arylmethanone synthesis via Friedel-Crafts type approaches are given, but numerous other standard chemistries are described within and were employed routinely.

[00524] While not intended to be exhaustive, representative synthetic organic transformations which can be used to prepare compounds of the invention are included below.

[00525] These representative transformations include; standard functional group manipulations; reductions such as nitro to amino; oxidations of functional groups including alcohols and pyridines; aryl substitutions via *IPSO* or other mechanisms for the introduction of a variety of groups including nitrile, methyl and halogen; protecting group introductions and removals; Grignard formation and reaction with an electrophile; metal-mediated cross couplings including but not limited to Buckwald, Suzuki and Sonigashira reactions; halogenations and other electrophilic aromatic substitution reactions; diazonium salt formations and reactions of these species; etherifications; cyclative condensations, dehydrations, oxidations and reductions leading to heteroaryl groups; aryl metallations and

transmetallations and reaction of the ensuing aryl-metal species with an electrophile such as an acid chloride or Weinreb amide; amidations; esterifications; nucleophilic substitution reactions; alkylations; acylations; sulfonamide formation; chlorosulfonylations; ester and related hydrolyses, and the like.

[00526] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are within the scope of the invention.

[00527] In the descriptions of the syntheses that follow, some precursors were obtained from commercial sources. These commercial sources include Aldrich Chemical Co., Acros Organics, Ryan Scientific Incorporated, Oakwood Products Incorporated, Lancaster Chemicals, Sigma Chemical Co., Lancaster Chemical Co., TCI-America, Alfa Aesar, Davos Chemicals, and GFS Chemicals.

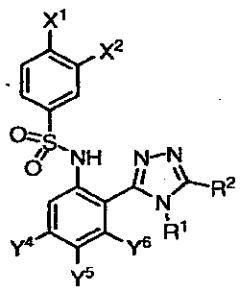
[00528] Compounds of the invention, including those listed in the table of activities, can be made by the methods and approaches described in the following experimental section, and by the use of standard organic chemistry transformations that are well known to those skilled in the art.

[00529] **Examples**

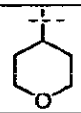
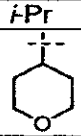
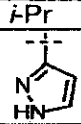
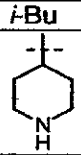
[00530] The above compounds and others within the scope of this invention can be made and tested for activity using the following procedures.

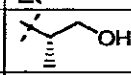
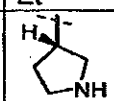
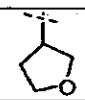
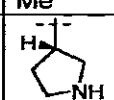
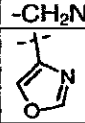
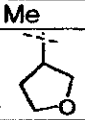
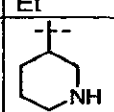
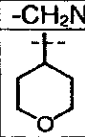
[00531] Exemplary compounds used in the method of the invention and in pharmaceutical compositions of the invention include but are not limited to the compounds listed in Table 1. Pharmaceutically acceptable salts of the compounds listed in Table 1 are also useful in the method of the invention and in pharmaceutical compositions of the invention.

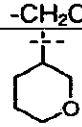
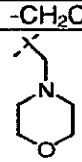
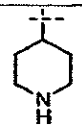
Table 1: Exemplary compounds

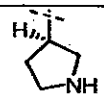
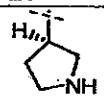
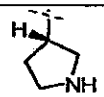
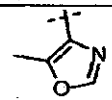
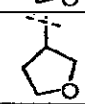
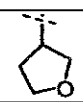
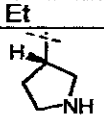
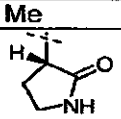
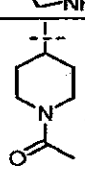


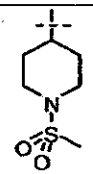
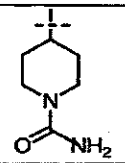
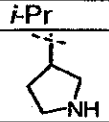
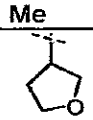
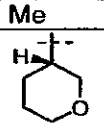
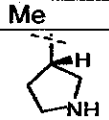
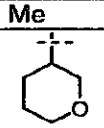
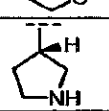
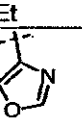
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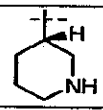
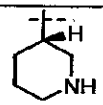
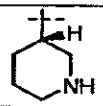
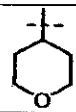
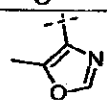
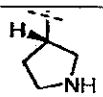
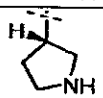
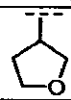
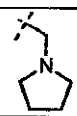
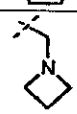
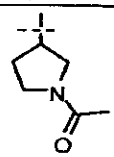
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1	*t*-Bu	H	H	Cl	H	*i*-Pr	H
2	*t*-Bu	H	H	Cl	H	Ph	H
3	*t*-Bu	H	H	Cl	H	*i*-Pr	Me
4	*t*-Bu	H	H	Cl	H	Ph	Me
5	*t*-Bu	H	H	Cl	H	Et	Me
6	*t*-Bu	H	H	Cl	H	Me	Me
7	*t*-Bu	H	H	Cl	H	cyclopropyl	Me
8	*t*-Bu	H	H	Cl	H	Me	*i*-Pr
9	*t*-Bu	H	H	Cl	H	Me	
10	*t*-Bu	H	H	Cl	H	Me	$-CH_2OCH_3$
11	*t*-Bu	H	H	Cl	H	*i*-Pr	*i*-Pr
12	*t*-Bu	H	H	Cl	H		Me
13	*t*-Bu	H	H	Cl	H	*i*-Pr	Et
14	*t*-Bu	H	H	Cl	H	cyclopentyl	Me
15	O*i*-Pr	H	H	Cl	H	*i*-Pr	Me
16	*t*-Bu	H	H	Cl	H		Me
17	O*i*-Pr	H	H	Cl	H	Et	Me
18	*t*-Bu	H	Cl	H	H	*i*-Pr	H
19	*t*-Bu	H	H	Cl	H	*i*-Bu	Me
20	*t*-Bu	H	H	Cl	H		Me
21	*t*-Bu	H	H	Cl	H		$-CH_2OCH_3$

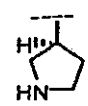
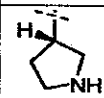
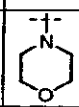
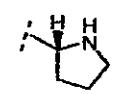
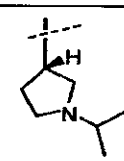
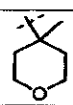
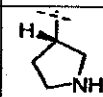
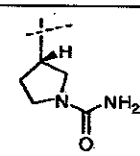
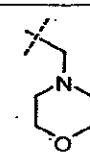
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23	*t*-Bu	H	F	H	H	Et	H
24	*t*-Bu	H	F	H	H	*i*-Pr	Me
25	*t*-Bu	H	H	Cl	F	Et	H
26	*t*-Bu	H	H	Cl	H		Me
27	*t*-Bu	H	H	Cl	H	$-CH_2CH_2NHC(O)CH_3$	Me
28	*t*-Bu	H	H	Cl	F	Me	Me
29	*t*-Bu	H	H	Cl	F	Et	Me
30	*t*-Bu	H	H	Cl	H	Me	H
31	*t*-Bu	H	H	Cl	H	Et	H
32	*t*-Bu	H	H	Cl	H		H
33	*t*-Bu	H	H	Cl	H	Me	
34	*t*-Bu	H	H	Cl	H	Me	
35	*t*-Bu	H	H	Cl	H		H
36	*t*-Bu	H	F	Cl	H	Me	Me
37	*t*-Bu	H	F	F	H		H
38	*t*-Bu	H	H	Cl	H	Et	Et
39	*t*-Bu	H	F	Cl	H	Me	$-CH_2N(CH_3)_2$
40	*t*-Bu	H	H	Cl	H	Me	
41	*t*-Bu	H	H	Cl	H	Me	$-CH_2CH_2OCH_3$
42	*t*-Bu	H	F	F	H		H
43	*t*-Bu	H	H	Cl	H	Et	*i*-Pr
44	*t*-Bu	H	F	Cl	H		H
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46	*t*-Bu	H	H	Cl	H	*i*-Pr	

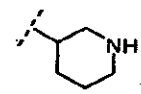
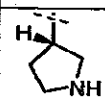
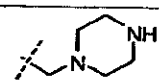
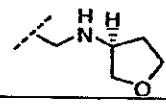
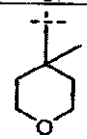
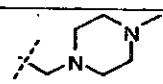
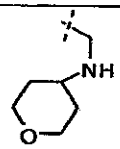
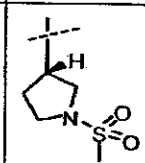
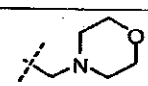
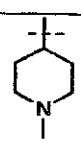
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48	*t*-Bu	H	F	Cl	H	Me	$-CH_2NHCH_2CH_3$
49	*t*-Bu	H	F	Cl	H	Me	$-CH_2NHCH(CH_3)_2$
50	*t*-Bu	H	F	Cl	H	Me	$-CH_2NHCH(CH_2CH_2)$
51	*t*-Bu	H	F	Cl	H	*i*-Pr	$-CH_2OCH_3$
52	*t*-Bu	H	F	Cl	H		$-CH_2OCH_3$
53	*t*-Bu	H	F	Cl	H		H
54	*t*-Bu	H	F	Cl	H		H
55	*t*-Bu	H	F	Cl	H	Me	$-C(O)NH_2$
56	*t*-Bu	H	F	Cl	H	Me	$-C(O)NHCH_3$
57	*t*-Bu	H	F	Cl	H	Me	$-C(CH_3)_2OH$
58	*t*-Bu	H	F	Cl	H	Me	$-C(O)CH_3$
59	*t*-Bu	H	F	Cl	H	Me	$-CH(OH)CH_3$
60	*t*-Bu	H	F	Cl	H	Me	
61	*t*-Bu	H	F	Cl	H	Me	
62	*t*-Bu	H	F	Cl	H	Me	$-CH_2CH_2OCH_3$
63	*t*-Bu	H	F	Cl	H	Me	
64	*t*-Bu	H	F	Cl	H	Me	$-CH_2C(O)OCH_2CH_3$
65	*t*-Bu	H	F	Cl	H	Me	$-CH_2C(CH_3)_2OH$
66	*t*-Bu	H	F	Cl	H	Me	
67	*t*-Bu	H	F	Cl	H	Me	$-CH_2SO_2CH_3$
68	O*i*-Pr	H	H	Cl	H	Me	Me
69	O*i*-Pr	H	H	Cl	H	*i*-Pr	H
70	*t*-Bu	H	H	Cl	H	Me	
71	*t*-Bu	H	F	F	H	Et	Me
72	*t*-Bu	H	F	H	H	Me	Me

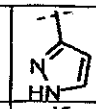
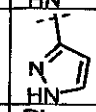
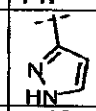
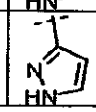
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74	*t*-Bu	H	F	H	H	Et	Me
75	*t*-Bu	H	H	Cl	H		H
76	*t*-Bu	H	F	Cl	H	Me	H
77	*t*-Bu	H	F	F	H		Me
78	*t*-Bu	H	F	Cl	H	*i*-Pr	H
79	*t*-Bu	H	F	Cl	H	Me	
80	*t*-Bu	H	F	Cl	H		Me
81	*t*-Bu	H	F	Cl	H		*i*-Pr
82	*t*-Bu	H	F	Cl	H	*i*-Pr	
83	*t*-Bu	H	H	Cl	H	$-CH_2H_2NH_2$	Me
84	*t*-Bu	H	H	Cl	H	cyclobutyl	Me
85	*t*-Bu	H	F	Cl	H		H
86	*t*-Bu	H	H	Cl	H	*i*-Pr	$-CF_3$
87	*t*-Bu	H	F	Cl	H	Et	*i*-Pr
88	*t*-Bu	H	F	Cl	H		Et
89	*t*-Bu	H	F	Cl	H	Me	$-CH_2CH_2SO_2CH_3$
90	*t*-Bu	H	F	Cl	H		H
91	*t*-Bu	H	H	Cl	H		Me
92	*t*-Bu	H	H	Cl	H	*i*-Pr	NH_2

93	*t*-Bu	H	H	Cl	H		Me
94	*t*-Bu	H	H	Cl	H		Me
95	*t*-Bu	H	Cl	H	H	*i*-Pr	Me
96	*t*-Bu	H	H	Cl	H	*i*-Pr	$-CH_2OCH_3$
97	*t*-Bu	H	H	Cl	H	Me	2-pyridyl
98	*t*-Bu	H	H	Cl	H	*i*-Pr	$-CH_2N(CH_3)_2$
99	*t*-Bu	H	H	Cl	H		Me
100	*t*-Bu	H	F	F	H	Me	Me
101	*t*-Bu	H	H	Cl	H		Me
102	*t*-Bu	H	H	Cl	H	Me	
103	*t*-Bu	H	H	Cl	H	Me	$-CH_2OCH(CH_3)_2$
104	*t*-Bu	H	H	Cl	H		H
105	*t*-Bu	H	H	Cl	H	Me	Et
106	*t*-Bu	H	F	Cl	H		Me
107	*t*-Bu	H	F	Cl	H	Me	$-CH_2OCH_3$
108	*t*-Bu	H	F	Cl	H		H
109	*t*-Bu	H	F	Cl	H		H
110	*t*-Bu	H	F	Cl	H	Me	Et
111	*t*-Bu	H	F	Cl	H	Me	

112	*t*-Bu	H	F	Cl	H		H
113	*t*-Bu	H	H	Cl	H		H
114	*t*-Bu	H	H	Cl	H		Me
115	*t*-Bu	H	F	Cl	H	Me	
116	*t*-Bu	H	F	Cl	H	Me	
117	*t*-Bu	H	H	Cl	H	Me	
118	*t*-Bu	H	H	Cl	H		*i*-Pr
119	*t*-Bu	H	H	Cl	H		Et
120	*t*-Bu	H	F	Cl	H		H
121	*t*-Bu	H	F	Cl	H	Me	
122	*t*-Bu	H	F	Cl	H	Me	
123	*t*-Bu	H	F	Cl	H	Me	-CH_2OH
124	*t*-Bu	H	H	Cl	H		Me
125	*t*-Bu	H	H	Cl	H	-$CH_2CH_2N(CH_3)_2$	Me
126	*t*-Bu	H	H	Cl	H	-$CH_2CH_2NHCH_3$	Me

127	*t*-Bu	H	H	Cl	H		Me
128	*t*-Bu	H	H	CN	H	Me	Et
129	*t*-Bu	H	H	$-C(O)NH_2$	H	Me	Et
130	*t*-Bu	H	H	$-CO_2H$	H	Me	Et
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134	O-*i*Pr	H	H	Cl	H		H
135		F	H	Cl	H	Me	Me
136	*t*-Bu	H	F	Cl	H	$-CH_2CH_2OCH_3$	H
137	*t*-Bu	H	F	Cl	H	Me	$-CH_2CH_2OH$
138	*t*-Bu	H	H	Cl	H	Me	$-CH_2NHCH(CH_3)_2$
139	*t*-Bu	H	F	Cl	H	Me	
140	*t*-Bu	H	F	Cl	H	Me	
141	*t*-Bu	H	H	Cl	H		H
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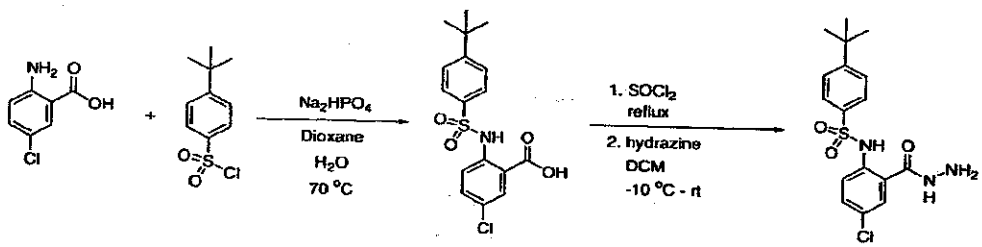
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146	*t*-Bu	H	F	Cl	H		*i*-Pr
147	*t*-Bu	H	F	Cl	H	Me	
148	*t*-Bu	H	F	Cl	H	Me	
149	*t*-Bu	H	F	Cl	H	Me	- $CH_2N(CH_3)CH_2CH_2OCH_3$
150	*t*-Bu	H	F	Cl	H	*i*-Pr	
151	*t*-Bu	H	F	Cl	H	Me	
152	*t*-Bu	H	F	Cl	H	Me	
153	*t*-Bu	H	H	Cl	H		H
154	*t*-Bu	H	F	Cl	H	*i*-Pr	
155	*t*-Bu	H	H	Cl	H		Me
156	t-Bu	H	Cl	H	H	CH=CH-CH=N-	

157	Cl	CF_3	Cl	H	H		H
158	Cl	CF_3	Cl	H	H		H
159	Cl	CF_3	Cl	H	H	Ph	H
160	Cl	CF_3	Cl	F	H		H
161	Cl	CF_3	Cl	F	H		$-CONH_2$

[00532] The above compounds and others within the scope of this invention can be made and tested for activity using the following procedures.

[00533] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR were recorded on a Varian Mercury 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parenthesis). 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. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1 mg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using acetonitrile / water with 1% formic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2 mM NH_4OAc in acetonitrile / water as delivery system.

[00534] General Procedure A – exemplified for 4-tert-Butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide



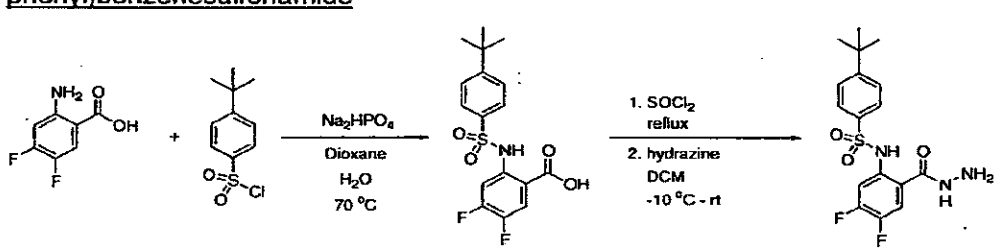
[00535] Step 1: 2-Amino-5-chlorobenzoic acid (200 g, 1.17 mol) was added to a solution of sodium hydrogen phosphate (497 g, 3.50 mol) in water (2.4 L) at 70 °C and was stirred until homogeneous (~10 min). 4-tert-Butylbenzenesulfonyl chloride (353 g, 1.52 mol), dissolved in 800 mL *p*-dioxane, was added to the stirring aniline solution in a steady stream over a ½ hour period via a 1 liter addition funnel. The resultant mixture was stirred at 70 °C overnight. The following day, upon LCMS verification of consumption of the aniline, the reaction mixture was divided into two equal portions for ease of handling. Each portion was poured in a slow stream into two liters of rapidly stirring 2 M HCl/H_2O in a four liter Erlenmeyer flask. The resultant precipitate was collected by vacuum filtration and washed well with water. The precipitate from each portion were subsequently combined and dried *in vacuo* to afford 320 g 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-benzoic acid as an off-white solid (87% yield): HPLC retention time = 2.76 minutes (Agilent Zorbax SB-C18, 2.1X50 mm, 5µ, 35 °C, using a 1 mL/min flow rate, a 2.5 minute gradient of 20 - 100% B with a 1.1 minute wash at 100% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 5% water/ 94.9% acetonitrile)); MS (ES) M+H expected 368.0, found 368.0.

[00536] Step 2: Thionyl chloride (300 mL, 4.11 mol) was introduced to a 1 liter round bottom flask fitted with a magnetic stir bar. 2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-benzoic acid (80 g, 218 mmol) was added under rapid agitation and the mixture was heated at reflux under a nitrogen atmosphere. The reaction progress was monitored by the addition of a few drops of the reaction mixture into ~1 mL of 2.0 M dimethylamine in THF,

followed by LCMS analysis. Complete conversion to the dimethyl amide was observed at 1.25 h. The crude mixture was subsequently concentrated *in vacuo* to produce a thick yellow oil which was then dissolved in 100 mL toluene and concentrated again to generate 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-benzoyl chloride as a pale yellow solid which was utilized directly in the next step.

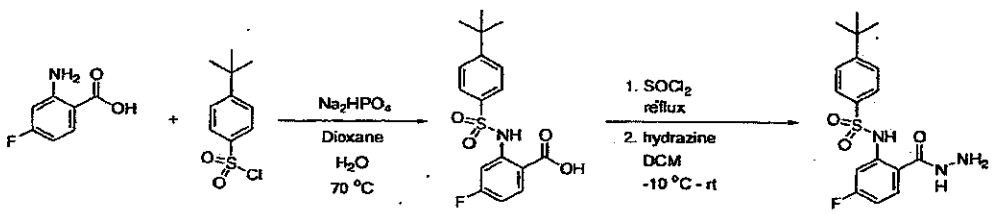
[00537] Step 3: The crude 2-(4-tert-butyl-benzenesulfonylamino)-5-chlorobenzoyl chloride was dissolved in dichloromethane (300 mL) and transferred to an addition funnel. Hydrazine hydrate (212 mL, 4.35 mol), dissolved in 1.2 L dichloromethane in a 4 L Erlenmeyer flask, was cooled to -10 °C in a dry ice- acetone bath and the acyl chloride solution was added in a slow stream to the stirring hydrazine solution over a 15 minute period. The cold bath was subsequently removed following the addition and LCMS analysis at 15 minutes indicated the reaction was complete. The resultant reaction mixture was quenched with water (500 mL), resulting in a voluminous white precipitate that was collected by vacuum filtration. The precipitate was slurried in 800 mL ethyl acetate and acetic acid was added while stirring until a homogeneous solution was formed. The solution was transferred to a separatory funnel and extracted with 3 X 100 mL of water. The aqueous phases were discarded and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to produce 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide (71 g) in an 85% yield: HPLC retention time = 2.49 minutes; MS (ES) M+H expected 382.0, found 382.0.

[00538] <u>4-tert-Butyl-N-(4,5-difluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide</u>



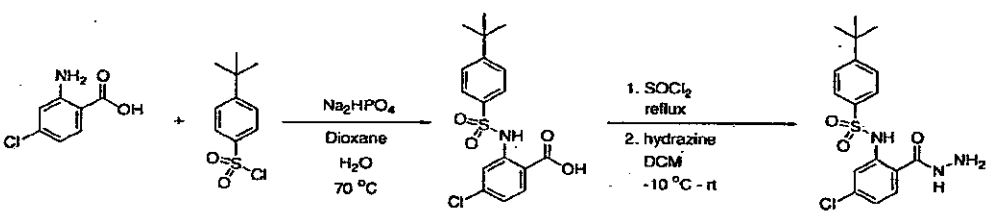
[00539] 4-tert-Butyl-N-(4,5-difluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-4,5-difluorobenzoic acid according to general procedure A.

[00540] 4-tert-Butyl-N-(5-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide



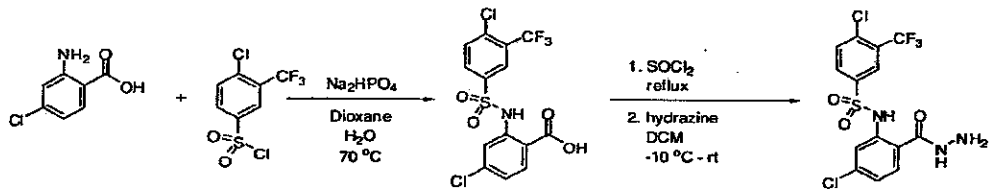
[00541] 4-tert-Butyl-N-(5-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-4-fluorobenzoic acid according to general procedure A.

[00542] 4-tert-Butyl-N-(5-chloro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide



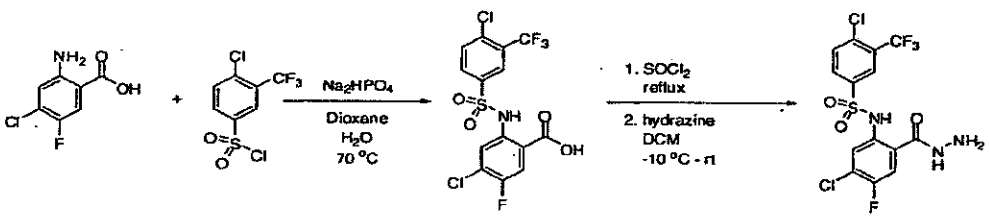
[00543] 4-tert-Butyl-N-(5-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-4-chlorobenzoic acid according to general procedure A.

[00544] 4-Chloro-N-(5-chloro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide



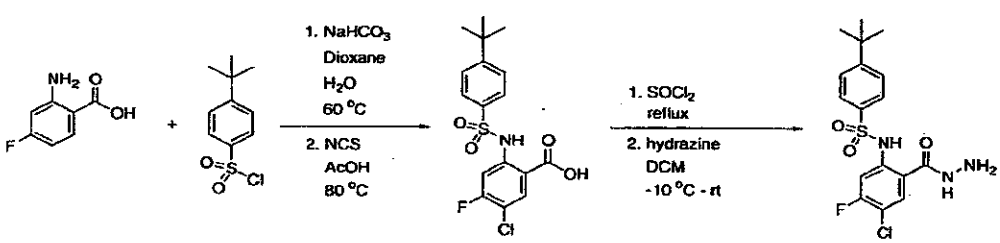
[00545] 4-Chloro-N-(5-chloro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide was synthesized from 2-amino-4-chlorobenzoic acid according to general procedure A.

[00546] 4-Chloro-N-(5-chloro-4-fluoro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide



[00547] 4-Chloro-N-(5-chloro-4-fluoro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide was synthesized from 2-amino-4-chloro-5-fluorobenzoic acid according to general procedure A.

[00548] General Procedure B as exemplified for 4-tert-Butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl) benzenesulfonamide



[00549] Step 1: 2-Amino-4-fluorobenzoic acid (25 g, 161 mmol) was added to a solution of sodium bicarbonate (54.1 g, 645 mmol) in water (2.4 L) at room temperature and was stirred until homogeneous. The resultant solution was heated to 60 °C in an oil bath. 4-tert-Butylbenzenesulfonyl

chloride (45.0 g, 193 mmol), dissolved in 200 mL *p*-dioxane, was subsequently added dropwise to the stirring aniline solution in a steady stream over a 30 min period. The reaction mixture was stirred at 60 °C overnight. The following day, upon LCMS verification of consumption of the aniline, the solution was poured in a slow stream into one liter of rapidly stirring 2 M HCl/H_2O. The resultant precipitate was collected by vacuum filtration, washed thoroughly with water, and dried *in vacuo* to afford 46 g of 2-(4-tert-butyl-benzenesulfonylamino)-4-fluoro-benzoic acid as an off-white solid (82% yield): HPLC retention time = 2.68; MS (ES) M+H expected 352.0, found 352.0.

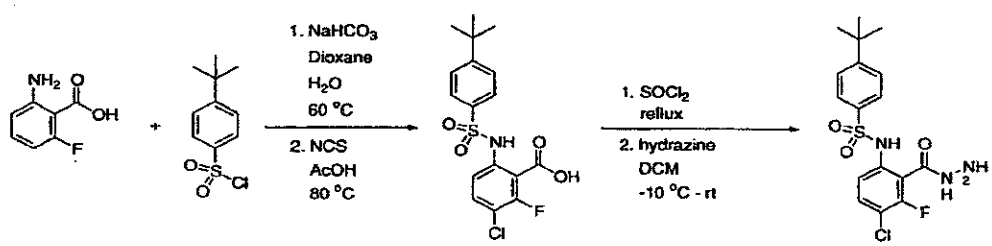
[00550] Step 2: 2-(4-tert-Butyl-benzenesulfonylamino)-4-fluoro-benzoic acid (23 g, 65.5 mmol) was added to 230 mL of stirring acetic acid in a 500 mL round bottom flask. N-chlorosuccinimide (17.5 g, 131 mmol) was then added and the mixture heated to 80 °C under a N_2 atmosphere. The reaction was determined to be complete in seven hours according to LCMS analysis. The heat bath was subsequently removed and the reaction was quenched via the addition of 250 mL of a 50% solution of sodium metabisulfite. The mixture immediately formed a thick white slurry which was allowed to stir for approximately 15 minutes. Vacuum filtration of the slurry resulted in a white solid that was washed with a small amount of water and dried in vacuo to generate 22 g of 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-benzoic acid (white solid, 87% yield): HPLC retention time = 2.87 minutes; MS (ES) M+H expected 386.0, found 386.0.

[00551] Step 3: Thionyl chloride (220 mL, 3.02 mol) was introduced to a 1 L round bottom flask fitted with a magnetic stir bar. 2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-4-fluoro-benzoic acid (22 g, 57.0 mmol) was added under rapid agitation and the mixture was heated at reflux under a nitrogen atmosphere. The reaction progress was monitored by the addition of a few drops of the reaction mixture into ~1 mL of 2.0 M dimethylamine in THF, followed by LCMS analysis. Complete conversion to the dimethyl amide was observed at 1.25 h. The crude mixture was subsequently concentrated *in vacuo* to produce an orange oil. Hexane (50 mL) was added to the flask and the mixture concentrated again to afford 2-(4-tert-butyl-

benzenesulfonylamino)-5-chloro-benzoyl chloride as an orange crystalline solid which was utilized direction in the next step.

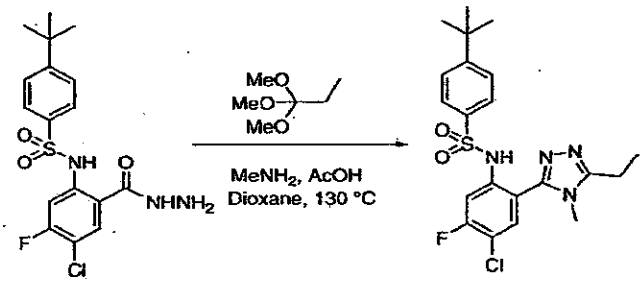
[00552] Step 4: The crude 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-benzoyl chloride (57.0 mmol) was dissolved in dichloromethane (100 mL) and transferred to an addition funnel. Anhydrous hydrazine (44 mL, 1.38 mol), dissolved in 300 mL dichloromethane in a one liter Erlenmeyer flask, was cooled to -10 °C in a dry ice- acetone bath and the acyl chloride solution was added in a slow stream to the stirring hydrazine solution over a 15 minute period. The cold bath was subsequently removed following the addition and LCMS analysis at 15 minutes indicated the reaction was complete. The resultant reaction mixture was quenched with water (200 mL), resulting in a voluminous white precipitate that was collected by vacuum filtration. The precipitate was slurried in 500 mL ethyl acetate and acetic acid was added while stirring until a homogeneous solution was formed. The solution was transferred to a separatory funnel and extracted with 2 X 50 mL of water. The aqueous phases were discarded and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to produce 4-tert-butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (16 g) in a 71% yield: HPLC retention time = 2.63 minutes; MS (ES) M+H expected 400.0, found 400.0.

[00553] <u>4-tert-Butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl) benzenesulfonamide</u>



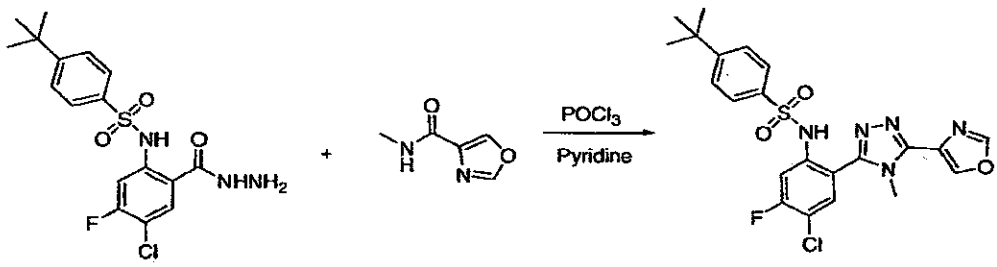
[00554] 4-tert-Butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-6-fluorobenzoic acid according to general procedure B.

[00555] General Procedure C as exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-ethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-5-fluoro-phenyl]-benzenesulfonamide



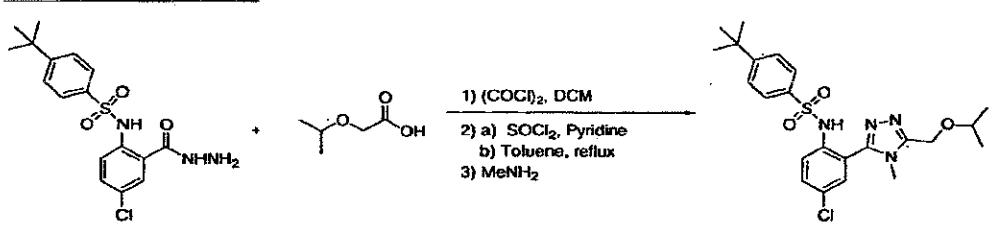
[00556] A 25 mL scintillation vial was charged with 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (1.0 g, 2.51 mmol) and trimethyl orthopropionate (0.534 mL, 3.76 mmol), and then stirred for 1 h at 45 °C. To the above reaction mixture was added methylamine (3.75 mL, 2.0 M in THF), AcOH (0.125 mL), and dioxane (10 mL). The vial was sealed, heated to 130 °C, and stirred overnight. The following day, the reaction mixture was cooled to 0 °C to induce precipitation of the product. The resultant white solid was filtered and dissolved in EtOAc (50 mL). The organics were subsequently washed with saturated $NaHCO_3$ solution (25 mL), saturated NH_4Cl solution (25 mL), water (25 mL), and brine (25 mL); dried with Na_2SO_4, and concentrated *in vacuo* to afford the title compound as a white solid (0.3 g) in 27% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 3H), 7.36 (d, 2H), 7.25 (d, 1H), 3.32 (s, 3H), 2.75 (q, 2H), 1.45 (t, 3H), 1.30 (s, 9H), MS (ES) M+H expected 451.0, found 451.0.

[00557] General Procedure D exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(4-methyl-5-oxazol-4-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00558] A 25 mL scintillation vial was charged with oxazole-4-carboxylic acid methylamide (132 mg, 1.0 mmol), $POCl_3$ (0.27 mL, 3 mmol), pyridine (0.48 mL, 6 mmol) and CH_3CN (10 mL). The vial was sealed, heated to 40 °C, and stirred for four hours. The volatiles were then evacuated *in vacuo* and to the residue was added 4-tert-butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (400 mg, 1.0 mmol), diisopropylamine (2.0 mL), and dioxane (2.0 mL). The vial was sealed, heated to 130 °C, and stirred for two hours. The volatiles were then removed in *vacuo*, and the residue was purified via automated silica gel chromatography and then HPLC to afford 4-tert-butyl-N-[4-chloro-5-fluoro-2-(4-methyl-5-oxazol-4-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.48 (d, 1H), 8.04 (d, 1H), 7.67 (d, 1H), 7.50 (d, 2H), 7.33 (d, 1H), 7.3 (d, 2H), 3.59 (s, 3H), 1.23 (s, 9H), MS (ES) M+H expected 490.1, found 490.0.

[00559] <u>General Procedure E exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-isopropoxymethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide</u>



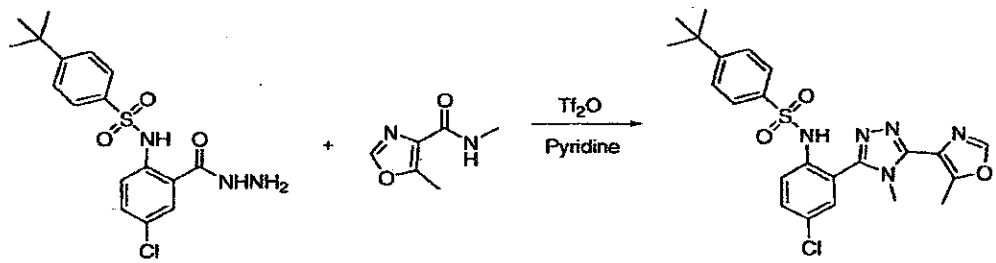
[00560] Step 1: Oxalyl chloride (0.19 mL, 2.20 mmol) was added to a solution of isopropoxyacetic acid (200 mg, 1.69 mmol) in dichloromethane (17 mL) and stirred at room temperature for 2 hours. The reaction was

concentrated and 3 mL of THF was added. The acid chloride solution was subsequently slowly added to a solution of 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (645 mg, 1.69 mmol) in 10 mL of THF at 0 °C. After the reaction was stirred for 1 h, it was quenched with water and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3x) and dichloromethane (2x), and the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude reside was purified by flash column chromatography (0-100% ethyl acetate in hexane) to yield 4-tert-butyl-N-{4-chloro-2-[N'-(2-isopropoxy-acetyl)-hydrazinocarbonyl]-phenyl}-benzenesulfonamide as a yellow solid.

[00561] Step 2: Thionyl chloride was added to a solution of 4-tert-butyl-N-{4-chloro-2-[N'-(2-isopropoxy-acetyl)-hydrazinocarbonyl]-phenyl}-benzenesulfonamide (150 mg, 0.312 mmol) and pyridine (66 µL, 0.811 mmol) in diethyl ether (3 mL). The resultant solution was stirred for 18 h at room temperature followed by removal of the volatiles *in vacuo*. 2 mL toluene was subsequently added and the reaction was heated at reflux for 5 h. The resultant solution was concentrated at reduced pressure and the residue purified via flash column chromatography (0-50% ethyl acetate in hexane) to afford 4-tert-butyl-N-[4-chloro-2-(5-isopropoxymethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide as a white solid.

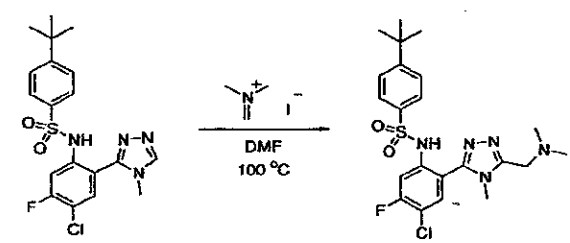
[00562] Step 3: In a pressure vessel, 4-tert-butyl-N-[4-chloro-2-(5-isopropoxymethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide (71 mg, 0.15 mmol) and methyl amine (40% in H_20, 1.5 mL, 0.6 mmol) were heated at 135 °C for 18 h. The reaction was cooled to room temperature, concentrated *in vacuo*, and the residue purified by flash column chromatography (0-50% ethyl acetate in hexane) to yield the title compound as a white solid: MS (ES) M+H expected 477.2, found 477.1.

[00563] General Procedure F exemplified for 4-tert-Butyl-N-{4-chloro-2-[4-methyl-5-(5-methyl-oxazol-4-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00564] A vial was charged with 5-methyl-oxazole-4-carboxylic acid methylamide (71 mg, 0.5 mmol), pyridine (0.12 mL, 1.5 mmol), and anhydrous dichloromethane (2.5 mL). The reaction vessel was cooled to -40 °C and trifluoromethanesulfonyl anhydride (0.11 mL, 0.65 mmol) was added. The reaction was subsequently warmed to -10 °C over 2.5 h and then 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (191 mg, 0.5 mmol) was added. The reaction was warmed to room temperature stirred an additional 2 h. The solvent was concentrated *in vacuo* and ethanol (5 mL) and diisopropylamine (0.5 mL) were added and the solution stirred at 90 °C overnight. The following day, the reaction was concentrated *in vacuo* and the crude material was purified by flash column chromatography (10 - 100% ethyl acetate and hexane), followed by preparative HPLC (10 - 90% gradient of MeCN-water) to yield the title compound: MS (ES) M+H expected 486.1, found 486.0.

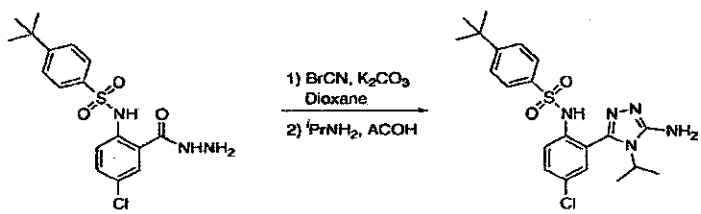
[00565] General Procedure G exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-dimethylaminomethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-5-fluoro-phenyl]-benzenesulfonamide



[00566] A 25 mL pear-shaped flask was charged with 4-tert-butyl-N-[4-chloro-5-fluoro-2-(4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (prepared according to general procedure C) (75 mg,

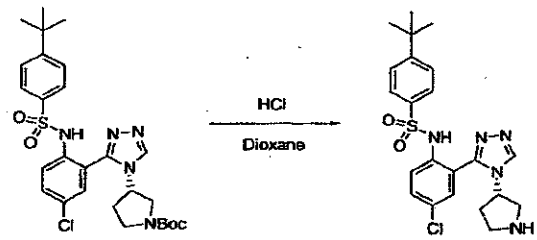
0.18 mmol), N,N-dimethylmethyleneiminium iodide (43 mg, 0.23 mmol), and DMF (0.44 mL). The flask was heated to 100 °C and stirred overnight. The following day, the solvent was evacuated *in vacuo* and the residue was purified via HPLC to afford 4-tert-butyl-N-[4-chloro-2-(5-dimethylaminomethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-5-fluoro-phenyl]-benzenesulfonamide as a white powder: ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, 1H), 7.48-7.54 (m, 4H), 7.28 (d, 1H), 3.70 (s, 2H), 3.46 (s, 3H), 2.36 (s, 6H), 1.33 (s, 9H), MS (ES) M+H expected 480.2, found 480.1.

[00567] General Procedure H exemplified for N-[2-(5-Amino-4-isopropyl-4H-[1,2,4]triazol-3-yl)-4-chloro-phenyl]-4-tert-butyl-benzenesulfonamide



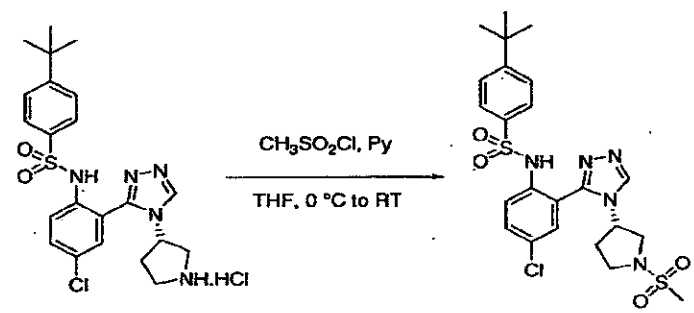
[00568] Cyanogen bromide (111 mg, 1.05 mmol) was added to a solution of 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (200 mg, 0.524 mmol) and potassium carbonate (145 mg, 1.05 mmol) in dioxane (2 mL) and the reaction was stirred for 18 h at room temperature. Isopropyl amine (0.18 mL, 2.09 mmol) and acetic acid (0.15 mL) were added and the reaction was heated at 135 °C for an additional 18 h. The resultant solution was partitioned between ethyl acetate/water and the organic phase was washed with 1N HCl, saturated sodium bicarbonate, and brine; dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was finally purified by flash column chromatography (10 - 100% ethyl acetate and hexane) then preparative HPLC (10 - 90% gradient of MeCN-water) to afford the title compound as a white solid: MS (ES) M+H expected 448.2, found 448.1.

[00569] General Procedure I exemplified for 4-tert-Butyl-N-[4-chloro-2-(4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00570] A 50 mL round-bottom flask was charged with 3-[3-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-phenyl]-[1,2,4]triazol-4-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared according to general procedure C, 750 mg, 1.34 mmol), followed by the addition of HCl in dioxane (13 mL, 4.0 M). The homogeneous solution was stirred overnight, the solvent evacuated *in vacuo*, and the residue was purified via HPLC to afford 4-tert-butyl-N-[4-chloro-5-fluoro-2-(4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide as a white powder: ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.02 (s, 1H), 9.67 (bs, 1H), 9.17 (s, 1H), 9.12 (bs, 1H), 7.71 (d, 2H), 7.51-7.61 (m, 4H), 7.20 (d, 1H), 4.72 (quint, 1H), 3.35-3.62 (m, 3H), 3.18-3.28 (m, 1H), 2.38-2.49 (m, 1H), 2.16-2.28 (m, 1H), 1.29 (s, 9H), MS (ES) M+H expect 460.2, found 460.1.

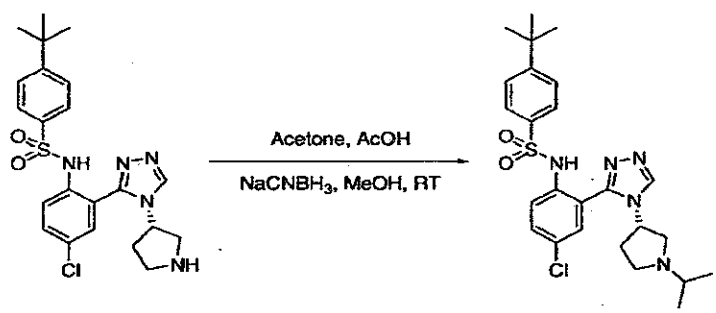
[00571] General Procedure J exemplified for 4-tert-Butyl-N-{4-chloro-2-[(S)-4-(1-methanesulfonyl-pyrrolidin-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00572] To 4-tert-butyl-N-[4-chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide hydrochloride (0.25 g, 0.505 mmol) in THF (8 mL) was added pyridine (0.60 mL, 7.4 mmol). The resultant

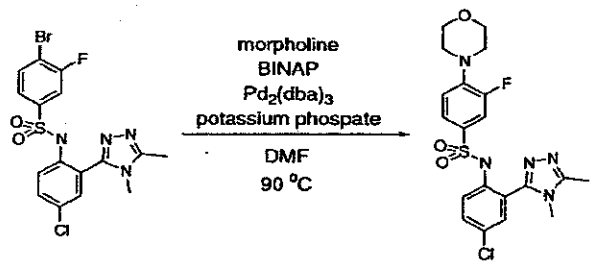
solution was stirred for 20 minutes at room temperature. The reaction mixture was subsequently cooled to 0 °C, methanesulfonyl chloride (0.595 mL, 7.6 mmol) was added, and the mixture was stirred overnight at room temperature. The following day, the volatiles were evaporated and the resultant residue was adsorbed onto silica gel and purified by automated normal-phase chromatography (using 50 → 100% EtOAc in hexanes) to obtain the title compound (0.183 g) in 67.5% yield: MS (ES) M+H expected 538.0, found 538.1.

[00573] General Procedure K exemplified for 4-tert-Butyl-N-[4-chloro-2-[(S)-4-(1-isopropyl-pyrrolidin-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



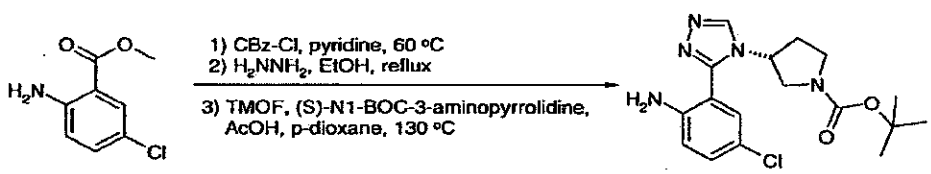
[00574] To a cooled solution of 4-tert-butyl-N-[4-chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (200 mg, 0.43 mmol) in MeOH (5 Ml) was added acetone (0.048 mL, 0.65 mmol) and then $NaCNBH_3$ (0.054 g, 0.86 mmol). The reaction mixture was stirred at room temperature for 2 h, evaporated to dryness, adsorbed onto silica gel, and purified by automated normal-phase chromatography (50% MeOH in EtOAc) and then preparative HPLC (20 → 95% CH_3CN in H_2O with 0.1% TFA). The pure fractions were combined and lyophilized to obtain title compound as a powder: MS (ES) M+H expected 502.0, found 502.1.

[00575] General Procedure L exemplified for N-[4-Chloro-2-(4,5-dimethyl-4H-[1,2,4]triazol-3-yl)-phenyl]-3-fluoro-4-morpholin-4-yl-benzenesulfonamide



A 25 mL scintillation vial was charged with 4-bromo-N-[4-chloro-2-(4,5-dimethyl-4H-[1,2,4]triazol-3-yl)-phenyl]-3-fluoro-benzenesulfonamide (synthesized according to general procedure C, 92 mg, 0.2 mmol), potassium phosphate monohydrate (276 mg, 1.2 mmol), BINAP (30 mg, 0.048 mmol), morpholine (87 mg, 1.0 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), and DMF (2 mL). The vial was sealed and stirred at 90 °C for 20 h. The crude product was purified by flash column chromatography (10 - 100% ethyl acetate and hexane) followed by preparative HPLC (10 - 90% gradient of MeCN-water) to afford the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$/HCl) δ 2.4 (s, 3 H), 2.7-3.7 (m, 8 H), 3.8 (s, 3 H), 6.7 (d, 1 H), 7.1-7.3 (m, 3 H), 7.4 (d, 1 H), 7.5 (d, 1 H), MS (ES) M+H expected 466.0, found 466.0.

[00576] General Procedure M exemplified for 3-[(S)-3-(2-Amino-5-chloro-phenyl)-[1,2,4]triazol-4-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



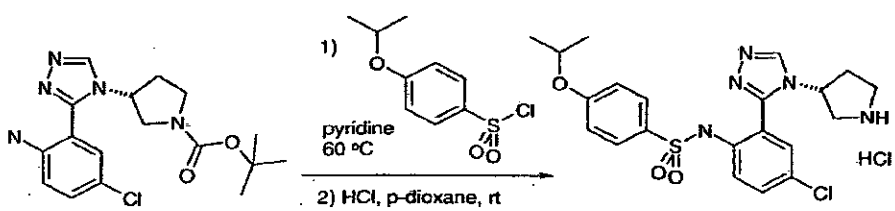
[00577] Step 1: 2-Amino-5-chlorobenzoic acid methyl ester (5 g, 27 mmol) was dissolved in 36 mL pyridine. CBz-Cl (4.2 mL, 29.6 mmol) was then added and the resultant solution was stirred at 60 °C overnight. The following day, LCMS analysis indicated the reaction was complete. The reaction mixture was subsequently poured in a slow stream into 200 mL of rapidly stirring 2 M HCl/H_2O. The mixture was transferred to a separatory funnel and extracted with 2 X 50 mL of EtOAc. The aqueous phase was discarded and the combined organics were dried over sodium sulfate and concentrated *in vacuo* to provide 6 g of 2-benzyloxycarbonylamino-5-chloro-benzoic acid

methyl ester (pale yellow oil, 70% yield): HPLC retention time = 3.15 minutes; MS (ES) M+H expected 320.0, found 320.0.

[00578] Step 2: 2-benzyloxycarbonylamino-5-chloro-benzoic acid methyl ester (3 g, 9.4 mmol) was dissolved in 30 mL ethanol. Hydrazine hydrate (1.5 mL, 30.0 mmol) was added and the resultant solution was heated at reflux under a nitrogen atmosphere for two hours, at which LCMS analysis showed complete conversion of the ester as well as the removal of the CBz protecting group. The reaction mixture was subsequently concentrated *in vacuo* to provide 1.6 g of 2-amino-5-chloro-benzoic acid hydrazide (light brown solid, 92% yield): HPLC retention time = 2.21; MS (ES) M+H expected 186.0, found 186.0.

[00579] Step 3: 2-Amino-5-chloro-benzoic acid hydrazide (0.8 g, 4.3 mmol) was dissolved in 8 mL *p*-dioxane in a 15 mL pressure vessel. Trimethyl orthoformate (0.71 mL, 6.5 mmol), (S)-N_1-Boc-3-aminopyrrolidine (4.0 g, 21.6 mmol), and acetic acid (5 drops) were added and the resultant solution was heated overnight in a 130 °C oil bath. The reaction mixture was subsequently concentrated *in vacuo* to produce a thick oil which was diluted with a small quantity of dichloromethane and purified via column chromatography (MeOH/DCM, 0% to 15 % gradient) to provide 1.4 g of 3-[(S)-3-(2-amino-5-chloro-phenyl)-[1,2,4]triazol-4-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (white semisolid, 77% yield): HPLC retention time = 1.98; MS (ES) M+H expected 364.0, found 364.1.

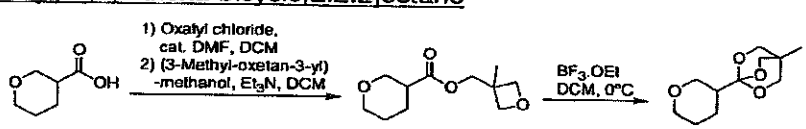
[00580] General Procedure N exemplified for N-[4-Chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-4-isopropoxy-benzenesulfonamide



[00581] Step 1: 3-[(S)-3-(2-Amino-5-chloro-phenyl)-[1,2,4]triazol-4-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.137 mmol) was dissolved in 0.5 mL pyridine in a 4 mL vial. 4-Isopropoxybenzenesulfonyl chloride (42 mg, 0.179 mmol) was added and the mixture heated at 60 °C overnight. Water (~3 mL) was added to the reaction mixture which induced the precipitation of a viscous oil. The mother liquor was discarded and the oil was dissolved in ~3 mL of acetonitrile. The resultant solution was purified by reversed phase HPLC and the pure fractions lyophilized to afford the desired sulfonamide: HPLC retention time = 2.71 minutes; MS (ES) M+H expected 562.0, found 562.1.

[00582] Step 2: The above sulfonamide was dissolved in 1 mL *p*-dioxane and 4 M HCl/*p*-dioxane (4 mL, 16 mmol) was added. The resultant mixture was stirred at room temperature for one hour, during which LCMS indicated complete removal of the BOC protecting group. The reaction mixture was subsequently concentrated *in vacuo* to generate a thick oil, which diluted with 10 mL of acetonitrile/H_2O and lyophilized to afford N-[4-chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-4-isopropoxy-benzenesulfonamide hydrochloride: HPLC retention time = 1.67 minutes; MS (ES) M+H expected 462.0, found 462.4.

[00583] General Procedure O exemplified for 4-Methyl-1-(tetrahydro-pyran-3-yl)-2,6,7-trioxa-bicyclo[2.2.2]octane

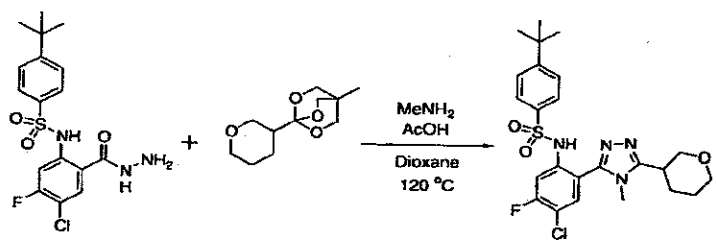


[00584] Step 1: To a stirred solution of tetrahydro-2H-pyran-3-carboxylic acid (231 mg, 1.77 mmol), under an inert atmosphere, in 8 mL of anhydrous DCM and 358 µL DMF was added oxalyl chloride (155 µL, 1.77 mmol). The mixture was stirred at room temperature for 4 h. This solution was then added via syringe to a 4 mL solution of DCM containing (3-methyl-oxetane-3-yl)-methanol (182 µL, 1.77 mmol) and Et_3N (0.62 mL, 4.44 mmol). The resulting mixture was stirred at room temperature for 4 hours. The solvent was subsequently evaporated *in vacuo* and the resultant residue was redissolved

in ethyl acetate and washed with saturated $NaHCO_3$, NH_4Cl solution, and brine. The combined organics were then dried over anhydrous Na_2SO_4 and concentrated to give a crude product, which was used directly in next step without further purification.

[00585] Step 2: The above crude tetrahydro-pyran-3-carboxylic acid 3-methyl-oxetan-3-ylmethyl ester (346 mg, 1.62 mmol) was dissolved in 6 mL of anhydrous DCM. To this solution at 0 °C, under a nitrogen atmosphere, was added BF_3•OEt_2 (41 µL, 0.324 mmol). The mixture was stirred at 0 °C for two hours then warmed to ambient temperature and stirred overnight. The next day, Et_3N (0.23 mL, 91.6 mmol) was added at 0 °C to quench the reaction. After stirring for 5 min, the solvent was removed *in vacuo*. The resultant residue was dissolved in ethyl acetate and washed with 3% of NH_4Cl, saturated $NaHCO_3$, and brine. The combined organics were subsequently dried over anhydrous Na_2SO_4 and concentrated to provide the desired orthoester.

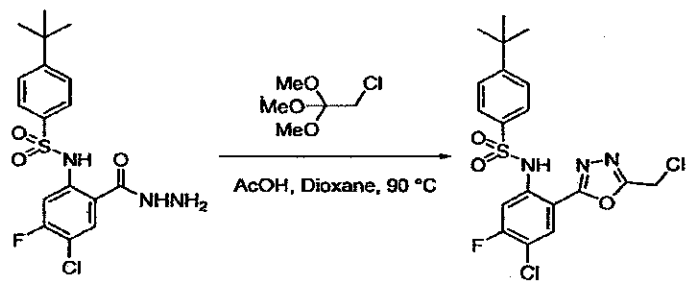
[00586] General Procedure P exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-[4-methyl-5-(tetrahydro-pyran-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl]-benzenesulfonamide



[00587] A 25 mL scintillation vial was charged with 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (253 mg, 0.633 mmol), 4-methyl-1-(tetrahydro-pyran-3-yl)-2,6,7-trioxa-bicyclo[2.2.2]octane (136 mg, 0.633 mmol), methylamine (31 µL, 0.886 mmol), AcOH (51 µL, 0.886 mmol), and dioxane (1.0 mL). The vial was sealed, heated to 120 °C, and stirred overnight. The following day, the volatiles were evacuated *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-[4-chloro-5-fluoro-2-[4-

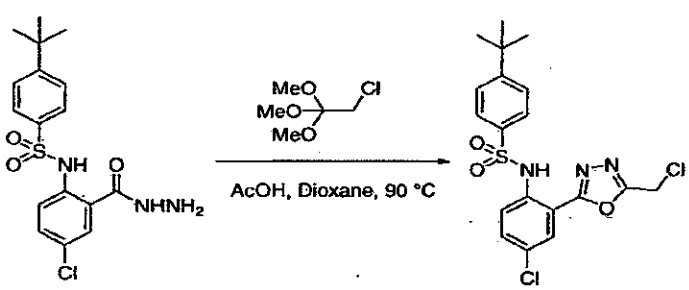
methyl-5-(tetrahydro-pyran-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: MS (ES) M+H expected 507.1, found 507.1.

[00588] General Procedure Q exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-5-fluoro-phenyl]-benzenesulfonamide



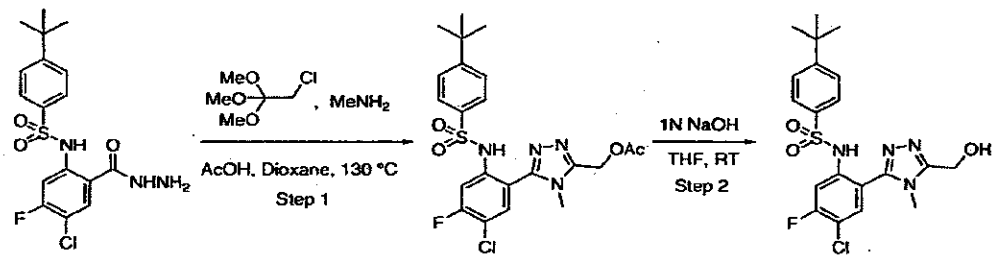
[00589] 2-Chloro-1,1,1-trimethoxy-ethane (0.507 mL, 3.76 mmol) and AcOH (1.5 mL) were added to 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (1.0 g, 2.51 mmol) in dioxane (6 mL) and stirred overnight at 90 °C. The reaction mixture was subsequently cooled to ambient temperature and stored for 1 day to promote precipitation of the product. The resultant white solid was filtered, washed with Et_2O (2 x 10 mL), and dried under vacuum to generate the title compound (0.74 g) in 65% yield as a white solid: MS (ES) M+H expected 458.0, found 458.3.

[00590] 4-tert-Butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide



[00591] 4-tert-Butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide was prepared according to general procedure Q: MS (ES) M+H expected 440.0, found 440.3.

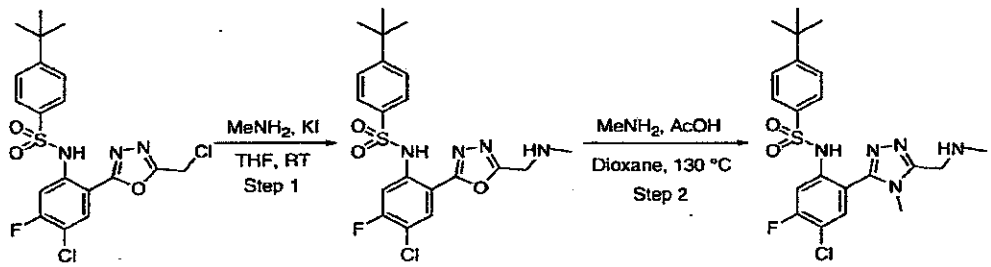
[00592] General Procedure R exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(5-hydroxymethyl-4-methyl-4H-1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00593] Step1: 2-Chloro-1,1,1-trimethoxy-ethane (0.220 mL, 3.76 mmol), $MeNH_2$ (0.625 mL, 2.0 M in THF) and AcOH (0.4 mL) were added to 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (0.50 g, 1.25 mmol) in dioxane (5 mL) and stirred 4 h at 130 °C. The resultant reaction mixture was evaporated to dryness, adsorbed onto silica gel, and purified by automated normal-phase chromatography (30% EtOAc in hexanes) to afford the 'triazole-acetate' as a minor product.

[00594] Step 2: To a solution of 'triazole-acetate' (20 mg) in THF (2 mL) was added 1 N aqueous NaOH (2 mL), and the solution was stirred at room temperature for 30 min. 2 N HCl (aqueous) (2 mL) was subsequently added and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organics were dried (Na_2SO_4), concentrated *in vacuo*, and purified by automated normal-phase chromatography (50% EtOAc in hexanes) to generate the title compound as white powder following lyophilization: MS (ES) M+H expected 453.0, found 453.1.

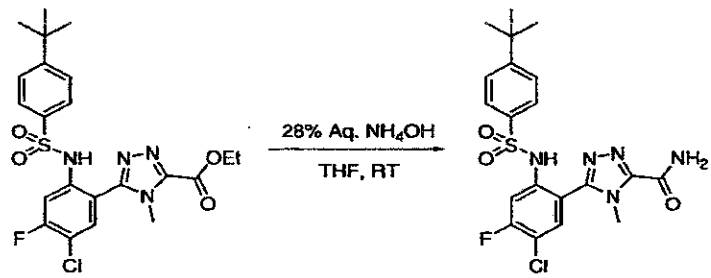
[00595] General Procedure S exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(4-methyl-5-methylaminomethyl-H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00596] Step 1: To a solution of 4-tert-butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-5-fluoro-phenyl]-benzenesulfonamide (400 mg, 0.875 mmol) in THF (5 mL) was added KI (0.145 g, 0.875 mmol) and $MeNH_2$ (1.31 mL, 2.62 mmol, 2.0 M in THF). The resultant solution was stirred at room temperature overnight. The following day, the reaction mixture was diluted with EtOAc (30 mL) and the organic layer was washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired 'methylaminomethyl-oxadiazole' (400 mg) as a white solid in quantitative yield: MS (ES) M+H expected 453.0, found 453.0.

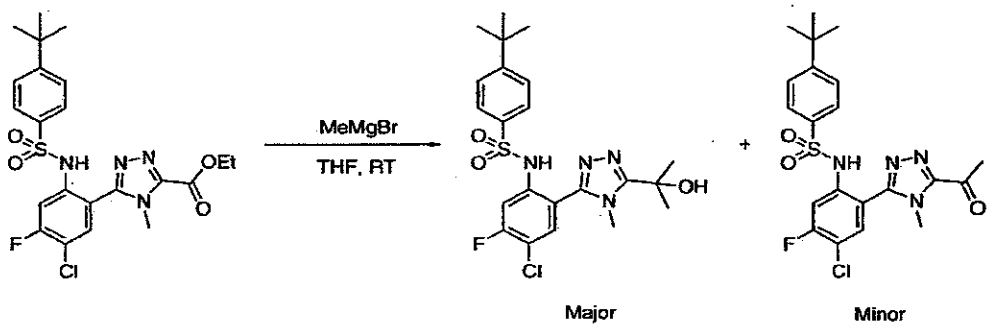
[00597] Step 2: To the above oxadiazole intermediate (100 mg, 0.22 mmol) in 1,4-dioxane (3 mL) was added $MeNH_2$ (1.1 mL, 2.0 M in THF), followed by AcOH (0.125 mL). The homogeneous solution was heated to 130 °C and stirred at for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL) and the organic layer was washed with saturated $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified via automated normal-phase chromatography (5% MeOH in EtOAc). The pure fractions were combined and lyophilized to produce the title compound as a powder: ^1H NMR (400 MHz, CD_3OD) δ 7.65 (d, 1H), 7.60-7.52 (m, 4H), 7.0 (d, 1H), 4.58 (s, 2H), 3.58 (s, 3H), 2.95 (s, 3H), 1.35 (s, 9H), MS (ES) M+H expected 466.0, found 466.1.

[00598] General Procedure T exemplified for 5-[2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazole-3-carboxylic acid amide



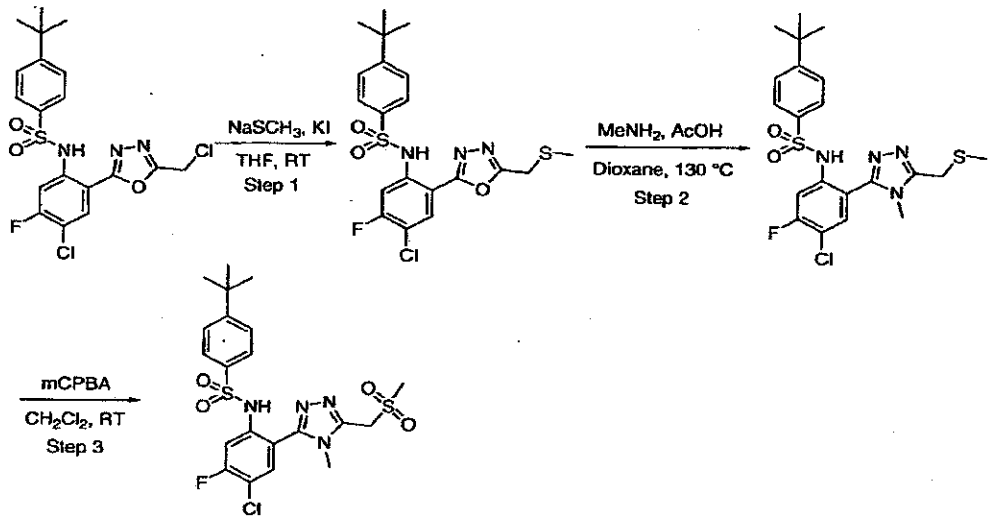
[00599] To a vial containing ethyl 5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester (synthesized according to general procedure C, 100 mg, 0.202 mmol) was added THF (2 mL) and 28% NH_4OH in water (2 mL), and the resultant solution was stirred at room temperature for 1 h. The reaction mixture was subsequently diluted with EtOAc (30 mL) and the organics were washed with water (2 x 10 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (50 → 100% gradient of EtOAc in hexanes). The pure fractions were collected and the solvent was removed. The isolated product was dissolved in MeCN/H_2O and the solvent removed via lyophilization to afford the title compound as a white powder: MS (ES) M+H expected 466.0, found 466.0.

[00600] General Procedure U exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-[5-(1-hydroxy-1-methyl-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide and N-[2-(5-Acetyl-4-methyl-4H-[1,2,4]triazol-3-yl)-4-chloro-5-fluoro-phenyl]-4-tert-butyl-benzenesulfonamide



[00601] To a solution of ethyl 5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester (synthesized according to general procedure C, 100 mg, 0.254 mmol) in THF (3 mL) at room temperature was added MeMgBr (3 mL, 3.0 M in Et_2O). The resultant solution was stirred 30 min, followed by the slow addition of saturated aqueous NH_4Cl solution to quench the excess MeMgBr. The aqueous layer was subsequently extracted with EtOAc (2 x 25 mL) and the combined organics were dried (Na_2SO_4), concentrated *in vacuo*, and purified by automated normal-phase chromatography (EtOAc/hexanes) to afford the tertiary alcohol (0.026g, 21% yield) as the major product and the methyl ketone as the minor product (0.020 g, 17% yield): MS (ES) M+H (major product) expected 481.0, found 481.0, MS (ES) M+H (minor product) expected 465.0, found 465.0.

[00602] General Procedure V exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(5-methanesulfonylmethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



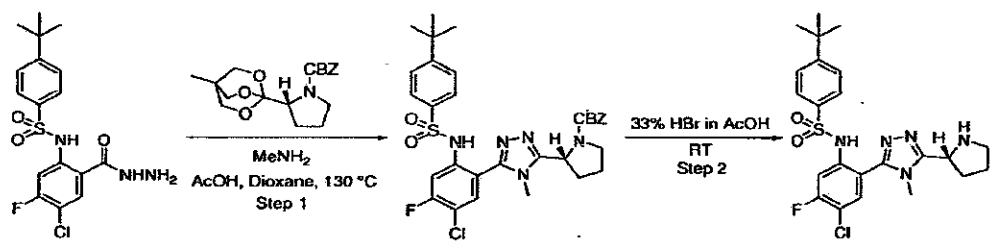
[00603] Step 1: KI (0.036 g, 0.218 mmol), followed by sodium thiomethoxide (0.046 g, 0.654 mmol) were added to 4-tert-butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-5-fluoro-phenyl]-benzenesulfonamide (100 mg, 0.218 mmol) in THF (3 mL) and stirred at room temperature overnight. The resultant reaction mixture was diluted with EtOAc (30 mL), and the organic layer was washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to generate the desired 'oxadiazole methylthioether' (100 mg) as a yellow thick syrup in quantitative yield: MS (ES) M+H expected 470.0, found 470.0.

[00604] Step 2: To the above 'oxadiazole methylthioether' (100 mg, 0.21 mmol) in 1,4-dioxane (3 mL) was added $MeNH_2$ (1.1 mL, 2.0 M in THF) and AcOH (0.128 mL) and the resultant mixture was stirred at 130 °C for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL), and the organic layer was washed with saturated $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified via automated normal-phase chromatography (EtOAc) to produce the

corresponding 'triazole methylthioether': MS (ES) M+H expected 483.0, found 483.4.

[00605] Step 3: To a solution of the above 'triazole methylthioether' (0.025 g, 0.05 mmol) in CH_2Cl_2 (3 mL) was added *m*CPBA (0.027g, 0.155 mmol) and the resultant mixture was stirred at room temperature overnight. The volatiles were subsequently removed and the product was purified utilizing preparative HPLC (20 → 95% CH_3CN in H_2O with 0.1% TFA). The pure fractions were combined and lyophilized to generate the title compound as a yellow powder: MS (ES) M+H expected 515.0, found 515.4.

[00606] General Procedure W exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-((R)-4-methyl-5-pyrrolidin-2-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide

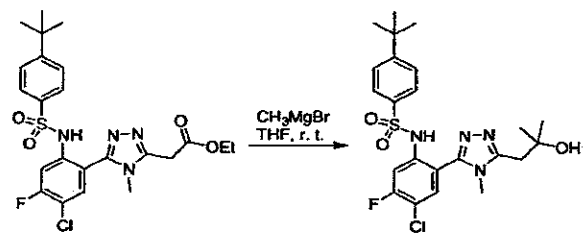


[00607] Step 1: (R)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-pyrrolidine-1-carboxylic acid benzyl ester (synthesized according to general procedure O, 0.296 g, 0.888 mmol), $MeNH_2$ (0.888 mL, 2.0 M in THF), and AcOH (0.125 mL) were added to 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (0.236 g, 0.59 mmol) in dioxane (5 mL) and the solution was stirred overnight at 130 °C. The following day, the reaction mixture was evaporated to dryness and the resultant crude triazole was utilized directly in the next step.

[00608] Step 2: To the above crude triazole was added 33% HBr in AcOH (3 mL) and the resultant reaction mixture was stirred overnight at room temperature. The following day, the volatiles were removed *in vacuo* and the resultant residue was dissolved in a small quantity of MeOH and purified via preparative HPLC (20 → 95% CH_3CN in H_2O with 0.1% TFA). The pure

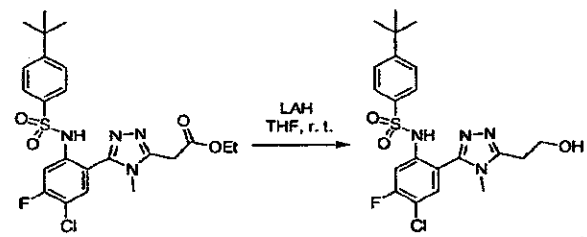
fractions were collected and lyophilized to afford the title compound as a yellow powder: MS (ES) M+H expected 492.0, found 492.4.

[00609] General Procedure X exemplified for 4-tert-Butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-2-methyl-propyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



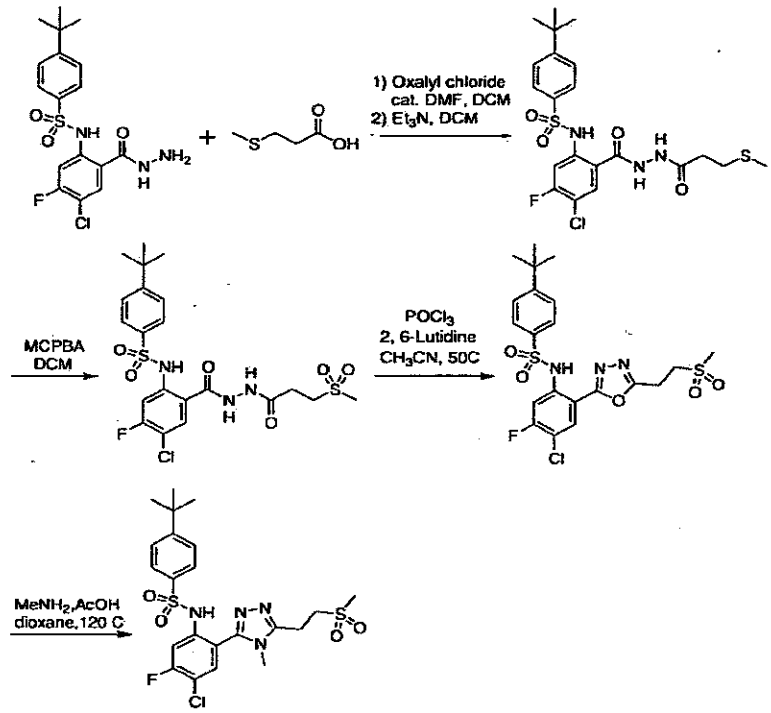
[00610] A 25 mL scintillation vial was charged with {5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazol-3-yl}-acetic acid ethyl ester (prepared according to general procedure P, 178 mg, 0.349 mmol) in 7 mL of anhydrous THF. To this solution under a nitrogen atmosphere was added of methyl magnesium bromide (0.47 mL, 3.0 M in THF) at room temperature. Upon complete consumption of the starting material (via LCMS), the reaction was quenched by the addition of an NH_4Cl solution. The solvent was subsequently removed *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-2-methyl-propyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.64 (d, 1H), 7.60 (d, 2H), 7.41 (d, 2H), 7.30 (d, 1H), 4.0 (s, 1H), 3.81 (s, 2H), 3.41 (s, 3H), 1.57 (s, 9H), 1.31 (s, 6H), MS (ES) M+H expected 495.2, found 495.4.

[00611] General Procedure Y exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-[5-(2-hydroxy-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00612] A 25 mL scintillation vial was charged with {5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazol-3-yl}-acetic acid ethyl ester (synthesized according to general procedure P, 95 mg, 0.186 mmol) in 2 mL of anhydrous MeOH. To this solution under a nitrogen atmosphere was added of lithium aluminum hydride (14 mg, 0.372 mmol) at room temperature. LCMS indicated completion of the reaction after 30 minutes and 1 mL of 20% H_2SO_4 was added. The solvent was subsequently removed *in vacuo* and the residue was extracted with DCM. The organic layer was then washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resultant residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: MS (ES) M+H expected 467.1, found 467.4.

[00613] General Procedure Z exemplified for 4-tert-Butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00614] Step 1: To a stirred solution of 3-methylsulfanyl-propionic acid (120 mg, 1.0 mmol) under an inert atmosphere in 6 mL of anhydrous DCM and DMF (200 µL) was added oxalyl chloride (89 µL, 1.0 mmol). The resultant solution was stirred at room temperature overnight and then added to a solution of 4-tert-butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (400 mg, 1.0 mmol) and Et_3N (0.35 mL, 2.5 mmol) at 0 °C. The resultant solution was stirred at room temperature for 4 hours and the solvent was removed *in vacuo*. The residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[N'-(3-methylsulfanyl-propionyl)-hydrazinocarbonyl]-phenyl}-benzenesulfonamide as an oil: MS (ES) M+H expected 502.1, found 502.0.

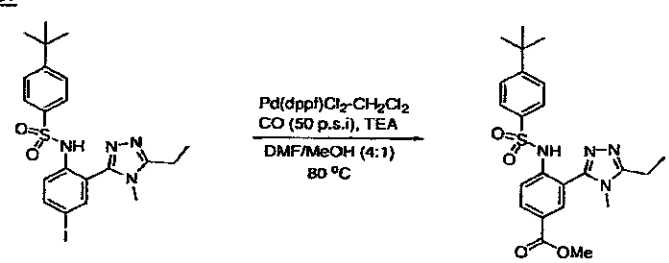
[00615] Step 2: To a solution of the above diamide (422 mg, 0.841 mmol) in 10 mL of DCM was added 3-chloroperoxybenzoic acid (386 mg, 1.72

mmol) at 0 °C. The reaction mixture was subsequently stirred at room temperature overnight. The following day, the product had precipitated from solution and was collected via vacuum filtration and used directly in the next step: MS (ES) M+H expected 534.1, found 534.0.

[00616] Step 3: A 25 mL scintillation vial was charged with the above crude sulfone (307 mg, 0.574 mmol), 2,6-lutidine (148 mg, 1.378 mmol), $POCl_3$ (106 mg, 0.689 mmol), and CH_3CN (1.0 mL). The vial was sealed, heated to 50 °C, and stirred overnight. The following day, the volatiles were evacuated *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-benzenesulfonamide as the desired product: MS (ES) M+H expected 516.1, found 516.0.

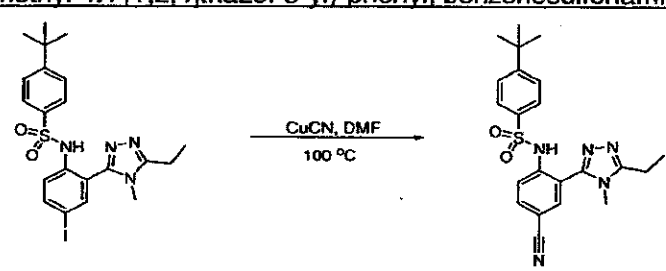
[00617] Step 4: A 25 mL scintillation vial was charged with 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-benzenesulfonamide (48 mg, 0.093 mmol), methylamine (13 µL, 0.372 mmol), AcOH (21 µL, 0.372 mmol), and dioxane (1.0 mL). The vial was sealed, heated to 120 °C, and stirred overnight. The following day, the volatiles were evacuated *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: MS (ES) M+H expected 529.1, found 529.0.

[00618] General Procedure AA exemplified for 4-(4-tert-Butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester



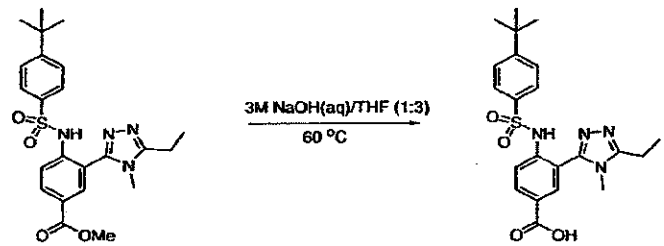
[00619] A 15 mL pressure vessel was charged with 4-tert-butyl-*N*-[4-iodo-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (prepared according to general procedure C, 551 mg, 1.05 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (1:1) (86 mg, 0.105 mmol), triethylamine (290 µL, 2.1 mmol), and DMF/MeOH (4:1) (5 mL). The vessel was placed under an atmosphere of CO (50 p.s.i.), heated to 80 °C, and stirred overnight. The following day, the volatiles were removed *in vacuo*, the residue dissolved in EtOAc, and the organics washed twice with 1 M HCl. The aqueous solution was then extracted three times with EtOAc. The EtOAc extractions were then pooled together and washed with brine. The organic solvent was then removed and the resultant residue was purified by silica gel chromatography to afford 4-(4-tert-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester as a yellow foam: MS (ES) M+H expected 457.2, found 457.1.

[00620] General Procedure BB exemplified for 4-tert-Butyl-*N*-[4-cyano-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



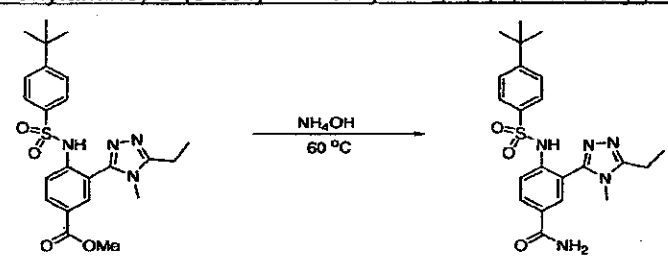
[00621] A 4 mL scintillation vial was charged with 4-tert-butyl-*N*-[4-iodo-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (prepared according to general procedure C, 18 mg, 0.034 mmol), CuCN (15 mg, 0.17 mmol), and DMF (500 µL). The reaction was then heated to 100 °C and stirred for 48 hours. The solution was then diluted with EtOAc and washed with an aqueous solution of EDTA (5% wt/wt). The organic layer was then concentrated and the residue purified by preparative TLC to afford 4-tert-butyl-*N*-[4-cyano-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide as a white solid: MS (ES) M+H expected 424.2, found 424.4.

[00622] General Procedure CC exemplified for 4-(4-tert-Butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid



[00623] A 10 mL scintillation vial was charged with 4-(4-tert-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester (20 mg, 0.044 mmol) and 3 M NaOH (aq)/THF (1:3) (1.5 mL). The reaction was heated to 60 °C and stirred overnight. The following day, the volatiles were removed *in vacuo* to about 200 µL at which point the solution was purified by preparative TLC to afford 4-(4-*tert*-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid as a light yellow solid: MS (ES) M+H expect 443.2, found 443.4.

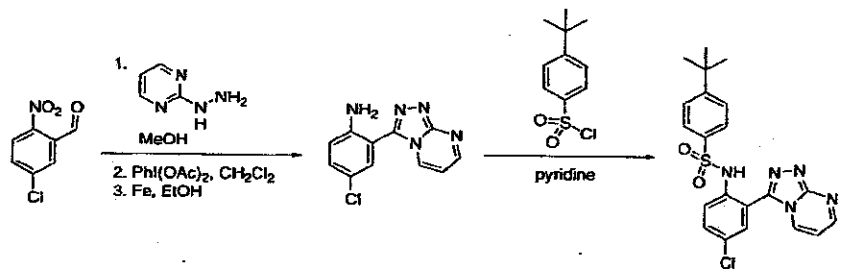
[00624] General Procedure DD exemplified for 4-(4-tert-Butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzamide



[00625] A 10 mL scintillation vial was charged with 4-(4-tert-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester (20 mg, 0.044 mmol) and 30% NH_3 in H_2O (1.5 mL). The reaction was heated to 60 °C and stirred overnight. The following day, the volatiles were removed *in vacuo* to about 200 µL at which point the solution was purified by preparative TLC to afford 4-(4-*tert*-butyl-benzenesulfonylamino)-3-

(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzamide as a colorless oil: MS (ES) M+H expected 442.2, found 442.4.

[00626] General Procedure EE exemplified for 4-tert-Butyl-*N*-(4-chloro-2-[1,2,4]triazolo[4,3-a]pyrimidin-3-yl-phenyl)-benzenesulfonamide



[00627] Step 1: A 5 mL scintillation vial was charged with 2-hydrazinopyrimidine (61 mg, 0.55 mmol), 2-nitro-5-chlorobenzaldehyde (112 mg, 0.60 mmol) and MeOH (500 µL) and heated to 60 °C for 30 minutes. The MeOH was then removed *in vacuo* and the resultant solid was washed with Et_2O. The crude solid (30 mg) was then suspended in CH_2Cl_2 (1 mL) and iodobenzene diacetate (39 mg, 0.12 mmol) was added. The reaction was stirred at room temperature for 30 minutes after which the solvent was removed *in vacuo*. The resultant residue was then dissolved in a 10% solution of saturated NH_4Cl(aq) in EtOH and iron (19 mg, 0.33 mmol) was then added and the reaction was stirred at 80 °C for 4 h. The solvent was then removed *in vacuo* and the product was purified by silica gel chromatography to afford 4-chloro-2-[1,2,4]triazolo[4,3-a]pyrimidin-3-yl-phenylamine as a light yellow oil.

[00628] Step 2: A 4 mL scintillation vial was charged with the above aniline (10 mg, 0.04 mmol), tert-butylphenylsulfonyl chloride (11 mg, 0.05 mmol), and pyridine (300 µL). The mixture was subsequently warmed to 60 °C and stirred overnight. The following day, the reaction mixture was diluted in EtOAc and washed with 1 N HCl (aqueous). The organic layer was then concentrated and the obtained residue was purified by preparative TLC to afford the desired sulfonamide: MS (ES) M+H expected 442.1, found 442.3.

[00629] The compounds in Table 2 were prepared by the indicated general procedure described above. MS (ES) $[M+H]^+$ data was collected and compared to the expected value to confirm the identity of the compound.

[00630] **Table 2 – Compounds prepared by General Procedures and MS Data**

Compound	General Procedure	$[M+H]^+$ expected	$[M+H]^+$ found
1	C	432.14	433.0
2	C	466.12	467.0
3	C	446.15	447.1
4	C	480.14	481.0
5	C	432.14	433.1
6	C	418.12	419.1
7	C	444.14	445.1
8	C	446.15	447.0
9	D	488.16	489.1
10	D	448.13	449.1
11	C	474.19	475.1
12	C	488.16	489.1
13	C	460.17	461.1
14	C	472.17	473.1
15	C	448.13	449.1
16	C	470.13	471.1
17	C	434.12	435.0
18	C	432.14	433.1
19	C	460.17	461.1
20	I	487.18	488.1
21	D	518.18	519.1
22	C	420.14	421.1
23	C	402.15	403.1
24	C	430.18	431.1
25	C	436.11	437.0
26	C	462.15	463.0
27	C	489.16	490.1
28	C	436.11	437.0
29	C	450.13	451.1
30	C	404.11	405.0
31	C	418.12	419.0
32	I	459.15	460.1
33	D	474.15	475.0
34	D	474.15	475.0
35	C	460.13	461.0
36	C	436.11	437.1
37	I	461.17	462.0
38	C	446.15	447.1

39	G	479.16	480.1
40	D	471.11	472.0
41	P	462.15	463.1
42	C	462.15	463.1
43	C	460.17	461.1
44	I	491.16	492.1
45	S	465.14	466.1
46	D	516.20	517.1
47	C	506.16	507.0
48	S	479.16	480.0
49	S	493.17	494.1
50	S	491.16	492.0
51	P	494.16	495.1
52	P	522.15	523.1
53	C	478.12	479.0
54	C	478.12	479.0
55	T	465.10	466.0
56	T	479.12	480.0
57	U	480.14	481.0
58	U	464.11	465.0
59	P	466.12	467.0
60	P	466.12	467.4
61	P	466.12	467.0
62	P	480.14	481.0
63	P	506.16	507.1
64	P	508.13	509.0
65	X	494.16	495.4
66	S	521.17	522.4
67	V	514.09	515.4
68	C	420.10	421.0
69	C	434.12	435.1
70	W	487.18	488.1
71	C	434.16	435.1
72	C	402.15	403.1
73	I	473.17	474.1
74	C	416.17	417.1
75	I	459.15	460.1
76	C	422.10	423.0
77	I	475.19	476.0
78	C	450.13	451.1
79	F	503.12	504.0
80	C	492.14	493.0
81	C	520.17	521.1
82	P	520.17	521.2
83	C	447.15	448.1
84	C	458.15	459.1
85	I	463.12	464.1
86	C	500.13	501.0

87	C	478.16	479.1
88	I	505.17	506.1
89	Z	528.11	529.0
90	C	491.12	492.0
91	C	529.19	530.1
92	H	447.15	448.1
93	J	565.16	566.1
94	J	530.19	531.1
95	C	446.15	447.1
96	D	476.16	477.1
97	D	481.13	482.1
98	G	489.20	490.1
99	I	473.17	474.1
100	C	420.14	421.1
101	C	474.15	475.1
102	D	474.15	475.1
103	E	476.16	477.1
104	C	474.15	475.1
105	C	432.14	433.1
106	I	491.16	492.1
107	P	466.12	467.1
108	C	492.14	493.1
109	I	477.14	478.1
110	C	450.13	451.1
111	D	489.10	490.0
112	I	491.16	492.1
113	I	473.17	474.1
114	I	487.18	488.2
115	P	492.14	493.1
116	P	506.16	507.1
117	F	485.13	486.0
118	I	501.20	502.1
119	I	487.18	488.1
120	C	478.12	479.1
121	S	505.17	506.1
122	S	491.16	492.1
123	R	452.11	453.0
124	C	515.18	516.1
125	C	475.18	476.1
126	C	461.17	462.1
127	I	473.17	474.1
128	BB	423.17	424.4
129	DD	441.18	442.4
130	CC	442.17	443.4
131	I	445.13	446.0
132	S	447.15	448.4
133	AA	456.18	457.1
134	N	461.13	462.1

135	L	465.10	466.0
136	C	466.12	467.4
137	Y	466.12	467.4
138	S	475.18	476.4
139	P	480.14	481.4
140	W	491.16	492.4
141	K	501.20	502.1
142	N	501.16	502.1
143	J	502.16	503.1
144	S	503.18	504.5
145	W	505.17	506.5
146	I	519.19	520.1
147	S	520.18	521.5
148	S	521.17	522.5
149	S	523.18	524.5
150	D	530.21	531.1
151	S	534.20	535.6
152	S	535.18	536.5
153	J	537.13	538.0
154	S	549.20	550.5
155	C	501.20	502.4
156	EE	441.1	442.1
157	C	502.00	502.9
158	C	516.01	516.9
159	C	512.01	512.9
160	C	519.99	520.9
161	T	563.00	563.9

[00631] **Measuring Efficacy of Chemokine Modulators**

[00632] *In Vitro Assays*

[00633] A variety of assays can be used to evaluate the compounds provided herein, including signaling assays, migration assays, ligand binding assays, and other assays of cellular response. Chemokine receptor signaling assays can be used to measure the ability of a compound, such as a potential CCR2 antagonist, to block CCR2 ligand- (e.g. MCP-1)-induced signaling or a potential CCR9 antagonist, to block CCR9 ligand- (e.g. TECK)-induced signaling. A migration assay can be used to measure the ability of a compound of interest, such as a possible chemokine antagonist, to block chemokine-mediated cell migration in vitro. The latter is believed to resemble chemokine-induced cell migration in vivo. A ligand binding assay can be used to measure the ability of a compound, such as a potential CCR2 antagonist, to

block the interaction of MCP-1 with its receptor or a potential CCR9 antagonist, to block the interaction of TECK with its receptor.

[00634] In a suitable assay, a chemokine protein (whether isolated or recombinant) is used which has at least one property, activity, or functional characteristic of a mammalian chemokine protein. The property can be a binding property (to, for example, a ligand or inhibitor), a signaling activity (e.g., activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium ion), cellular response function (e.g., stimulation of chemotaxis or inflammatory mediator release by leukocytes), and the like.

[00635] The assay can be a cell-based assay that utilizes cells stably or transiently transfected with a vector or expression cassette having a nucleic acid sequence that encodes the chemokine receptor. Cell lines naturally expressing the chemokine can also be used. The cells are maintained under conditions appropriate for expression of the receptor and are contacted with a putative 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 (for example, relative to background in the absence of a putative agent, or relative to a known ligand). Optionally, a cellular fraction, such as a membrane fraction, containing the receptor can be used in lieu of whole cells.

[00636] Detection of binding or complex formation can be detected directly or indirectly. For example, the putative agent can be labeled with a suitable label (e.g., fluorescent label, chemiluminescent 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 (e.g., MCP-1 or TECK) as a competitor.

[00637] Binding inhibition assays can be used to evaluate the present compounds. In these assays, the compounds are evaluated as inhibitors of ligand binding using, for example, MCP-1 or TECK. In one embodiment, the CCR2 receptor is contacted with a ligand such as MCP-1 and a measure of ligand binding is made. The receptor is then contacted with a test agent in the

presence of a ligand (e.g., MCP-1) and a second measurement of binding is made. In another embodiment, the CCR9 receptor is contacted with a ligand such as TECK and a measure of ligand binding is made. The receptor is then contacted with a test agent in the presence of a ligand (e.g., TECK) and a second measurement of binding is made. A reduction in the extent of ligand binding is indicative of inhibition of binding by the test agent. The binding inhibition assays can be carried out using whole cells which express the chemokine, or a membrane fraction from cells which express the chemokine.

[00638] The binding of a G protein coupled receptor by, for example, an agonist, can result in a signaling event by the receptor. Accordingly, signaling assays can also be used to evaluate the compounds of the present invention and induction of signaling function by an agent can be monitored using any suitable method. For example, G protein activity, such as hydrolysis of GTP to GDP, or later signaling events triggered by receptor binding can be assayed by known methods (see, for example, PCT/US97/15915; Neote et al., *Cell*, 72:415425 (1993); Van Riper et al., *J. Exp. Med.*, 177:851-856 (1993) and Dahinden et al., *J. Exp. Med.*, 179:751-756 (1994)).

[00639] Chemotaxis assays can also be used to assess receptor function and evaluate the compounds provided herein. These assays are based on the functional migration of cells in vitro or in vivo induced by an agent, and can be used to assess the binding and/or effect on chemotaxis of ligands, inhibitors, or agonists. A variety of chemotaxis assays are known in the art, and any suitable assay can be used to evaluate the compounds of the present invention. Examples of suitable assays include those described in PCT/US97/15915; Springer et al., WO 94/20142; Berman *et al.*, *Immunol. Invest.*, 17:625-677 (1988); and Kavanaugh *et al.*, *J. Immunol.*, 146:4149-4156 (1991)).

[00640] Calcium signaling assays measure calcium concentration over time, preferably before and after receptor binding. These assays can be used to quantify the generation of a receptor-signaling mediator, Ca^{++}, following receptor binding (or absence thereof). These assays are useful in determining the ability of a compound, such as those of the present invention, to generate the receptor signaling mediator by binding to a receptor of

interest. Also, these assays are useful in determining the ability of a compound, such as those of the present invention, to inhibit generation of the receptor signaling mediator by interfering with binding between a receptor of interest and a ligand.

[00641] In calcium signaling assays used to determine the ability of a compound to interfere with binding between a chemokine receptor and a known chemokine ligand, chemokine receptor-expressing cells (CCR2-expressing cells such as THP-1 cells or CCR9-expressing cells such as T cell line MOLT-4 cells) are first incubated with a compound of interest, such as a potential chemokine antagonist, at increasing concentrations. The cell number can be from 10^5 to 5 x 10^5 cells per well in a 96-well microtiter plate. The concentration of the compound being tested may range from 0 to 100 μM. After a period of incubation (which can range from 5 to 60 minutes), the treated cells are placed in a Fluorometric Imaging Plate Reader (FLIPR®) (available from Molecular Devices Corp., Sunnyvale, CA) according to the manufacturer's instruction. The FLIPR® system is well known to those skilled in the art as a standard method of performing assays. The cells are then stimulated with an appropriate amount of the chemokine ligand (MCP-1 for CCR2 or TECK for CCR9) at 5-100 nM final concentration, and the signal of intracellular calcium increase (also called calcium flux) is recorded. The efficacy of a compound as an inhibitor of binding between the chemokine and the ligand can be calculated as an IC_{50} (the concentration needed to cause 50% inhibition in signaling) or IC_{90} (at 90% inhibition).

[00642] In vitro cell migration assays can be performed (but are not limited to this format) using the 96-well microchamber (called ChemoTX™). The ChemoTX™ system is well known to those skilled in the art as a type of chemotactic/cell migration instrument. In this assay, CCR2-expressing cells (such as THP-1) or CCR9-expressing cells (such as MOLT-4) are first incubated with a compound of interest, such as a possible CCR2 or CCR9 antagonist, respectively, at increasing concentrations. Typically, fifty thousand cells per well are used, but the amount can range from 10^3-10^6 cells per well. The chemokine ligand (for example, CCR2 ligand MCP-1, typically at 0.1 nM (but can range from 5-100 nM); or CCR9 ligand TECK, typically at

50 nM (but can range from 5-100 nM)), is placed at the lower chamber and the migration apparatus is assembled. Twenty microliters of test compound-treated cells are then placed onto the membrane. Migration is allowed to take place at 37 °C for a period of time, typically 1.5 hours for CCR2 or 2.5 hours for CCR9. At the end of the incubation, the number of cells that migrated across the membrane into the lower chamber is then quantified. The efficacy of a compound as an inhibitor of chemokine-mediated cell migration is calculated as an IC_{50} (the concentration needed to reduce cell migration by 50%) or IC_{90} (for 90% inhibition).

[00643] In vivo efficacy models for human IBD

[00644] T cell infiltration into the small intestine and colon have been linked to the pathogenesis of human inflammatory bowel diseases which include Coeliac disease, Crohn's disease and ulcerative colitis. Blocking trafficking of relevant T cell populations to the intestine is believed to be an effective approach to treat human IBD. CCR9 is expressed on gut-homing T cells in peripheral blood, elevated in patients with small bowel inflammation such as Crohn's disease and Coeliac disease. CCR9 ligand TECK is expressed in the small intestine. It is thus believed that this ligand-receptor pair plays a role in IBD development by mediating migration of T cells to the intestine. Several animal models exist and can be used for evaluating compounds of interest, such as potential CCR9 antagonists, for an ability to affect such T cell migration and/or condition or disease, which might allow efficacy predictions of antagonists in humans.

[00645] *Animal models with pathology similar to human ulcerative colitis*

[00646] A murine model described by Panwala and coworkers (Panwala, et al., *J Immunol.*, 161(10):5733-44 (1998)) involves genetic deletion of the murine multi-drug resistant gene (MDR). MDR knockout mice (MDR-/-) are susceptible to developing a severe, spontaneous intestinal inflammation when maintained under specific pathogen-free facility conditions. The intestinal inflammation seen in MDR-/- mice has a pathology similar to that of human inflammatory bowel disease (IBD) and is defined by Th1 type T cells infiltration into the lamina propria of the large intestine.

[00647] Another murine model was described by Davidson *et al., J. Exp. Med.*, 184(1):241-51(1986). In this model, the murine IL-10 gene was deleted and mice rendered deficient in the production of interleukin 10 (IL-10-/-). These mice develop a chronic inflammatory bowel disease (IBD) that predominates in the colon and shares histopathological features with human IBD.

[00648] Another murine model for IBD has been described by *Powrie et al., Int Immunol.*, 5(11):1461-71 (1993), in which a subset of CD4+ T cells (called CD45RB(high)) from immunocompetent mice are purified and adoptively transferred into immunodeficient mice (such as C.B-17 scid mice). The animal restored with the CD45RBhighCD4+ T cell population developed a lethal wasting disease with severe mononuclear cell infiltrates in the colon, pathologically similar with human IBD.

[00649] *Murine models with pathology similar to human Crohn's disease*

[00650] The TNF ARE(-/-) model. The role of TNF in Crohn's disease in human has been demonstrated more recently by success of treatment using anti-TNF alpha antibody by Targan *et al., N. Engl. J. Med.*, 337(15):1029-35 (1997). Mice with aberrant production of TNF-alpha due to genetic alteration in the TNF gene (ARE-/-) develop Crohn's-like inflammatory bowel diseases (*see* Kontoyiannis *et al., Immunity*, 10(3):387-98 (1999)).

[00651] The SAMP/yit model. This is model described by Kosiewicz *et al., J. Clin. Invest.*, 107(6):695-702 (2001). The mouse strain, SAMP/Yit, spontaneously develops a chronic inflammation localized to the terminal ileum. The resulting ileitis is characterized by massive infiltration of activated T lymphocytes into the lamina propria, and bears a remarkable resemblance to human Crohn's disease.

[00652] **Examples of in vitro assays**

[00653] *Reagents*

[00654] THP-1 cells and MOLT-4 cells were obtained from the American Type Culture Collection (Manassas, VA) and cultured in RPMI tissue culture medium supplemented with 10% fetal calf serum (FCS) in a humidified 5% CO_2 incubator at 37 °C. Recombinant human chemokine proteins MCP-1 and

TECK were obtained from R&D Systems (Minneapolis, MN). ^{125}I-labeled MCP-1 protein was obtained from Amersham (Piscataway, NJ). ChemoTX® chemotaxis microchambers were purchased from Neuro Probe (Gaithersburg, MD). CyQUANT® cell proliferation kits were purchased from Molecular Probes (Eugene, Oregon). Calcium indicator dye Fluo-4 AM was purchased from Molecular Devices (Mountain View, CA).

[00655] *Conventional migration assay*

[00656] Conventional migration assay was used to determine the efficacy of potential receptor antagonists in blocking migration mediated through chemokines (such as CCR2 or CCR9). This assay was routinely performed using the ChemoTX® microchamber system with a 5-μm pore-sized polycarbonate membrane. To begin such an assay, chemokine expressing cells (such as THP-1 cells for CCR2 assay or MOLT-4 cells for CCR9 assay) were harvested by centrifugation of cell suspension at 1000 RPM on a GS-6R Beckman centrifuge. The cell pellet was resuspended in chemotaxis buffer (HBSS with 0.1% BSA) at $10x10^6$ cells/mL for CCR2 assay ($5 x10^6$ cells/mL for CCR9 assay). Test compounds at desired concentrations were prepared from 10 mM stock solutions by serial dilutions in chemotaxis buffer. An equal volume of cells and compounds were mixed and incubated at room temperature for 15 minutes. Afterwards, 20 μL of the mixture was transferred onto the porous membrane of a migration microchamber, with 29 μL of chemokine ligand (0.1 nM chemokine MCP-1 protein for CCR2 assay or 50 nm chemokine TECK protein for CCR9 assay) placed at the lower chamber. Following an incubation at 37 °C (90-minute for CCR2;150-minute for CCR9), during which cells migrated against the chemokine gradient, the assay was terminated by removing the cell drops from atop the filter. To quantify cells migrated across the membrane, 5 μL of 7X CyQUANT® solution was added to each well in the lower chamber, and the fluorescence signal measured on a Spectrafluor Plus fluorescence plate reader (TECAN, Durham, NC). The degree of inhibition was determined by comparing migration signals between compound-treated and untreated cells. IC_{50} calculation was further

performed by non-linear squares regression analysis using Graphpad Prism (Graphpad Software, San Diego, CA).

[00657] *BiRAM Assay*

[00658] The primary screen to identify chemokine antagonists was carried out using BiRAM assay (WO 02101350, US2004023286), which detects potential hits by their ability to activate cell migration under inhibitory chemokine concentration. To begin such an assay, chemokine expressing cells (such as THP-1 cells for CCR2 assay or MOLT-4 cells for CCR9 assay) were harvested by centrifugation of cell suspension at 1000 RPM on a GS-6R Beckman centrifuge. The cell pellet was resuspended in chemotaxis buffer (HBSS/0.1% BSA) at 10 x 10^6 cells/mL for CCR2 assay (5 x 10^6 cells/mL for CCR9 assay). Twenty-five microliters of cells was mixed with an equal volume of a test compound diluted to 20 μM in the same buffer. Twenty microliters of the mixture was transferred onto the filter in the upper chemotaxis chamber, with 29 μL of chemokine solution containing chemokine ligand (100 nM chemokine MCP-1 and MIP-1α protein for CCR2 assay or 500 nm chemokine TECK protein for CCR9 assay) was placed in the lower chamber. Following an incubation at 37 °C (90-minute for CCR2; 150-minute for CCR9), the assay was terminated by removing the cell drops from atop the filter. To quantify cells migrated across the membrane, 5 μL of 7X CyQUANT® solution was added to each well in the lower chamber, and the fluorescence signal measured on a Spectrafluor Plus fluorescence plate reader (TECAN, Durham, NC).

[00659] For selection of potential hits, the level of migration activation was calculated as a RAM index-the ratio between the signal of a particular well and the median signal of the whole plate. Compounds with a RAM index of greater than 1.5 for CCR2 assay (1.8 for CCR9 assay) were regarded as RAM positive, and were selected for IC_{50} determinations in conventional functional assays.

[00660] *Calcium flux assay*

[00661] Calcium flux assay measures an increase in intracellular calcium following ligand-induced receptor activation. In the screen of chemokine antagonists, it was used as a secondary assay carried out on a FLIPR® machine (Molecular Devices, Mountain View, CA). To begin an assay, chemokine expressing cells (such as THP-1 cells for CCR2 assay or MOLT-4 cells for CCR9 assay) were harvested by centrifugation of cell suspension, and resuspended to 1.5 x 10^6 cells/mL in HBSS (with 1% fetal calf serum). Cells were then labeled with a calcium indicator dye Fluo-4 AM for 45 minutes at 37 °C with gentle shaking. Following incubation, cells were pelletted, washed once with HBSS and resuspended in the same buffer at a density of 1.6 x 10^6 cells/mL. One hundred microliters of labeled cells were mixed with 10 µL of test compound at the appropriate concentrations on an assay plate. Chemokine protein (MCP-1 at a final concentration of 0.1 nM for CCR2 assay or TECK at a final concentration of 25 nM for CCR9 assay) to activate the receptor. The degree of inhibition was determined by comparing calcium signals between compound-treated and untreated cells. IC_{50} calculations were further performed by non-linear squares regression analysis using Graphpad Prism (Graphpad Software, San Diego, CA).

[00662] **Ligand binding assay**

[00663] Ligand binding assay was used to determine the ability of potential CCR2 antagonists to block the interaction between CCR2 and its ligand MCP-1. CCR2 expressing THP-1 cells were centrifuged and resuspended in assay buffer (20 mM HEPES pH 7.1, 140 mM NaCl, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and with 0.2% bovine serum albumin) to a concentration of 2.2 x 10^5 cells/mL. Binding assays were set up as follows. First, 0.09 mL of cells (1 x 10^5 THP-1 cells/well) was added to the assay plates containing the compounds, giving a final concentration of ~2-10 µM each compound for screening (or part of a dose response for compound IC_{50} determinations). Then 0.09 mL of ^{125}I labeled MCP-1 (obtained from Amersham; Piscataway, NJ) diluted in assay buffer to a final concentration of ~50 pM, yielding ~30,000 cpm per well, was added, the plates sealed and incubated for approximately 3 hours at 4 °C on a shaker platform. Reactions were aspirated onto GF/B

glass filters pre-soaked in 0.3% polyethyleneimine (PEI) solution, on a vacuum cell harvester (Packard Instruments; Meriden, CT). Scintillation fluid (50 µL; Microscint 20, Packard Instruments) was added to each well, the plates were sealed and radioactivity measured in a Top Count scintillation counter (Packard Instruments). Control wells containing either diluent only (for total counts) or excess MCP-1 (1 µg/mL, for non-specific binding) were used to calculate the percent of total inhibition for compound. The computer program Prism from GraphPad, Inc. (San Diego, Ca) was used to calculate IC_{50} values. IC_{50} values are those concentrations required to reduce the binding of labeled MCP-1 to the receptor by 50%.

[00664] Discovery of chemokine antagonists

[00665] The discovery of chemokine antagonists was carried out in two steps: First, BiRAM assay was used to screen a compound library in a high-throughput manner. The assay detected compounds by their ability to cause a positive migration signal under BiRAM condition. Secondly, BiRAM positive compounds were tested to determine their IC_{50} values using the conventional migration, calcium flux assays and ligand binding assays.

[00666] For instance, in a screen of approximately 100,000 compounds, 2000 individual wells representing approximately 2% of total compounds showed a desired RAM index (greater than 1.5 for CCR2; greater than 1.8 for CCR9). These compounds were cheery-picked and retested in duplicate wells by RAM assay. A total of 156 compounds were confirmed BiRAM positives.

[00667] Since a BiRAM positive signal indicates only the presence of a receptor antagonist and not how strongly it blocks receptor functions, the BiRAM positive compounds were further tested for potency in conventional migration, calcium flux and ligand binding assays. IC_{50} determinations on this subset discovered several compounds with an IC_{50} less than 1 µM and that did not inhibit other chemokine receptors examined at significant levels.

[00668] In Vivo Efficacy

[00669] A 17-day study of type II collagen-induced arthritis is conducted to evaluate the effects of a modulator on arthritis-induced clinical ankle

swelling. Rat collagen-induced arthritis is an experimental model of polyarthritis that has been widely used for preclinical testing of numerous anti-arthritic agents (see Trentham et al., *J. Exp. Med.*, **146(3):**857-868 (1977), Bendele et al., *Toxicologic Pathol.*, **27:**134-142 (1999), Bendele et al., *Arthritis Rheum.*, **42:**498-506 (1999)). The hallmarks of this model are reliable onset and progression of robust, easily measurable polyarticular inflammation, marked cartilage destruction in association with pannus formation and mild to moderate bone resorption and periosteal bone proliferation.

[00670] Female Lewis rats (approximately 0.2 kilograms) are anesthetized with isoflurane and injected with Freund's Incomplete Adjuvant containing 2 mg/mL bovine type II collagen at the base of the tail and two sites on the back on days 0 and 6 of this 17-day study. The test modulator is dosed daily by sub-cutaneous injection from day 9 to day 17 at a dose of 100 mg/kg and a volume of 1 mL/kg in the following vehicle (24.5 % Cremaphore EL, 24.5% common oil, 1% Benzylalcohol and 50% Distilled water). Caliper measurements of the ankle joint diameter are taken daily, and reducing joint swelling is taken as a measure of efficacy.

[00671] The MDR1a-knockout mice, which lack the P-glycoprotein gene, spontaneously develop colitis under specific pathogen-free condition. The pathology in these animals has been characterized as Th1-type T cell-mediated inflammation similar to ulcerative colitis in humans. Disease normally begins to develop at around 8-10 weeks after birth. However the ages at which disease emerges and the ultimate penetrance level often vary considerably among different animal facilities.

[00672] In a study using the MDR1a-knockout mice, a CCR9 antagonist is evaluated by prophylactic administration for its ability to delay disease onset. Female mice (n=34) are dosed with 50 mg/kg twice a day by subcutaneous injections for 14 consecutive weeks starting at age 10 weeks. The study is evaluated for IBD-associated growth retardation.

[00673] *Evaluation of a test modulator in a rat model of thioglycollate-induced peritoneal inflammation*

[00674] A 2-day study of thioglycollate-induced inflammation is conducted to evaluate the effects of the test modulator. The hallmarks of this model are reliable onset and progression of robust, easily measurable inflammatory cellular infiltrate. For the induction of inflammatory peritonitis in Lewis rats, Brewer-Thioglycollate (1.0 mL, 4 % solution in distilled water) is injected intra peritoneal (i.p.). Before this injection, the treatment group received test modulator or vehicle and the control group received the same volume of PBS as i.p. injection. After 2 days, a peritoneal lavage ias performed with ice-cold PBS containing 1 mM EDTA. The recovered cells are counted with a cell counter (Coulter Counter; Coulter Pharmaceutical, Palo Alto, CA) and monocytes/macrophages were identified by flow cytometry using light-scatter properties.

[00675] *Evaluation of a test modulator in a mouse model of bacterial infection*

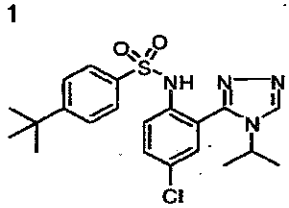
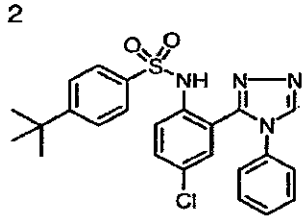
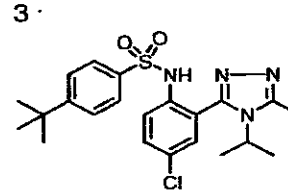
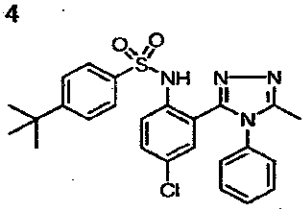
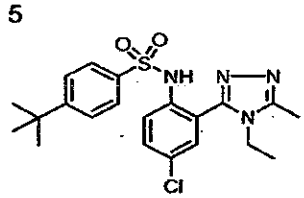
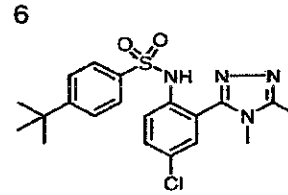
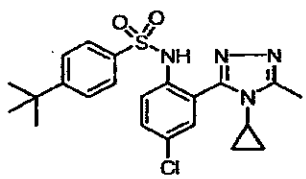
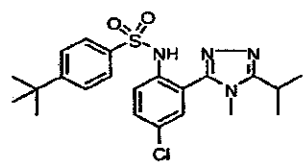
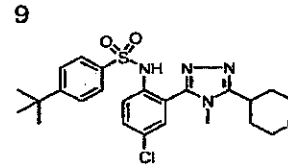
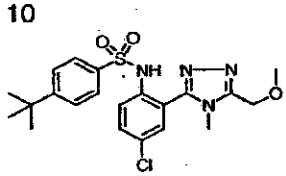
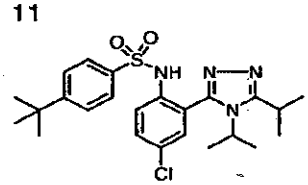
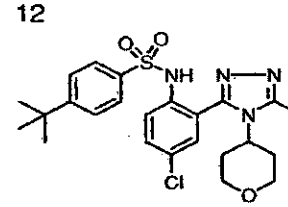
[00676] A 1-day study of streptococcus *pneumoniae* infection is conducted to evaluate the effects of the test modulator. The model measures bacterial infection and spread in an animal following pulmonary infection with live bacterial cultures, measured by inflammatory cellular infiltrate, and assessment of bacterial burden. C57/B6 mice are inoculated intra nasally with LD50 400 CFU at day 0. Groups are either test modulator or vehicle control treated 1 day prior to bacterial inoculation and twice daily throughout the study. Bacterial burden is measured at 24 hours by plating serial dilutions of homogenized lung tissue on agar plates and counting colonies.

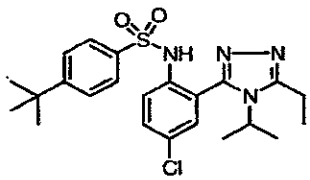
[00677] Pharmacologics to be used in conjunction with CCR2 compounds

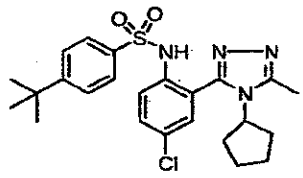
[00678] Pharmacological agents that can be used in conjunction with the CCR2 antagonists of the current invention include those used for the treatments of atherosclerosis, restenosis, multiple sclerosis, pulmonary fibrosis, inflammatory bowel disease, rheumatoid arthritis, graft-versus-host disease, renal fibrosis, psoriasis, transplantation rejection, obesity, diabetes, hypercholesterolemia and cancer.

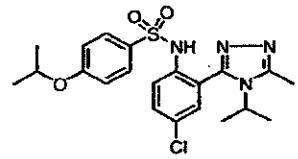
[00679] In the tables below, structures and activity are provided for representative compounds described herein. Activity is provided as follows for either or both of the chemotaxis assay and/or calcium mobilization assays, described above.

[00680] **Table 3: Compounds with CCR9 activity in one of the chemotaxis, binding or calcium mobilization assays, with IC50 < 1000 nM**

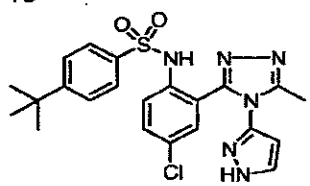
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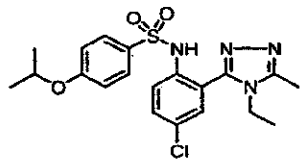




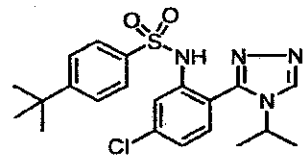
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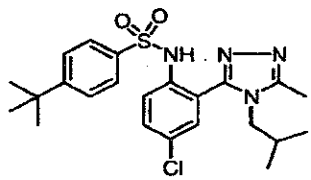
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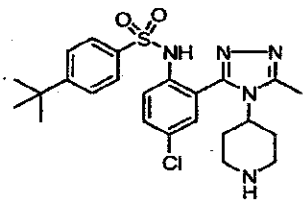
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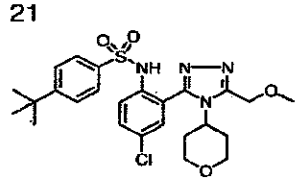
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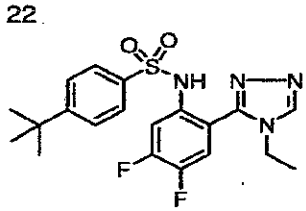
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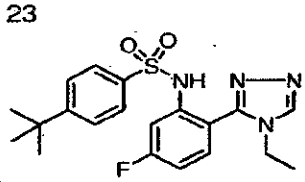
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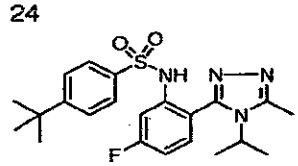
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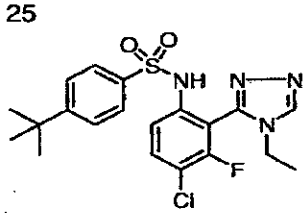
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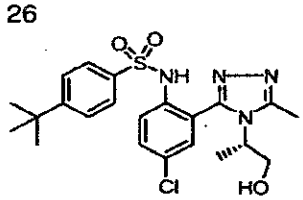
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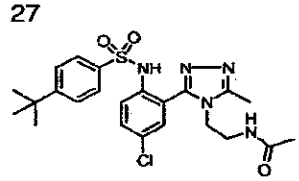
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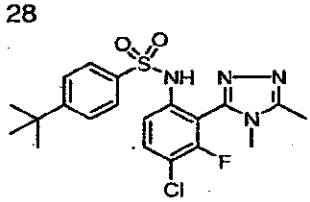
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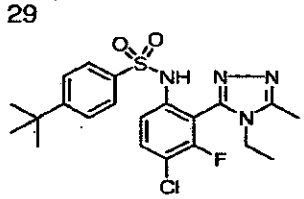
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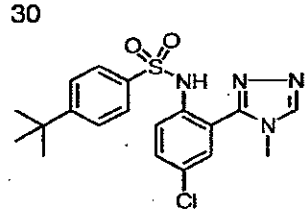
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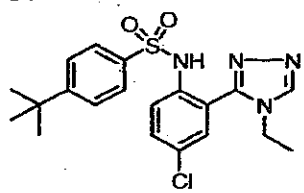
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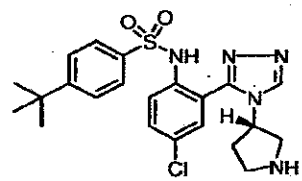
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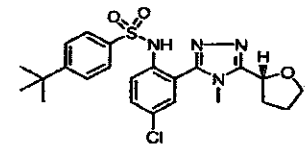
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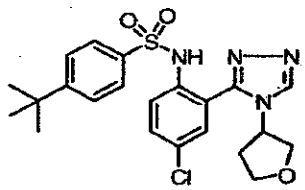
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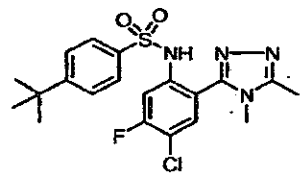
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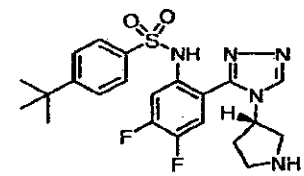
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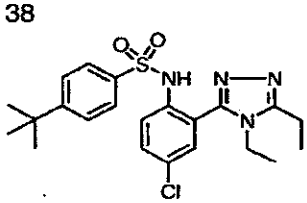
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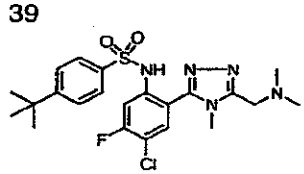
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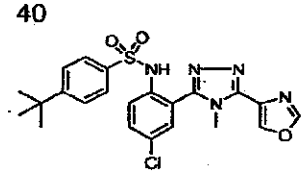
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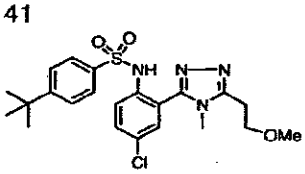
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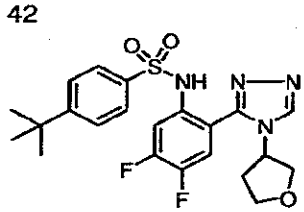
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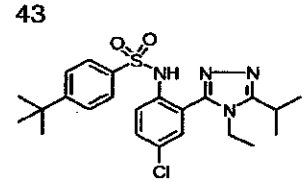
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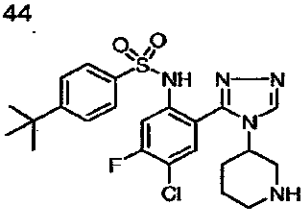
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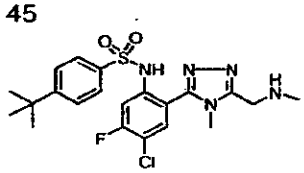
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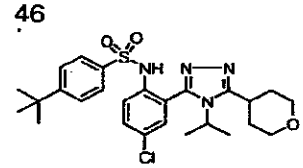
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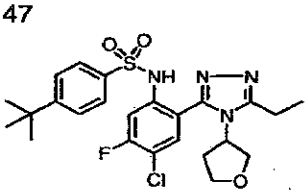
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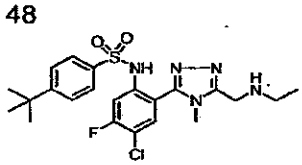
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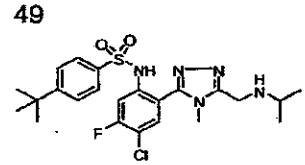
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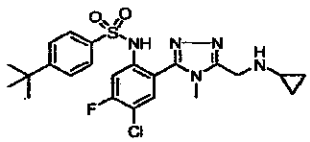
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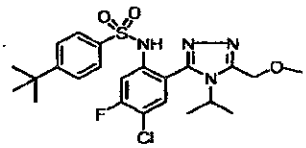
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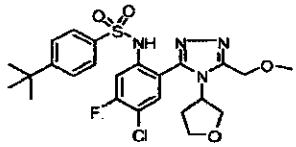
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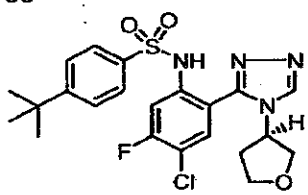
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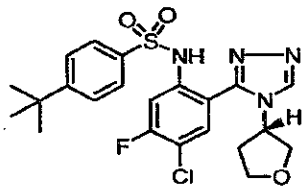
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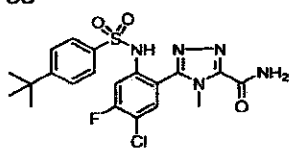
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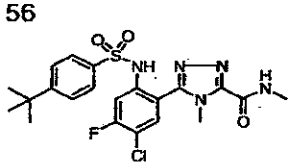
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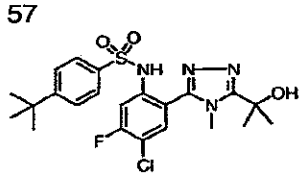
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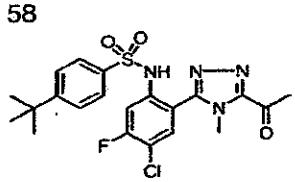
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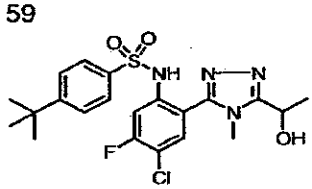
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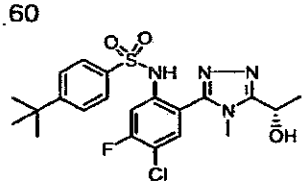
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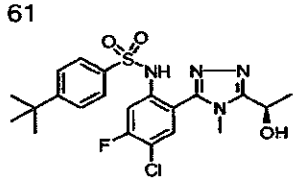
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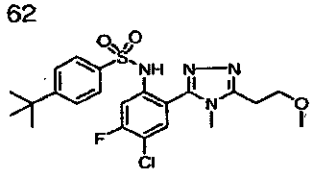
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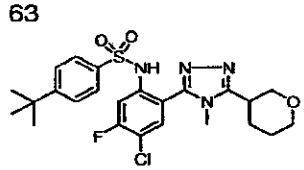
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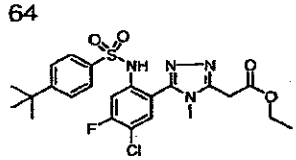
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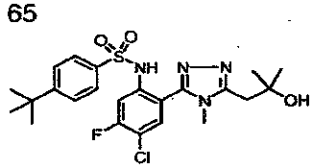
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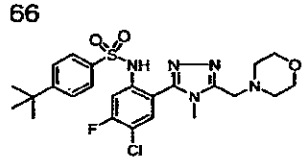
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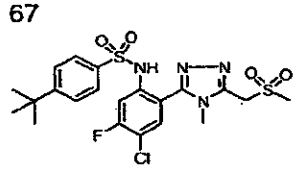
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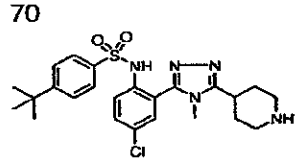
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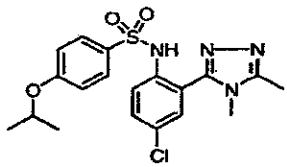


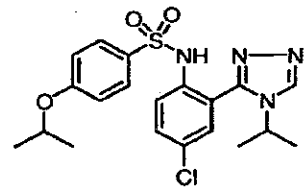
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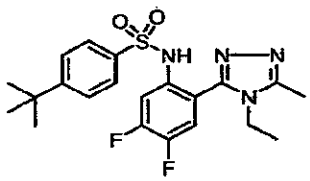
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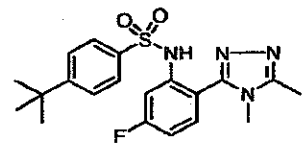




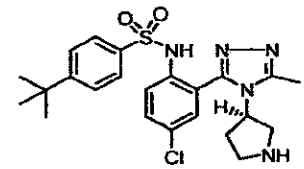
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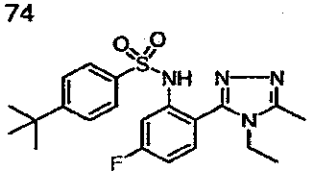
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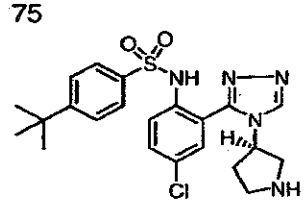
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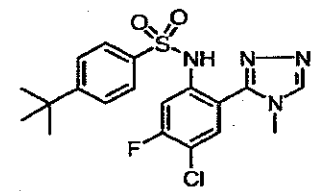
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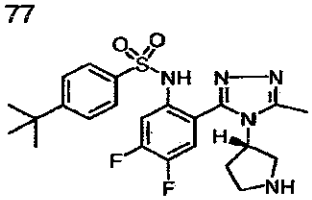
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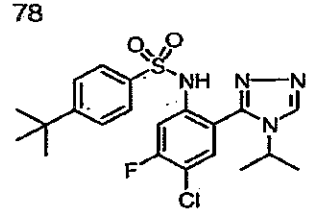
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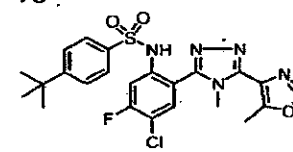
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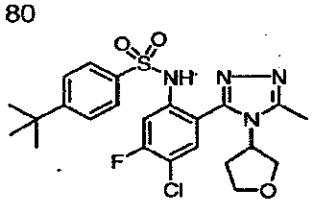
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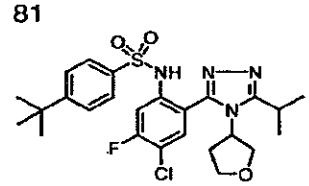
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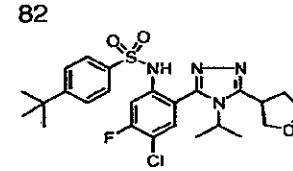
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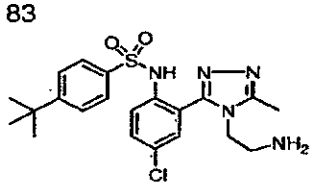
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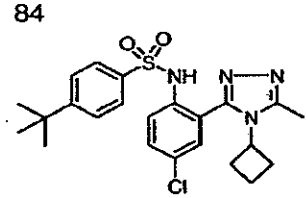
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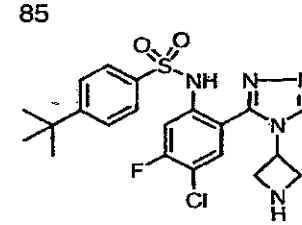
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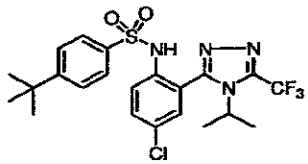
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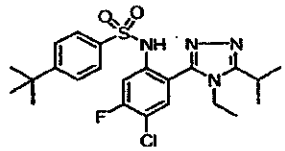
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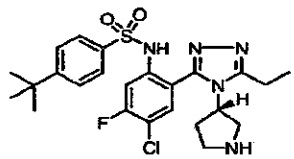
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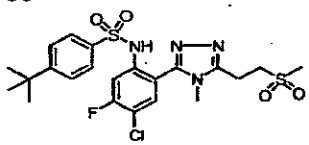
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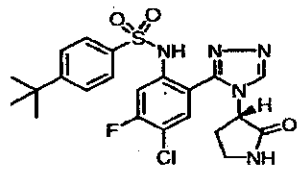
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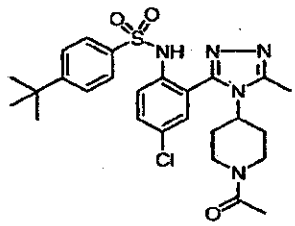
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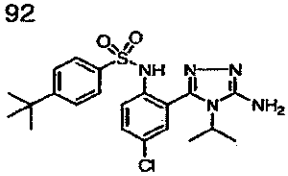
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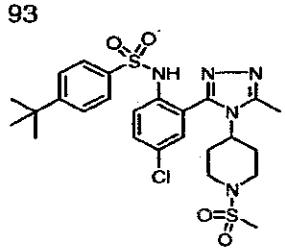
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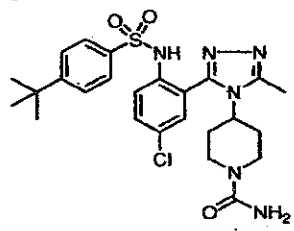
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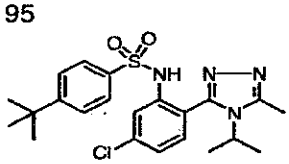
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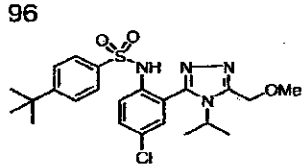
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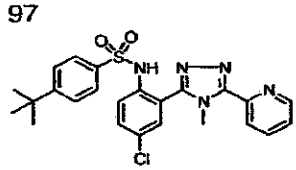
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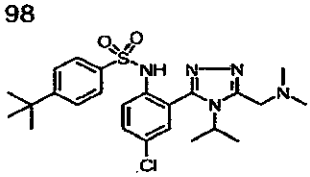
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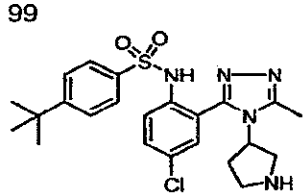
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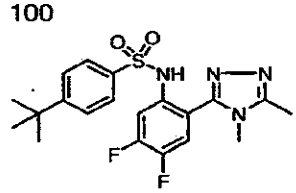
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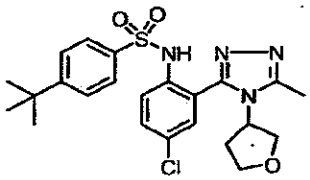
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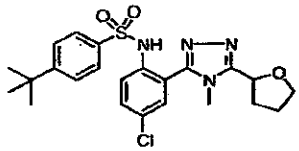
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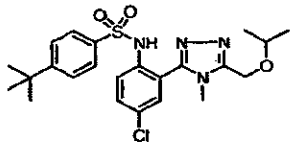
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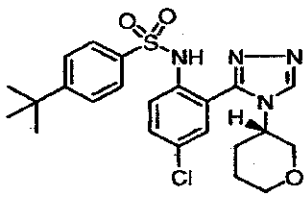
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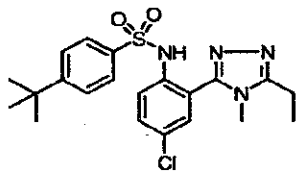
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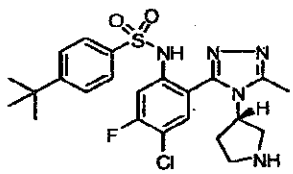
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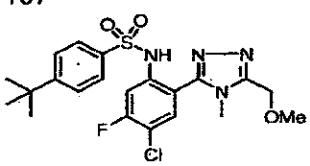
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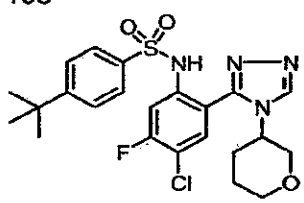
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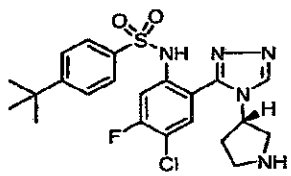
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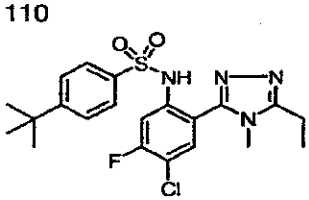
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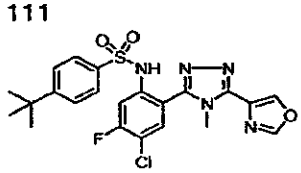
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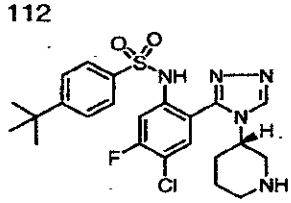
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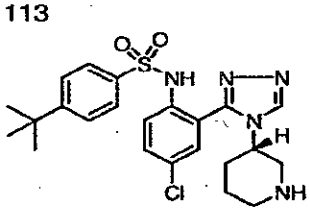
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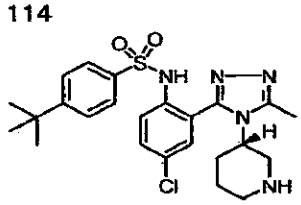
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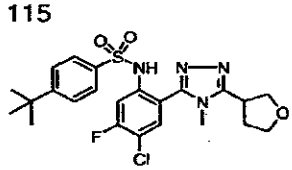
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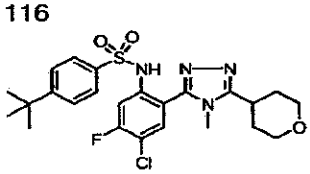
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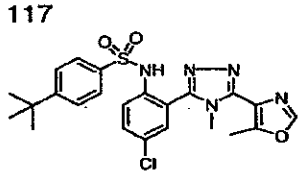
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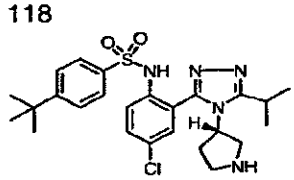
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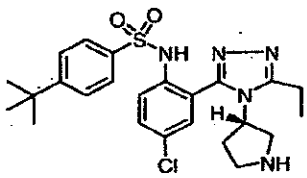
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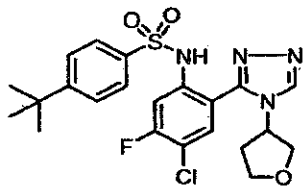


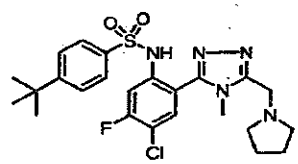
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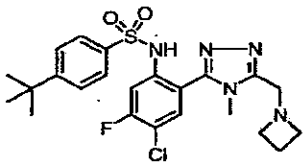
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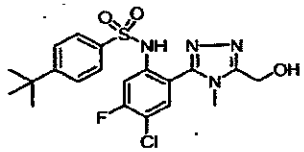




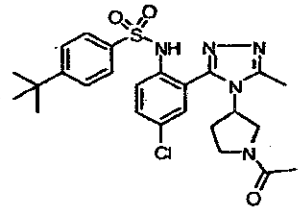
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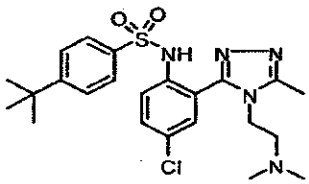
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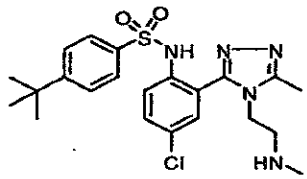
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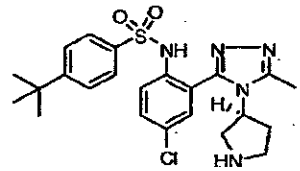
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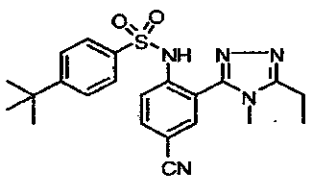
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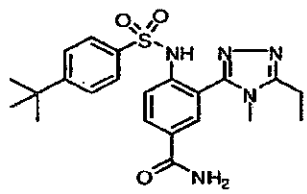
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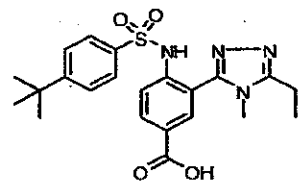
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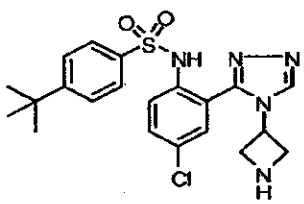
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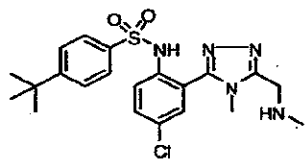
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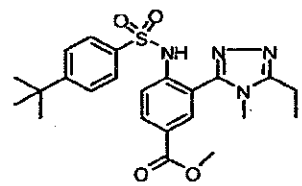
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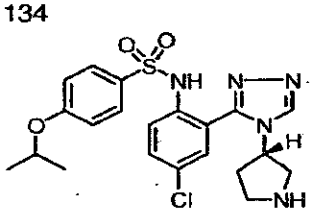
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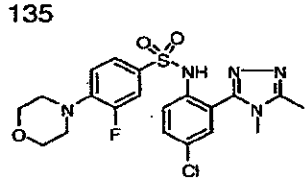
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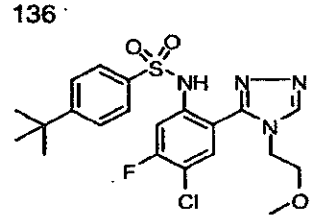
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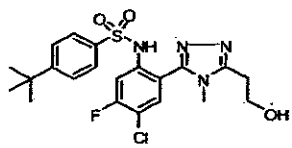
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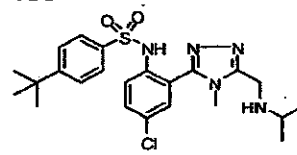
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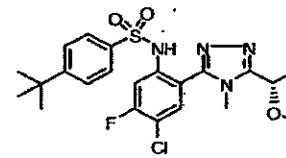
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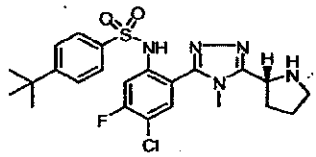
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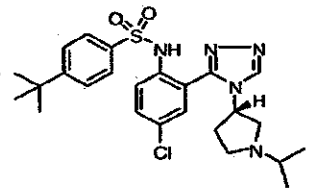
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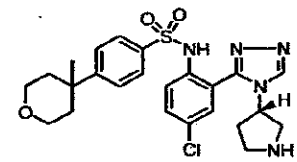
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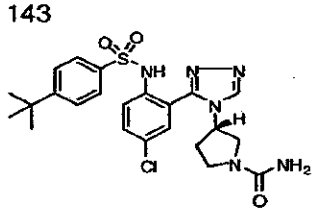
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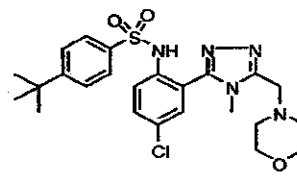
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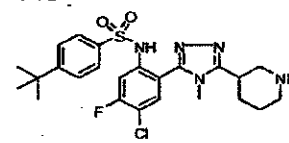
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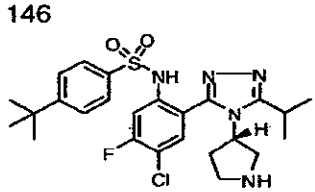
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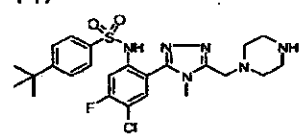
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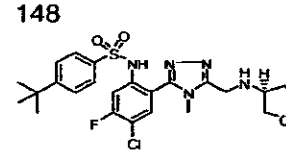
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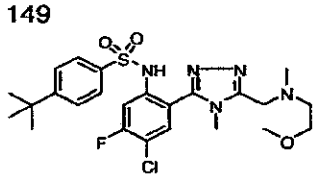
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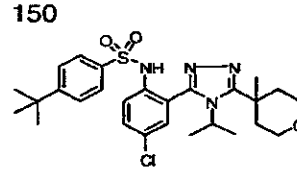
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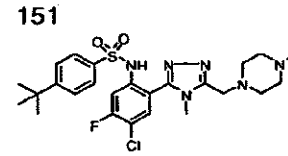
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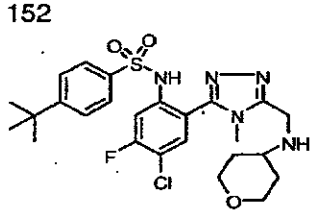
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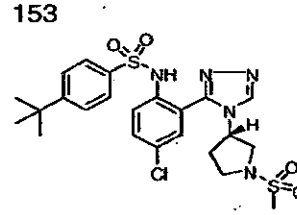
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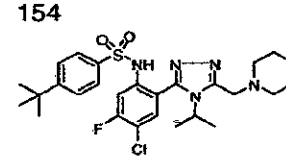
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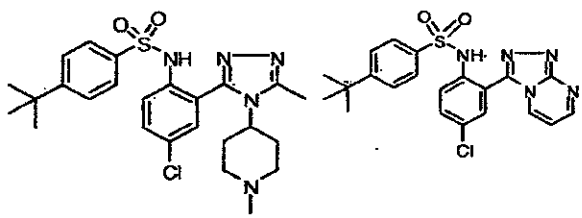


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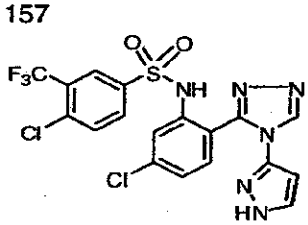
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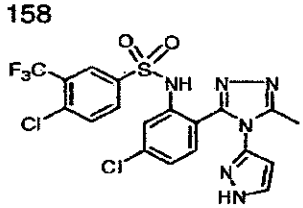


[00681] Table 4: Compounds with CCR2 activity in one of the chemotaxis, binding or calcium mobilization assays, with IC50 < 1000 nM

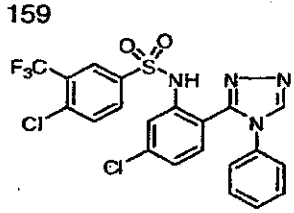
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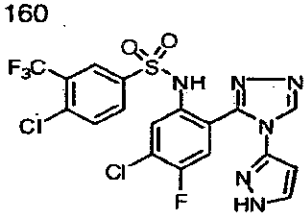
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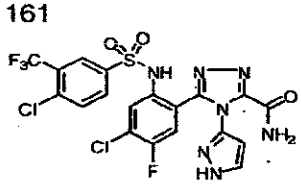
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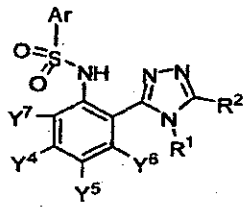
161



[00682] It is therefore intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of this invention.

Claims

1. A compound of the formula (I), or a salt thereof:



(I)

where

Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl;

Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^5C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

R^{15} and R^{16}, R^{16} and R^{17} or R^{15} and R^{17} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

R^1 is selected from the group consisting of $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or

unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^2 is selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, $-NR^7C(O)NR^8R^9$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3-to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3-to 10-membered heterocyclyl;

R^7 and R^8, R^8 and R^9 or R^7 and R^9 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring; and

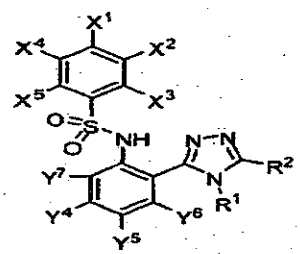
where R^1 and R^2 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

wherein the substituents for substituted alkyl, substituted alkenyl, and substituted alkynyl are selected from halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R", oxo (=O or -O-), -OR', -OC(O)R', -OC(O)NR'R" $-NO_2$, -NR'C(O)R", -NR'"C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R'"$, -NR'"S(O)NR'R", $-NR'"S(O)_2NR'R"$, -SR',-S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR'", -SiR'R"R'", $-N_3$, unsubstituted C_{6-10} aryl, unsubstituted 5- to 10-membered heteroaryl, and unsubstituted 3- to 10-membered heterocyclyl; and

the substituents for substituted aryl, substituted heteroaryl and substituted heterocyclyl are selected from halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R", oxo (=O or -O-), -OR', -OC(O)R', -OC(O)NR'R", $-NO_2$, -NR'C(O)R", -NR'"C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R"$, -NR'"S(O)NR'R", $NR'"S(O)_2NR'R"$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR'", -SiR'R"R'", $-N_3$, unsubstituted C_{1-8} alkyl, unsubstituted C_{2-8} alkenyl, unsubstituted

C_{2-8} alkynyl, unsubstituted C_{6-10} aryl, unsubstituted 5- to 10-membered heteroaryl, and unsubstituted 3- to 10-membered heterocyclyl;
wherein R', R" and R"' each independently is selected from hydrogen, unsubstituted C_{1-8} alkyl, unsubstituted C_{2-8} alkenyl, unsubstituted C_{2-8} alkynyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted heterocyclyl, unsubstituted arylalkyl and unsubstituted aryloxyalkyl,
wherein substituted or unsubstituted C_{1-8} alkyl may be linear, cyclic, or branched or a combination thereof.

2. The compound of claim 1, or a salt thereof, of the formula (II):



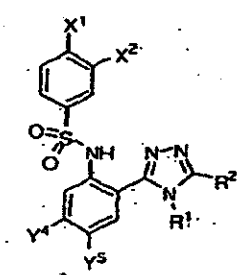
(II)

where
X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;
R^{18}, R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-}

$_{10}$ aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and R^{18} and R^{19}, R^{19} and R^{20} or R^{18} and R^{20} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

3. The compound of claim 2, or a salt-thereof, where
X^1 is selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3-to 10-membered heterocyclyl;
Y^7 is hydrogen;
Y^4, Y^5, and Y^6 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$;
R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3-to 10-membered heterocyclyl, substituted or unsubstituted, C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and
R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, unsubstituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

4. The compound of claim 2, or a salt thereof, of the formula (III):



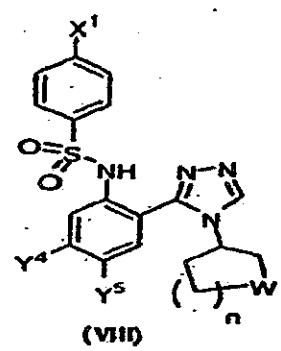
(III)

where at least one of X^1 and X^2 is other than hydrogen and at least one of Y^4 and Y^5 is other than hydrogen.

5. The compound of claim 4, or a salt thereof, of the formula (III): where X^2 is hydrogen or halogen; Y^4 is hydrogen, halogen or -CN; and X^1 and Y^5 are other than hydrogen.

6. The compound of claim 5, or a salt thereof, where
X1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl; $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl;
Y^5 is selected from the group consisting of halogen, -CN, $-CO_2R^{15}$, and $-C(O)NR^{15}R^{16}$;
R^1 is selected from the group consisting of substituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and
R^2 is hydrogen.

7. The compound of claim 6, or a salt thereof, of the formula (VIII)



(VIII)

where W is NH or O; and n is 0, 1, or 2.

8. The compound of claim 4, or a salt thereof, where

X^1 is halogen;

X^2 is halogen or $-CF_3$;

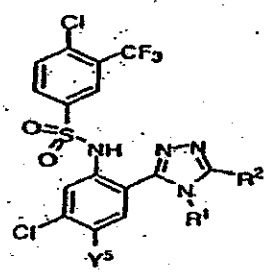
Y^4 is halogen;

Y^5 is hydrogen or halogen;

R^1 is aryl or heteroaryl; and

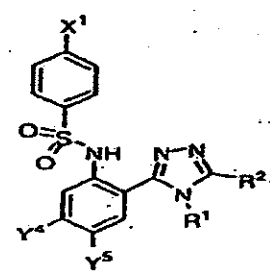
R^2 is hydrogen or substituted or unsubstituted C_{1-8} alkyl.

9. The compound of claim 8, or a salt thereof, of the formula (V):



(V)

10. The compound of claim 2, or a salt thereof, of the formula (IV):



(IV)

where Y^4 is hydrogen or fluoro; and X^1 and Y^5 are other than hydrogen.

11. The compound of claim 10, or a salt thereof, where

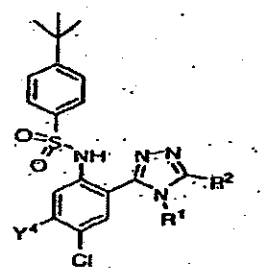
X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

Y^5 is selected from the group consisting of halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$;

R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted, 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and

R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocycyclyl substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

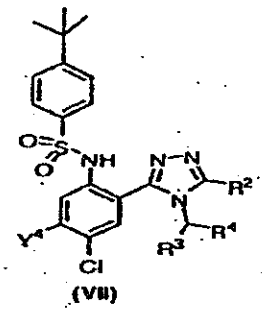
12. The compound of claim 11, or a salt thereof, of the formula (VI):



(VI)

where Y^4 is hydrogen or halogen.

13. The compound of claim 12, or a salt thereof, of the formula (VII):



(VII)

where

Y^4 is hydrogen or halogen; and

R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4 -10 member heterocyclic. 5-10 member heteroaryl ring or 6-10 membered aryl ring.

14. The compound of claim 13, or salt thereof, where R^2 is hydrogen.

15. The compound of claim 1, selected from the group consisting of
4-tert-butyl-N-(4-chloro-2-(4,5-diisopropyl-4H-1.2.4-triazol-3-yl)phenyl)benzenesulfonamide;
4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;
4-tert-butyl-N-(4-chloro-2-(4-cyclopentyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;
4-tert-butyl-N-(4-chloro-2-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;
4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;
4-tert-butyl-N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2.4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4'-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

N-(2-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)ethyl)acetamide;

(R)- 4,-tert- butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4,5-difluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(1-hydroxypropan-2-yl)-S-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(1,5-difluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4,5-diethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1-,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)-3- -fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-memthyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide.

4-tert-butyl-N-(4-chloro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-chloro-2-(4-isopropopyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-fluoro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

ethyl 2-(5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)acetate;

5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazole-3-carboxamide:

5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-N,4-dimethyl-4H-1,2,4-triazole-3-carboxamide;

(R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-tiazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert- butyl-N-(4-chloro-2-(5-((cyclopropylamino)methyl)-4-methyl-4H-1-2-4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((ethylamino)methyl-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4- tert- butyl-N-(4- chloro- 5- fluoro- 2-(4-(tetrahydro-2H-pyran-3- yl)-4H-1,2,4-triazol- 3- yl) phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamido;

4-tert-butyl-N-4-chloro-5-fluoro-2-(4-methyl-5-(methylsulfonylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4- tert- butyl- N-(4-chloro- 5- fluoro- 2-(4-methyl-5-(tetrahydro-2H-pyran-3- yl)-4H-1,2,4- triazol- 3- yl)phenyl)benzenesulfonamide;

4- tert- butyl- N-(4-chloro- 5- fluoro- 2-(4-methyl-5-(tetrahydro-2H-pyran-4- yl)-4H-1,2,4- triazol- 3- yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hyoroxy-2-methylpropyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxypropan)-2-yl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzene-sulfonamide;

4- tert- butyl- N-(4- chloro- 5- fluoro- 2-(5-(2- methoxyethyl)- 4- methyl-4H-1,2,4-triazol- 3- yl) phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(hydroxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5(methoxymethyl)-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzensulfonamide;

N-(2-(5-(azetidin-1-ylmethyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(5-acetyl-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

(S)-4-tert-butyl-N-(4,5-difluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-4.5-difluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4,triazol-3-yl)phenyl)benzenesulfonamido;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluororophenyl)benzenesulfonamide:

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-oxopyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-(4-methyltetrahydro-2H-pyran-4-yl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-cyclobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-trifluoromethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-methylpipenridin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(2-(methylsulfonyl)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide

N-(2-(4-(1-acetylpiperidin-4-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(4-(2-aminoethyl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(methoxymethy))-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2.4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(isopropoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-y))phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydrofuran3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)piperidine-1-carboxamide;

4-tert-butyl-N-(4-chloro-2-(4-(2-(dimethylamino)ethyl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(2-(methylamino)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(2-(4-(1-acetylpyrrolidin-3-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(5-amino-4-isopropyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-cyano-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzamide:

4-(4-tert-butylphenylsulfonamido)-3-5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoic acid;

N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

methyl 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoate;

N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-3-fluoro-4-morpholinobenzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxyethyl)4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4- tert- butyl- N-(4- chidro- 2-(5-((isopropylamino) methyl)- 4- methyl- 4H- 1,2,4-triazol- 3- yl) phenyl) benzenesulfonamide ;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

(R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

(S)-4-tert-butyl-N-(4-chloro-2-(4-(1-isopropylpyrrolidin-3-yl)-4H-1,2,4-triazo)-3-yl)phenyl)benzenesulfonamide:

(S)-3-(3-(2-(4-tert-butylphehylsulfonamido)-5-chlorophenyl)-4H-1,2,4-triazol-4-yl)pyrrolidine-1-carboxamide:

4-tert-butyl-N-(4-clhloro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperazin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide:

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydrofuran-3-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl) benzenesulfonamide:

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(((2-methoxyethyl)(methyl)amino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl) benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((-4-methylpiperazin-1-y))methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl) benzenesulfonamide:

(S)-4-tert-butyl-N-(4-chloro-2-(4-(1-(methylsulfonyl)pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chlorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

4-chloro-N-(5-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

4-chloro-N-(5-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chloro-4-fluorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

5-(4-chloro-2-(4-chloro-3-(trifluoromethyl)phenylsulfonamido)-5-fluorophenyl)-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazole-3-carboxamide; and

N-(2-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-4-tert-butylbenzensulfonamide.

16. The compound of claim 15, which is (S)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl) benzenesulfonamide or a salt thereof.

17. The compound of claim 15, which is (S)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl) benzenesulfonamide.

18. A composition comprising a pharmaceutically acceptable carrier and a compound of claim 1.

19. A compound as defined in any one of claims 1 to 17, or a salt thereof, or a composition as defined in claim 18, for use in a method of treating a CCR2-mediated condition or disease or a CCR9-mediated condition or disease.

20. A compound or composition according to claim 19 wherein the method of treating comprises oral, parenteral, rectal, transdermal, sublingual, nasal or topical administration.

21. The compound or composition of claim 19, where the disease or condition is selected from the group consisting of atherosclerosis, restenosis, multiple sclerosis, inflammatory bowel disease, renal fibrosis, rheumatoid arthritis, obesity, diabetes, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, idiopathic pneumonia syndrome, pulmonary fibrosis, transplantation rejection, graft-versus-host disease, cancer, neuropathic pain, Crohn's disease, and ulcerative colitis.

22. A compound or composition according to claim 19 wherein the compound or composition is for administration with an anti-inflammatory or analgesic agent.