The present invention relates to certain substituted (1,2,4-oxadiazol-3-yl)indolin-2-yl carboxylic acid derivatives of Formula (1a) and pharmaceutically acceptable salts thereof, which exhibit useful pharmacological properties, for example, as agonists of the SIPI receptor.

Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the treatment of SIPI receptor-associated disorders, for example, psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, microbial infections or diseases and viral infections or diseases.

**FIGURE 1**

![Chemical Structure](image)
Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published: with international search report (Art. 21(3))
FIELD OF THE INVENTION

The present invention relates to certain substituted (1,2,4-oxadiazol-3-yl)indolin-2-yl carboxylic acid derivatives of Formula (Ia) and pharmaceutically acceptable salts thereof, which exhibit useful pharmacological properties, for example, as agonists of the S1P1 receptor. Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the treatment of disorders associated with the S1P1 receptor, for example, psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, microbial infections or diseases and viral infections or diseases.

BACKGROUND OF THE INVENTION

The present invention relates to compounds that are S1P1 receptor agonists having at least immunosuppressive, anti-inflammatory, and/or hemostatic activities, e.g. by virtue of modulating leukocyte trafficking, sequestering lymphocytes in secondary lymphoid tissues, and/or enhancing vascular integrity.

The present application is in part focused on addressing an unmet need for immunosuppressive agents such as may be orally available which have therapeutic efficacy for at least autoimmune diseases and disorders, inflammatory diseases and disorders (e.g., acute and chronic inflammatory conditions), transplant rejection, cancer, and/or conditions that have an underlying defect in vascular integrity or that are associated with angiogenesis such as may be pathologic (e.g., as may occur in inflammation, tumor development, and atherosclerosis) with fewer side effects such as the impairment of immune responses to systemic infection.

The sphingosine-1-phosphate (SIP) receptors 1-5 constitute a family of G protein-coupled receptors with a seven-transmembrane domain. These receptors, referred to as S1P1 to S1P5 (formerly termed endothelial differentiation gene (EDG) receptor-1, -5, -3, -6, and -8, respectively; Chun et al., Pharmacological Reviews, 54:265-269, 2002), are activated via binding by sphingosine-1-phosphate, which is produced by the sphingosine kinase-catalyzed phosphorylation of sphingosine. S1P1, S1P4, and S1P5 receptors activate Gi but not Gq, whereas S1P2 and S1P3 receptors activate both Gi and Gq. The S1P3 receptor, but not the S1P1 receptor, responds to an agonist with an increase in intracellular calcium.

SIP receptor agonists having agonist activity on the S1P1 receptor have been shown to rapidly and reversibly induce lymphopenia (also referred to as peripheral lymphocyte lowering
(PLL); Hale et al, Bioorg. Med. Chem. Lett., 14:3351-3355, 2004). This is attended by clinically useful immunosuppression by virtue of sequestering T- and B-cells in secondary lymphoid tissue (lymph nodes and Peyer's patches) and thus apart from sites of inflammation and organ grafts (Rosen et al, Immunol. Rev., 195:160-177, 2003; Schwab et al, Nature Immunol, 8:1295-1301, 2007). This lymphocyte sequestration, for example in lymph nodes, is thought to be a consequence of concurrent agonist-driven functional antagonism of the S1P1 receptor on T-cells (whereby the ability of SIP to mobilize T-cell egress from lymph nodes is reduced) and persistent agonism of the S1P1 receptor on lymph node endothelium (such that barrier function opposing transmigration of lymphocytes is increased) (Matloubian et al, Nature, 427:355-360, 2004; Baumruker et al, Expert Opin. Investig. Drugs, 16:283-289, 2007).

It has been reported that agonism of the S1P1 receptor alone is sufficient to achieve lymphocyte sequestration (Sanna et al, J Biol Chem., 279:13839-13848, 2004) and that this occurs without impairment of immune responses to systemic infection (Brinkmann et al, Transplantation, 72:764-769, 2001; Brinkmann et al, Transplant Proc, 33:530-531, 2001).

That agonism of endothelial S1P1 receptors has a broader role in promoting vascular integrity is supported by work implicating the S1P1 receptor in capillary integrity in mouse skin and lung (Sanna et al, Nat Chem Biol, 2:434-441, 2006). Vascular integrity can be compromised by inflammatory processes, for example as may derive from sepsis, major trauma and surgery so as to lead to acute lung injury or respiratory distress syndrome (Johan Groeneveld, Vascul Pharmacol, 39:247-256, 2003).

An exemplary SIP receptor agonist having agonist activity on the S1P1 receptor is FTY720 (fingolimod), an immunosuppressive agent currently in clinical trials (Martini et al, Expert Opin. Investig. Drugs, 16:505-518, 2007). FTY720 acts as a prodrug which is phosphorylated in vivo; the phosphorylated derivative is an agonist for S1P1, S1P3, S1P4, and S1P5 receptors (but not the S1P2 receptor) (Chiba, Pharmacology & Therapeutics, 108:308-319, 2005). FTY720 has been shown to rapidly and reversibly induce lymphopenia (also referred to as peripheral lymphocyte lowering (PLL); Hale et al, Bioorg. Med. Chem. Lett., 14:3351-3355, 2004). This is attended by clinically useful immunosuppression by virtue of sequestering T- and B-cells in secondary lymphoid tissue (lymph nodes and Peyer's patches) and thus apart from sites of inflammation and organ grafts (Rosen et al, Immunol. Rev., 195:160-177, 2003; Schwab et al, Nature Immunol, 8:1295-1301, 2007).


FTY720 has been reported to have therapeutic efficacy in at least: a rat model for autoimmune myocarditis and a mouse model for acute viral myocarditis (Kiyabuyashi et al, J.

Additionally, FTY720 has been reported to have therapeutic efficacy in experimental autoimmune encephalomyelitis (EAE) in rats and mice, a model for human multiple sclerosis (Brinkmann et al, J. Biol. Chem., 277:21453-21457, 2002; Fujino et al, J. Pharmacol. Exp. Ther., 305:70-77, 2003; Webb et al, J. Neuroimmunol, 153:108-121, 2004; Rausch et al, J.

Recently, FTY720 has been reported to have anti-viral activity. Specific data has been presented in the lymphocytic choriomeningitis virus (LCMV) mouse model, wherein the mice were infected with either the Armstrong or the clone 13 strain of LCMV (Premenko-Lanier et al, Nature, 454, 894, 2008).

FTY720 has been reported to impair migration of dendritic cells infected with Francisella tularensis to the mediastinal lymph node, thereby reducing the bacterial colonization of it. Francisella tularensis is associated with tularemia, ulceroglandular infection, respiratory infection and a typhoidal disease (E. Bar-Haim et al, PLoS Pathogens, 4(11): e1000211, doi:10.1371/journal.ppat.1000211, 1, 2008).

It has also been recently reported that a short-term high dose of FTY720 rapidly reduced ocular infiltrates in experimental autoimmune uveoretinitis. When given in the early stages of ocular inflammation, FTY720 rapidly prevented retinal damage. It was reported to not only prevent infiltration of target organs, but also reduce existing infiltration (Raveney et al, Arch. Ophthalmol. 126(10), 1390, 2008).

It has been reported that treatment with FTY720 relieved ovariectomy-induced osteoporosis in mice by reducing the number of mature osteoclasts attached to the bone surface. The data provided evidence that SIP controlled the migratory behaviour of osteoclast precursors, dynamically regulating bone mineral homeostasis (Ishii et al, Nature, advance online publication, 8 February 2009, doi:10.1038/nature07713).

Agonism of the SIPI receptor has been implicated in enhancement of survival of oligodendrocyte progenitor cells. Survival of oligodendrocyte progenitor cells is a required component of the remyelination process. Remyelination of multiple sclerosis lesions is considered to promote recovery from clinical relapses. (Miron et al, Ann. Neurol., 63:61-71, 2008; Coelho et al, J. Pharmacol Exp. Ther., 323:626-635, 2007; Dev et al, Pharmacology
and Therapeutics, 117:77-93, 2008). It also has been shown that the SIPI receptor plays a role in platelet-derived growth factor (PDGF)-induced oligodendrocyte progenitor cell mitogenesis (Jung et al, *Gu*a, 55:1656-1667, 2007).

Agonism of the SIPI receptor has also been reported to mediate migration of neural stem cells toward injured areas of the central nervous system (CNS), including in a rat model of spinal cord injury (Kimura et al, *Stem Cells*, 25:1 15-124, 2007).

Agonism of the SIPI receptor has been implicated in the inhibition of keratinocyte proliferation (Sauer et al, *J. Biol. Chem.*, 279:38471-38479, 2004), consistent with reports that SIP inhibits keratinocyte proliferation (Kim et al, *Cell Signal*, 16:89-95, 2004). The hyperproliferation of keratinocytes at the entrance to the hair follicle, which can then become blocked, and an associated inflammation are significant pathogenetic factors of acne (Koreck et al, *Dermatology*, 206:96-105, 2003; Webster, *Cutis*, 76:4-7, 2005).

FTY720 has been reported to have therapeutic efficacy in inhibiting pathologic angiogenesis, such as that as may occur in tumor development. Inhibition of angiogenesis by FTY720 is thought to involve agonism of the SIPI receptor (Oo et al, *J. Biol. Chem.*, 282:9082-9089, 2007; Schmid et al, *J. Cell Biochem.*, 101:259-270, 2007). FTY720 has been reported to have therapeutic efficacy for inhibiting primary and metastatic tumor growth in a mouse model of melanoma (LaMontagne et al, *Cancer Res.*, 66:221-231, 2006). FTY720 has been reported to have therapeutic efficacy in a mouse model for metastatic hepatocellular carcinoma (Lee et al, *Clin. Cancer Res.*, 11:84588466, 2005).

It has been reported that oral administration of FTY720 to mice potently blocked VEGF-induced vascular permeability, an important process associated with angiogenesis, inflammation, and pathological conditions such as sepsis, hypoxia, and solid tumor growth (T Sanchez et al, *J. Biol. Chem.*, 278(47), 47281-47290, 2003).

Cyclosporin A and FK506 (calcineurin inhibitors) are drugs used to prevent rejection of transplanted organs. Although they are effective in delaying or suppressing transplant rejection, classical immunosuppressants such as cyclosporin A and FK506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, /β-cell toxicity and gastrointestinal discomfort. There is an unmet need in organ transplantation for an immunosuppressant without these side effects which is effective as a monotherapy or in combination with a classical immunosuppressant for inhibiting migration of, e.g., alloantigen-reactive T-cells to the grafted tissue, thereby prolonging graft survival.

FTY720 has been shown to have therapeutic efficacy in transplant rejection both as a monotherapy and in synergistic combination with a classical immunosuppressant, including cyclosporin A, FK506 and RAD (an mTOR inhibitor). It has been shown that, unlike the classical immunosuppressants cyclosporin A, FK506 and RAD, FTY720 has efficacy for prolonging graft survival without inducing general immunosuppression, and this difference in
drug action is believed to be relevant to the synergism observed for the combination (Brinkmann et al, Transplant Proc, 33:530-531, 2001; Brinkmann et al, Transplantation, 72:764-769, 2001).

Agonism of the SIPI receptor has been reported to have therapeutic efficacy for prolonging allograft survival in mouse and rat skin allograft models (Lima et al, Transplant Proc, 36:1015-1017, 2004; Yan et al, Bioorg. & Med. Chem. Lett., 16:3679-3683, 2006). FTY720 has been reported to have therapeutic efficacy for prolonging allograft survival in a rat cardiac allograft model (Suzuki et al, Transpl. Immunol, 4:252-255, 1996). FTY720 has been reported to act synergistically with cyclosporin A to prolong rat skin allograft survival (Yanagawa et al, J. Immunol, 160:5493-5499, 1998), to act synergistically with cyclosporin A and with FK506 to prolong rat cardiac allograft survival, and to act synergistically with cyclosporin A to prolong canine renal allograft survival and monkey renal allograft survival (Chiba et al, Cell Mol Biol, 3:11-19, 2006). KRP-203, an SIP receptor agonist has been reported to have therapeutic efficacy for prolonging allograft survival in a rat skin allograft model and both as monotherapy and in synergistic combination with cyclosporin A in a rat cardiac allograft model (Shimizu et al, Circulation, 111:222-229, 2005). KRP-203 also has been reported to have therapeutic efficacy in combination with mycophenolate mofetil (MMF; a prodrug for which the active metabolite is mycophenolic acid, an inhibitor of purine biosynthesis) for prolonging allograft survival both in a rat renal allograft model and in a rat cardiac allograft model (Suzuki et al, J. Heart Lung Transplant, 25:302-209, 2006; Fujishiro et al, J. Heart Lung Transplant, 25:825-833, 2006). It has been reported that an agonist of the SIPI receptor, AUY954, in combination with a subtherapeutic dose of RAD001 (Certican/Everolimus, an mTOR inhibitor) can prolong rat cardiac allograft survival (Pan et al, Chemistry & Biology, 13:1227-1234, 2006). In a rat small bowel allograft model, FTY720 has been reported to act synergistically with cyclosporin A to prolong small bowel allograft survival (Sakagawa et al, Transpl. Immunol, 13:161-168, 2004). FTY720 has been reported to have therapeutic efficacy in a mouse islet graft model (Fu et al, Transplantation, 73:1425-1430, 2002; Liu et al, Microsurgery, 27:300-304; 2007) and in a study using human islet cells to evidence no detrimental effects on human islet function (Truong et al, American Journal of Transplantation, 7:2031-2038, 2007).

FTY720 has been reported to reduce the nociceptive behavior in the spared nerve injury model for neuropathic pain which does not depend on prostaglandin synthesis (O. Costu et al, Journal of Cellular and Molecular Medicine, 12(3), 995-1004, 2008).

FTY720 has been reported to impair initiation of murine contact hypersensitivity (CHS). Adoptive transfer of immunized lymph node cells from mice treated with FTY720 during the sensitization phase was virtually incapable of inducing CHS response in recipients (D. Nakashima et al, J. Investigative Dermatology, 128(12), 2833-2841, 2008).
It has been reported that prophylactic oral administration of FTY720 (1 mg/kg, three
times a week), completely prevented the development of experimental autoimmune myasthenia
gravis (EAMG) in C57BL/6 mice (T. Kohono et al, Biological & Pharmaceutical Bulletin,
28(4), 736-739, 2005).

In one embodiment, the present invention encompasses compounds which are agonists
of the SlP1 receptor having selectivity over the S1P3 receptor. The S1P3 receptor, and not the
SlP1 receptor, has been directly implicated in bradycardia (Sanna et al, J. Biol. Chem.,
279:13839-13848, 2004). An SlP1 receptor agonist selective over at least the S1P3 receptor has
advantages over current therapies by virtue of an enhanced therapeutic window, allowing better
tolerability with higher dosing and thus improving efficacy as therapy. The present invention
encompasses compounds which are agonists of the SlP1 receptor and which exhibit no or
substantially no activity for bradycardia.

SlP1 receptor agonists are useful to treat or prevent conditions where suppression of the
immune system or agonism of the SlP1 receptor is in order, such as diseases and disorders
mediated by lymphocytes, transplant rejection, autoimmune diseases and disorders,
inflammatory diseases and disorders, and conditions that have an underlying defect in vascular
integrity or that relate to angiogenesis such as may be pathologic.

In one embodiment, the present invention encompasses compounds which are agonists
of the SlP1 receptor having good overall physical properties and biological activities and having
an effectiveness that is substantially at least that of prior compounds with activity at the SlP1
receptor.

Citation of any reference throughout this application is not to be construed as an
admission that such reference is prior art to the present application.

SUMMARY OF THE INVENTION

The present invention encompasses compounds of Formula (Ia) and pharmaceutically
acceptable salts, solvates, and hydrates thereof:

![Chemical Structure](image)

(Ia)

wherein:

Y is N or CH;

Z is N or CR¹;
R¹, R², and R³ are each independently selected from the group consisting of H, Ci-C₆ alkoxy, Q-C₆ alkylsulfonyl, C₁-C₆ alkylthio, Q-C₆ alkylamino, cyano, C₃-C₇ cycloalkyl, Ci-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, heteroaryl, and heterocyclyl, wherein said C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one C₃-C₇ cycloalkyl group.

The present invention encompasses compounds which are SIPI receptor agonists having at least immunosuppressive, anti-inflammatory and/or hemostatic activities, e.g. by virtue of modulating leukocyte trafficking, sequestering lymphocytes in secondary lymphoid tissues, and/or enhancing vascular integrity.

SIPI receptor agonists are useful to treat or prevent conditions where suppression of the immune system or agonism of the SIPI receptor is in order, such as diseases and disorders mediated by lymphocytes, transplant rejection, autoimmune diseases and disorders, inflammatory diseases and disorders (e.g., acute and chronic inflammatory conditions), cancer, and conditions that have an underlying defect in vascular integrity or that are associated with angiogenesis such as may be pathologic (e.g., as may occur in inflammation, tumor development and atherosclerosis). Such conditions where suppression of the immune system or agonism of the SIPI receptor is in order include diseases and disorders mediated by lymphocytes, conditions that have an underlying defect in vascular integrity, autoimmune diseases and disorders, inflammatory diseases and disorders (e.g., acute and chronic inflammatory conditions), acute or chronic rejection of cells, tissue or solid organ grafts, arthritis including psoriatic arthritis and rheumatoid arthritis, diabetes including type I diabetes, demyelinating disease including multiple sclerosis, ischemia-reperfusion injury including renal and cardiac ischemia-reperfusion injury, inflammatory skin disease including psoriasis, atopic dermatitis and acne, hyperproliferative skin disease including acne, inflammatory bowel disease including Crohn's disease and ulcerative colitis, systemic lupus erythematosus, asthma, uveitis, myocarditis, allergy, atherosclerosis, brain inflammation including Alzheimer's disease and brain inflammatory reaction following traumatic brain injury, central nervous system disease including spinal cord injury or cerebral infarction, pathologic angiogenesis including as may occur in primary and metastatic tumor growth, rheumatoid arthritis, diabetic retinopathy and atherosclerosis, cancer, chronic pulmonary disease, acute lung injury, acute respiratory disease syndrome, sepsis, and the like.

One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for treating a disorder associated with the SIPI receptor in an individual comprising administering to the individual in
need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating a disorder associated with the SIPI receptor in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof, wherein the disorder is selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, hypertensive nephropathy, glomerulosclerosis, myocardial ischemia-reperfusion injury, and acne.

One aspect of the present invention pertains to methods for treating a disease or disorder mediated by lymphocytes in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating an autoimmune disease or disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating an inflammatory disease or disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating a disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof, wherein the disorder is selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, and acne.

One aspect of the present invention pertains to methods for treating a microbial infection or disease associated with the SIPI receptor in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating a viral infection or disease associated with the SIPI receptor in an individual comprising administering to the
individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating psoriasis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating rheumatoid arthritis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating Crohn's disease in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating transplant rejection in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating multiple sclerosis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating systemic lupus erythematosus in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating ulcerative colitis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating type I diabetes in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating acne in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.
One aspect of the present invention pertains to methods for treating gastritis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating polymyositis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating thyroiditis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating vitiligo in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating biliary cirrhosis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating hypertensive nephropathy in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating glomerulosclerosis in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating myocardial ischemia-reperfusion injury in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a disorder associated with the SIPI receptor.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a disorder associated with the SIPI receptor selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's
disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, hypertensive nephropathy, glomerulosclerosis, myocardial ischemia-reperfusion injury, and acne.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a disease or disorder mediated by lymphocytes.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of an autoimmune disease or disorder.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of an inflammatory disease or disorder.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of cancer.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a microbial infection or disease associated with the SIPI receptor.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of a viral infection or disease associated with the SIPI receptor.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of psoriasis, rheumatoid arthritis, Crohn’s disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, and acne.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of psoriasis.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of rheumatoid arthritis.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of Crohn’s disease.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of transplant rejection.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of multiple sclerosis.
One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of systemic lupus erythematosus.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of ulcerative colitis.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of type I diabetes.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of acne.

One aspect of the present invention pertains to the use of compounds of the present invention in the manufacture of a medicament for the treatment of myocardial ischemia-reperfusion injury.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a disorder associated with the SIPI receptor.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a disorder associated with the SIPI receptor selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, hypertensive nephropathy, glomerulosclerosis, myocardial ischemia-reperfusion injury, and acne.
One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a disease or disorder mediated by lymphocytes.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of an autoimmune disease or disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of an inflammatory disease or disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of cancer.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a microbial infection or disease associated with the SIPI receptor.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a viral infection or disease associated with the SIPI receptor.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of psoriasis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of rheumatoid arthritis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of Crohn's disease.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of transplant rejection.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of multiple sclerosis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of systemic lupus erythematosus.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of ulcerative colitis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of type I diabetes.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of acne.
One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of gastritis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of polymyositis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of thyroiditis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of vitiligo.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of hepatitis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of biliary cirrhosis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of hypertensive nephropathy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of glomerulosclerosis.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of hypertensive nephropathy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of myocardial ischemia-reperfusion injury.

One aspect of the present invention pertains to processes for preparing a composition comprising admixing a compound of the present invention and a pharmaceutically acceptable carrier.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 shows the results of an experiment which measured the ability of Compound 1 to lower the absolute count of peripheral lymphocytes in mouse compared to saline and vehicle.

Figure 2 shows the results of an experiment which measured the ability of Compound 2 to lower the absolute count of peripheral lymphocytes in mouse compared to saline and vehicle.

Figure 3 shows a general synthetic scheme for the preparation of compounds of Formula (Ia). Oxidation of the hydroxymethyl indoline starting material afforded the aldehyde which was converted via a Wittig reaction to the 3-β-butoxy-3-oxoprop-1-enyl indoline. This was further converted to the corresponding 3-β-butoxy-3-oxopropyl indoline by palladium-catalyzed reduction. Following bromination of the aromatic ring, the cyano group was introduced by a metal-catalyzed coupling reaction and subsequently converted to the amidoxime.
group. Condensation of the precursor with acid chlorides, followed by deprotection, provided substituted (l,2,4-oxadiazol-3-yl)indolin-2-yl carboxylic acid derivatives of Formula (Ia).

DETAILED DESCRIPTION OF THE INVENTION

5 DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term "agonist" is intended to mean a moiety that interacts with and activates a G-protein-coupled receptor, such as the SIPl receptor, such as can thereby initiate a physiological or pharmacological response characteristic of that receptor. For example, an agonist may activate an intracellular response upon binding to the receptor, or enhances GTP binding to a membrane. In certain embodiments, an agonist of the invention is an SIPl receptor agonist that is capable of facilitating sustained SIPl receptor internalization (see e.g., Matioubian et al, Nature, 427, 355).

The term "antagonist" is intended to mean a moiety that competitively binds to the receptor at the same site as an agonist (for example, the endogenous ligand), but which does not activate the intracellular response initiated by the active form of the receptor and can thereby inhibit the intracellular responses by an agonist or partial agonist. An antagonist does not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term "hydrate" as used herein means a salt of the invention that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The term "solvate" as used herein means a salt of the invention that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

The term "in need of treatment" and the term "in need thereof" when referring to treatment are used interchangeably to mean a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.
The term "individual" is intended to mean any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates and most preferably humans.

The term "inverse agonist" is intended to mean a moiety that binds to the endogenous form of the receptor or to the constitutively activated form of the receptor and which inhibits the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of an agonist or partial agonist, or decreases GTP binding to a membrane. In some embodiments, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%. In some embodiments, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 50%. In some embodiments, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

The term "modulate or modulating" is intended to mean an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term "pharmaceutical composition" is intended to mean a composition comprising at least one active ingredient; including but not limited to, salts, solvates, and hydrates of compounds of the present invention, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term "therapeutically effective amount" is intended to mean the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, caregiver or by an individual, which includes one or more of the following:

(1) Preventing the disease, for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) Inhibiting the disease, for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and

(3) Ameliorating the disease, for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

CHEMICAL GROUP, MOIETY OR RADICAL
The term "C₁-C₆ alkoxy" is intended to mean a C₁-C₆ alkyl radical, as defined herein, attached directly to an oxygen atom. Some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples include methoxy, ethoxy, \( \alpha \)-propoxy, isopropoxy, \( \beta \)-butoxy, tert-butoxy, isobutoxy, sec-butoxy, and the like.

The term "C₁-C₆ alkyl" is intended to mean a straight or branched carbon radical containing 1 to 6 carbons. Some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples of an alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, H-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, tert-pentyl, neo-pentyl, 1-methylbutyl \( \{ \text{i.e.,} \) \[CH(\text{CH}_3)\text{CH}_2\text{CH}_3\] \], 2-methylbutyl \( \{ \text{i.e.,} \) \[CH_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3\] \], n-hexyl, and the like.

The term "C₁-C₆ alkylsulfonyl" is intended to mean a C₁-C₆ alkyl radical attached to the sulfur of a sulfone radical having the formula: -S(O)₂- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, M-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, and the like.

The term "C₁-C₆ alkylthio" is intended to mean a C₁-C₆ alkyl radical attached to a sulfur atom \( \{ \text{i.e.,} \) \(-\text{S}-\) \) wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfanyl \( \{ \text{i.e.,} \) \( \text{CH}_3\text{S} \) \), ethylsulfanyl, \( \text{n-,propylsulfanyl, isopropylsulfanyl, n-butylsulfanyl, sec-butylsulfanyl, isobutylsulfanyl, tert-butylsulfanyl, and the like.} \)

The term "C₁-C₆ alkyaminoo" is intended to mean one alkyl radical attached to an -NH-radical wherein the alkyl radical has the same meaning as described herein. Some examples include, but are not limited to, methylamino, ethylamino, \( \alpha \)-propylamino, isopropylamino, \( \text{n-,butylamino, sec-butylamino, isobutylamino, tert-butylamino, and the like.} \)

The term "cyano" is intended to mean the group -CN.

The term "C₃-C₇ cycloalkyl" is intended to mean a saturated ring radical containing 3 to 7 carbons. Some embodiments contain 3 to 6 carbons. Some embodiments contain 3 to 5 carbons. Some embodiments contain 5 to 7 carbons. Some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term "C₁-C₆ haloalkoxy" is intended to mean a Q-C₆ haloalkyl, as defined herein, which is directly attached to an oxygen atom. Examples include, but are not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, and the like.

The term "C₁-C₆ haloalkyl" is intended to mean an C₆ alkyl group, defined herein, wherein the alkyl is substituted with between one halogen up to fully substituted wherein a fully substituted C₁-C₆ haloalkyl can be represented by the formula \( \text{C}_n\text{L}_{2n+1} \) wherein L is a halogen and "n" is 1, 2, 3, 4, 5 or 6. When more than one halogen is present, the halogens may be the
same or different and selected from the group consisting of fluoro, chloro, bromo or iodo, preferably fluoro. Some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, and the like.

The term "halogen" or "halo" is intended to mean a fluoro, chloro, bromo or iodo group.

The term "heteroaryl" is intended to mean an aromatic ring system containing 5 to 14 aromatic ring atoms that may be a single ring, two fused rings or three fused rings, wherein at least one aromatic ring atom is a heteroatom selected from, for example, the group consisting of N, O, S, a nitrogen optionally substituted with H, C1-C4 alkyl, or C1-C4 alkyl. Some embodiments contain 5 to 6 ring atoms, for example, furanyl, thiienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyraziny, pyrimidinyl, pyridazinyl, triazinyl, and the like. Some embodiments contain 8 to 14 ring atoms for example quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, triazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl, 1H-benzimidazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, isobenzofuran, and the like.

The term "heterocyclic" or "heterocyclyl" is intended to mean a non-aromatic ring containing 3 to 8 ring atoms wherein one, two or three ring atoms are heteroatoms selected from, for example, the group consisting of N, O, S(=O), S(=O)2, and NH, wherein the N is optionally substituted as described herein. In some embodiments, the nitrogen is optionally substituted with C1-C4 acyl or Q-C4 alkyl. In some embodiments, ring carbon atoms are optionally substituted with oxo thus forming a carbonyl group. In some embodiments, ring sulfur atoms are optionally substituted with oxo atoms thus forming a thiocarbonyl group. The heterocyclic group can be attached/bonded to any available ring atom, for example, ring carbon, ring nitrogen and the like. In some embodiments the heterocyclic group is a 3-, 4-, 5-, 6- or 7-membered ring. Examples of a heterocyclic group include, but are not limited to, aziridin-1-yl, aziridin-2-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl, [1,3]-dioxolan-2-yl, thiomorpholin-4-yl, [1,4]oxazepan-4-yl, 1,1-dioxothiomorpholin-4-yl, azepan-1-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, and the like.

**COMPOUNDS OF THE INVENTION:**
One aspect of the present invention pertains to certain compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

\[
\begin{align*}
\text{R}^3, \text{R}^3, \text{Y}, \text{and Z have the same definitions as described herein, supra and infra.} \\
\text{It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables \( \{ \text{e.g., R}^1, \text{R}^2, \text{R}^3, \text{Y}, \text{and Z} \} \) contained within the generic chemical formula described herein, for example, (Ia, Ic, etc.), are specifically embraced by the present invention just as if each and every combination was individually explicitly recited, to the extent that such combinations embrace compounds that result in stable compounds (\text{i.e., compounds that can be isolated, characterized and tested for biological activity}). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each and every subcombination of chemical groups and subcombination of uses and medical indications was individually and explicitly recited herein. \\
\text{As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group. The non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is "substituted" it may have up to the full valence of substitution, for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, "substituted with one or more substituents" refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one substituent, the substituents can be identical or they can be different.}
\end{align*}
\]
Compounds of the invention also include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

It is understood and appreciated that compounds of Formula (Ia) and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including but not limited to racemates. It is understood that Formula (Ia) is intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

The Variables Y and Z

In some embodiments, Y is N or CH; and Z is N or CR^1.

In some embodiments, Y is N; and Z is N.

In some embodiments, Y is N; and Z is CR^1.

In some embodiments, Y is CH; and Z is N.

In some embodiments, Y is CH; and Z is CR^1.

In some embodiments, Y is N.

In some embodiments, Y is CH.

In some embodiments, Z is N.

In some embodiments, Z is CR^1.

The Groups R^1, R^2, R^3

In some embodiments, R^1, R^2, and R^3 are each independently selected from the group consisting of H, C^1-C^6 alkoxy, Ci-C^6 alkyl, C^1-C^6 alkylsulfonfyl, C^1, C^6 alkylthio, Q-C^6 alkylamino, cyano, C^3-C^7 cycloalkyl, Ci-C^6 haloalkoxy, C^1-C^6 haloalkyl, halogen, heteroaryl, and heterocyclyl, wherein said C^1-C^6 alkyl and Q-C^6 alkoxy are each optionally substituted with one C^3-C^7 cycloalkyl group.

In some embodiments, R^1, R^2, and R^3 are each independently selected from the group consisting of H, C^1-C^6 alkoxy, C^1-C^6 alkyl, C^1-C^6 alkylsulfonfyl, cyano, C^3-C^7 cycloalkyl, C^1-C^6 haloalkoxy, C^1-C^6 haloalkyl, halogen, and heteroaryl.
In some embodiments, R\(^1\), R\(^2\), and R\(^3\) are each independently selected from the group consisting of H, chloro, cyano, cyclopentyl, difluoromethoxy, ethyl, methoxy, methylsulfonyl, thien-2-yl, trifluoromethoxy, and trifluoromethyl.

The Group R\(^1\)

In some embodiments, R\(^1\) is selected from the group consisting of H, Ci-C\(_6\) alkoxy, Q - C\(_6\) alkyl, Ci-C\(_6\) alkylsulfonyl, Q-C\(_6\) alkylthio, C\(_{1-6}\) alkylamino, cyano, C\(_5\)-C\(_7\) cycloalkyl, Ci-C\(_6\) haloalkoxy, C\(_1\)-C\(_6\) haloalkyl, halogen, heteroaryl, and heterocyclyl, wherein the Ci-C\(_6\) alkyl and Ci-C\(_6\) alkoxy are each optionally substituted with one C\(_3\)-C\(_7\) cycloalkyl group.

In some embodiments, R\(^1\) is selected from the group consisting of H, Q-C\(_6\) alkoxy, Q - C\(_6\) alkylsulfonyl, Q-C\(_6\) alkylthio, C\(_{1-6}\) alkylamino, cyano, Ci-C\(_6\) haloalkoxy, C\(_1\)-C\(_6\) haloalkyl, and halogen.

In some embodiments, R\(^1\) is selected from the group consisting of H, Ci-C\(_6\) alkoxy, Q - C\(_6\) alkylsulfonyl, cyano, Q-C\(_6\) haloalkoxy, C\(_1\)-C\(_6\) haloalkyl, and halogen.

In some embodiments, R\(^1\) is selected from the group consisting of H, chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

The Group R\(^2\)

In some embodiments, R\(^2\) is selected from the group consisting of H, C\(_1\)-C\(_6\) alkoxy, Q - C\(_6\) alkyl, C\(_1\)-C\(_6\) alkylsulfonyl, Q-C\(_6\) alkylthio, C\(_1\)-C\(_6\) alkylamino, cyano, C\(_5\)-C\(_7\) cycloalkyl, C\(_1\)-C\(_6\) haloalkoxy, C\(_1\)-C\(_6\) haloalkyl, halogen, heteroaryl, and heterocyclyl, wherein the C\(_1\)-C\(_6\) alkyl and C\(_1\)-C\(_6\) alkoxy are each optionally substituted with one C\(_3\)-C\(_7\) cycloalkyl group.

In some embodiments, R\(^2\) is selected from the group consisting of H, C\(_1\)-C\(_6\) alkoxy, Q - C\(_6\) alkyl, C\(_5\)-C\(_7\) cycloalkyl, Ci-C\(_6\) haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the C\(_1\)-C\(_6\) alkyl and C\(_1\)-C\(_6\) alkoxy are each optionally substituted with one C\(_3\)-C\(_7\) cycloalkyl group.
In some embodiments, R₂ is selected from the group consisting of H, Ci-C₆ alkoxy, Q-C₆ alkyl, C₃-C₇ cycloalkyl, Ci-C₆ haloalkoxy, halogen, and heteroaryl.

In some embodiments, R₂ is selected from the group consisting of H, chloro, cyclopentyl, cyclopropylmethoxy, cyclopropylmethyl, ethyl, methoxy, pyrrolidin-1-yl, thien-2-yl, and trifluoromethoxy.

In some embodiments, R₂ is selected from the group consisting of H, chloro, cyclopentyl, difluoromethoxy, ethyl, methoxy, thien-2-yl, and trifluoromethoxy.

In some embodiments, R₂ is H.

In some embodiments, R₂ is chloro.

In some embodiments, R₂ is cyclopentyl.

In some embodiments, R₂ is cyclopropylmethoxy.

In some embodiments, R₂ is cyclopropylmethyl.

In some embodiments, R₂ is difluoromethoxy.

In some embodiments, R₂ is ethyl.

In some embodiments, R₂ is methoxy.

In some embodiments, R₂ is pyrrolidin-1-yl.

In some embodiments, R₂ is thien-2-yl.

In some embodiments, R₂ is trifluoromethoxy.

The Group R³

In some embodiments, R³ is selected from the group consisting of H, Ci-C₆ alkoxy, Q-C₆ alkyl, Ci-C₆ alkylsulfonyl, Ci-C₆ alkylthio, C₃-C₇ alkylamino, cyano, C₃-C₇ cycloalkyl, Ci-C₆ haloalkoxy, C₃-C₇ haloalkyl, halogen, heteroaryl, and heterocyclyl, wherein the Q-C₆ alkyl and Ci-C₆ alkoxy are each optionally substituted with one C₃-C₇ cycloalkyl group.

In some embodiments, R³ is selected from the group consisting of H, Q-C₆ alkoxy, Q-C₆ alkylsulfonyl, Ci-C₆ alkylthio, Ci-C₆ alkylamino, cyano, Ci-C₆ haloalkoxy, Q-C₆ haloalkyl, and halogen.

In some embodiments, R³ is selected from the group consisting of H, Ci-C₆ alkoxy, Q-C₆ alkylsulfonyl, cyano, Q-C₆ haloalkoxy, Q-C₆ haloalkyl, and halogen.

In some embodiments, R³ is selected from the group consisting of H, chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R³ is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R³ is H.

In some embodiments, R³ is chloro.

In some embodiments, R³ is cyano.

In some embodiments, R³ is ethylamino.
In some embodiments, \( R_3 \) is methoxy.
In some embodiments, \( R_3 \) is methylthio.
In some embodiments, \( R_3 \) is methylsulfonyl.
In some embodiments, \( R_3 \) is trifluoromethoxy.
In some embodiments, \( R_3 \) is trifluoromethyl.

**Certain Combinations**

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

\[
\begin{align*}
\text{Y} & : \text{N or CH;} \\
\text{Z} & : \text{N or CR}_1; \\
\text{R}_1 & : \text{selected from the group consisting of H, C}_1\text{-C}_6 \text{ alkoxy, Ci-C}_6 \text{ alkylsulfonyl, Ci-C}_6 \text{ alkylthio, Ci-C}_6 \text{ alkylamino, cyano, Ci-C}_6 \text{ haloalkoxy, Ci-C}_6 \text{ haloalkyl, and halogen;} \\
\text{R}_2 & : \text{selected from the group consisting of H, C}_1\text{-C}_6 \text{ alkoxy, Ci-C}_6 \text{ alkyl, C}_3\text{-C}_7 \text{ cycloalkyl, Ci-C}_6 \text{ haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the Ci-C}_6 \text{ alkyl and C}_1\text{-C}_6 \text{ alkoxy are each optionally substituted with one C}_3\text{-C}_7 \text{ cycloalkyl group;} \\
\text{and} \\
\text{R}_3 & : \text{selected from the group consisting of H, Ci-C}_6 \text{ alkoxy, Ci-C}_6 \text{ alkylsulfonyl, Ci-C}_6 \text{ alkylthio, Ci-C}_6 \text{ alkylamino, cyano, Q-C}_6 \text{ haloalkoxy, Ci-C}_6 \text{ haloalkyl, and halogen.}
\end{align*}
\]

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

\[
\begin{align*}
\text{Y} & : \text{N or CH;} \\
\text{Z} & : \text{N or CR}_1; \\
\text{R}_1 & : \text{selected from the group consisting of chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.}
\end{align*}
\]
R² is selected from the group consisting of H, C₁⁻₆ alkoxy, C₁⁻₆ alkyl, C₃⁻₇ cycloalkyl, Ci-C₆ haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the C₁⁻₆ alkyl and C₁⁻₆ alkoxy are each optionally substituted with one C₃⁻₇ cycloalkyl group; and

R³ is selected from the group consisting of H, C₁⁻₆ alkoxy, Ci-C₆ alkylsulfonyl, Q-C₆ alkythio, Ci-C₆ alkylamino, cyano, Ci-C₆ haloalkoxy, Ci-C₆ haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

Y is N or CH;
Z is N or CR¹;
R¹ is selected from the group consisting of H, Ci-C₆ alkoxy, Ci-C₆ alkylsulfonyl, C₁⁻C₆ alkythio, C₁⁻C₆ alkylamino, cyano, C₁⁻C₆ haloalkoxy, Q-C₆ haloalkyl, and halogen;

R² is selected from the group consisting of H, chloro, cyclopentyl, cyclopropymethoxy, cyclopropymethyl, ethyl, methoxy, pyrrolidin-1-yl, thien-2-yl, and trifluoromethoxy; and

R³ is selected from the group consisting of H, C₁⁻C₆ alkoxy, C₁⁻C₆ alkylsulfonyl, C₁⁻C₆ alkythio, Ci-C₆ alkylamino, cyano, C₁⁻C₆ haloalkoxy, C₁⁻C₆ haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

Y is N or CH;
Z is N or CR¹;
R¹ is selected from the group consisting of H, C₁⁻C₆ alkoxy, C₁⁻C₆ alkylsulfonyl, C₁⁻C₆ alkythio, C₁⁻C₆ alkylamino, cyano, C₁⁻C₆ haloalkoxy, C₁⁻C₆ haloalkyl, and halogen;

R² is selected from the group consisting of H, C₁⁻C₆ alkoxy, C₁⁻C₆ alkyl, C₃⁻C₇ cycloalkyl, C₁⁻C₆ haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the C₁⁻C₆ alkyl and C₁⁻C₆ alkoxy are each optionally substituted with one C₃⁻C₇ cycloalkyl group; and

R³ is selected from the group consisting of H, chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.
Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

- \( Y \) is N or CH;
- \( Z \) is N or CR;
- \( R^1 \) is selected from the group consisting of chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl;
- \( R^2 \) is selected from the group consisting of H, chloro, cyclopentyl, cyclopropylmethyl, cyclopropylmethyl, ethyl, methoxy, pyrrolidin-1-yl, thien-2-yl, and trifluoromethoxy; and
- \( R^3 \) is selected from the group consisting of H, chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

![Chemical Structure](Ic)

wherein:

- \( R^1 \) is selected from the group consisting of H, Ci-C₆ alkoxy, Ci-C₆ alkylsulfonyl, Ci-C₆ alkythio, Ci-C₆ alkylamino, cyano, C₁-C₆ haloalkoxy, Q-C₆ haloalkyl, and halogen;
- \( R^2 \) is selected from the group consisting of H, Ci-C₆ alkoxy, Ci-C₆ alkyl, C₃-C₇ cycloalkyl, Ci-C₆ haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the C₁-C₆ alkyl and C₇ Ci-C₆ alkoxy are each optionally substituted with one C₃-C₇ cycloalkyl group; and
- \( R^3 \) is selected from the group consisting of H, C₁-C₆ alkoxy, Ci-C₆ alkylsulfonyl, Q-C₆ alkythio, Q-C₆ alkylamino, cyano, Q-C₆ haloalkoxy, Q-C₆ haloalkyl, and halogen.
R^1 is selected from the group consisting of H, C\textsubscript{i}-C\textsubscript{6} alkoxy, C\textsubscript{1}-C\textsubscript{6} alkylsulfonyl, C\textsubscript{1}-C\textsubscript{6} alkylthio, C\textsubscript{1}-C\textsubscript{6} alkylamino, cyano, C\textsubscript{1}-C\textsubscript{6} haloalkoxy, Q-C\textsubscript{6} haloalkyl, and halogen;

R^2 is selected from the group consisting of H, C\textsubscript{i}-C\textsubscript{6} alkoxy, C\textsubscript{i}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{7} cycloalkyl, C\textsubscript{1}-C\textsubscript{6} haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the C\textsubscript{i}-C\textsubscript{6} alkyl and Q-C\textsubscript{6} alkoxy are each optionally substituted with one C\textsubscript{3}-C\textsubscript{7} cycloalkyl group; and

R^3 is selected from the group consisting of H, C\textsubscript{i}-C\textsubscript{6} alkoxy, Q-C\textsubscript{6} alkylsulfonyl, Q-C\textsubscript{6} alkylthio, Q-C\textsubscript{6} alkylamino, cyano, C\textsubscript{i}-C\textsubscript{6} haloalkoxy, Q-C\textsubscript{6} haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof wherein:

R^1, R^2, and R^3 are each independently selected from the group consisting of H, C\textsubscript{i}-C\textsubscript{6} alkoxy, Q-C\textsubscript{6} alkyl, Q-C\textsubscript{6} alkylsulfonyl, cyano, C\textsubscript{3}-C\textsubscript{7} cycloalkyl, Q-C\textsubscript{6} haloalkoxy, C\textsubscript{i}-C\textsubscript{6} haloalkyl, halogen, and heteroaryl.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof wherein:

R^1 is selected from the group consisting of H, C\textsubscript{i}-C\textsubscript{6} alkoxy, C\textsubscript{1}-C\textsubscript{6} alkylsulfonyl, cyano, C\textsubscript{i}-C\textsubscript{6} haloalkoxy, C\textsubscript{i}-C\textsubscript{6} haloalkyl, and halogen;

R^2 is selected from the group consisting of H, Q-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{7} cycloalkyl, C\textsubscript{i}-C\textsubscript{6} haloalkoxy, halogen, and heteroaryl; and

R^3 is selected from the group consisting of H, C\textsubscript{i}-C\textsubscript{6} alkoxy, C\textsubscript{i}-C\textsubscript{6} alkylsulfonyl, cyano, C\textsubscript{i}-C\textsubscript{6} haloalkoxy, C\textsubscript{i}-C\textsubscript{6} haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof wherein:

R^1 is selected from the group consisting of chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl;

R^2 is selected from the group consisting of H, Q-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{7} cycloalkyl, Q-C\textsubscript{6} haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the C\textsubscript{i}-C\textsubscript{6} alkyl and Q-C\textsubscript{6} alkoxy are each optionally substituted with one C\textsubscript{3}-C\textsubscript{7} cycloalkyl group; and
Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

R<sub>1</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkoxy, Q-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, Ci-C<sub>6</sub> alkenylamino, cyano, Q-C<sub>6</sub> haloalkoxy, Ci-C<sub>6</sub> haloalkyl, and halogen;

R<sub>2</sub> is selected from the group consisting of H, chloro, cyclopentyl, cyclopropylmethoxy, cyclopropylmethyl, ethyl, methoxy, pyrrolidin-1-yl, thien-2-yl, and trifluoromethoxy; and

R<sub>3</sub> is selected from the group consisting of H, Q-C<sub>6</sub> alkoxy, Ci-C<sub>6</sub> alkylsulfonyl, Q-C<sub>6</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkenylamino, cyano, Q-C<sub>6</sub> haloalkoxy, Q-C<sub>6</sub> haloalkyl, and halogen.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

R<sub>1</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkoxy, Q-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, Ci-C<sub>6</sub> alkenylamino, cyano, Q-C<sub>6</sub> haloalkoxy, Ci-C<sub>6</sub> haloalkyl, and halogen;

R<sub>2</sub> is selected from the group consisting of H, Q-C<sub>6</sub> alkoxy, Ci-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, Q-C<sub>6</sub> haloalkoxy, halogen, heteroaryl, and heterocyclyl, wherein the Q-C<sub>6</sub> alkyl and Q-C<sub>6</sub> alkoxy are each optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group; and

R<sub>3</sub> is selected from the group consisting of H, chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

R<sub>1</sub> is selected from the group consisting of chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy, and trifluoromethyl;
Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

R\textsuperscript{1}, R\textsuperscript{2}, and R\textsuperscript{3} are each independently selected from the group consisting of H, chloro, cyano, cyclopentyl, difluoromethoxy, ethyl, methoxy, methylsulfonyl, thien-2-yl, trifluoromethoxy, and trifluoromethyl.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

R\textsuperscript{1} is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl;

R\textsuperscript{2} is selected from the group consisting of H, chloro, cyclopentyl, difluoromethoxy, ethyl, methoxy, and thien-2-yl; and

R\textsuperscript{3} is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

Some embodiments of the present invention include every combination of one or more compounds selected from the following group shown in Table A.
<table>
<thead>
<tr>
<th>Cmpd No.</th>
<th>Chemical Structure</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(S)-3-(5-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(S)-3-(5-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(4-methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>Cmpd No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>8</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(S)-3-(5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(S)-3-(5-(5-(4-methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>10</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(S)-3-(5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>11</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(3-chloro-4-cyclopentylphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>12</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
<tr>
<td>13</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>(R)-3-(5-(5-(4-ethyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid</td>
</tr>
</tbody>
</table>
Additionally, individual compounds and chemical genera of the present invention, for example, those compounds found in Table A including diastereomers and enantiomers thereof, encompass all pharmaceutically acceptable salts, solvates, and hydrates, thereof.

It is understood that the present invention embraces each diastereomer, each enantiomer and mixtures thereof of each compound and generic formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral carbon. Separation of the individual isomers (such as, by chiral HPLC, recrystallization of diastereomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective syntheses and the like) of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

The compounds of the Formula (Ia) of the present invention may be prepared according to relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., Protecting Groups in Organic Synthesis, 3rd Edition, 1999 [Wiley]; incorporated herein by reference in its entirety).

### PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically
acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a
compound of the present invention and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a
pharmaceutical composition comprising admixing at least one compound according to any of
the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing
the active compound(s) with liquids or finely divided solid carriers, or both, in the required
proportions and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents,
tabletting lubricants and disintegrants may be used in tablets and capsules for oral
administration. Liquid preparations for oral administration may be in the form of solutions,
emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be
in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle
before use. Additional additives such as suspending or emulsifying agents, non-aqueous
vehicles (including edible oils), preservatives and flavorings and colorants may be added to the
liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of
the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and
sealing an appropriate vial or ampule. These are just a few examples of the many appropriate
methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical
compositions using techniques well known to those in the art. Suitable pharmaceutically
acceptable carriers, outside those mentioned herein, are known in the art; for example, see

While it is possible that, for use in the prophylaxis or treatment, a compound of the
invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable
however to present the compound or active ingredient as a pharmaceutical formulation or
composition further comprising a pharmaceutically acceptable carrier.

The invention thus further provides pharmaceutical formulations comprising a
compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative
thereof together with one or more pharmaceutically acceptable carriers thereof and/or
prophylactic ingredients. The carrier(s) must be “acceptable” in the sense of being compatible
with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical
(including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-
cutaneous and intravenous) administration or in a form suitable for administration by inhalation,
insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate
by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use; in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or suspensions, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a salt, solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as S1P receptor modulators. The term "active ingredient" is defined in the context of a "pharmaceutical composition" and is intended to mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits and as is customary and known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention.
Representative doses of the present invention include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate by the patient's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient or an active salt, solvate or hydrate derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in one model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, whether an acute or chronic disease state is being treated or prophylaxis is conducted or whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors including those cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimens outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as 2, 3, 4 or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following
dosage forms may comprise, as the active component, either a compound of the invention or a
pharmaceutically acceptable salt, solvate or hydrate of a compound of the invention. Typical
procedures for making and identifying suitable hydrates and solvates, outside those mentioned
herein, are well known to those in the art; see for example, pages 202-209 of K.J. Guillory,
"Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: *Polymorphism in
incorporated herein by reference in its entirety.

For preparing pharmaceutical compositions from the compounds of the present
invention, the suitable pharmaceutically acceptable carrier can be either solid, liquid or a
mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets,
suppositories and dispersible granules. A solid carrier can be one or more substances which may
also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders,
preservatives, tablet disintegrating agents, or encapsulating materials.

In powders, the carrier is a finely divided solid which is in a mixture with the finely
divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding
capacity in suitable proportions and compacted to the desired shape and size.

The powders and tablets may contain varying percentage amounts of the active
compound. A representative amount in a powder or tablet may be from 0.5 to about 90 percent
of the active compound. However, an artisan would know when amounts outside of this range
are necessary. Suitable carriers for powders and tablets include magnesium carbonate,
magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth,
methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like.
The term "preparation" is intended to include the formulation of the active compound with
encapsulating material as carrier providing a capsule in which the active component, with or
without carriers, is surrounded by a carrier, which is thus in association with it. Similarly,
cachets and lozenges are included. Tablets, powders, capsules, pills, cachets and lozenges can be
used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid
glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously
therein (e.g., by stirring). The molten homogenous mixture is then poured into convenient sized
molds, allowed to cool and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries,
tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient
such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions and emulsions, for example,
water or water-propylene glycol solutions. For example, parenteral injection liquid preparations
can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed 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.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.
Formulations suitable for topical administration in the mouth include lozenges comprising the active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols (e.g., nasal aerosols, by inhalation), this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. Solutions or dispersions of the compounds of the present invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative thereof in water, water/alcohol mixtures or suitable saline solutions, for example, can be employed using customary additives (e.g., benzyl alcohol or other suitable preservatives), absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants (e.g., carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and the like). The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder (e.g., a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP)). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form (e.g., capsules, cartridges) as for gelatin or blister packs from which the powder may be administered by means of an inhaler.
The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

In some embodiments, the compositions are tablets or capsules for oral administration.

In some embodiments, the compositions are liquids for intravenous administration.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluensulfonic and the like, such as those pharmaceutically acceptable salts listed by Berge et al., *Journal of Pharmaceutical Sciences*, 66:1-19 (1977), incorporated herein by reference in its entirety.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and that when administered into an individual undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems Vol. 14 of the A.C.S. Symposium Series; and in *Bioresversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at
least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

It is noted that when SIPI receptor agonists are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as SIPI receptor agonists, for the treatment of an SIPI receptor-associated disease or disorder in companionship animals (e.g., cats, dogs, etc.) and in livestock animals (e.g., cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

HYDRATES AND SOLVATES

It is understood that when the phrase "pharmaceutically acceptable salts, solvates, and hydrates" is used in reference to a particular formula herein, it is intended to embrace solvates and/or hydrates of compounds of the particular formula, pharmaceutically acceptable salts of compounds of the particular formula as well as solvates and/or hydrates of pharmaceutically acceptable salts of compounds of the particular formula. It is also understood by a person of ordinary skill in the art that hydrates are a subgenus of solvates.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be apparent to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt or as a solvate or hydrate thereof. Moreover, various hydrates and solvates of the compounds of the invention and their salts will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of KJ. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999, incorporated herein by reference in its entirety. Accordingly, one aspect of the present invention pertains to hydrates and solvates of compounds of the present invention and/or their pharmaceutically acceptable salts, as described herein, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (PXRD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).
OTHER UTILITIES

Another object of the present invention relates to radiolabeled compounds of the present invention that are useful not only in radio-imaging but also in assays, both in vitro and in vivo, for localizing and quantitating the SIPI receptor in tissue samples, including human and for identifying SIPI receptor ligands by inhibition binding of a radiolabeled compound. It is a further object of this invention to develop novel SIPI receptor assays which comprise such radiolabeled compounds.

The present invention embraces isotopically-labeled compounds of the present invention. Isotopically or radiolabeled compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Suitable radionuclides that may be incorporated in compounds of the present invention include, but are not limited to, $^3$H (also written as D for deuterium), $^3$H (also written as T for tritium), $^{11}$C, $^{12}$C, $^{13}$N, $^{18}$O, $^{17}$O, $^{19}$F, $^{35}$S, $^{36}$Cl, $^{75}$Br, $^{76}$Br, $^{77}$Br, $^{123}$I, $^{124}$I, $^{125}$I and $^{131}$I. The radionuclide that is incorporated in the instant radiolabeled compounds will depend on the specific application of that radiolabeled compound. For example, for in vitro SIPI receptor labeling and competition assays, compounds that incorporate $^3$H, $^{14}$C, $^{82}$Br, $^{125}$I, $^{131}$I or $^{35}$S will generally be most useful. For radio-imaging applications $^{14}$C, $^{18}$F, $^{125}$I, $^{123}$I, $^{124}$I, $^{131}$I, $^{75}$Br, $^{76}$Br or $^{77}$Br will generally be most useful.

It is understood that a "radiolabeled" or "labeled compound" is a compound of Formula (Ia), (Ic), etc., containing at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of $^3$H, $^{14}$C, $^{125}$I, $^{35}$S and $^{82}$Br.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide $^3$H and/or $^{14}$C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in Figure 3 and the examples infra, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Other synthetic methods that are useful are discussed infra. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or a scarcer radio-isotope or nonradioactive isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. Certain synthetic methods, for example, for incorporating activity levels of tritium into target molecules, are as follows:
A. Catalytic Reduction with Tritium Gas: This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride \(^{3}H\): This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

C. Reduction with Lithium Aluminum Hydride \(^{3}H\): This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

D. Tritium Gas Exposure Labeling: This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. \(N\)-Methylation using Methyl Iodide \(^{3}H\): This procedure is usually employed to prepare 0-methyl or \(N\)-methyl \(^{3}H\) products by treating appropriate precursors with high specific activity methyl iodide \(^{3}H\). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of \(^{125}\)I into target molecules include:

A. Sandmeyer and like reactions: This procedure transforms an aryl amine or a heteroaryl amine into a diazonium salt, such as a diazonium tetrafluoroborate salt and subsequently to \(^{125}\)I labeled compound using Na\(^{125}\)I. A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.

B. Ortho \(^{125}\)Iodination of phenols: This procedure allows for the incorporation of \(^{125}\)I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd. Radiopharm.*, 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with \(^{125}\)I: This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction \([i.e. \ Pd(Ph_3P)_4]\) or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin \(\{e.g., (CH_3)_3SnSn(CH_3)_3\}\). A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

A radiolabeled SIPI receptor compound of Formula (Ia) or can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound \(\{i.e., \ test \ compound\}\) can be evaluated for its ability to reduce binding of the "radiolabeled compound of Formula (Ia)" to the SIPI receptor. Accordingly, the ability of a test compound to compete with the "radiolabeled compound of Formula (Ia)" for the binding to the SIPI receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the SIPI receptor. In one embodiment the labeled compound has an IC\(_{50}\) less than about 500 \(\mu\)M, in another embodiment the labeled compound has an IC\(_{50}\) less than about 100 \(\mu\)M, in yet another embodiment the
labeled compound has an IC$_{50}$ less than about 10 µM, in yet another embodiment the labeled
compound has an IC$_{50}$ less than about 1 µM and in still yet another embodiment the labeled
inhibitor has an IC$_{50}$ less than about 0.1 µM.

Other uses of the disclosed receptors and methods will become apparent to those of skill
in the art based upon, inter alia, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be
performed any particular number of times or in any particular sequence. Additional objects,
advantages and novel features of this invention will become apparent to those skilled in the art
upon examination of the following examples thereof, which are intended to be illustrative and
not intended to be limiting.

EXAMPLES

Example 1: Syntheses of Compounds of the Present Invention.

Illustrated syntheses for compounds of the present invention are shown in Figure 3
where the variables have the same definitions as used throughout this disclosure.

The compounds of the invention and their syntheses are further illustrated by the
following examples. The following examples are provided to further define the invention
without, however, limiting the invention to the particulars of these examples. The compounds
described herein, supra and infra, are named according to the CS ChemDraw Ultra Version
7.0.1, AutoNom version 2.2, CS ChemDraw Ultra Version 9.0.7. In certain instances common
names are used and it is understood that these common names would be recognized by those
skilled in the art.

Chemistry: Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a
Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse)
and z-gradient. Proton nuclear magnetic resonance (¹H NMR) spectra were also recorded on a
Bruker Avance-500 equipped with a BBI (Broad Band Inverse) and z-gradient. Chemical shifts
are given in parts per million (ppm) with the residual solvent signal used as reference. NMR
abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q
= quartet, m = multiplet, bs = broad singlet, bt = broad triplet. Microwave irradiations were
carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer
chromatography (TLC) was performed on silica gel 60 F$_{254}$ (Merck), preparatory thin-layer
chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman)
and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-
0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

Celite® 545 was used for filtration of palladium.

LCMS spec: HPLC-pumps: LC-IOAD VP, Shimadzu Inc.; HPLC system controller:
SCL-IOA VP, Shimadzu Inc; UV-Detector: SPD-IOA VP, Shimadzu Inc; Autosampler: CTC
Example 1.1: Preparation of (R)-3-(5-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 1).

Step A: Preparation of (S)-tert-Butyl 2-formylindoline-1-carboxylate.

To an ice cold solution of (S)-tert-butyl 2-(hydroxymethyl)indoline-1-carboxylate (1.0 g, 4.01 mmol) in DCM (12 mL) was added Dess-Martin periodinane (1.87 g, 4.41 mmol). The ice bath was removed after 10 min, and the solution was stirred for 2 h at room temperature. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc; 100:0 to 90:10) to provide the title compound (0.78 g, 79%). LCMS m/z = 148.7 [M+H-Boc]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.51 (s, 9H), 3.13 (m, IH), 3.33-3.46 (m, IH), 4.73-4.86 (m, IH), 6.97 (t, J = 7.3 Hz, IH), 7.13 (d, J = 7.3 Hz, IH), 7.21 (bs, IH), 7.90 (bs, IH), 9.64 (bs, 1 H).

Step B: Preparation of (S)-tert-Butyl 2-(3-tert-Butoxy-3-oxoprop-l-etyl)indoline-1-carboxylate

(S)-tert-Butyl 2-formylindoline-1-carboxylate (0.75 g, 3.03 mmol) and (tert-butoxycarbonylmethylene)triphenylphosphorane (1.71 g, 4.55 mmol) were dissolved in anhydrous DCM (15 mL) under N₂ and stirred for 1 h at room temperature. The solution was washed with 3% NH₄Cl (2 x 10 mL), dried with MgSO₄, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc; 100:0 to 90:10) to provide the title compound (0.95 g, 91%). LCMS m/z = 368.1 [M+Na]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.45 (s, 9H), 1.53 (bs, 9H), 2.45 (d, J = 15.5 Hz, IH), 3.42-3.49 (m, IH), 4.99 (bs, IH), 5.79 (d, J = 15.3 Hz, IH), 6.77 (dd, J = 15.8 and 6.3 Hz, IH), 6.95 (t, J = 6.8 Hz, IH), 7.12 (d, J = 7.5 Hz, IH), 7.19 (t, J = 7.3 Hz, IH), 7.81 (bs, IH).

Step C: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)indoline-1-carboxylate.

To a solution of (S)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl-ethyl)indoline-1-carboxylate (0.95 g, 2.75 mmol) in EtOAc was added 10% Pd/C (0.1 g, 5 mol %). The reaction was carried out under an atmosphere of H₂ (balloon) and stirred at room temperature for 8 h before it was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to provide the title compound (0.92 g, 96%). LCMS m/z = 348.0 [M+H]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.42 (s, 9H), 1.57 (bs, 9H), 1.94 (m, 2H), 2.20-2.26 (m, 2H), 2.70 (d, J = 16.0 Hz, IH), 3.27-3.35 (m, IH), 4.46 (bs, IH), 6.93 (t, J = 7.3 Hz, IH), 7.14 (m, 2H), 7.72 (bs, IH).

Step D: Preparation of (R)-tert-Butyl 5-Bromo-2-(3-tert-butoxy-3-oxopropyl)indoline-1-carboxylate.
NBS (0.47 g, 2.65 mmol) was added to a solution of (R)-tert-butyl-2-(3-tert-butoxy-3-oxopropyl)indoline-1-carboxylate (0.92 g, 2.65 mmol) in DMF (3 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and quenched with water (3 mL). The reaction was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water, brine, dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc; 100: 0 to 95:5) to provide the title compound (0.85 g, 75%). LCMS m/z = 448.1 [M+Na]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.42 (s, 9H), 1.56 (bs, 9H), 1.84-2.01 (m, 2H), 2.18-2.26 (m, 2H), 2.69 (d, J = 15.5 Hz, IH), 3.24-3.33 (m, IH), 4.46 (bs, IH), 7.22-7.28 (m, 2H), 7.60 (bs, IH).

Step E: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-cyanoindoline-1-carboxylate.

(R)-tert-Butyl 5-bromo-2-(3-tert-butoxy-3-oxopropyl)indoline-1-carboxylate (0.63 g, 1.48 mmol), CuI (28 mg, 0.148 mmol), NaCN (0.145g, 2.96 mmol), and Pd(PPh₃)₄ (85 mg, 0.074 mmol) were charged into a round bottomed flask. Propionitrile (5 mL) was added and the mixture was heated under reflux for 15 h under N₂ atmosphere. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), and filtered through Celite®. The filtrate was washed with H₂O and brine, dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc; 100: 0 to 80:20) to provide the title compound (0.38 g, 69%). LCMS m/z = 373.1 [M+H]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.42 (s, 9H), 1.57 (bs, 9H), 1.90 (m, IH), 2.00 (m, IH), 2.20 (t, J = 7.8 Hz, 2H), 2.76 (d, J = 15.5 Hz, IH), 3.26-3.34 (m, IH), 4.51 (bs, IH), 7.38 (s, IH), 7.47 (d, J = 8.0 Hz, IH), 7.75 (bs, IH).

Step F: Preparation of (R)-tert-Etyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(N-hydroxy carbamimidoyl)indoline-1-carboxylate.

A solution of (i?)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-cyanoindoline-1-carboxylate (0.34 g, 0.91 mmol) and hydroxylamine (50% in H₂O, 0.6 g, 9.1 mmol) in EtOH (5 mL) was sealed in a heavy walled tube and heated at 70 °C for 2 h. After removal of the solvent, the residue was purified using strong cationic exchange resin to provide the title compound (0.24 g, 65%). LCMS m/z = 406.3 [M+H]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.42 (s, 9H), 1.57 (bs, 9H), 1.86-1.92 (m, IH), 1.94-2.02 (m, IH), 2.20 (t, J = 7.6 Hz, 2H), 2.72 (d, J = 15.4 Hz, IH), 3.26-3.34 (m, IH), 3.47 (s, IH), 4.49 (bs, IH), 4.87 (bs, 2H), 7.41 (d, J = 8.0 Hz, IH), 7.42 (s, IH), 7.68 (bs, 1 H).

Step G: Preparation of (R)-tert-Butyl 5-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2-(3-tert-butoxy-3-oxopropyl)indoline-1-carboxylate.

A mixture of (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)5-(N′-hydroxy carbamimidoyl)indoline-1-carboxylate (0.14 g, 0.345 mmol), 3,5-bis(trifluoromethyl)benzoyl chloride (95 mg, 0.345 mmol), triethylamine (40 mg, 0.39 mmol), and molecular sieves (0.3 g) in THF was stirred at 70 °C for 24 h. The reaction was filtered and...
washed with EtOAc. The organics were washed with 1 N HCl and H2O, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc; 100:0 to 90:10) to provide the title compound (0.16 g, 74%). LCMS m/z = 628.4 [M+H]+; 1H NMR (400 MHz, CDCl3) δ ppm 1.43 (s, 9H), 1.60 (bs, 9H), 1.94-2.06 (m, 2H), 2.24 (t, J = 7.8 Hz, 2H), 2.82 (d, J = 16.4 Hz, IH), 3.34-3.44 (m, IH), 4.55 (bs, IH), 7.83 (bs, IH), 7.94 (s, IH), 8.02 (d, J = 8.6 Hz, IH), 8.10 (s, IH), 8.66 (s, 2 H).

**Step H: Preparation of (R)-3-(5-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid.**

A solution of (R)-tert-butyl 5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate (0.14 g, 0.22 mol) and TFA (1 mL) in DCM (3 mL) was stirred for 2 h at room temperature. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc/MeOH; 90:10:0 to 70:20:10) to provide the title compound (70 mg, 67%). LCMS m/z = 472.2 [M+H]+; 1H NMR (400 MHz, DMSO-^d_6) δ ppm 1.79 (q, J = 7.8 Hz, 2H), 2.24-2.34 (m, 2H), 2.68 (dd, J = 16.4 and 7.6 Hz, IH), 3.12-3.20 (m, IH), 3.88-3.94 (m, IH), 6.54 (s, IH), 6.55 (d, J = 8.0 Hz, IH), 7.70 (s, IH), 7.72 (d, J = 8.2 Hz, IH), 8.52 (s, IH), 8.68 (s, 2H), 12.09 (s, IH).

**Example 1.2: Preparation of (S)-3-(5-(3-Cyano-5-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 3).**

The title compound was prepared from (R)-tert-butyl 2-(hydroxymethyl)indoline-1-carboxylate in a similar manner to the one described in Example 1.1. LCMS m/z = 472.3 [M+H]+; 1H NMR (400 MHz, Acetonitrile- d_3) δ ppm 1.86 (q, J = 7.3 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 2.74 (dd, J = 16.2, 8.3 Hz, IH), 3.22 (dd, J = 15.9, 8.8 Hz, IH), 3.97 (quintet, J = 8.3 Hz, IH), 6.63 (d, J= 8.6 Hz, IH), 7.78-7.80 (m, 2H), 8.28 (s, IH), 8.68 (s, 2H).

**Example 1.3: Preparation of (R)-3-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 2).**

The title compound was prepared from (S)-tert-butyl 2-(hydroxymethyl)indoline-1-carboxylate and 3-cyano-5-(trifluoromethyl)benzoyl chloride in a similar manner to the one described in Example 1.1. LCMS m/z = 445.1 [M+H]+; 1H NMR (400 MHz, CDCl3) δ ppm 1.97-2.05 (m, 2H), 2.48-2.54 (m, 2H), 2.79 (dd, J = 15.6, 8.0 Hz, IH), 3.27 (dd, J = 15.9, 8.8 Hz, IH), 4.04-4.12 (m, IH), 4.47 (bs, IH), 6.65 (d, J = 8.3 Hz, IH), 7.71 (s, IH), 7.85 (d, J = 7.8 Hz, IH), 8.26 (s, IH), 8.42 (s, 2H).

**Example 1.4: Preparation of (S)-3-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 4).**
The title compound was prepared from (R)-tert-buty\(2\)-(hydroxymethyl)indoline-1-carboxylate and 3-cyano-5-(trifluoromethyl)benzoyl chloride in a similar manner to the one described in Example 1.1, the title compound was obtained. LCMS \(m/z = 445.5\) [M+H]+; \(^1\)H NMR (400 MHz, DMSCW) \(\delta\) ppm 1.72-1.80 (m, 2H), 2.28-2.38 (m, 2H), 2.68 (dd, \(J = 15.8, 7.6\) Hz, IH), 3.16 (dd, \(J = 15.9, 9.2\) Hz, IH), 3.85-3.93 (m, IH), 6.54 (d, \(J = 4.0\) Hz, IH), 6.56 (s, IH), 7.70-7.68 (m, 2H), 8.39 (bs, IH), 8.40 (bs, IH), 8.64 (m, IH), 12.1 (s, IH).

**Example 1.5: Preparation of (i?)-3-(5-(5-(4-Chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.**

**Step A: Preparation of (i?)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.**

4-Chloro-3-(trifluoromethoxy)benzoic acid (0.024 g, 0.099 mmol), HATU (0.038 g, 0.099 mmol) and triethylamine (0.029 mL, 0.207 mmol) were stirred in dioxane for 30 minutes, then (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(N'-hydroxycarbamimidoyl)indoline-1-carboxylate (0.040 g, 0.099 mmol) was added. The reaction was heated to 100 °C for overnight. Upon cooling to room temperature, the reaction was treated with water. The precipitate was collected by vacuum filtration and purified by preparative TLC to give the title compound (0.010 g) as an oil. LCMS \(m/z = 610.8\) [M+H]+.

**Step B: Preparation of (i?)-3-(5-(5-(4-Methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 5).**

(R)-tert-Butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate (0.017 g) was dissolved in DCM/TFA (20% TFA) and stirred for 3 h. The mixture was purified by preparative HPLC/MS to give the title compound as a solid. LCMS \(m/z = 454.2\) [M+H]+.

**Example 1.6: Preparation of (R)-3-(5-(5-(4-Methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 6).**

**Step A: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.**

The title compound was prepared from 4-methoxy-3-(trifluoromethoxy)benzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS \(m/z = 606.6\) [M+H]+.

**Step B: Preparation of (i?)-3-(5-(5-(4-Methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid (Compound 6).**

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS \(m/z = 450.4\) [M+H]+; \(^1\)H...
NMR (400 MHz, DMSO-^6) δ ppm 1.71-1.82 (m, 2H), 2.25-2.39 (m, 2H), 2.67 (dd, J = 15.92, 7.71 Hz, IH), 3.16 (dd, J = 15.98, 8.40 Hz, IH), 3.84-3.94 (m, IH), 3.99 (s, 3H), 6.54 (d, J = 7.96 Hz, IH), 7.51 (d,J= 8.97 Hz, IH), 7.63-7.74 (m, 2H), 8.03 (s, IH), 8.17 (dd, J = 8.65, 2.08 Hz, IH).

Example 1.7: Preparation of (R)-3-(5-(5-(4-(Difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 7).

Step A: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

The title compound was prepared as an oil from 4-(difluoromethoxy)-3-methoxybenzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS m/z = 588.4 [M+H]^+.

Step B: Preparation of (R)-3-(5-(5-(4-(Difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 7).

From (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS m/z = 432.4 [M+H]^+; ^1H NMR (400 MHz, DMSO-^6) δ ppm 1.58-1.77 (m, 2H), 1.95 (t, J = 7.26 Hz, 2H), 2.63 (dd, J = 15.54, 7.33 Hz, IH), 3.10 (dd, J = 15.98, 9.03 Hz, IH), 3.80-3.90 (m, IH), 3.98 (s, 3H), 6.51 (d, J = 7.96 Hz, IH), 6.63 (bs, IH), 7.06-7.47 (m, 2H), 7.61-7.69 (m, 2H), 7.73-7.83 (m, 2H).

Example 1.8: Preparation of (5)-3-(5-(5-(4-Chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 8).

Step A: Preparation of (S)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

The title compound was prepared as an oil from 4-chloro-3-(trifluoromethoxy)-benzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS m/z = 610.8 [M+H]^+.

Step B: Preparation of (5)-3-(5-(4-Chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 8).

The title compound was prepared from (S)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS m/z = 454.3 [M+H]^+; ^1H NMR (400 MHz, DMSO-^6) δ ppm 1.71-1.81 (m, 2H), 2.24-2.41 (m, 2H), 2.68 (dd, J = 16.17, 7.33 Hz, IH), 3.16 (dd, J = 16.11, 9.54 Hz, IH), 3.85-3.95 (m, IH), 6.55 /α,J= 8.08 Hz, IH), 7.64-7.73 (m, 2H), 7.98-8.03 (m, IH), 8.17-8.22 (m, 2H).
Example 1.9: Preparation of (£)-3-(5-(4-Methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 9).

Step A: Preparation of (S)-<i>tert-Butyl</i> 2-(3-<i>tert-Butoxy-3-oxopropyl</i>)<i>-5-(5-(4-Methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate</i>.

The title compound was prepared from 4-methoxy-3-(trifluoromethoxy)benzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS <i>m/z</i> = 606.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.43 (s, 9H), 1.59 (s, 9H), 1.89-2.08 (m, 2H), 2.19-2.27 (m, 2H), 2.81 (dd, <i>J</i> = 16.36, 1.83 Hz, IH), 3.38 (dd, <i>J</i> = 16.36, 9.79 Hz, IH), 3.99 (s, 3H), 4.49-4.59 (m, IH), 7.14 (d, <i>J</i> = 8.72 Hz, IH), 7.70-7.86 (m, 2H), 7.92 (s, IH), 7.99 (dd, <i>J</i> = 8.34, 1.39 Hz, IH), 8.07-8.10 (m, IH), 8.13 (dd, <i>J</i> = 8.59, 2.15 Hz, IH).

Step B: Preparation of (S)-3-(5-(5-(4-Methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 9).

The title compound was prepared from (S)-<i>tert-buty</i>· 2-(3-<i>tert-butoxy-3-oxopropyl</i>)<i>-5-(5-(4-methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate</i> using a similar method to the one described in Example 1.5, Step B. LCMS <i>m/z</i> = 450.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-<i>d</i>₆) δ ppm 1.72-1.80 (m, 2H), 2.27-2.38 (m, 2H), 2.68 (dd, <i>J</i> = 16.42, 7.45 Hz, IH), 3.16 (dd, <i>J</i> = 15.85, 8.91 Hz, IH), 3.84-3.94 (m, 3H), 3.99 (s, 3H), 6.55 (d, <i>J</i> = 7.96 Hz, IH), 7.51 (d, <i>J</i> = 8.84 Hz, IH), 7.64-7.70 (m, 2H), 8.01-8.06 (m, IH), 8.17 (dd, <i>J</i> = 8.72, 2.15 Hz, IH).

Example 1.10: Preparation of (£)-3-(5-(5-(4-Difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 10).

Step A: Preparation of (S)-<i>tert-Butyl</i> 2-(3-<i>terf-Butoxy-3-oxopropyl</i>)<i>-5-(5-(4-difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate</i>.

The title compound was prepared as an oil from 4-(difluoromethoxy)-3-methoxybenzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS <i>m/z</i> = 588.6 [M+H]<sup>+</sup>.

Step B: Preparation of (S)-3-(5-(5-(4-(Difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 10).

The title compound was prepared from (S)-<i>tert-buty</i>· 2-(3-<i>tert-butoxy-3-oxopropyl</i>)<i>-5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate</i> using a similar method to the one described in Example 1.5, Step B. LCMS <i>m/z</i> = 432.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-<i>d</i>₆) δ ppm 1.70-1.82 (m, 2H), 2.24-2.42 (m, 2H), 2.68 (dd, <i>J</i> = 15.85, 7.39 Hz, IH), 3.16 (dd, <i>J</i> = 16.36, 9.16 Hz, IH), 3.84-3.95 (m, 3H), 3.98 (s, 3H), 6.55 (d, <i>J</i> = 7.96 Hz, IH), 7.05-7.48 (m, 2H), 7.66-7.73 (m, 2H), 7.75-7.82 (m, 2H).
Example 1.11: Preparation of (R)-3-(5-(3-Chloro-4-cyclopentylphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 11).

Step A: Preparation of (R)-tert-Butyl 5-(5-(4-Bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)-2-(3-tert-butoxy-3-oxopropyl)indoline-1-carboxylate.

The title compound was prepared from 4-bromo-3-chlorobenzoic acid using a similar method to the one described in Example 1.5, Step A and was purified using silica gel column chromatography to give a solid. LCMS m/z = 604.3 [M+H]+.

Step B: Preparation of (K)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(3-chloro-4-cyclopentylphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

To a solution of (R)-tert-butyl 5-(5-(4-bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)-2-(3-tert-butoxy-3-oxopropyl)indoline-1-carboxylate (0.077 g, 0.127 mmol) in THF was added cyclopentylzinc(II) bromide (0.764 mL, 0.382 mmol) and bis(tri-butylphosphate)palladium(0) (3.25 mg, 6.36 μmol) at room temperature. After stirring at reflux for 2 h, the reaction was quenched with saturated NaHCO₃ (aq) and filtered through celite®. The filtrate was extracted with EtOAc, dried over MgSO₄, concentrated and purified by silica gel column chromatography to give the title compound as a solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.43 (s, 9H), 1.60 (s, 9H), 1.89-2.05 (m, 2H), 2.20-2.30 (m, 4H), 3.16 (dd, J = 16.11, 7.89 Hz, 2H), 3.16 (dd, J = 16.29, 9.09 Hz, 2H), 3.44 (quintet, J = 8.31 Hz, 2H), 3.83-3.96 (m, 2H), 6.56 (d, J = 7.96 Hz, 2H), 7.63-7.73 (m, 3H), 8.05 (dd, J = 8.15, 1.83 Hz, 2H), 8.11 (d, J = 1.77 Hz, 2H).

Step C: Preparation of (R)-3-(5-(3-Chloro-4-cyclopentylphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 11).

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(3-chloro-4-cyclopentylphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS m/z = 438.5 [M+H]+; ¹H NMR (400 MHz, DMSO-^δ) δ ppm 1.52-1.89 (m, 8H), 2.01-2.14 (m, 2H), 2.24-2.42 (m, 2H), 2.68 (dd, J = 16.11, 7.89 Hz, 2H), 3.16 (dd, J = 16.29, 9.09 Hz, 2H), 3.44 (quintet, J = 8.31 Hz, 2H), 3.83-3.96 (m, 2H), 6.56 (d, J = 7.96 Hz, 2H), 7.63-7.73 (m, 3H), 8.05 (dd, J = 8.15, 1.83 Hz, 2H), 8.11 (d, J = 1.77 Hz, 2H).

Example 1.12: Preparation of (R)-3-(5-(4-Cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 12).

Step A: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

The title compound was prepared from 4-chloro-3-(trifluoromethyl)benzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS m/z = 594.4 [M+H]+; ¹H NMR (400 MHz, CD₃OD) δ ppm 1.43 (s, 9H), 1.60 (s, 9H), 1.89-2.05 (m, 2H), 2.20-2.30 (m,
2H), 2.89 (d, J = 15.79 Hz, IH), 3.36-3.50 (m, IH), 4.50-4.62 (m, IH), 7.73-7.85 (m, IH), 7.90 (d, J = 8.46 Hz, IH), 7.94-8.03 (m, 2H), 8.36-8.48 (m, IH), 8.55 (s, IH).

**Step B: Preparation of (R)-tert-Butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-cyclo pentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.**

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.11, Step B. 

**Example 1.11, Step B.** 1H NMR (400 MHz, CDCl₃) δ ppm 1.43 (s, 9H), 1.60 (s, 9H), 1.61-1.71 (m, 2H), 1.72-1.84 (m, 2H), 1.85-2.09 (m, 4H), 2.10-2.20 (m, 2H), 2.20-2.31 (m, 2H), 2.82 (d, J = 14.65 Hz, IH), 3.31-3.53 (m, 2H), 4.54 (bs, IH), 7.65 (d, J = 8.34 Hz, IH), 7.80 (bs, IH), 7.94 (s, IH), 8.01 (d, J = 8.46 Hz, IH), 8.29 (dd, J = 8.27, 1.45 Hz, IH), 8.45 (d, J = 1.26 Hz, IH).

**Step C: Preparation of (R)-3-(5-(5-(4-Cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 12).**

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-cyclo pentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS m/z = 472.6 [M+H]+; 1H NMR (400 MHz, DMSO-4) δ ppm 1.60-1.81 (m, 6H), 1.82-1.95 (m, 2H), 2.00-2.12 (m, 2H), 2.24-2.41 (m, 2H), 2.68 (dd, J = 16.17, 7.45 Hz, IH), 3.16 (dd, J = 16.29, 9.22 Hz, IH), 3.28-3.41 (m, IH), 3.83-3.96 (m, IH), 6.56 (d, J = 8.08 Hz, IH), 7.65-7.74 (m, 2H), 7.91 (d, J = 8.34 Hz, IH), 8.27-8.33 (m, IH), 8.32-8.40 (m, IH).

**Example 1.13: Preparation of (R)-3-(5-(5-(4-Ethyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 13).**

**Step A: Preparation of (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-ethyl-3-( trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.**

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate and diethyl zinc (1 M in THF) using a similar method to the one described in Example 1.11, Step B. LCMS m/z = 588.7 [M+H]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.32 (t, J = 7.52 Hz, 3H), 1.43 (s, 9H), 1.60 (s, 9H), 1.87-2.11 (m, 2H), 2.24 (t, J = 8.27 Hz, 2H), 2.82 (dd, J = 16.29, 1.77 Hz, IH), 2.92 (q, J = 7.45 Hz, 2H), 3.38 (dd, J = 16.29, 9.85 Hz, IH), 4.55 (bs, IH), 7.55 (d, J = 8.08 Hz, IH), 7.80 (bs, IH), 7.94 (s, IH), 8.01 (dd, J = 8.46, 1.52 Hz, IH), 8.29 (dd, J = 8.08, 1.64 Hz, IH), 8.46 (d, J = 1.26 Hz, 1H).

**Step B: Preparation of (R)-3-(5-(5-(4-Ethyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 13).**

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-ethyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a
similar method to the one described in Example 1.5, Step B. LCMS m/z = 432.4 [M+H]+; 1H NMR (400 MHz, DMSCW, 6) δ ppm 1.27 (t, J = 7.52 Hz, 3H), 1.77 (q, J = 7.54 Hz, 2H), 2.23-2.41 (m, 2H), 2.68 (dd, J = 16.23, 7.64 Hz, IH), 2.88 (q, J = 7.24 Hz, 2H), 3.17 (dd, J = 16.17, 9.22 Hz, IH), 3.84-3.96 (m, IH), 6.56 (d, J = 7.96 Hz, IH), 7.65-7.74 (m, 2H), 7.80 (d, J = 8.08 Hz, IH), 8.29-8.39 (m, 2H).

Example 1.14: Preparation of (R)-3-(5-(5-(4-Ethyl-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 14).

Step A: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

The title compound was prepared from 4-bromo-3-chlorobenzoic acid using a similar method to the one described in Example 1.5, Step A. LCMS m/z = 604.5 [M+H]+.

Step B: Preparation of (R)-tert-Butyl 2-(3-tert-Butoxy-3-oxopropyl)-5-(5-(4-ethyl-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate and diethyl zinc (1 M in THF) using a similar method to the one described in Example 1.11, Step B. LCMS m/z = 958.6 [M+H]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.34-1.45 (m, 12H), 1.60 (s, 9H), 1.88-2.10 (m, 2H), 2.24 (t, J = 8.34 Hz, 2H), 2.82 (dd, J = 16.36, 1.71 Hz, IH), 3.11-3.25 (m, 5H), 3.39 (dd, J = 16.29, 9.85 Hz, IH), 4.55 (bs, IH), 7.62 (d, J = 8.08 Hz, IH), 7.80 (bs, IH), 7.94 (s, IH), 8.00 (d, J = 1.14 Hz, IH), 8.36 (dd, J = 8.08, 1.77 Hz, IH), 8.88 (d, J = 1.77 Hz, IH).

Step C: Preparation of (R)-3-(5-(5-(4-Ethyl-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 14).

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-ethyl-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS m/z = 442.3 [M+H]+.

Example 1.15: Preparation of (i?)-3-(5-(5-(4-(thiophen-2-yl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 15).

Step A: Preparation of (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-(thiophen-2-yl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate.

The title compound was prepared from (R)-tert-butyl 2-(3-tert-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate and thiophene-2-ylzinc(II) bromide (0.050 M in THF) using a similar method to the one described in Example 1.11, Step B. LCMS m/z = 642.5 [M+H]+; 1H NMR (400 MHz, CDCl₃) δ ppm 1.43 (s, 9H), 1.60 (s, 9H), 1.92-2.09 (m, 2H), 2.20-2.28 (m, 2H), 2.83 (dd, J = 16.48, 1.71 Hz, IH), 3.39 (dd, J = 16.11, 9.92 Hz, IH), 4.49-4.60 (m, IH), 7.13 (dd, J = 5.12, 3.60 Hz, IH), 7.24 (d, J = 8.08 Hz, IH), 8.29-8.39 (m, 2H).
3.54 Hz, IH), 7.48 (dd, J = 5.18, 1.14 Hz, IH), 7.71 (d, J = 8.08 Hz, IH), 7.81 (bs, IH), 7.95 (s, IH), 8.00-8.06 (m, IH), 8.36 (dd, J = 8.08, 1.64 Hz, IH), 8.61 (d, J = 1.64 Hz, IH).

**Step B: Preparation of \((/?)-3-(5-(4-(Thiophen-2-yl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 15).**

The title compound was prepared from \((/?)-tert/-butyl\) 2-(3-tert/-butoxy-3-oxopropyl)-5-(5-(4-(thiophen-2-yl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS \(m/z = 486.3\) [M+H]+; \(^1\)H NMR (400 MHz, DMSO) 
\[ \delta \text{ ppm} = 1.77 \text{ (q, } J = 7.54 \text{ Hz, 2H}), \ 2.25-2.41 \text{ (m, 2H)}, \ 2.69 \text{ (dd, } J = 16.36, 7.64 \text{ Hz, IH}), \ 3.17 \text{ (dd, } J = 16.23, 9.03 \text{ Hz, IH}), \ 3.83-3.97 \text{ (m, IH)}, \ 6.57 \text{ (d, } J = 7.96 \text{ Hz, IH}), \ 7.22 \text{ (dd, } J = 5.05, 3.66 \text{ Hz, IH}), \ 7.30 \text{ (d, } J = 3.54 \text{ Hz, IH}), \ 7.68-7.76 \text{ (m, 2H)}, \ 7.81 \text{ (dd, } J = 5.05, 1.14 \text{ Hz, IH}), \ 7.86 \text{ (d, } J = 8.08 \text{ Hz, IH}), \ 8.44 \text{ (d, } J = 8.08 \text{ Hz, IH}), \ 8.46-8.51 \text{ (m, IH).}

**Example 1.16: Preparation of \((R)-3-(5-(5-(4-Chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic Acid (Compound 16).**

The title compound was prepared from \((R)-tert/-butyl\) 2-(3-tert/-butoxy-3-oxopropyl)-5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxylate using a similar method to the one described in Example 1.5, Step B. LCMS \(m/z = 438.2\) [M+H]+; \(^1\)H NMR (400 MHz, DMSO) 
\[ \delta \text{ ppm} = 1.76 \text{ (q, } J = 7.54 \text{ Hz, 2H}), \ 2.24-2.41 \text{ (m, 2H)}, \ 2.68 \text{ (dd, } J = 16.55, 7.58 \text{ Hz, IH}), \ 3.16 \text{ (dd, } J = 16.42, 9.22 \text{ Hz, IH}), \ 3.84-3.95 \text{ (m, IH)}, \ 6.56 \text{ (d, } J = 8.08 \text{ Hz, IH}), \ 7.65-7.74 \text{ (m, 2H)}, \ 8.03 \text{ (d, } J = 8.34 \text{ Hz, IH}), \ 8.38-8.48 \text{ (m, 2H).}

**Example 2: Homogeneous Time-Resolved Fluorescence (HTRF®) Assay For Direct cAMP Measurement.**

Compounds were screened for agonists of the SIPI receptor (e.g., human SIPI receptor) using the HTRF® assay for direct cAMP measurement (Gabriel et al, Assay and Drug Development Technologies, 1:291-303, 2003) and recombinant CHO-K1 cells stably transfected with SIPI receptors. CHO-K1 cells were obtained from ATCC® (Manassas, VA; Catalog # CCL-61). An agonist of the SIPI receptor was detected in the HTRF® assay for direct cAMP measurement as a compound which decreased cAMP concentration. The HTRF® assay also was used to determine EC\(_{50}\) values for SIPI receptor agonists.

**Principle of the assay:** The HTRF® assay kit was purchased from Cisbio-US, Inc. (Bedford, MA; Catalog # 62AM4PEC). The HTRF® assay supported by the kit is a competitive immunoassay between endogenous cAMP produced by the CHO-K1 cells and tracer cAMP labeled with the dye d2. The tracer binding is visualized by a monoclonal anti-cAMP antibody labeled with Cryptate. The specific signal (i.e., fluorescence resonance energy transfer, FRET) is inversely proportional to the concentration of unlabeled cAMP in the standard or sample.
Standard curve: The fluorescence ratio (665 nm/620 nm) of the standards (0.17 to 712 nM cAMP) included in the assay was calculated and used to generate a cAMP standard curve according to the kit manufacturer's instructions. The fluorescence ratio of the samples (test compound or compound buffer) was calculated and used to deduce respective cAMP concentrations by reference to the cAMP standard curve.

Setup of the assay: The HTRF® assay was carried out using a two-step protocol essentially according to the kit manufacturer's instructions, in 20 µL total volume per well in 384-well plate format (ProxiPlates; PerkinElmer, Fremont, CA; catalog # 6008280). To each of the experimental wells was transferred 1500 recombinant CHO-K1 cells in 5 µL phosphate buffered saline containing calcium chloride and magnesium chloride ("PBS+"; Invitrogen, Carlsbad, CA; catalog # 14040) supplemented with IBMX (250 µM) and rolipram (20 µM) (phosphodiesterase inhibitors; Sigma-Aldrich, St. Louis, MO; catalog # 15879 and catalog # R6520, respectively), followed by test compound in 5 µL compound buffer (PBS+ supplemented with 10 µL NKH477 (water-soluble forskolin derivative; SignaGen Laboratories, Gaithersburg, MD; catalog # PKI-NKH477-010)) or 5 µL compound buffer. The plate was then incubated at room temperature for 1 hour. To each well was then added 5 µL cAMP-d2 conjugate in lysis buffer and 5 µL Cryptate conjugate in lysis buffer according to the kit manufacturer's instructions. The plate was then further incubated at room temperature for 1 hour, after which the assay plate was read.

Assay readout: HTRF® readout was accomplished using a PHERAnstar (BMG LABTECH Inc., Durham, NC) or EnVision™ (PerkinElmer, Fremont CA) microplate reader.

Certain compounds of the present invention and their corresponding activity values are shown in Table B.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>EC_{50} S1P1 (HTRF®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.4 nM</td>
</tr>
<tr>
<td>4</td>
<td>0.8 nM</td>
</tr>
</tbody>
</table>

Compounds of the invention had activity values ranging from about 0.5 to about 2.4 nM in this assay.

Example 3: Cellular/Functional Ca^{2+} Assay for Agonist Activity on S1P3 Receptor.

A compound of the invention can be shown to have no or substantially no agonist activity at the S1P3 receptor using in assay a human neuroblastoma cell line which endogenously expresses S1P3 (predominantly), S1P2 and S1P5 receptors, but not SIPl or S1P4 receptors, based on mRNA analysis (Villulas et al, J. Neurosci. Res., 73:215-226, 2003). Of
these, S1P3 and S1P2 receptors respond to agonists, such as S1P, with an intracellular calcium increase. No or substantially no increase of intracellular calcium in response to a test compound is indicative of the test compound exhibiting no or substantially no agonist activity on the S1P3 receptor. Such an assay can be performed commercially, e.g. by Caliper LifeSciences (Hopkinton, MA).

Assay: The human neuroblastoma cells are washed and resuspended in physiological buffer. The cells are then loaded with dye that measures intracellular calcium. S1P is used as a reference agonist. After addition of S1P or a test compound, fluorescence is measured at 485 nm excitation / 525 nm emission every 2 s for at least 60 s. Calcium ionophore A23187 is then added as an internal positive control.

Example 4: Effect of compounds in Peripheral Lymphocyte Lowering (PLL) Assay.

A compound of the invention can be shown to induce peripheral lymphocyte lowering (PLL).

A. Mouse PLL Assay.

Animals: Male BALB/c mice (6 to 7 weeks of age at start of study) (Charles River Laboratories, Wilmington, MA) were housed four per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange, CA, Rodent Diet 8604) and water. Mice were allowed one week of habituation to the animal facility before testing.

PLL Assay: Mice were administered one of the following viap.o.: saline, vehicle (100% PEG400) or 1 mg/kg of Compound 1 or Compound 2 in vehicle, in a total volume of 5 mL/kg. Peripheral blood samples were collected at 5 hours post dose. The mice were anesthetized with isoflurane and bled retro-orbitally (300 μL) into 1.5 mL EDTA tubes. A complete cell count (CBC) (including lymphocyte count) was obtained using CELL-DYN® 3700 (Abbott Laboratories, Abbott Park, IL). Results are presented in Figures 1 and 2, in which peripheral blood lymphocyte (PBL) count is shown for the 5 hour group. Reduction of the peripheral blood lymphocyte count by the test compound in comparison with vehicle is indicative of the test compound exhibiting activity for inducing peripheral lymphocyte lowering.

It is apparent from inspection of Figures 1 and 2 that Compound 1 and Compound 2 exhibited activity for inducing peripheral lymphocyte lowering (lymphopenia) in the mouse.

B. Rat PLL Assay.

Animals: Male Sprague-Dawley rats (7 weeks of age at start of study) (Charles River Laboratories) are housed two per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange, CA, Rodent Diet 8604) and water. Rats are allowed one week of habituation to the animal facility before testing.
PLL Assay: Rats are orally administered vehicle or test compound (e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg) in vehicle, in a total volume of 5 mL/kg. Peripheral blood samples are collected at 1, 3, 5, 8, 16 and 24 hours post dose. At each time point, the rats are anesthetized with isoflurane and bled retro-orbitally (200 µL) into 1.5 mL EDTA tubes. A complete cell count (CBC) (including lymphocyte count) is obtained using CELL-DYN® 3700 (Abbott Laboratories, Abbott Park, IL). Reduction of the peripheral blood lymphocyte count by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic activity for inducing peripheral lymphocyte lowering.

Example 5: Effect of Compounds on Experimental Autoimmune Encephalomyelitis (EAE).

A compound of the invention can be shown to have therapeutic efficacy in multiple sclerosis by showing it to have therapeutic efficacy in experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis. In certain exemplary well-established models, EAE is induced in rodents by injection of myelin oligodendrocyte glycoprotein (MOG) peptide, by injection of myelin basic protein (MBP) or by injection of proteolipid protein (PLP) peptide.

A. MOG-induced EAE in Mice.

Animals: Female C57BL/6 mice (8 to 10 weeks of age at start of study) (Jackson Laboratory, Bar Harbor, ME) are housed four per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange, CA, Rodent Diet 8604) and water. Mice are allowed one week of habituation to the animal facility before testing.

Induction of EAE: Mice are immunized subcutaneously, 50 µL per hind flank, with a total of 100 µg MOG_{35-55} peptide emulsified 1:1 with Complete Freund's adjuvant containing 4 mg/mL heat-killed Mycobacterium tuberculosis. Mice also receive 200 ng pertussis toxin intraperitoneally on the day of immunization and 48 hours later.

Clinical scoring: Severity of disease symptoms is scored as follows (in increasing order of severity): 0 = normal; 1 = limp tail OR hind limb weakness; 2 = limp tail AND limb weakness / weakness of 2 or more limbs; 3 = severe limb weakness or single limb paralysis; 4 = paralysis of 2 or more limbs; 5 = death.

Drug treatment: Mice are dosed orally, with vehicle or a test compound, once a day from day 3 until day 21. Dosing volume is 5mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg. Mice are weighed daily. Mice are monitored daily from day 7 onward for disease symptoms. After the last dose on day 21, disease progression is monitored daily for 2 more weeks. Reduction of the severity of disease symptoms by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in EAE.
B. PLP-induced EAE in Mice.

Animals: Female SJL/J mice (8 to 10 weeks of age at start of study) (Jackson Laboratory, Bar Harbor, ME) are housed four per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange, CA, Rodent Diet 8604) and water. Mice are allowed one week of habituation to the animal facility before testing.

Induction of EAE: Mice are immunized subcutaneously with 100 µg PLP139-151 peptide emulsified 1:1 with Complete Freund’s adjuvant containing 4 mg/mL heat-killed Mycobacterium tuberculosis. Mice also receive 200 ng pertussis toxin intravenously on the day of immunization.

Clinical scoring: Severity of disease symptoms is scored as follows (in increasing order of severity): 0 = normal; 1 = limp tail OR hind limb weakness; 2 = limp tail AND limb weakness / weakness of 2 or more limbs; 3 = severe limb weakness or single limb paralysis; 4 = paralysis of 2 or more limbs; 5 = death.

Drug treatment: Mice are dosed orally, with vehicle or a test compound, once a day from day 3 until day 21. Dosing volume is 5mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg. Mice are weighed daily. Mice are monitored daily from day 7 onward for disease symptoms. After the last dose on day 21, disease progression is monitored daily for two more weeks.

C. MBP-induced EAE in Rats.

Animals: Male Lewis rats (325-375 g at start of study) (Harlan, San Diego, CA) are housed two per cage and maintained in a humidity- (30-70%) and temperature- (20-22 °C) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 A.M.) with free access to food (Harlan-Teklad Western Res., Orange, CA, Rodent Diet 8604) and water. Rats are allowed one week of habituation to the animal facility before testing. During the study, rats are weighed daily prior to clinical scoring at 11 am.

Induction of EAE: Myelin basic protein (MBP; guinea pig) is dissolved in sterile saline at a concentration of 1 mg/ml, and then emulsified 1:1 with Complete Freund’s adjuvant (1mg/ml). 50 µL of this emulsion is administered by intraplantar (ipl) injection into both hind paws of each rat, for a total injected volume of 100 µL per rat and a total dose of 50 µg of MBP per rat.

Clinical scoring: Severity of disease symptoms is scored daily after body weighing and before drug dosing. Severity of disease symptoms is scored as follows (in increasing order of severity): 0 = normal; 1 = tail OR limb weakness; 2 = tail AND limb weakness; 3 = severe hind limb weakness or single limb paralysis; 4 = loss of tail tone and paralysis of 2 or more limbs; 5 = death.
**Drug treatment:** Rats are dosed orally, with vehicle or a test compound, 1 hour prior to MBP injection on day 0 and daily thereafter, after clinical scoring, for the duration of the study. Dosing volume is 5 mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg. Reduction of the severity of disease symptoms by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in EAE.

**Example 6: Effect of Compounds on Type I Diabetes.**

A compound of the invention can be shown to have therapeutic efficacy in Type I diabetes using an animal model for Type I diabetes, such as cyclophosphamide induced Type I diabetes in mice.

**Animals:** Baseline blood glucose measurements are taken from 9-10 week old female NOD/Ltj mice (Jackson Laboratory, Bar Harbor, ME) to ensure that they are normoglycemic (blood glucose is 80-120 mg/dL) prior to initiation of the experiment. Blood glucose is measured from tail bleeds using a OneTouch® Ultra® meter and test strips (LifeScan, Milpitas, CA).

Cyclophosphamide **induction of type I diabetes:** On day 0 and day 14, normoglycemic NOD mice are injected intraperitoneally with 4 mg of cyclophosphamide monohydrate (200 mg/kg) dissolved in 0.9% saline. If mice are diabetic (blood glucose is >250 mg/dL), they are not given a booster dose of cyclophosphamide on day 14.

**Drug treatment:** Mice are dosed orally, with vehicle or test compound, once a day from day 0 until day 25. Compounds are suspended in 0.5% methyl cellulose vehicle using a sonicator to ensure uniform suspension. Mice are weighed twice weekly and are dosed according to weight. Dosing volume is 5 mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg. Blood glucose is measured twice weekly. After dosing is completed at day 25, the mice continue to be monitored and blood glucose measurements are taken once a week for 3 weeks. Promotion of normoglycemia by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in Type I diabetes.

**Example 7: Allograft Survival.**

A compound of the invention can be shown to have therapeutic efficacy in prolonging allograft survival by showing it to have therapeutic efficacy in prolonging, e.g., survival of a skin allograft in an animal model.

**Animals:** Female BALBc/J mice (6 to 7 weeks of age at start of study) (Jackson Laboratory, Bar Harbor, ME) are housed four per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange, CA, Rodent Diet 8604) and water. Female C57BL/6 mice (8 to 10 weeks of age at start of study) (Jackson Laboratory, Bar Harbor, ME)
are similarly housed and maintained. Mice are allowed one week of habituation to the animal facility before testing.

**Skin allograft:** Balbc/J and C57BL/6 mice are used as donors and recipients, respectively, in a model of skin allograft transplantation. Donor Balbc/J mice are anesthetized, and 0.5 cm-diameter full thickness areas of abdominal skin are surgically removed. Skin grafts harvested from the Balbc/J mice are sutured onto the dorsum of anesthetized recipient C57BL/6 mice. Sutured allografts are covered with Vaseline gauze and Bolster dressing for 7 days. The allografted mice are divided into eight groups of 8 mice each.

**Clinical scoring:** Skin allografts are inspected and digital images recorded daily until rejection, which is defined as the first day on which more than 80% of the graft is necrotic. Histological analysis of the rejected graft is carried out on hematoxylin and eosin (H & E)-stained sections. In an optional related study, on post-transplantation day 5, isolated lymphocytes from peripheral lymph nodes and spleen are counted and characterized for activation markers (e.g., T-cell activation markers) by flow cytometry. Also on day 5, grafts are removed from transplanted recipients, cut into small fragments, digested with collagenase and sedimented over Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden) to isolate graft-infiltrating lymphocytes, which are counted and characterized for activation markers (e.g., T-cell activation markers) by flow cytometry. Histological analysis of the graft on day 5 can be carried out on hematoxylin and eosin (H&E)-stained sections.

**Drug treatment:** Mice are dosed orally, with vehicle or test compound, once a day from the day of transplantation until the end of the study, e.g. until day 14, 21 or 28. Dosing volume is 5 mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg. Delay of time of rejection of the skin allograft by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in prolonging skin allograft survival.

Example 8: Effect of Compounds on Colitis.

Compounds can be commercially tested for efficacy in at least DSS-induced colitis and TNBS-induced colitis, e.g. by the Jackson Laboratory (Bar Harbor, ME).

A. Mouse Model for Colitis.

**Animals:** Male BALB/c mice (6 weeks of age at start of study) (Jackson Laboratory, Bar Harbor, ME) are housed four per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange CA, Rodent Diet 8604) and water. Mice are allowed one week of habituation to the animal facility before testing.

**TNBS induction of colitis:** Mice are weighed for baseline body weights and fasted later that day beginning at 6:15 pm just prior to lights-out (day 0). Body weights are taken again the following morning (day 1) at approximately 7:30 am. Mice are anesthetized with isoflurane prior to induction of colitis. Colitis is induced in the mice by intracolonic injection of about 150 mg/kg TNBS in 50% ethanol (in a volume of 150 µL) using an intubation needle (22 guage, 1.5 in) inserted completely into the anus with the mouse held by the tail in a vertical position. The mouse is held vertically for 30 additional seconds to allow thorough absorption and minimize leakage, after which the mouse is returned to its cage. Mice are then fed, following the preceding approximately 14 hour of fasting. Each morning thereafter, the mice are weighed. In control experiments, mice receive 50% ethanol alone using the same protocol.

**Drug treatment:** Drug treatment begins on day 2. Mice are dosed orally, with vehicle or a test compound, once a day from day 2 until the conclusion of the experiment on, e.g., day 7, 14 or 21. Dosing volume is 5 mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg.

**Clinical scoring:** Upon conclusion of the experiment, colons are extracted and measured. Mice are euthanized with CO2 and colon is removed from anus to cecum. Excised colon is measured for entire length, length from anus to end of inflamed area and length of inflamed (affected) area. After measurements, colon is cleared of excrement by flushing with saline and then cut open to clear more thoroughly. Colon is then weighed and preserved in neutral buffered formalin (NBF; 10% formalin, pH 6.7-7.0). The colon tissue is embedded in paraffin and processed for hematoxylin and eosin (H & E)-stained sections. Severity of disease symptoms is scored histologically from the stained sections as follows: 0 = no evidence of inflammation; 1 = low level of leukocyte infiltration with infiltration seen in <10% of high-power fields AND no structural changes; 2=moderate leukocyte infiltration with infiltration seen in 10% to 25% of high-power fields AND crypt elongation AND bowel wall thickening that does not extend beyond the mucosal layer AND no ulcerations; 3 = high level of leukocyte infiltration seen in 25% to 50% of high-power fields AND crypt elongation AND infiltration beyond the mucosal layer AND thickening of the bowel wall AND superficial ulcerations; 4 = marked degree of transmural leukocyte infiltration seen in >50% of high-power fields AND elongated and distorted crypts AND bowel-wall...
thickening AND extensive ulcerations. Reduction of the severity of the disease symptoms by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in colitis.

B. Rat Model for Colitis.

**Animals:** Male Wistar rats (175-200 g at start of study) (Charles River Laboratories, Wilmington, MA) are housed two per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30am) with free access to food (Harlan Teklad, Orange CA, Rodent Diet 8604) and water. Rats are allowed one week of habitation to the animal facility before testing.

**TNBS induction of colitis:** Rats are weighed for baseline body weights and fasted later that day beginning at 6:15 pm just prior to lights-out (day 0). Body weights are taken again the following morning (day 1) at approximately 7:30 am. Rats are anesthesitized with isoflurane prior to induction of colitis. Colitis is induced in the rats by intracolonic injection of about 60 mg/kg TNBS in 50% ethanol (in a volume of 500 µL) using a fabricated intubation needle (7.5 Fr umbilical catheter and 14 g hub) inserted 8cm into the anus with the rat held by the tail in a vertical position. The rat is held vertically for an additional 30 seconds to allow thorough absorption and minimize leakage, after which the rat is returned to its cage. Rats are then fed, following the preceding approximately 14 h of fasting. Each morning thereafter, the rats are weighed. In control experiments, rats receive 50% ethanol alone using the same protocol..

**Drug treatment:** Drug treatment begins on day 2. Rats are dosed orally, with vehicle or test compound, once a day from day 2 until the conclusion of the experiment on, e.g., day 7, 14 or 21. Dosing volume is 5 mL/kg. Test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg.

**Clinical scoring:** Upon conclusion of the experiment, colons are extracted and measured. Rats are euthanized with CO₂ and colon is removed from anus to cecum. Excised colon is measured for entire length, length from anus to end of inflamed area, and length of inflamed (affected) area. After measurements, colon is cleared of excrement by flushing with saline and then cut open to clear more thoroughly. Colon is then weighed and preserved in neutral buffered formalin (NBF; 10% formalin, pH 6.7-7.0). The colon tissue is embedded in paraffin and processed for hematoxylin and eosin (H & E)-stained sections. Severity of disease symptoms is scored histologically from the stained sections as follows: 0 = no evidence of inflammation; 1 = low level of leukocyte infiltration with infiltration seen in <10% of high-power fields AND no structural changes; 2 = moderate leukocyte infiltration with infiltration seen in 10% to 25% of high-power fields AND crypt elongation AND bowel wall thickening that does not extend beyond the mucosal layer AND no ulcerations; 3 = high level of leukocyte infiltration seen in 25% to 50% of high-power fields AND crypt elongation AND infiltration beyond the mucosal layer AND thickening of the bowel wall AND superficial ulcerations; 4 = marked degree of transmural leukocyte infiltration seen in >50%
of high-power fields AND elongated and distorted crypts AND bowel-wall thickening AND extensive ulcerations. Reduction of the severity of the disease symptoms by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in colitis.

Example 9: Effects of Compounds on Cardiac Telemetry in the Rat.

Animals: Male Sprague-Dawley rats (250-300 g at time of surgery) are implanted by Charles River Laboratories (Wilmington, MA) with cardiac transmitting devices (Data Sciences PhysioTel C50-PXT) into the peritoneal space, with a pressure-sensing catheter inserted into the descending aorta. Rats are allowed at least one week to recover. Rats are housed in individual cages and maintained in a humidity- (30-70%) and temperature- (20-22 °C) controlled facility on a 12 h:12 h light/dark cycle (lights on at 7:00 am) with free access to food (Harlan-Teklad, Orange, CA, Rodent Diet 8604) and water. Rats are allowed one week of habituation to the animal facility before testing.

Measurement of cardiovascular parameters: The implanted transmitting devices transmit continuous measurements of blood pressure (systolic, diastolic, mean arterial, pulse), heart rate, body temperature, and motor activity in freely moving conscious animals. These data are transmitted via radiofrequency to a computer which bin the data into 1 minute averages using DataSciences ART software. Telemetry recording occurs over a 21-h period, starting at noon and continuing until 9:00 am the following day. A maximum of eight rats are tested at a time, and the same eight rats are utilized for all treatment groups in a within-subject design.

Drug treatment: Rats are injected orally with vehicle or compound at 1:00pm. A full study (vehicle + 3 doses) requires four separate testing sessions, which occur on Mondays-Tuesdays and Thursdays-Fridays. During each of the testing sessions, the eight rats are divided into four treatment groups such that each group comprises N = 2 for any given session. Rats are re-tested in subsequent testing sessions in a crossover design such that by the end of the four sessions, all animals receive all treatments in a pseudo-random order, and each group comprises N = 8.

Exemplary bradycardia assay: It is expressly contemplated that the rats can be used to show that a compound of the invention has no or substantially no activity for bradycardia. By way of illustration and not limitation, the rats are administered vehicle or a test compound and heart rate is then measured over a 120 minute period. No or substantially no reduction of heart rate in response to the test compound in comparison with vehicle is indicative of the test compound exhibiting no or substantially no activity for bradycardia.

Those skilled in the art will recognize that various modifications, additions, substitutions and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the
invention. All documents referenced above, including, but not limited to, printed publications and provisional and regular patent applications, are incorporated herein by reference in their entirety.
What is claimed is:

1. A compound selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

   ![Chemical Structure](image)

   \[ \text{(Ia)} \]

   wherein:
   - Y is N or CH;
   - Z is N or CR¹;
   - R¹, R², and R³ are each independently selected from the group consisting of H, Ci-C₆ alkoxy, Ci-C₆ alkyl, Q-C₆ alkylsulfonyl, C₁-C₆ alkylthio, cyano, C₃-C₇ cycloalkyl, Q-C₆ haloalkoxy, Ci-C₆ haloalkyl, halogen, heteroaryl, and heterocyclyl, wherein said Ci-C₆ alkyl and Q-C₆ alkoxy are each optionally substituted with one C₃-C₇ cycloalkyl group.

2. The compound according to claim 1, wherein Y is CH.

3. The compound according to claim 1 or 2, wherein Z is CR¹.

4. The compound according to any one of claims 1 to 3, wherein R¹, R², and R³ are each independently selected from the group consisting of H, Ci-C₆ alkoxy, Ci-C₆ alkyl, C₁-C₆ alkylsulfonyl, cyan, C₃-C₇ cycloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, halogen, and heteroaryl.

5. The compound according to any one of claims 1 to 3, wherein R¹, R², and R³ are each independently selected from the group consisting of H, chloro, cyano, cyclopentyl, difluoromethoxy, ethyl, methoxy, methylsulfonyl, thien-2-yl, trifluoromethoxy, and trifluoromethyl.

6. The compound according to any one of claims 1 to 5, wherein R¹ is selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkylsulfonyl, cyan, C₁-C₆ haloalkoxy, Q-C₆ haloalkyl, and halogen.
7. The compound according to any one of claims 1 to 5, wherein R1 is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

8. The compound according to any one of claims 1 to 7, wherein R2 is selected from the group consisting of H, C1-C6 alkoxy, C1-C6 alkyl, C3-C7 cycloalkyl, Ci-C6 haloalkoxy, halogen, and heteroaryl.

9. The compound according to any one of claims 1 to 7, wherein R2 is selected from the group consisting of H, chloro, cyclopentyl, difluoromethoxy, ethyl, methoxy, thien-2-yl, and trifluoromethoxy.

10. The compound according to any one of claims 1 to 9, wherein R3 is selected from the group consisting of H, C1-C6 alkoxy, C1-C6 alkylsulfonyl, cyano, Ci-C6 haloalkoxy, C1-C6 haloalkyl, and halogen.

11. The compound according to any one of claims 1 to 9, wherein R3 is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

12. The compound according to claim 1, selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

   Y is N or CH;
   Z is N or CR1;
   R1 is selected from the group consisting of H, Ci-C6 alkoxy, C1-C6 alkylsulfonyl, C1-C6 alklythio, C1-C6 alkylamino, cyano, C1-C6 haloalkoxy, Q-C6 haloalkyl, and halogen;
   R2 is selected from the group consisting of H, C1-C6 alkoxy, C1-C6 alkyl, C3-C7 cycloalkyl, C1-C6 haloalkoxy, halogen, heteroaryl and heterocyclyl, wherein said C1-C6 alkyl and C1-C6 alkoxy are each optionally substituted with one C3-C7 cycloalkyl group; and
   R3 is selected from the group consisting of H, C1-C6 alkoxy, C1-C6 alkylsulfonyl, Ci-C6 alklythio, C1-C6 alkylamino, cyano, C1-C6 haloalkoxy and C1-C6 haloalkyl, and halogen.

13. The compound according to claim 1, selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:
Y is N or CH;
Z is N or CR;

R1 is selected from the group consisting of chloro, cyano, ethylamino, methoxy, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl;

R2 is selected from the group consisting of H, Q-C6 alkoxy, Ci-C6 alkyl, C3-C7 cycloalkyl, C1-C6 haloalkoxy, halogen, heteroaryl and heterocyclyl, wherein said C1-C6 alkyl and Q-C6 alkoxy are each optionally substituted with one C3-C7 cycloalkyl group; and

R3 is selected from the group consisting of H, Ci-C6 alkoxy, Ci-C6 alkylsulfonyl, C1-C6 alkylthio, Q-C6 alkylamino, cyano, Q-C6 haloalkoxy and Q-C6 haloalkyl and halogen.

14. The compound according to claim 1, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

\[
\text{(Ic)}
\]

wherein:

R1, R2, and R3 are each independently selected from the group consisting of H, Ci-C6 alkoxy, Ci-C6 alkyl, Ci-C6 alkylsulfonyl, cyano, C3-C7 cycloalkyl, Q-C6 haloalkoxy, C1-C6 haloalkyl, halogen, and heteroaryl.

15. The compound according to claim 14, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof wherein:

R1 is selected from the group consisting of H, Q-C6 alkoxy, C1-C6 alkylsulfonyl, cyano, C1-C6 haloalkoxy, Ci-C6 haloalkyl, and halogen;

R2 is selected from the group consisting of H, Ci-C6 alkoxy, C1-C6 alkyl, C3-C7 cycloalkyl, Ci-C6 haloalkoxy, halogen, and heteroaryl; and

R3 is selected from the group consisting of H, Ci-C6 alkoxy, Ci-C6 alkylsulfonyl, cyano, Q-C6 haloalkoxy, Q-C6 haloalkyl, and halogen.

16. The compound according to claim 14, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof wherein:
R₁, R₂, and R₃ are each independently selected from the group consisting of H, chloro, cyano, cyclopentyl, difluoromethoxy, ethyl, methoxy, methylsulfonyl, thien-2-yl, trifluoromethoxy, and trifluoromethyl.

17. The compound according to claim 14, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:
R₁ is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl;
R₂ is selected from the group consisting of H, chloro, cyclopentyl, difluoromethoxy, ethyl, methoxy, thien-2-yl, and trifluoromethoxy; and
R₃ is selected from the group consisting of H, chloro, cyano, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

18. The compound according to claim 14, selected from compounds of Formula (Ic) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:
R₁ is selected from the group consisting of chloro, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl;
R₂ is selected from the group consisting of H, chloro, cyclopentyl, difluoromethoxy, ethyl, methoxy, and thien-2-yl; and
R₃ is H, cyano, and trifluoromethyl.

19. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:
(R)-3-(5-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(i?)-3-(5-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(5)-3-(5-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid; and
(S)-3-(5-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid.

20. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:
(i?)-3-(5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(4-methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(5)-3-(5-(5-(4-chloro-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(S)-3-(5-(5-(4-(methoxy-3-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(S)-3-(5-(5-(4-(difluoromethoxy)-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(5-(3-chloro-^cyclopentylphenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(5-(4-ethyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(5-(4-ethyl-3-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid;
(R)-3-(5-(5-(4-(thiophen-2-yl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid; and
(i?)-3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)indolin-2-yl)propanoic acid.

21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20, and a pharmaceutically acceptable carrier.

22. A method for treating a disorder associated with the SIPI receptor in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

23. A method for treating a disorder associated with the SIPI receptor in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21, wherein said disorder is selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes,
hypertensive nephropathy, glomerulosclerosis, myocardial ischemia-reperfusion injury, and acne.

24. A method for treating a disease or disorder mediated by lymphocytes in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

25. A method for treating an autoimmune disease or disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

26. A method for treating an inflammatory disease or disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

27. A method for treating psoriasis in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

28. A method for treating rheumatoid arthritis in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

29. A method for treating Crohn's disease in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

30. A method for treating transplant rejection in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.
31. A method for treating multiple sclerosis in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

32. A method for treating systemic lupus erythematosus in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

33. A method for treating ulcerative colitis in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

34. A method for treating type I diabetes in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 21.

35. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a disorder associated with the SIPl receptor.

36. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a disorder associated with the SIPl receptor selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, hypertensive nephropathy, glomerulosclerosis, myocardial ischemia-reperfusion injury, and acne.

37. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a disease or disorder mediated by lymphocytes.

38. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of an autoimmune disease or disorder.

39. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of an inflammatory disease or disorder.
40. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of psoriasis.

41. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of rheumatoid arthritis.

42. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of Crohn's disease.

43. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of transplant rejection.

44. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of multiple sclerosis.

45. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of systemic lupus erythematosus.

46. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of ulcerative colitis.

47. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of type I diabetes.

48. A compound according to any one of claims 1 to 20 for use in a method for the treatment of the human or animal body by therapy.

49. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a disorder associated with the SIPI receptor.

50. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a disorder associated with the SIPI receptor selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, hypertensive nephropathy, glomerulosclerosis, myocardial ischemia-reperfusion injury, and acne.
51. A compound according to any one of claims 1 to 20 for use in a method for the treatment of a disease or disorder mediated by lymphocytes.

52. A compound according to any one of claims 1 to 20 for use in a method for the treatment of an autoimmune disease or disorder.

53. A compound according to any one of claims 1 to 20 for use in a method for the treatment of an inflammatory disease or disorder.

54. A compound according to any one of claims 1 to 20 for use in a method for the treatment of psoriasis.

55. A compound according to any one of claims 1 to 20 for use in a method for the treatment of rheumatoid arthritis.

56. A compound according to any one of claims 1 to 20 for use in a method for the treatment of Crohn's disease.

57. A compound according to any one of claims 1 to 20 for use in a method for the treatment of transplant rejection.

58. A compound according to any one of claims 1 to 20 for use in a method for the treatment of multiple sclerosis.

59. A compound according to any one of claims 1 to 20 for use in a method for the treatment of systemic lupus erythematosus.

60. A compound according to any one of claims 1 to 20 for use in a method for the treatment of ulcerative colitis.

61. A compound according to any one of claims 1 to 20 for use in a method for the treatment of type I diabetes.

62. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 20, and a pharmaceutically acceptable carrier.
Mouse Peripheral Lymphocyte Lowering (PLL) Assay (p.o., 5 h)

- 1 mg/kg Compound 1
- 100% PEG 400 Vehicle
- Saline

Absolute Lymphocyte Count (1000/µl)
### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04 C07D413/14 A61K31/4196 A61P1/00 A61P3/10 A61P17/06 A61P19/00 A61P37/00 A61P37/06

According to International Patent Classification (IPC) and its national classification and IPC.

### B. FIELDS SEARCHED

Minimum documentation/field (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2009/080729 A (GLAXO GROUP LTD [GB]); HEER JAG PAUL [GB]; HEIGHTMAN THOMAS</td>
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<td>WO 2009/078983 A (ARENA PHARM INC [US]); JONES ROBERT M [US]; BUZARD DANIEL J</td>
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- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **L** document which may throw doubts on patentability of the invention claimed in the international patent application
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

15 September 2009

Date of mailing of the international search report

22/09/2009

Name and mailing address of the ISA/Authorized officer

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Gettins, Marc

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