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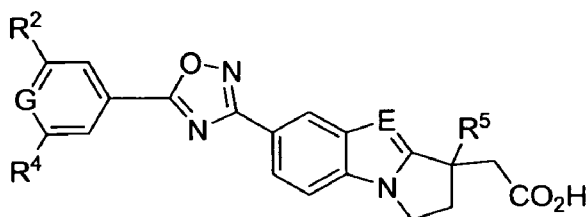
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(54) Title: DISUBSTITUTED OXADIAZOLE DERIVATIVES USEFUL IN THE TREATMENT OF AUTOIMMUNE AND IN-
 FLAMMATORY DISORDERS



(Ia)

(57) Abstract: The present invention relates to certain disubstituted oxadiazole derivatives of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates 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 S1P1-associated disorders, for example, psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, biliary cirrhosis, microbial infections and associated diseases, viral infections and associated diseases, diseases and disorders mediated by lymphocytes, auto immune diseases, inflammatory diseases, and cancer.

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**DISUBSTITUTED OXADIAZOLE DERIVATIVES USEFUL IN THE TREATMENT OF
AUTOIMMUNE AND INFLAMMATORY DISORDERS**

FIELD OF THE INVENTION

5 The present invention relates to certain disubstituted oxadiazole derivatives of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates 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
10 invention in the treatment of S1P1-associated disorders, for example, psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, biliary cirrhosis, microbial infections and associated diseases, viral infections and associated diseases,
15 diseases and disorders mediated by lymphocytes, auto immune diseases, inflammatory diseases, and cancer.

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
20 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
25 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 (S1P) receptors 1-5 constitute a family of G protein-coupled receptors with a seven-transmembrane domain. These receptors, referred to as S1P1 to
30 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,
35 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.

S1P 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 S1P 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 S1P 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).

In clinical trials, FTY720 elicited an adverse event (*i.e.*, transient asymptomatic bradycardia) due to its agonism of the S1P3 receptor (Budde *et al.*, *J. Am. Soc. Nephrol.*, 13:1073-1083, 2002; Sanna *et al.*, *J. Biol. Chem.*, 279:13839-13848, 2004; Ogawa *et al.*, *BBRC*, 361:621-628, 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 (Kiyabayashi *et al.*, *J. Cardiovasc. Pharmacol.*, 35:410-416, 2000; Miyamoto *et al.*, *J. Am. Coll. Cardiol.*, 37:1713-1718, 2001); mouse models for inflammatory bowel disease including colitis (Mizushima *et al.*, *Inflamm. Bowel Dis.*, 10:182-192, 2004; Deguchi *et al.*, *Oncology Reports*, 16:699-703, 2006; Fujii *et al.*, *Am. J. Physiol. Gastrointest. Liver Physiol.*, 291:G267-G274, 2006; Daniel *et al.*, *J. Immunol.*, 178:2458-2468, 2007); a rat model for progressive mesangioproliferative glomerulonephritis (Martini *et al.*, *Am. J. Physiol. Renal Physiol.*, 292:F1761-F1770, 2007); a mouse model for asthma, suggested to be primarily through the S1P1 receptor on the basis of work using the S1P1 receptor agonist SEW2871 (Idzko *et al.*, *J. Clin. Invest.*, 116:2935-2944, 2006); a mouse model for airway inflammation and induction of bronchial hyperresponsiveness (Sawicka *et al.*, *J. Immunol.*, 171:6206-6214, 2003); a mouse model for atopic dermatitis (Kohno *et al.*, *Biol. Pharm. Bull.*, 27:1392-1396, 2004); a mouse model for ischemia-reperfusion injury (Kaudel *et al.*, *Transplant. Proc.*, 39:499-502, 2007); a mouse model for systemic lupus erythematosus (SLE) (Okazaki *et al.*, *J. Rheumatol.*, 29:707-716, 2002; Herzinger *et al.*, *Am. J. Clin. Dermatol.*, 8:329-336, 2007); rat models for rheumatoid arthritis (Matsuura *et al.*, *Int. J. Immunopharmacol.*, 22:323-331, 2000; Matsuura *et al.*, *Inflamm. Res.*, 49:404-410, 2000); a rat model for autoimmune uveitis (Kurose *et al.*, *Exp. Eye Res.*, 70:7-15, 2000); mouse models for type I diabetes (Fu *et al.*, *Transplantation*, 73:1425-1430, 2002; Maki *et al.*, *Transplantation*, 74:1684-1686, 2002; Yang *et al.*, *Clinical Immunology*, 107:30-35, 2003; Maki *et al.*, *Transplantation*, 79:1051-1055, 2005); mouse models for atherosclerosis (Nofer *et al.*, *Circulation*, 115:501-508, 2007; Keul *et al.*, *Arterioscler. Thromb. Vasc. Biol.*, 27:607-613, 2007); a rat model for brain inflammatory reaction following traumatic brain injury (TBI) (Zhang *et al.*, *J. Cell. Mol. Med.*, 11:307-314, 2007); and mouse models for graft coronary artery disease and graft-versus-host disease (GVHD) (Hwang *et al.*, *Circulation*, 100:1322-1329, 1999; Taylor *et al.*, *Blood*, 110:3480-3488, 2007). *In vitro* results suggest that FTY720 may have therapeutic efficacy for β -amyloid-related inflammatory diseases including Alzheimer's disease (Kaneider *et al.*, *FASEB J.*, 18:309-311, 2004). KRP-203, an S1P receptor agonist having agonist activity on the S1P1 receptor, has been reported to have therapeutic efficacy in a rat model for autoimmune myocarditis (Ogawa *et al.*, *BBRC*, 361:621-628, 2007). Using the S1P1 receptor agonist SEW2871, it has been shown that agonism of endothelial S1P1 receptors prevents proinflammatory monocyte/endothelial interactions in type I diabetic vascular endothelium (Whetzel *et al.*, *Circ. Res.*, 99:731-739, 2006) and protects the vasculature against TNF α -mediated monocyte/endothelial interactions (Bolick *et al.*, *Arterioscler. Thromb. Vasc. Biol.*, 25:976-981, 2005).

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. Magn. Reson. Imaging*, 20:16-24, 2004; Kataoka *et al.*, *Cellular & Molecular Immunology*, 2:439-448, 2005; Brinkmann *et al.*, *Pharmacology & Therapeutics*, 115:84-105, 2007;
- 5 Baumruker *et al.*, *Expert Opin. Investig. Drugs*, 16:283-289, 2007; Balatoni *et al.*, *Brain Research Bulletin*, 74:307-316, 2007). Furthermore, FTY720 has been found to have therapeutic efficacy for multiple sclerosis in clinical trials. In Phase II clinical trials for relapsing-remitting multiple sclerosis, FTY720 was found to reduce the number of lesions detected by magnetic resonance imaging (MRI) and clinical disease activity in patients with multiple sclerosis
- 10 (Kappos *et al.*, *N. Engl. J. Med.*, 355:1124-1140, 2006; Martini *et al.*, *Expert Opin. Investig. Drugs*, 16:505-518, 2007; Zhang *et al.*, *Mini-Reviews in Medicinal Chemistry*, 7:845-850, 2007; Brinkmann, *Pharmacology & Therapeutics*, 115:84-105, 2007). FTY720 is currently in Phase III studies of relapsing-remitting multiple sclerosis (Brinkmann, *Pharmacology & Therapeutics*, 115:84-105, 2007; Baumruker *et al.*, *Expert. Opin. Investig. Drugs*, 16:283-289, 2007; Dev *et al.*, *Pharmacology and Therapeutics*, 117:77-93, 2008).
- 15

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).

- 20 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, 2008).

- 25 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).

- 30 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 S1P controlled the migratory behavior of osteoclast precursors, dynamically regulating bone mineral homeostasis (Ishii *et al.*, *Nature*, advance online publication, 8 February 2009, doi:10.1038/nature07713).

- 35 Agonism of the S1P1 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 S1P1 receptor plays a role in platelet-derived growth factor (PDGF)-induced oligodendrocyte progenitor cell mitogenesis
5 (Jung *et al.*, *Glia*, 55:1656-1667, 2007).

Agonism of the S1P1 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*, 25:115-124, 2007).

Agonism of the S1P1 receptor has been implicated in the inhibition of keratinocyte proliferation (Sauer *et al.*, *J. Biol. Chem.*, 279:38471-38479, 2004), consistent with reports that
10 S1P 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 S1P1 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
20 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
25 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
30 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
35 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 S1P1 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 S1P 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 S1P1 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).

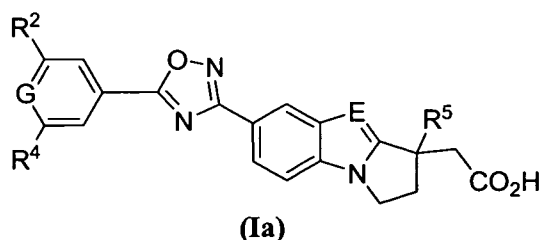
In one embodiment, the present invention encompasses compounds which are agonists of the S1P1 receptor having selectivity over the S1P3 receptor. The S1P3 receptor, and not the S1P1 receptor, has been directly implicated in bradycardia (Sanna *et al.*, *J. Biol. Chem.*, 279:13839-13848, 2004). An S1P1 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 S1P1 receptor and which exhibit no or substantially no activity for bradycardia.

S1P1 receptor agonists are useful for treating or preventing conditions where suppression of the immune system or agonism of the S1P1 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.

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:



wherein:

E is N or CR¹;

G is N or CR³;

R¹ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, cyano, C₁-C₆ haloalkyl, C₁-C₆ haloacyl, and halogen;

R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkyloxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen; and

R^5 is H or halogen.

- 5 The present invention encompasses compounds which 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.

- S1P1 receptor agonists are useful for treating or preventing conditions where
10 suppression of the immune system or agonism of the S1P1 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,
15 tumor development and atherosclerosis). Such conditions where suppression of the immune system or agonism of the S1P1 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;
20 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
25 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, atherosclerosis; cancer; chronic pulmonary disease;
30 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 an S1P1 receptor-associated disorder in an individual comprising administering to the individual in need thereof a
35 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 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.

5 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.

10 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.

15 One aspect of the present invention pertains to methods for treating a microbial infection or 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.

20 One aspect of the present invention pertains to methods for treating a viral infection or 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.

25 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. Examples of cancer include, but are not limited to, lung cancer, colon cancer, breast cancer, prostate cancer, pancreatic cancer, and hepatocellular carcinoma.

30 One aspect of the present invention pertains to methods for treating a disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof, 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, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

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

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

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

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

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

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

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

35 One aspect of the present invention pertains to methods for treating hypertensive nephropathy in an individual comprising administering to said 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 said 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 said 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 said 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 said 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 said 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 hepatitis in an individual comprising administering to said 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 said 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 an S1P1 receptor-associated 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 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 a microbial infection or disease.

5 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.

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. Examples of cancer include, but are not limited to, lung cancer, colon cancer, breast cancer, prostate cancer, pancreatic cancer, and hepatocellular carcinoma.

10 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 S1P1 receptor-associated disorder selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy,
15 glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

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.

20 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.

25 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.

30 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.

35 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 the use of compounds of the present invention in the manufacture of a medicament for the treatment of hypertensive nephropathy.

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 glomerulosclerosis.

5 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 gastritis.

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 polymyositis.

10 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 thyroiditis.

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 vitiligo.

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 hepatitis.

15 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 biliary cirrhosis.

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.

20 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of an S1P1 receptor-associated disorder.

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.

25 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 a microbial infection or disease.

30 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.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of cancer. Examples of cancer include, but are not limited to, lung cancer, colon cancer, breast cancer, prostate cancer, pancreatic cancer, and hepatocellular carcinoma.

35 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of an S1P1 receptor-associated disorder selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection,

multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

5 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.

10 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.

15 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.

20 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 myocardial ischemia-reperfusion injury.

25 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 gastritis.

30 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.

35 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 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 the exemplified enantiomer of Compound 4 (Example 1.3) to lower the absolute count of peripheral lymphocytes in rats compared to vehicle.

Figure 2 shows a general synthetic scheme for the preparation of compounds of Formula (**Ia**) wherein E is CR¹. The synthetic scheme shows the coupling of carboxylic acids or acid chlorides with *N*-hydroxy-carbamimidoyl intermediates and subsequent formation of the oxadiazole ring to provide ester intermediates. The esters can be converted to carboxylic acid using methods known in the art, for example, *t*-butyl esters are converted to carboxylic acids by treatment with an acid, such as TFA in the presence or absence of thioanisole or cysteine, methyl esters are converted to carboxylic acids by treatment with a base, such as LiOH, NaOH, KOH, and the like. The acid can then be converted to compounds of Formula (**Ia**) by using appropriate electrophiles known in the art, such as *N*-halosuccinimide.

Figure 3 shows alternative routes to give compounds of Formula (**Ia**) by introducing the R¹ group before the ester is hydrolyzed to the carboxylic acid and by subsequently introducing the alkyl group through a halogen intermediate.

Figure 4 shows synthetic methods to give compounds of Formula (**Ia**) wherein R¹ is alkylsulfonyl, cyano, or haloalkyl.

Figure 5 shows a general synthetic scheme for the preparation of compounds of Formula (**Ia**) wherein E is N.

DETAILED DESCRIPTION OF THE INVENTION

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 S1P1 receptor, such as can thereby initiate a physiological or pharmacological response characteristic of that receptor. For example, an agonist activates 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 S1P1 receptor agonist that is capable of

facilitating sustained S1P1 receptor internalization (see *e.g.*, Matloubian *et al.*, Nature, 427, 355, 2004).

5 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.

10 The term “**hydrate**” as used herein means a compound of the invention or a salt thereof, 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 compound of the invention or a salt, thereof, 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.

15 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.

25 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.

30 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, 35 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

5 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
10 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
15 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
20 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).

25 **CHEMICAL GROUP, MOIETY OR RADICAL**

The term “**C₁-C₆ acyl**” is intended to mean a C₁-C₆ alkyl radical attached to the carbon of a carbonyl group wherein the definition of alkyl has the same definition as described herein; some examples include, but are not limited to, acetyl, propionyl, *n*-butanoyl, *sec*-butanoyl, pivaloyl, pentanoyl, and the like.

30 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, *n*-propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, isobutoxy, *sec*-butoxy, and the like.

35 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, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isopentyl, *tert*-pentyl, *neo*-pentyl, 1-methylbutyl [*i.e.*, -CH(CH₃)CH₂CH₂CH₃], 2-methylbutyl [*i.e.*, -CH₂CH(CH₃)CH₂CH₃], *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, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl, *tert*-butylsulfonyl, and the like.

The term “**cyano**” is intended to mean the group -CN.

The term “**C₃-C₇ cycloalkoxy**” is intended to mean a saturated ring radical containing 3 to 7 carbons directly bonded to an oxygen atom. Some examples include cyclopropyl-O-, cyclobutyl-O-, cyclopentyl-O-, cyclohexyl-O-, and the like.

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 C₁-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.

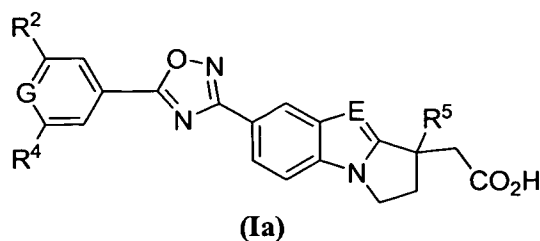
The term “**C₁-C₆ haloalkyl**” is intended to mean an C₁-C₆ alkyl group, defined herein, wherein the alkyl is substituted with between one halogen up to fully substituted wherein a fully substituted C₁-C₆ haloalkyl can be represented by the formula C_zL_{2z+1} wherein L is a halogen and “z” is 1, 2, 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 “**C₁-C₆ haloacyl**” is intended to mean a C₁-C₆ haloalkyl radical attached to the carbon of a carbonyl group wherein the definition of haloalkyl has the same definition as described herein; some examples include, but are not limited to, 2,2,2-trifluoroacetyl, 3,3,3-trifluoropropanoyl, 2,2-difluoropropanoyl, 2,2,3,3,3-pentafluoropropanoyl, 3,3,3-trifluoro-2-(trifluoromethyl)propanoyl, and the like.

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

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:



wherein:

- 5 E, G, R², R⁴, and R⁵ have the same definitions as described herein, *supra* and *infra*.

It is understood that the present invention embraces compounds, solvates and/or hydrates of compounds, pharmaceutically acceptable salts of compounds, and solvates and/or hydrates of pharmaceutically acceptable salts of compounds, wherein the compounds are as described herein.

- 10 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
- 15 represented by the variables (*e.g.*, E, G, R¹, R², R³, R⁴, and R⁵) contained within the generic chemical formulae described herein, for example, (Ia), (Ib), (Ic), (Ie), (Ig), (Ii), (Ik), (IIa), (IIIa), (IIIb), (IIIc), (IIId), *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 stable compounds (*i.e.*, compounds that can be isolated, characterized
- 20 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.

- 25 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
- 30 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.

Compounds of the invention also include tautomeric forms, such as keto-enol tautomers
5 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.

The present disclosure includes all isotopes of atoms occurring in the present compounds, intermediates, salts and crystalline forms thereof. Isotopes include those atoms
10 having the same atomic number but different mass numbers. One aspect of the present invention includes every combination of one or more atoms in the present compounds, intermediates, salts, and crystalline forms thereof that is replaced with an atom having the same atomic number but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as ^1H or ^{12}C , found in one the present compounds,
15 intermediates, salts, and crystalline forms thereof, with a different atom that is not the most naturally abundant isotope, such as ^2H or ^3H (replacing ^1H), or ^{11}C , ^{13}C , or ^{14}C (replacing ^{12}C). A compound wherein such a replacement has taken place is commonly referred to as being an isotopically-labeled compound. Isotopic-labeling of the present compounds, intermediates, salts, and crystalline forms thereof can be accomplished using any one of a variety of different
20 synthetic methods known to those of ordinary skill in the art and they are readily credited with understanding the synthetic methods and available reagents needed to conduct such isotopic-labeling. By way of general example, and without limitation, isotopes of hydrogen include ^2H (deuterium) and ^3H (tritium). Isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C . Isotopes of nitrogen include ^{13}N and ^{15}N . Isotopes of oxygen include ^{15}O , ^{17}O , and ^{18}O . An isotope of fluorine
25 includes ^{18}F . An isotope of sulfur includes ^{35}S . An isotope of chlorine includes ^{36}Cl . Isotopes of bromine include ^{75}Br , ^{76}Br , ^{77}Br , and ^{82}Br . Isotopes of iodine include ^{123}I , ^{124}I , ^{125}I , and ^{131}I . Another aspect of the present invention includes compositions, such as, those prepared during synthesis, preformulation, and the like, and pharmaceutical compositions, such as, those prepared with the intent of using in a mammal for the treatment of one or more of the disorders
30 described herein, comprising one or more of the present compounds, intermediates, salts, and crystalline forms thereof, wherein the naturally occurring distribution of the isotopes in the composition is perturbed. Another aspect of the present invention includes compositions and pharmaceutical compositions comprising compounds as described herein wherein the compound is enriched at one or more positions with an isotope other than the most naturally abundant
35 isotope. Methods are readily available to measure such isotope perturbations or enrichments, such as, mass spectrometry, and for isotopes that are radio-isotopes additional methods are available, such as, radio-detectors used in connection with HPLC or GC.

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

5 Formula (Ia) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof unless stated or shown otherwise.

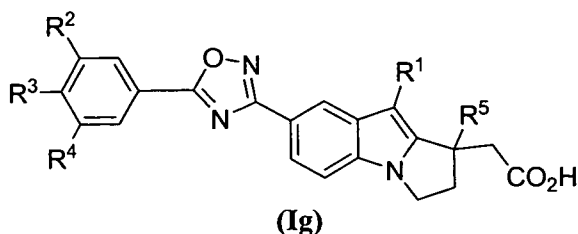
The Variables E and G

In some embodiments, E is N.

10 In some embodiments, E is CR¹.

In some embodiments, E is CR¹; and G is CR³.

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



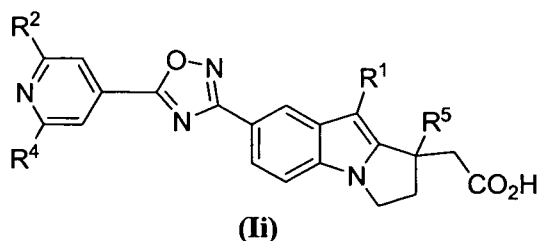
15 wherein each variable in Formula (Ig) has the same meaning as described herein, *supra* and *infra*.

In some embodiments, G is N.

In some embodiments, G is CR³.

In some embodiments, E is CR¹; and G is N.

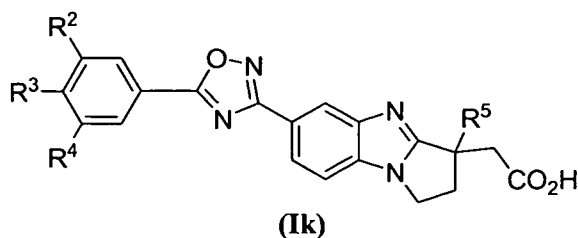
20 Some embodiments of the present invention pertain to compounds of Formula (Ii) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein each variable in Formula (Ii) has the same meaning as described herein, *supra* and *infra*.

25 In some embodiments, E is N; and G is CR³.

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



wherein each variable in Formula **(Ik)** has the same meaning as described herein, *supra* and *infra*.

5 **The Group R¹**

In some embodiments, R¹ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ haloalkyl, C₁-C₆ haloacyl, cyano, and halogen.

In some embodiments, R¹ is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl.

10 In some embodiments, R¹ is chloro or fluoro.

In some embodiments, R¹ is chloro

In some embodiments, R¹ is cyano.

In some embodiments, R¹ is fluoro.

In some embodiments, R¹ is iodo

15 In some embodiments, R¹ is methyl.

In some embodiments, R¹ is methylsulfonyl.

In some embodiments, R¹ is trifluoroacetyl.

In some embodiments, R¹ is trifluoromethyl.

20 **The Group R²**

In some embodiments, R² is selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyloxy, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, and halogen.

25 In some embodiments, R² is selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R² is selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R² is selected from the group consisting of cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

30 In some embodiments, R² is selected from the group consisting of cyano, cyclohexyl, cyclopentyl, and isopropoxy.

In some embodiments, R² is selected from the group consisting of CN and trifluoromethoxy.

In some embodiments, R^2 is selected from the group consisting of chloro, cyano, fluoro, methyl, and trifluoromethyl.

In some embodiments, R^2 is H.

In some embodiments, R^2 is cyano.

5 In some embodiments, R^2 is fluoro.

In some embodiments, R^2 is methoxy.

In some embodiments, R^2 is methyl.

In some embodiments, R^2 is chloro.

In some embodiments, R^2 is trifluoromethyl.

10 In some embodiments, R^2 is trifluoromethoxy.

The Group R^3

15 In some embodiments, R^3 is selected from the group consisting of H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkyloxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

In some embodiments, R^3 is selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^3 is selected from the group consisting of H, cyclohexyl, cyclopentyl, and isopropoxy.

20 In some embodiments, R^3 is selected from the group consisting of cyano, isopropoxy, cyclopentyl, and cyclohexyl.

In some embodiments, R^3 is H.

In some embodiments, R^3 is cyano.

In some embodiments, R^3 is cyclopentyl.

25 In some embodiments, R^3 is cyclohexyl.

In some embodiments, R^3 is isopropoxy.

In some embodiments, R^3 is trifluoromethyl.

In some embodiments, R^3 is trifluoromethoxy.

The Group R^4

30 In some embodiments, R^4 is selected from the group consisting of H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkyloxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

35 In some embodiments, R^4 is selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^4 is selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^4 is selected from the group consisting of cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^4 is selected from the group consisting of cyano and trifluoromethoxy.

5 In some embodiments, R^4 is selected from the group consisting of H, chloro, methoxy, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^4 is H.

In some embodiments, R^4 is cyano.

In some embodiments, R^4 is methoxy.

10 In some embodiments, R^4 is methyl.

In some embodiments, R^4 is chloro.

In some embodiments, R^4 is trifluoromethyl.

In some embodiments, R^4 is trifluoromethoxy.

15 **The Group R^5**

In some embodiments, R^5 is H or halogen.

In some embodiments, R^5 is H or fluoro.

In some embodiments, R^5 is H.

In some embodiments, R^5 is fluoro.

20

Certain Combinations

In some embodiments, R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkyloxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

25 In some embodiments, R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, fluoro, iodo, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

30 In some embodiments, R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^2 and R^4 are each independently selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, R^2 and R^4 are each independently selected from the group consisting of cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl; and R^3 is H.

35 In some embodiments, R^2 and R^4 are each independently C_1 - C_6 alkyl or halogen.

In some embodiments, R^2 and R^4 are each independently chloro or methyl.

In some embodiments, R^2 and R^3 are each independently selected from the group consisting of cyano, isopropoxy, cyclohexyl, and cyclopentyl; and R^4 is H.

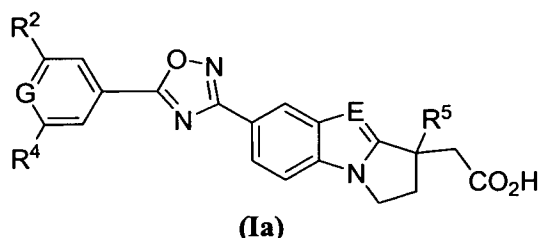
In some embodiments, R^2 is cyano; R^3 is isopropoxy, cyclohexyl, or cyclopentyl; and R^4 is H.

5 In some embodiments, R^1 is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl;

R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, fluoro, iodo, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl; and

10 R^5 is H or F.

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



15 wherein:

E is N or CR^1 ;

G is N or CR^3 ;

R^1 is selected from the group consisting of methyl, trifluoromethyl, cyano, trifluoroacetyl, methylsulfonyl, chloro, iodo, and fluoro;

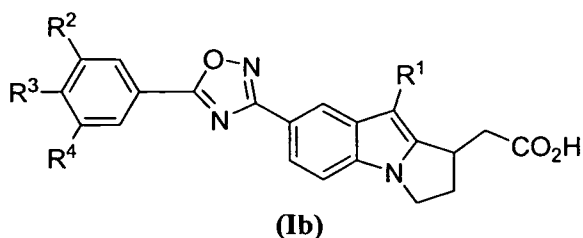
20 R^2 is selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl;

R^3 is selected from the group consisting of H, cyclohexyl, cyclopentyl, and isopropoxy;

R^4 is selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl; and

25 R^4 is H or fluoro.

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

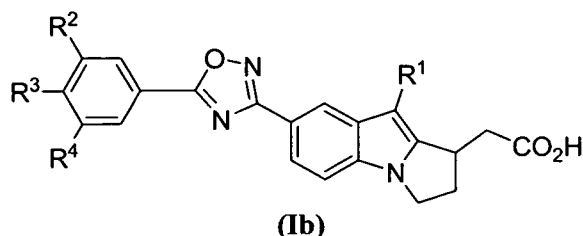


wherein:

R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloacyl, cyano, and halogen; and

5 R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, C_1 - C_6 alkoxy, cyano, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

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

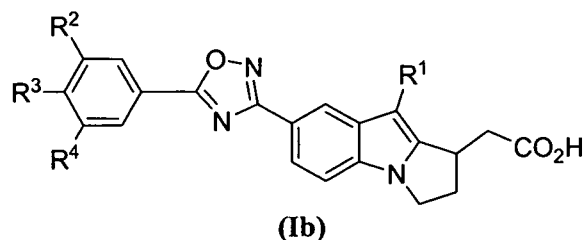


wherein:

R^1 is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl; and

15 R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, fluoro, iodo, isopropoxy, methoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

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



wherein:

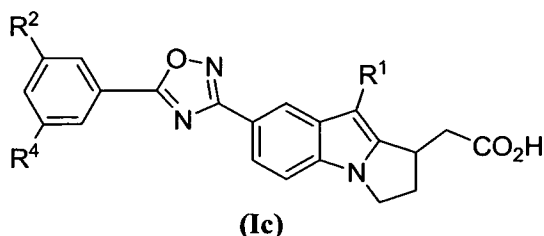
25 R^1 is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl;

R^2 is selected from the group consisting of H, chloro, cyano, fluoro, methoxy, trifluoromethoxy, and trifluoromethyl;

R^3 is selected from the group consisting of H, cyclohexyl, cyclopentyl, and isopropoxy; and

5 R^4 is selected from the group consisting of H, chloro, cyano, fluoro, methoxy, trifluoromethoxy, and trifluoromethyl.

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

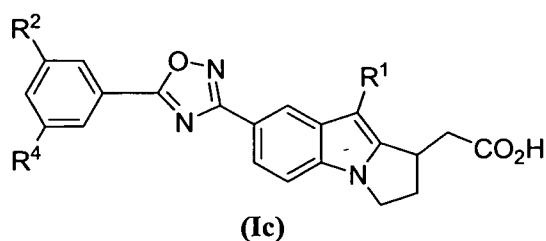


wherein:

R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 haloalkyl, cyano, and halogen; and

15 R^2 and R^4 are each independently selected from the group consisting of cyano, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

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

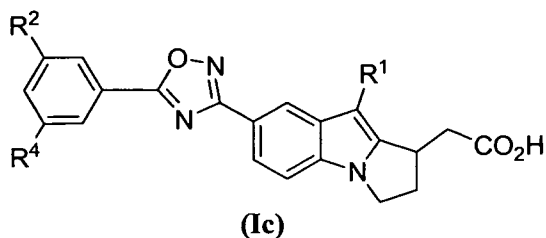


wherein:

R^1 is selected from the group consisting of methyl, trifluoromethyl, cyano, methylsulfonyl, chloro, iodo, and fluoro;

25 R^2 and R^4 are each independently selected from the group consisting of chloro, cyano, methoxy, 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:



5 wherein:

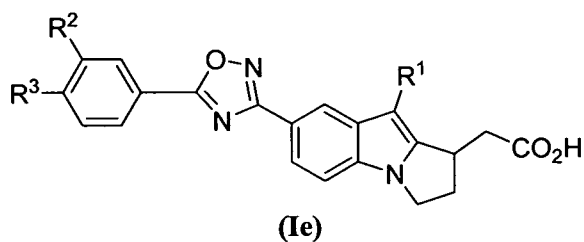
R^1 is selected from the group consisting of methyl, trifluoromethyl, cyano, methylsulfonyl, chloro, iodo, and fluoro;

R^2 is cyano; and

R^4 is trifluoromethoxy.

10

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



15

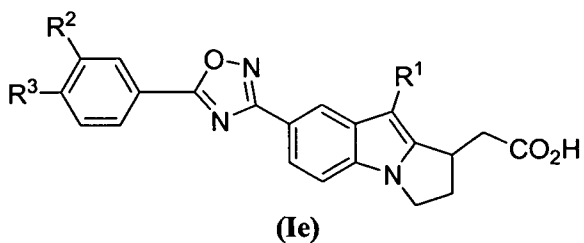
wherein:

R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloacyl, cyano, and halogen; and

R^2 and R^3 are each independently selected from the group consisting of C_1 - C_6 alkoxy, cyano, C_3 - C_7 cycloalkyl, and halogen.

20

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



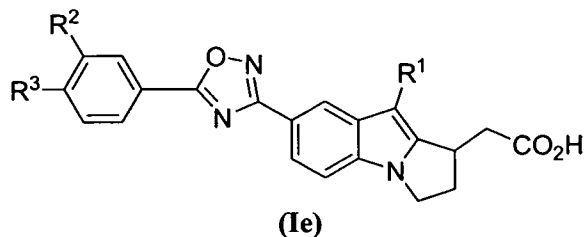
25

wherein:

R^1 is C_1 - C_6 haloacyl or halogen; and

R^2 and R^3 are each independently selected from the group consisting of C_1 - C_6 alkoxy, cyano, and C_3 - C_7 cycloalkyl.

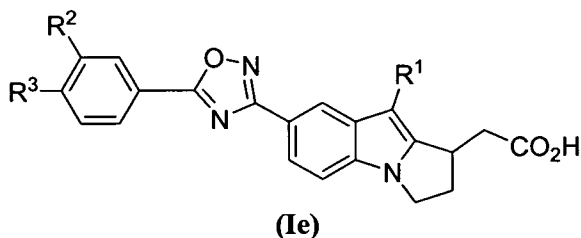
- 5 Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

- 10 R^1 is C_1 - C_6 haloacyl or halogen;
 R^2 is cyano, C_1 - C_6 haloalkyl, or halogen; and
 R^3 is C_1 - C_6 alkoxy or C_3 - C_7 cycloalkyl.

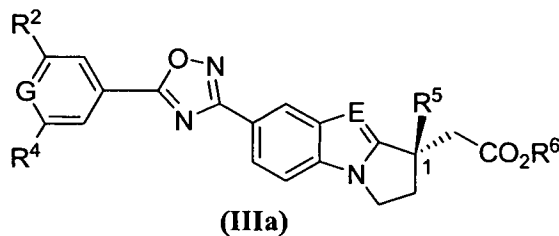
- 15 Some embodiments of the present invention pertain to compounds selected from compounds of Formula (Ie) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

- 20 R^1 is chloro or trifluoroacetyl;
 R^2 is cyano, fluoro, or trifluoromethyl; and
 R^3 is cyclohexyl, cyclopentyl, isopropoxy, or methoxy.

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



wherein:

E is N or CR¹;

G is N or CR³;

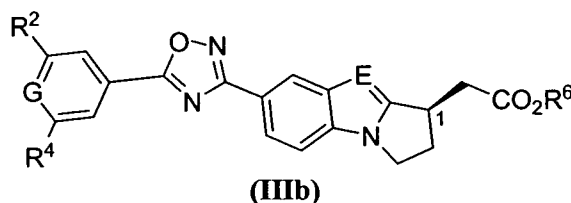
R¹ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ haloalkyl, C₁-C₆ haloacyl, cyano, and halogen;

R², R³, and R⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyloxy, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, and halogen;

R⁵ is H or halogen; and

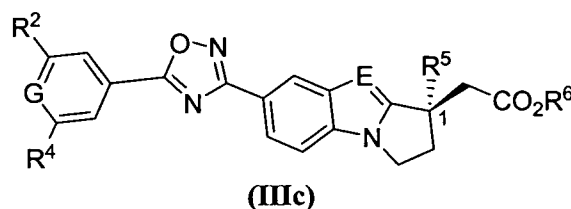
R⁶ is H or C₁-C₆ alkyl.

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



wherein each variable in Formula (IIIb) has the same meaning as described herein, *supra* and *infra*.

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



wherein:

E is N or CR¹;

G is N or CR³;

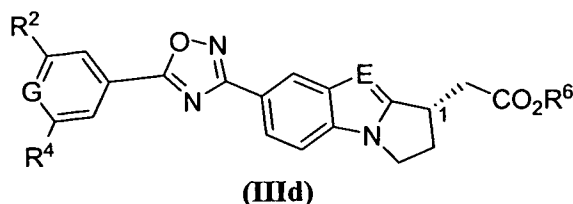
R¹ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ haloalkyl, C₁-C₆ haloacyl, cyano, and halogen;

R², R³, and R⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyloxy, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, and halogen;

R⁵ is H or halogen; and

R⁶ is H or C₁-C₆ alkyl.

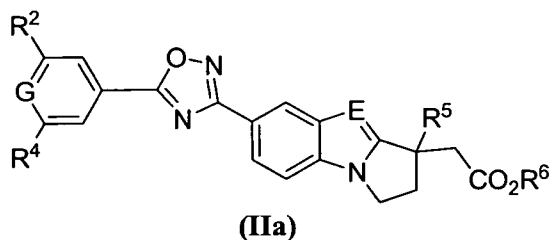
Some embodiments of the present invention pertain to compounds of Formula (III_d) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein each variable in Formula (III_d) has the same meaning as described herein, *supra* and *infra*.

Esters and Prodrugs

One aspect of the present invention pertains to compounds selected from compounds of Formula (II_a) and pharmaceutically acceptable salts, solvates, and hydrates thereof, useful as synthetic intermediates in the preparation of compounds of Formula (I_a) and/or useful as prodrugs for the oral delivery of compounds of Formula (I_a):



wherein:

E, G, R², R⁴, and R⁵ have the same definitions as described herein, *supra* and *infra*, and R⁶ is C₁-C₆ alkyl.

One aspect of the present invention pertains to compounds selected from compounds of Formula (II_a) and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In some embodiments, R⁶ is methyl.

In some embodiments, R⁶ is *tert*-butyl.

It is appreciated that all of the embodiments described herein, *supra* and *infra*, that relate to the common variables shared between compounds of Formula (I_a) and (II_a) namely, E, G, R², R⁴, and R⁵, apply to compounds of Formula (II_a) just as if they were each individually disclosed herewith with specific reference to Formula (II_a).

One aspect of the present invention pertains to compounds of Formula (II_a) as synthetic intermediates useful in the preparation of compounds of Formula (I_a).

One aspect of the present invention pertains to compounds of Formula (II_a) as esters of compounds, described and shown herein, such as compounds in Table A, where R⁶ is methyl.

One aspect of the present invention pertains to compounds of Formula (II_a) as esters of compounds, described and shown herein, such as compounds in Table A, where R⁶ is *tert*-butyl.

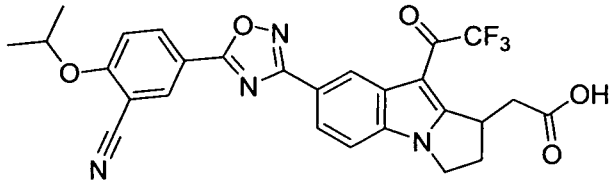
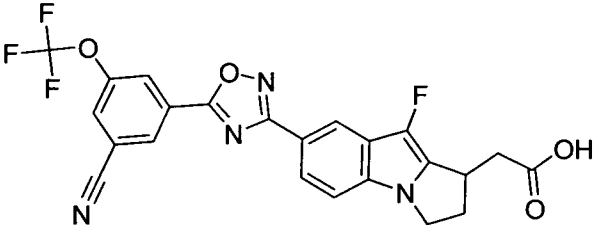
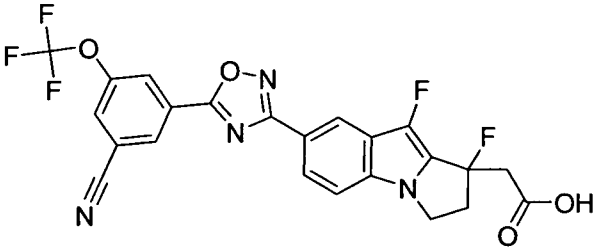
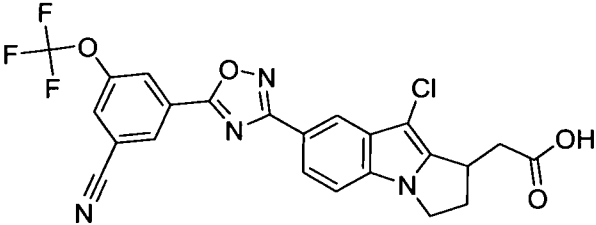
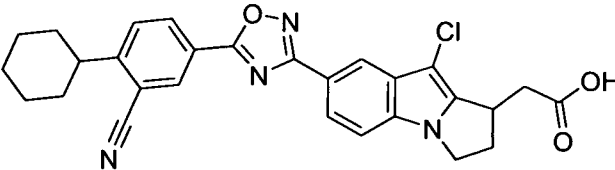
One aspect of the present invention pertains to compounds of Formula (IIa) as prodrugs useful for the oral delivery of compounds of Formula (Ia).

One aspect of the present invention pertains to compounds of Formula (IIa) useful as prodrugs of compounds of Formula (Ia).

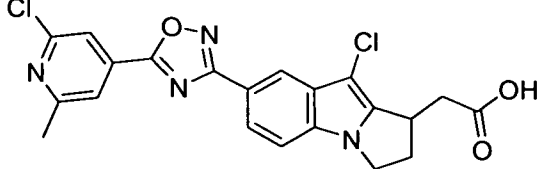
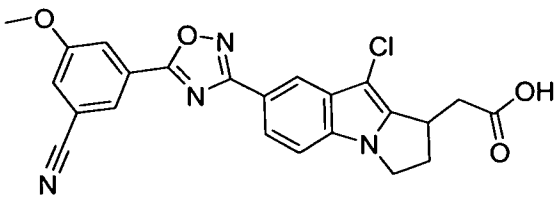
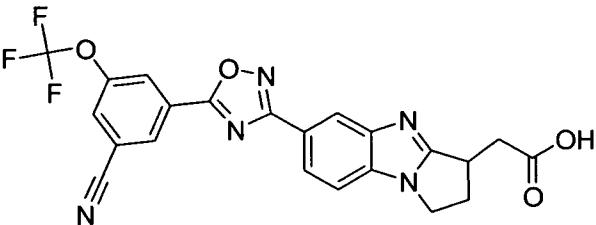
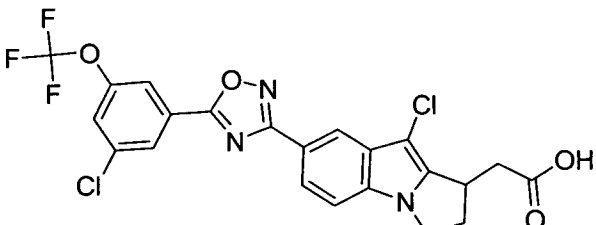
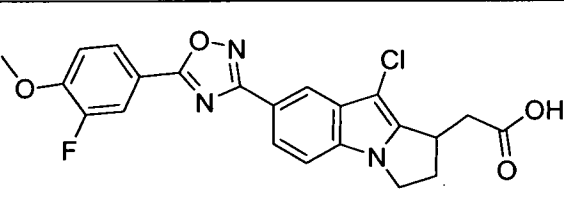
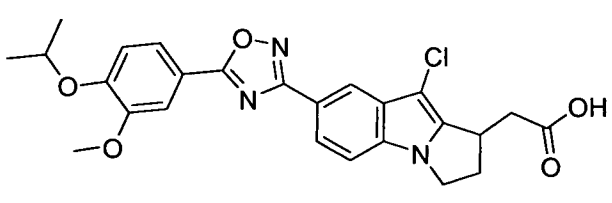
5

Some embodiments of the present invention include every combination of one or more compounds selected from the following group shown in **Table A**.

Table A

Cmpd No.	Chemical Structure	Chemical Name
1		2-(7-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-9-(2,2,2-trifluoroacetyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
2		2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-fluoro-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
3		2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1,9-difluoro-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
4		2-(9-chloro-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
5		2-(9-chloro-7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
6		2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid
7		2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid
8		2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid
9		2-(9-cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid
10		2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid
11		2-(7-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid
12		2-(9-chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1 <i>H</i> -pyrrolo[1,2- <i>a</i>]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
13		2-(9-chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
14		2-(9-chloro-7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
15		2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazol-3-yl)acetic acid
16		2-(9-chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
17		2-(9-chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid
18		2-(9-chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid

C(1) Ring Carbon Stereochemistry

Certain compounds of the present invention contain the fused tricyclic system referred to as 2,3-dihydro-1H-pyrrolo[1,2-a]indole. Certain other compounds of the present invention contain the fused tricyclic system referred to as 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole. Present on one of the rings of both of the fused tricyclic systems is a -CH₂CO₂H group. The ring carbon to which the -CH₂CO₂H acid group is bonded is referred to herein as the C(1) ring carbon. It is understood that the stereochemistry for the C(1) ring carbon contained in the 2,3-dihydro-1H-pyrrolo[1,2-a]indole or 2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole

ring system can be either *R* or *S*, see Formulae (IIIa) through (IIIId) for specific designation of C(1).

A. C(1) Ring Carbon *R* Stereochemistry

In some embodiments, the stereochemistry for the C(1) ring carbon is *R*.

5 Some embodiments of the present invention include every combination of one or more compounds selected from the following group and pharmaceutically acceptable salts, solvates, and hydrates thereof: (*R*)-2-(7-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-9-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-fluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1,9-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(7-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-3-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(9-chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; and (*R*)-2-(9-chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid.

B. C(1) Ring Carbon “*S*” Stereochemistry

In some embodiments, the stereochemistry for the C(1) ring carbon is *S*.

Some embodiments of the present invention include every combination of one or more compounds selected from the following group and pharmaceutically acceptable salts, solvates, and hydrates thereof: (*S*)-2-(7-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-9-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-fluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1,9-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(7-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-3-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; (*S*)-2-(9-chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; and (*S*)-2-(9-chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid.

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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

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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]).

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, tableting 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 Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*)

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.

5 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.

10 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
15 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
20 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
25 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
30 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
35 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 S1P1 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.

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 percentages 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-butanediol. 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.

5 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,
10 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
15 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
20 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
25 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.

30 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.

35 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, ethenesulfonic, 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*-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed by Berge *et al.*, *Journal of Pharmaceutical Sciences*, 66:1-19 (1977).

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 *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

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 S1P1 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 S1P1 receptor agonists, for the treatment of an S1P1 receptor-associated disease or disorder in companion 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 when referring 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 and solvates and hydrates of pharmaceutically acceptable salts of compounds of the particular formula. It is understood by one of ordinary skill in the art that hydrates is a subset of solvates.

The compounds of the present invention can be administered 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 K.J. 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. Accordingly, one aspect of the present invention pertains to hydrates and solvates of compounds of Formula (Ia) or Formula (IIa) and/or their pharmaceutical 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 (XRPD), 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).

POLYMOPHS AND PSEUDOPOLYMORPHS

Polymorphism is the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.

Polymorphs show the same properties in the liquid or gaseous state but they behave differently
5 in the solid state.

Besides single-component polymorphs, drugs can also exist as salts and other multicomponent crystalline phases. For example, solvates and hydrates may contain an API host and either solvent or water molecules, respectively, as guests. Analogously, when the guest compound is a solid at room temperature, the resulting form is often called a cocrystal. Salts,
10 solvates, hydrates, and cocrystals may show polymorphism as well. Crystalline phases that share the same API host, but differ with respect to their guests, may be referred to as pseudopolymorphs of one another.

Solvates contain molecules of the solvent of crystallization in a definite crystal lattice. Solvates, in which the solvent of crystallization is water, are termed hydrates. Because water is a
15 constituent of the atmosphere, hydrates of drugs may be formed rather easily.

By way of example, Stahly recently published a polymorph screen of 245 compounds consisting of a "wide variety of structural types" that revealed about 90% of the compounds exhibiting multiple solid forms. Overall, approximately half the compounds were polymorphic, often having one to three forms. About one-third of the compounds formed hydrates, and about
20 one-third formed solvates. Data from cocrystal screens of 64 compounds showed that 60% formed cocrystals other than hydrates or solvates. (G. P. Stahly, *Crystal Growth & Design* (2007), 7(6), 1007-1026.)

OTHER UTILITIES

Another object of the present invention relates to radiolabeled compounds of the present
25 invention that are useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the S1P1 receptor in tissue samples, including human and for identifying S1P1 receptor ligands by inhibition binding of a radiolabeled compound. It is a further object of this invention to develop novel S1P1 receptor assays which comprise such
30 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
35 commonly found in nature. Suitable radionuclides that may be incorporated in compounds of the present invention include, but are not limited, to ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{75}Br , ^{76}Br , ^{77}Br , ^{82}Br ,

¹²³I, ¹²⁴I, ¹²⁵I, and ¹³¹I. 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* S1P1 receptor labeling and competition assays, compounds that incorporate ³H, ¹⁴C, ⁸²Br, ¹²⁵I, ¹³¹I, or ³⁵S will generally be most useful. For radio-imaging applications ¹¹C, ¹⁸F, ¹²⁵I, ¹²³I, ¹²⁴I, ¹³¹I, ⁷⁵Br, ⁷⁶Br, or ⁷⁷Br will generally be most useful.

It is understood that a "radiolabeled" or "labeled compound" is a compound of Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ik), (IIa), (IIb), (IIc), (IIId), etc. containing at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ³H, ¹⁴C, ¹²⁵I, ³⁵S, and ⁸²Br.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ³H and/or ¹⁴C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ²H) 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 Figures 2 to 5 and 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 [³H]: 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 [³H]: 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 [³H]: This procedure is usually employed to prepare *O*-methyl or *N*-methyl [³H] products by treating appropriate precursors with high

specific activity methyl iodide [^3H]. 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:

5 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.

10 B. Ortho ^{125}I 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.* $\text{Pd}(\text{Ph}_3\text{P})_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [*e.g.*,
15 $(\text{CH}_3)_3\text{SnSn}(\text{CH}_3)_3$]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

A radiolabeled S1P1 receptor compound of Formula (Ia) or Formula (IIa) 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
20 the “radiolabeled compound of Formula (Ia) or Formula (IIa)” to the S1P1 receptor. Accordingly, the ability of a test compound to compete with the “radiolabeled compound of Formula (Ia) or Formula (IIa)” for the binding to the S1P1 receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the S1P1 receptor. In one
25 embodiment the labeled compound has an IC_{50} less than about 500 μM , in another embodiment the labeled compound has an IC_{50} less than about 100 μM , 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 .

30 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
35 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 Figures 2 through 5 where the variables have the same definitions as used throughout this disclosure.

5

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 AutoNom version 2.2, or 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 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, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet, bs = broad singlet, br = broad. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was performed 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-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2.

Example 1.1: Preparation of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Intermediate 1).

Step A: Preparation of 7-Bromo-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-one.

To a solution of ethyl 5-bromo-1H-indole-2-carboxylate (30 g, 112 mmol) in toluene (500 mL) was added portionwise sodium hydride (60% dispersion in mineral oil, 9.40 g, 235 mmol). Vigorous gas evolution was observed. The resulting white suspension was heated to 110 °C. Butyl acrylate (35.1 mL, 246 mmol) was added dropwise (using a syringe pump) over 24 h while stirring vigorously at an internal temperature of 110 °C. Additional butyl acrylate (10 mL)

was added in one portion and stirring was continued at 110 °C for 4 h followed by additional sodium hydride (60% dispersion in mineral oil, 5 g) and butyl acrylate (10 mL). 4 h later another 6 mL of butyl acrylate was added. Stirring was continued at 110 °C for a total of 48 h. The reaction was cooled in an ice-bath, and 2 M HCl (400 mL) was added carefully. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 200 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting orange residue was dissolved in acetic acid (900 mL) and water (100 mL). The orange solution was refluxed for 16 h. The solvents were removed under reduced pressure. To the residue was added dichloromethane (300 mL). The resulting precipitate was collected by filtration and rinsed twice with dichloromethane to provide the title compound. LCMS m/z = 250.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.20 (t, J = 6.1 Hz, 2H), 4.46 (t, J = 6.1 Hz, 2H), 6.92 (s, 1H), 7.46 (dd, J = 8.8, 1.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H).

Step B: Preparation of 1-Oxo-2,3-dihydro-1H-pyrrolo[1,2-a]indole-7-carbonitrile.

To a suspension of 7-bromo-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-one (6.7 g, 26.8 mmol) in *N*-methylpyrrolidinone (20 mL) was added CuCN (3.12 g, 34.8 mmol). The mixture was heated under microwave irradiation in a sealed, thick-walled glass tube at 200 °C for 2 h. The reaction was diluted with dichloromethane (400 mL). Celite® was added and the mixture was stirred vigorously for 5 min. The solids were removed by filtration. The dichloromethane was removed under reduced pressure. The remaining brown liquid was poured into water (800 mL). The precipitate was collected by filtration, rinsed with water, and dried under reduced pressure to give the title compound as a beige solid (5.16 g). LCMS m/z = 197.0 [M+H]⁺.

Step C: Preparation of *tert*-Butyl 2-(7-Cyano-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-ylidene)acetate.

To a solution of 1-oxo-2,3-dihydro-1H-pyrrolo[1,2-a]indole-7-carbonitrile (3.30 g, 16.82 mmol) in THF (50 mL) was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (15.83 g, 42.0 mmol). The mixture was stirred at 65 °C for 22 h and concentrated. The residue was purified by silica gel flash chromatography to provide the title compound as a pale yellow solid. LCMS m/z = 295.1 [M+H]⁺.

Step D: Preparation of *tert*-Butyl 2-(7-Cyano-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

tert-Butyl 2-(7-cyano-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-ylidene)acetate (4.6 g, 15.63 mmol) was dissolved in EtOAc (100 mL). The flask was flushed with nitrogen gas. Degussa wet (50 wt% water) 10% Pd/C (1.663 g, 1.563 mmol) was added and the mixture was agitated on a Parr shaker under 70 psi hydrogen for 16 h. The mixture was filtered through Celite® and concentrated. To the residue was added further 10% Pd/C and the hydrogenation

was repeated at 70 psi for 6 h. The reaction mixture was filtered and concentrated to provide the title compound as an orange solid. LCMS m/z = 297.3 $[M+H]^+$.

Step E: Preparation of *tert*-Butyl 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

5 To a solution of *tert*-Butyl 2-(7-cyano-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (4.95 g, 16.70 mmol) in ethanol (60 mL) was added a 50 wt% aqueous solution of hydroxylamine (10.24 mL, 167 mmol). The resulting solution was stirred in a sealed flask at 70 °C for 4 h. The solution was concentrated under reduced pressure to provide the title compound as a yellow solid. LCMS m/z = 330.4 $[M+H]^+$.

10 **Step F: Preparation of 3-Cyano-5-(trifluoromethoxy)benzoyl Chloride.**

To a solution of 3-cyano-5-(trifluoromethoxy)benzoic acid (11.0 g, 47.6 mmol) in dichloromethane (100 mL) was added DMF (10 drops). The solution was cooled in an ice-bath and a 2.0 M dichloromethane solution of oxalyl chloride (29.7 mL, 59.5 mmol) was added over 5 min. After addition was complete, the cooling bath was removed and the mixture was stirred
15 at 23 °C for 4 h. The solvent was removed under reduced pressure to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.82 (s, 1H), 8.17 (s, 1H), 8.36 (s, 1H).

Step G: Preparation of *tert*-Butyl 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a solution of *tert*-butyl 2-(7-(*N*'-hydroxycarbamimidoyl)-2,3-dihydro-1*H*-
20 pyrrolo[1,2-*a*]indol-1-yl)acetate (7.95 g, 24.14 mmol) in dioxane (175 mL) was added 3-cyano-5-(trifluoromethoxy)benzoyl chloride (6.02 g, 24.14 mmol) and triethylamine (11.77 mL, 84 mmol). The resulting suspension was stirred at 75 °C for 3.5 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with 0.5 M HCl (200 mL), and then brine. The organic layer was dried over MgSO₄, filtered,
25 and concentrated under reduced pressure to provide a beige solid. Crystallization from dichloromethane/hexanes yielded the title compound as a white solid. LCMS m/z = 525.5 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.50 (s, 9H), 2.29-2.38 (m, 1H), 2.56 (dd, J = 15.7, 8.1 Hz, 1H), 2.77 (dd, J = 15.9, 6.8 Hz, 1H), 2.88-2.96 (m, 1H), 3.76 (quintet, J = 7.5 Hz, 1H), 4.06-4.12 (m, 1H), 4.18-4.23 (m, 1H), 6.29 (s, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.72 (s, 1H), 7.93
30 (dd, J = 8.6, 1.5 Hz, 1H), 8.31 (s, 1H), 8.39 (s, 1H), 8.47 (t, J = 1.3 Hz, 1H).

Step H: Preparation of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

To a solution of *tert*-butyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (0.55 g, 1.049 mmol) and
35 thioanisole (1.232 mL, 10.49 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (3.12 mL, 41.9 mmol). The resulting suspension was stirred at 23 °C for 3 h. The volatiles were removed under reduced pressure. The residue was taken up in hexanes and stirred overnight.

The resulting solid was collected by filtration and rinsed with hexanes to provide a racemic mixture of the title compound. LCMS $m/z = 469.3$ $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.23-2.32 (m, 1H), 2.63 (dd, $J = 16.4, 8.1$ Hz, 1H), 2.77 (dd, $J = 16.7, 6.8$ Hz, 1H), 2.78-2.87 (m, 1H), 3.65 (quintet, $J = 7.5$ Hz, 1H), 4.05-4.11 (m, 1H), 4.21-4.27 (m, 1H), 6.31 (s, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.80 (dd, $J = 8.6, 1.5$ Hz, 1H), 8.27 (d, $J = 1.0$ Hz, 1H), 8.43 (s, 2H), 8.66 (t, $J = 1.3$ Hz, 1H), 12.39 (s, 1H).

Resolution via Chiral HPLC.

Column: normal phase preparative ChiralPak AD-H, 250 x 20 mm ID, 5 μ m particle size

Eluent: 100% acetonitrile with 0.05% trifluoroacetic acid

10 Gradient: isocratic

Flow: 13 mL/min

Detector: 280 nm

Retention Times: 1st enantiomer: 7.9 min; 2nd enantiomer: 14.9 min

15 **Example 1.2: Preparation of 2-(7-(5-(3-Cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-9-(2,2,2-trifluoroacetyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 1).**

Step A: Preparation of Isopropyl 3-Bromo-4-isopropoxybenzoate.

A mixture of 3-bromo-4-hydroxybenzoic acid (20.00 g, 92 mmol), cesium carbonate (90 g, 276 mmol) 2-bromopropane (21.61 mL, 230 mmol) in DMF (200 mL) were stirred at 80 °C for 16 h in a 500 mL round bottomed flask. After cooling down, the reaction mixture was filtered by vacuum filtration through Celite[®] and washed with EtOAc (3 x 100 mL). The solvent was removed under reduced pressure. The residue was taken up in EtOAc, washed with water (3 x 100 mL), dried (MgSO₄), filtered by vacuum filtration through a glass fiber paper and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (24.3 g) as a colorless oil. LCMS $m/z = 301.3$ $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.34 (m, 12H), 4.76-4.85 (m, 1H), 5.09-5.18 (m, 1H), 7.22 (d, $J = 8.97$ Hz, 1H), 7.92 (dd, $J = 8.72, 2.15$ Hz, 1H), 8.09 (d, $J = 2.15$ Hz, 1H).

Step B: Preparation of Isopropyl 3-Cyano-4-isopropoxybenzoate.

Isopropyl 3-bromo-4-isopropoxybenzoate (23.8 g, 79 mmol) and CuCN (9.20 g, 103 mmol) in anhydrous *N*-methyl-2-pyrrolidinone (158 mL) were heated to 200 °C for 16 h in a 500 mL round bottomed flask. After 16 h the reaction mixture was poured into 1 M HCl and extracted into EtOAc (3 x 200 mL). The organic layers were combined and washed with 1 M HCl (3 x 200 mL) and washed with saturated NaCl (1 x 200 mL), dried (MgSO₄), filtered by vacuum filtration through a glass fiber paper and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (17.46 g) as a tan solid. LCMS $m/z = 248.1$ $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.34 (d, $J = 6.19$ Hz,

6H), 1.38 (d, $J = 6.06$ Hz, 6H), 4.88-4.96 (m, 1H), 5.10-5.18 (m, 1H), 7.39 (d, $J = 8.84$ Hz, 1H), 8.12-8.21 (m, 2H).

Step C: Preparation of 3-Cyano-4-isopropoxybenzoic Acid.

To a solution of isopropyl 3-cyano-4-isopropoxybenzoate (17.46 g, 70.6 mmol) in dioxane (100 mL) was added LiOH (1.0 M, 212 mL, 212 mmol). The reaction was stirred at 30 °C for 1.5 h in a 1 L round bottomed flask. After 1.5 h, the reaction was cooled down to room temperature and poured into 1 M HCl and extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with saturated NaCl (1 x 200 mL), dried (MgSO₄), and filtered by vacuum filtration through a glass fiber paper. The solvent was removed under reduced pressure to give the title compound (14 g) as a solid. LCMS $m/z = 206.1$ [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.36 (d, $J = 6.06$ Hz, 6H), 4.85-4.96 (m, 1H), 7.37 (d, $J = 8.72$ Hz, 1H), 8.12-8.22 (m, 2H), 13.17 (s, 1H).

Step D: Preparation of *tert*-Butyl 2-(7-(5-(3-Cyano-5-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

To a solution of *tert*-butyl 2-(7-(*N*-hydroxycarbamimidoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.148 g, 0.45 mmol) in dioxane (2.71 mL) and 3-cyano-4-isopropoxybenzoic acid (0.120 g, 0.585 mmol) was added TEA (0.627 mL, 4.50 mmol) followed by 1-propylphosphonic acid cyclic anhydride (0.292 mL, 0.495 mmol). The reaction was heated to reflux for 2 h. The mixture was diluted with EtOAc, washed with water (3x) and brine. The organics were dried over MgSO₄ and concentrated. The residue was purified by column chromatography to give a white solid. LCMS $m/z = 499.8$ [M+H]⁺.

Step E: Preparation of 2-(7-(5-(3-Cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-9-(2,2,2-trifluoroacetyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

To a solution of *tert*-butyl 2-(7-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.465 g, 0.933 mmol) in CH₂Cl₂ (3.11 mL) was added triisopropylsilane (1.918 mL, 9.33 mmol) and TFA (3.59 mL, 46.6 mmol). The reaction was stirred overnight and concentrated under reduced pressure. The residue was purified via preparative LCMS, to give the title compound as a pink solid. LCMS $m/z = 539.2$ [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.39 (d, $J = 6.06$ Hz, 6H), 2.40-2.47 (m, 1H), 2.70-2.83 (m, 2H), 2.87-3.00 (m, 1H), 3.91-4.01 (m, 1H), 4.38 (t, $J = 8.40$ Hz, 2H), 4.92-5.03 (m, 1H), 7.56 (d, $J = 9.22$ Hz, 1H), 7.79 (d, $J = 8.46$ Hz, 1H), 8.07 (dd, $J = 8.53, 1.58$ Hz, 1H), 8.43 (dd, $J = 9.03, 2.21$ Hz, 1H), 8.52 (d, $J = 2.27$ Hz, 1H), 8.79 (s, 1H), 12.45 (s, 1H).

Example 1.3: Preparation of an Enantiomer of 2-(9-Chloro-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 4).

The 2nd enantiomer of **Intermediate 1** (as described in Example 1.1, eluting at 14.9 min from chiral HPLC) (0.117 g, 0.25 mmol) was dissolved in anhydrous THF (4.0 mL). The

reaction mixture was cooled to 0 °C and added 1-chloropyrrolidine-2,5-dione (0.035 g, 0.263 mmol). The reaction mixture was warmed to 25 °C and stirred for 18 h. The mixture was diluted with MTBE (100 mL), washed with 2 M sodium thiosulfate (20 mL), water (20 mL), and brine (20 mL). The organics were dried over MgSO₄ and concentrated under reduced pressure to give the title compound (0.119 g) as a yellow solid. LCMS *m/z* = 502.8 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.30-2.43 (m, 1H), 2.63 (dd, *J* = 16.48, 9.54 Hz, 1H), 2.82-2.94 (m, 1H), 2.99 (dd, *J* = 16.42, 4.17 Hz, 1H), 3.69-3.84 (m, 1H), 4.07-4.19 (m, 1H), 4.24-4.33 (m, 1H), 7.58 (d, *J* = 8.59 Hz, 1H), 7.90 (dd, *J* = 8.59, 1.52 Hz, 1H), 8.18 (d, *J* = 1.14 Hz, 1H), 8.40 (s, 1H), 8.45 (s, 1H), 8.69 (t, *J* = 1.33 Hz, 1H), 12.40 (bs, 1H).

Example 1.4: Preparation of 2-(9-Chloro-7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 5).

Step A: Preparation of *tert*-Butyl 2-(7-(5-(3-Cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

3-Cyano-4-cyclohexylbenzoic acid (33 mg, 0.14 mmol) was dissolved in DMA (1.0 mL) and CDI (46.7 mg, 0.29 mmol) was added. The reaction was warmed to 60 °C and stirred for 1 h. *tert*-Butyl 2-(7-(*N'*-hydroxycarbamimidoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (47.4 g, 144 mmol) was added and the reaction was stirred at 90 °C for 3 h. The reaction was concentrated to an oil and purified by column chromatography to give the title compound (22.6 mg). LCMS *m/z* = 523.3 [M+H]⁺.

Step B: Preparation of 2-(7-(5-(3-Cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

tert-Butyl 2-(7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (22.6 mg, 0.043 mmol) was dissolved in DCM (0.5 mL) and D/L-cysteine (16 mg, 0.130 mmol) was added. The reaction mixture was cooled to 0 °C and TFA (0.223 mL, 2.90 mmol) was added. The reaction was stirred at room temperature for 6 h. The DCM was removed under reduced pressure and the remaining solution was diluted with water causing a white precipitate to form. The solids were collected by filtration, rinsed with water, and dried to give the title compound (18 mg). LCMS *m/z* = 467.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.08-1.65 (m, 5H), 1.71-1.80 (m, 1H), 1.81-1.92 (m, 4H), 2.22-2.34 (m, 1H), 2.62 (dd, *J* = 16.4, 7.70, 1H), 2.72-2.87 (m, 2H), 2.92-3.02 (m, 1H), 3.65 (quintet, *J* = 7.5 Hz, 1H), 4.04-4.13 (m, 1H), 4.20-4.27 (m, 1H), 6.31 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.78-7.85 (m, 2H), 8.28 (s, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 8.53 (s, 1H), 12.3 (bs, 1H).

Step C: Preparation of 2-(9-Chloro-7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

2-(7-(5-(3-Cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid (12.8 mg, 0.027 mmol) was dissolved in DCM (1.0 mL),

and cooled to 0 °C. NCS (3.66 mg, 0.027 mmol) was added and the reaction was stirred for 30 minutes. The reaction was diluted with water and the DCM layer was washed two additional times with water. The organic layer was dried over sodium sulfate, filtered, and concentrated to give the title compound (13.0 mg). LCMS m/z = 501.4 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.10-1.63 (m, 5H), 1.80-1.86 (m, 1H), 1.89-2.01 (m, 4H), 2.38-2.48 (m, 1H), 2.67 (dd, J = 16.8, 10.2 Hz, 1H), 2.98-3.13 (m, 2H), 3.35 (dd, J = 16.8, 3.8 Hz, 1H), 3.83-3.92 (m, 1H), 4.06-4.14 (m, 1H), 4.20-4.27 (m, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 8.00 (dd, J = 8.6, 1.6 Hz, 1H), 8.37 (dd, J = 8.2, 1.8 Hz, 1H), 8.41 (d, J = 1.3 Hz, 1H), 8.50 (d, J = 1.8 Hz, 1H).

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Example 1.5: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-fluoro-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 2).

To a solution of the 1st enantiomer of **Intermediate 1** (as described in Example 1.1, eluting at 7.9 min from chiral HPLC) (50 mg, 0.107 mmol) in DMF (1 mL) was added 1-fluoropyridinium trifluoromethanesulfonate (23.8 mg, 0.096 mmol). The reaction was stirred at 23 °C for 4 h then at 40 °C for 18 h. The mixture was purified by preparative HPLC to give the title compound (7 mg) as a white solid. LCMS m/z = 487.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.28-2.36 (m, 1H), 2.67 (dd, J = 16.2, 8.2 Hz, 1H), 2.78-2.87 (m, 2H), 3.77-3.84 (m, 1H), 4.06-4.13 (m, 1H), 4.22-4.28 (m, 1H), 7.53 (dd, J = 8.7, 2.0 Hz, 1H), 7.86 (dd, J = 8.6, 1.6 Hz, 1H), 8.24 (d, J = 1.0 Hz, 1H), 8.40-8.41 (m, 1H), 8.44-8.45 (m, 1H), 8.69 (t, J = 1.4 Hz, 1H), 11.54 (bs, 1H).

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Example 1.6: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1,9-difluoro-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 3).

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To a suspension of the 1st enantiomer of **Intermediate 1** (as described in Example 1.1, eluting at 7.9 min from chiral HPLC) (50 mg, 0.107 mmol) in dimethoxyethane (1 mL) was added 1-fluoropyridinium trifluoromethanesulfonate (33 mg, 0.134 mmol). The reaction was stirred at 55 °C for 4 h. The mixture was purified by preparative HPLC to give the title compound (10.8 mg) as a pink solid. LCMS m/z = 505.3 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.94-2.02 (m, 1H), 2.24-2.33 (m, 1H), 2.79 (dd, J = 18.6, 3.4 Hz, 1H), 3.09 (dd, J = 18.6, 9.4 Hz, 1H), 3.33-3.41 (m, 1H), 3.68-3.74 (m, 1H), 7.22 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 8.26 (dd, J = 8.5, 1.3 Hz, 1H), 8.42-8.46 (m, 2H), 8.71 (t, J = 1.4 Hz, 1H).

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Example 1.7: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid (Compound 6).

Step A: Preparation of an Enantiomer of Methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

The 2nd enantiomer of **Intermediate 1** (as described in Example 1.1, eluting at 14.9 min from chiral HPLC) (0.5 g, 1.067 mmol) was suspended in MeOH (3 mL) and toluene (3 mL) solution. TMS-diazomethane (2 M solution in hexanes) (0.854 mL, 1.708 mmol) was slowly added to the mixture at room temperature. It slowly became a clear brown solution during addition. The reaction mixture was stirred for another 30 min. The solvent was removed under reduced pressure to give the title compound as a light pink solid (475 mg). LCMS m/z = 483.1 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) 2.30-2.38 (m, 1H), 2.65 (dd, J = 16.2, 8.4 Hz, 1H), 2.88 (dd, J = 16.1, 6.4 Hz, 1H), 2.92-2.98 (m, 1H), 3.76 (s, 3H), 3.75-3.85 (m, 1H), 4.06-4.14 (m, 1H), 4.18-4.27 (m, 1H), 6.29 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H), 7.94 (dd, J = 8.5 and 1.6 Hz, 1H), 8.31 (s, 1H), 8.39 (d, J = 1.4 Hz, 1H), 8.46 (t, J = 1.3 Hz, 1H).

Step B: Preparation of an Enantiomer of Methyl 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a solution of the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (470 mg, 0.974 mmol) in DCM (8 mL) was slowly added 1-iodopyrrolidine-2,5-dione (230 mg, 1.023 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 30 min, then diluted with DCM. The organic layer was washed with aqueous sodium thiosulfate solution, water and dried. The solvent was evaporated to give the title compound as light brown solid (548 mg). LCMS m/z = 609.4 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) 2.39-2.48 (m, 1H), 2.60 (dd, J = 16.5 and 10.6 Hz, 1H), 2.96-3.05 (m, 1H), 3.32 (dd, J = 16.4 and 3.6 Hz, 1H), 3.75 (s, 3H), 3.75-3.82 (m, 1H), 4.12-4.18 (m, 1H), 4.22-4.30 (m, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H), 7.90 (dd, J = 8.5 and 1.6 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.32 (s, 1H), 8.48 (t, J = 1.3 Hz, 1H).

Step C: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

The above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (75 mg, 0.123 mmol) in dioxane (1 mL) was added 1 M LiOH aqueous solution (0.493 mmol, 0.493 mL) at room temperature. The reaction mixture was stirred at the

temperature for 3 h, diluted with water, and acidified with 0.5 M citric acid aqueous solution to pH 4. The solid collected was purified by preparative HPLC to give the title compound (50 mg). LCMS m/z = 594.9 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) 2.35-2.43 (m, 1H), 2.60 (dd, J = 16.5, 10.3 Hz, 1H), 2.85-2.94 (m, 1H), 3.05 (dd, J = 16.5, 3.4 Hz, 1H), 3.60-3.68 (m, 1H), 4.14-4.20 (m, 1H), 4.25-4.34 (m, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.90 (dd, J = 8.5, 1.5 Hz, 1H), 8.00 (d, J = 1.3 Hz, 1H), 8.40 (s, 1H), 8.44 (s, 1H), 8.69 (t, J = 1.3 Hz, 1H), 12.40 (bs, 1H).

Example 1.8: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 7).

Step A: Preparation of an Enantiomer of Methyl 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

To a mixture of the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (464 mg, 0.763 mmol) and bis(tri-*t*-butylphosphine)palladium(0) (39.0 mg, 0.076 mmol) in THF was added methylzinc(II) chloride in THF solution (2 M) (1.144 mL, 2.288 mmol) at room temperature under nitrogen protection. The reaction mixture was heated at 70 °C for 2 h, cooled down, quenched with saturated NaHCO₃ solution, and filtered through Celite®. The filtrate was extracted with ethyl acetate. The combined organics were dried then concentrated. The residue was purified by column chromatography to give the title compound as an off-white solid (255 mg). LCMS m/z = 497.2 $[M+H]^+$; 1H NMR (400 MHz, CDCl₃) 2.34 (s, 3H), 2.34-2.42 (m, 1H), 2.56 (dd, J = 15.9 and 9.8 Hz, 1H), 2.88-2.97 (m, 1H), 2.98 (dd, J = 15.9 and 4.8 Hz, 1H), 3.75 (s, 3H), 3.75-3.85 (m, 1H), 4.02-4.08 (m, 1H), 4.12-4.18 (m, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H), 7.94 (dd, J = 8.5 and 1.5 Hz, 1H), 8.31 (s, 1H), 8.33 (d, J = 1.5 Hz, 1H), 8.48 (t, J = 1.3 Hz, 1H).

Step B: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

The above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (200 mg, 0.403 mmol) in dioxane (2 mL) was added 1 M LiOH aqueous solution (1.61 mmol, 1.61 mL) at room temperature. The reaction mixture was stirred at the temperature for 3 h, diluted with water, acidified with 0.5 M citric acid aqueous solution to pH 4. The solid was collected and dried to give the title compound as a light yellow solid (182 mg). LCMS m/z = 483.3 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) 2.29 (s, 3H), 2.29-2.35 (m, 1H), 2.56 (dd, J = 16.0, 9.0 Hz, 1H), 2.78-2.86 (m, 2H), 3.65-3.72 (m, 1H), 4.03-4.08 (m, 1H), 4.14-4.20 (m, 1H),

7.45 (d, $J = 8.5$ Hz, 1H), 7.80 (dd, $J = 8.5, 1.3$ Hz, 1H), 8.21 (d, $J = 1.3$ Hz, 1H), 8.40 (s, 1H), 8.44 (s, 1H), 8.68 (t, $J = 1.3$ Hz, 1H), 12.30 (bs, 1H).

Example 1.9: Preparation of an Enantiomer of 2-(9-Cyano-7-(5-(3-cyano-5-

(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid (Compound 9).

Step A: Preparation of an Enantiomer of Methyl 2-(9-cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a mixture of the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate and dicyanozinc (17.5 mg, 0.148 mmol) in DMA (0.5 mL) under a nitrogen atmosphere was added tetrakis(triphenylphosphine)palladium(0) (8.5 mg, 0.1 eq). The reaction mixture was heated in a heavy-walled sealed tube under microwave irradiation at 140 °C for 1.5 h. The reaction was diluted with EtOAc, washed with H₂O and 1 N HCl, dried, and concentrated. The residue was purified by preparative TLC to give the title compound (8.5 mg). LCMS $m/z = 508.2$ $[M+H]^+$.

Step B: Preparation of an Enantiomer of 2-(9-Cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

To a solution of the above-mentioned enantiomer of methyl 2-(9-cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (8.2 mg, 0.016 mmol) in acetonitrile/H₂O (0.2 mL/4 μ L, 2%) was added LiBr (21 mg, 0.24 mmol), and followed by Et₃N (6.5 μ L, 0.048 mmol). The reaction was stirred at 85 °C for 3 h. The reaction was diluted with DCM (5 mL), washed with H₂O (twice) and 1 N HCl, dried with anhydrous MgSO₄, and concentrated. The solid residue was washed with IPA to the title compound (2.1 mg). LCMS $m/z = 494.3$ $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) δ 2.44-2.54 (m, 1H), 2.69 (dd, $J = 16.5$ and 9.4 Hz, 1H), 3.01-3.10 (m, 1H), 3.19 (dd, $J = 16.3$ and 4.2 Hz, 1H), 3.94-4.02 (m, 1H), 4.11-4.18 (m, 1H), 4.26-4.33 (m, 1H), 7.40 (d, $J = 8.6$, 1H), 7.74 (s, 1H), 8.05 (dd, $J = 8.5$ and 1.4 Hz, 1H), 8.33 (s, 1H), 8.48 (s, 1H), 8.53 (s, 1H).

Example 1.10: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-

(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid (Compound 8).

Step A: Preparation of an Enantiomer of Methyl 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a mixture of potassium fluoride (196 mg, 3.37 mmol) and copper(I) iodide (626 mg, 3.29 mmol) in 5 mL DMA, trimethyl(trifluoromethyl)silane (514 μ L, 3.29 mmol) was added. After stirring at 50 °C for 40 min, the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (200 mg, 0.329 mmol) was added and the mixture was continue to be stirred at 80 °C. After 30 min, the mixture was quenched with ice and purified by preparative HPLC. Fractions containing the title compound were partially concentrated and the residue was extracted with 1 M NaHCO₃ solution and CH₂Cl₂. The organics were dried over MgSO₄, filtered, and concentrated to give the title compound (28.0 mg) as a white solid. LCMS m/z = 551.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 2.47-2.53 (m, 1H), 2.62-2.69 (m, 1H), 2.96-3.06 (m, 2H), 3.73 (s, 3H), 3.90-3.99 (m, 1H), 4.15-4.28 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 0.9 Hz, 1H), 8.05 (dd, J = 8.6, 1.6 Hz, 1H), 8.33 (d, J = 0.9 Hz, 1H), 8.48-8.52 (m, 2H).

Step B: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

To a solution of the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (3.7 mg, 6.72 μ mol) in CH₃CN (0.5 mL, with 2% H₂O) were added lithium bromide (50 mg, 0.576 mmol) and triethylamine (10 μ L, 0.072 mmol). After stirring at 80 °C (oil bath) for 1 h, the mixture was purified by preparative HPLC. Appropriate fractions were partly concentrated and the residue was extracted with 1 M HCl and CH₂Cl₂. The organics were dried over MgSO₄, filtered, and concentrated to give the title compound (0.7 mg) as a white solid. LCMS m/z = 537.2 [M+H]⁺.

Example 1.11: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid (Compound 10).

Step A: Preparation of an Enantiomer of Methyl 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

A mixture of the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (105 mg, 0.173 mmol), sodium methanesulfinate (176 mg, 1.724 mmol), copper (I) trifluoromethanesulfonate benzene complex (10 mg, 0.020 mmol), and *N*¹,*N*²-dimethylethane-1,2-diamine (5 μ L, 0.046 mmol) in DMSO (3 mL) was stirred at 80 °C (oil bath) overnight. The mixture was purified by preparative HPLC. Appropriate fractions were partly concentrated and the residue was extracted with 1 M NaHCO₃ and CH₂Cl₂. The organics were dried over MgSO₄, filtered, and

concentrated to give the title compound (7.1 mg) as a white solid. LCMS m/z = 561.2 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ ppm 2.52-2.59 (m, 1H), 2.88-2.94 (m, 1H), 2.98-3.05 (m, 1H), 3.21 (s, 3H), 3.21-3.29 (m, 1H), 3.68 (s, 3H), 4.07-4.13 (m, 1H), 4.19-4.33 (m, 2H), 7.43 (d, J = 8.6 Hz, 1H), 7.74 (s, 1H), 8.11 (dd, J = 8.6, 1.5 Hz, 1H), 8.34 (s, 1H), 8.50 (m, 1H), 8.73 (m, 1H).

5 **Step B: Preparation of an Enantiomer of 2-(7-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.**

A mixture of the above-mentioned enantiomer of methyl 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (5.4 mg, 9.63 μ mol), lithium bromide (25 mg, 0.288 mmol),
10 and triethylamine (5 μ L, 0.036 mmol) in 1 mL CH_3CN with 2% H_2O was stirred at 80 °C for 30 min. The mixture was purified by preparative HPLC. Appropriate fractions were partly concentrated and the residue was extracted with 1 M HCl and CH_2Cl_2 . The organics were dried over $MgSO_4$, filtered, and concentrated to give the title compound (3.8 mg) as a white solid.
15 LCMS m/z = 547.3 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ ppm 2.56-2.63 (m, 1H), 2.93-3.07 (m, 2H), 3.22 (s, 3H), 3.31-3.36 (m, 1H), 4.08-4.13 (m, 1H), 4.20-4.33 (m, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.74 (s, 1H), 8.11 (dd, J = 8.5, 1.5 Hz, 1H), 8.34 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 8.72 (s, 1H).

20 **Example 1.12: Preparation of 2-(9-Chloro-7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 14).**

Step A: Preparation of *tert*-Butyl 2-(7-(5-(3-Cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

3-Cyano-5-methoxybenzoic acid (0.027 g, 0.152 mmol) was dissolved in DMA (1.0
25 mL). HATU (0.075 g, 0.197 mmol) and triethylamine (0.042 mL, 0.304 mmol) were added. After stirring for 30 minutes, *tert*-butyl 2-(7-(*N'*-hydroxycarbamimidoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.05 g, 0.152 mmol) was added and the reaction was stirred at room temperature for 1 h. The reaction was warmed to 90 °C and stirred for 48 h. The reaction mixture was concentrated and the residue was purified by column chromatography to give the
30 title compound (47.7 mg). LCMS m/z = 471.4 $[M+H]^+$.

Step B: Preparation of 2-(9-Chloro-7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

tert-Butyl 2-(7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (47.7 mg, 0.101 mmol) was taken up in DCM (1.0 mL) and
35 cooled to 0 °C. NCS (13.5 mg, 0.101 mmol) was added and the reaction was stirred for 30 minutes and then diluted with saturated aqueous sodium thiosulfate. The DCM layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by column

chromatography and the resultant material was taken up into a mixture of D/L-cysteine (120 mg) and TFA (2.0 mL). After 10 minutes at room temperature, the reaction was diluted with water and the resulting solid was isolated by filtration to give the title compound (11.2 mg).

LCMS m/z = 449.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 2.31-2.42 (m, 1H), 2.63 (dd, J = 16.4, 9.6 Hz, 1H), 2.82-2.92 (m, 1H), 2.95-3.04 (m, 1H), 3.69-3.81 (m, 1H), 3.96 (s, 3H), 4.08-4.17 (m, 1H), 4.23-4.33 (m, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 8.17 (s, 2H), 12.3 (bs, 1H).

Example 1.13: Preparation of 2-(9-Chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 13).

Step A: Preparation of *tert*-Butyl 2-(7-(5-(2-Chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

To a solution of *tert*-butyl 2-(7-(*N'*-hydroxycarbamimidoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.075 g, 0.228 mmol) and triethylamine (0.111 mL, 0.797 mmol) in THF was added 2-chloro-6-methylisonicotinoyl chloride (0.032 mL, 0.228 mmol). The resulting suspension was stirred overnight. The mixture was concentrated and dissolved in DMF, then heated at 90 °C for 4 h. The solvent was removed and the residue was taken up in EtOAc. The organics were washed with 1 M HCl followed by brine (twice). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel to yield the title compound as a white solid (0.078 g). LCMS m/z = 465.3 $[M+H]^+$; 1H NMR (400 MHz, CDCl₃) δ ppm 1.51 (s, 9H), 2.29-2.39 (m, 1H), 2.57 (dd, J = 15.79, 8.21 Hz, 1H), 2.69 (s, 3H), 2.78 (dd, J = 15.92, 6.82 Hz, 1H), 2.93 (m, 1H), 3.77 (m, 1H), 4.09 (dt, J = 10.10, 7.58 Hz, 1H), 4.21 (m, 1H), 6.29 (s, 1H), 7.34 (d, J = 8.34 Hz, 1H), 7.87 (s, 1H), 7.91-7.97 (m, 2H), 8.40 (d, J = 1.52 Hz, 1H).

Step B: Preparation of *tert*-Butyl 2-(9-Chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

To a solution of *tert*-butyl 2-(7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.075 g, 0.161 mmol) in anhydrous DCM (3.23 mL) cooled to 0 °C was added 1-chloropyrrolidine-2,5-dione (0.023 g, 0.169 mmol). After stirring the reaction mixture at 0 °C for 1 h, the reaction mixture was warmed to room temperature for about 15 min, after which the reaction mixture was quenched with 2 M sodium thiosulfate (4.03 mL, 8.07 mmol). The mixture was extracted with MTBE (50 mL). The organic layer was washed with 2 M sodium thiosulfate (2 x 10 mL), water (10 mL), brine (10 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the title compound as a yellow solid (48 mg). LCMS m/z = 499.1 $[M+H]^+$; 1H NMR (400 MHz, Acetone- d_6) δ ppm 1.44 (s, 9H), 2.50 (m, 1H), 2.65 (d, J = 6.57 Hz, 1H), 2.68 (s, 3H), 3.01 (dd, J = 12.88, 4.67 Hz, 1H), 3.07 (dd, J = 16.04, 4.04 Hz, 1H), 3.84

(m, 1H), 4.21 (ddd, $J = 10.17, 8.02, 6.95$ Hz, 1H), 4.35 (ddd, $J = 10.20, 8.56, 4.74$ Hz, 1H), 7.53 (d, $J = 8.59$ Hz, 1H), 7.94 - 7.99 (m, 2H), 8.02 (s, 1H), 8.31 (d, $J = 1.39$ Hz, 1H).

Step C: Preparation of 2-(9-Chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

5 *tert*-Butyl 2-(9-chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.044 g, 0.088 mmol) was dissolved in a pre-mixed solution of DCM (2 mL, 31.1 mmol), TFA (1.0 mL, 12.98 mmol), and thioanisole (0.104 mL, 0.881 mmol) and stirred at room temperature for 1 h. Toluene (20 mL) was added and the solvent was evaporated under reduced pressure at 25 °C to give a residue which was
10 coevaporated with toluene (20 mL) again at 25 °C to give a solid residue. The solid residue was suspended in DCM (10 mL) and hexane (40 mL) was added to give a grey suspension. The solvent was evaporated under reduced pressure at 25 °C to a volume of 10 mL. The solid was filtered, washed with hexanes (3 times), and dried under reduced pressure to give the title compound as a grey solid (0.038 g). LCMS $m/z = 443.3$ $[M+H]^+$; 1H NMR (400 MHz, DMSO-
15 d_6) δ ppm 2.36 (m, 1H), 2.63 (s, 3H), 2.65 (d, $J = 9.60$ Hz, 1H), 2.82-2.92 (m, 1H), 2.99 (dd, $J = 16.48, 4.23$ Hz, 1H), 3.70-3.82 (m, 2H), 4.28 (m, 1H), 7.59 (d, $J = 8.46$ Hz, 1H), 7.90 (dd, $J = 8.59, 1.64$ Hz, 1H), 8.00 (s, 1H), 8.05 (s, 1H), 8.19 (d, $J = 1.26$ Hz, 1H), 12.40 (bs, 1H).

Example 1.14: Preparation of 2-(9-Chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 12).

Step A: Preparation of *tert*-Butyl 2-(7-(5-(4-Cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

4-Cyclopentyl-3-(trifluoromethyl)benzoic acid (58.8 mg, 0.228 mmol), oxalyl chloride
25 (0.040 mL, 0.455 mmol) and DMF (1.175 μ L, 0.015 mmol) in DCM (1.00 mL) were stirred at room temperature for 1 h in a 20 mL sealed scintillation vial. After 1 h, the solvent was removed under reduced pressure to give 4-cyclopentyl-3-(trifluoromethyl)benzoyl chloride, which was immediately added to a solution of *tert*-butyl 2-(7-(*N*-hydroxycarbamimidoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (50 mg, 0.152 mmol) and TEA (0.023 mL, 0.167 mmol) in THF
30 (1.00 mL). The reaction was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue was dissolved in DMF (1.00 mL). The reaction was then heated to 75 °C for 16 h. The reaction was then taken up in EtOAc (5 mL) and washed with water (2 x 5 mL), dried over $MgSO_4$, filtered by vacuum filtration through a glass fiber paper and concentrated under reduced pressure. The residue was purified by silica gel column
35 chromatography to give the title compound as an off-white solid (35 mg). LCMS $m/z = 552.5$ $[M+H]^+$.

Step B: Preparation of *tert*-Butyl 2-(9-Chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a solution of *tert*-butyl 2-(7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (23.4 mg, 0.042 mmol) in DCM (1.00 mL) at 0 °C in a 20 mL sealed scintillation vial, NCS (5.66 mg, 0.042 mmol) was added and the reaction was allowed to continue at 0 °C for 1 h. The mixture was taken up in DCM (5 mL) and washed with water (3 x 5 mL) then saturated sodium thiosulfate (aq) (1 x 5mL), dried over MgSO₄, and filtered by vacuum filtration through a glass fiber paper. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as a yellow oil (18.3 mg). LCMS *m/z* = 586.2 [M+H]⁺.

Step C: Preparation 2-(9-Chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

A solution of 2-amino-3-mercaptopropanoic acid (11.35 mg, 0.094 mmol) in TFA (1 mL) was cooled down to 0 °C. The cold solution was added to *tert*-butyl 2-(9-chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (18.3 mg, 0.031 mmol) in a 20 mL sealed scintillation vial and stirred at 0 °C for 1 h. The mixture was poured into ice water and stirred for 30 minutes. The resulting precipitate was collected by vacuum filtration, washed with water (2 x 5 mL), *n*-hexane (3 x 5 mL), and dried (vacuum oven) to give the title compound as a tan solid (14.0mg). LCMS *m/z* = 530.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.63-1.79 (m, 4H), 1.84-1.96 (m, 2H), 2.03-2.14 (m, 2H), 2.31-2.42 (m, 1H), 2.63 (dd, *J* = 16.55, 9.60 Hz, 1H), 2.83-2.93 (m, 1H), 2.99 (dd, *J* = 16.42, 4.29 Hz, 1H), 3.29-3.42 (m, 1H), 3.70-3.81 (m, 1H), 4.09-4.17 (m, 1H), 4.24-4.32 (m, 1H), 7.58 (d, *J* = 8.59 Hz, 1H), 7.88-7.96 (m, 2H), 8.18 (d, *J* = 1.01 Hz, 1H), 8.36 (d, *J* = 1.26 Hz, 1H), 8.42 (d, *J* = 8.34 Hz, 1H), 12.40 (s, 1H).

Example 1.15: Preparation of 2-(7-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid (Compound 11).

Step A: Preparation of *tert*-Butyl 2-(7-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a stirred solution of 3,5-bis(trifluoromethyl)benzoic acid (39.2 mg, 0.152 mmol) and HATU (69.3 mg, 0.182 mmol) in DMF (1 mL) was added DIEA (52.9 μL, 0.304 mmol). After 15 min, *tert*-butyl 2-(7-(*N*'-hydroxycarbamimidoyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (50 mg, 0.152 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, and then heated at 65 °C for 1 h. The solvent was evaporated, and the residue was purified by column chromatography to give the title compound (53 mg). LCMS *m/z*

= 552.6 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.51 (s, 9H), 2.28-2.38 (m, 1H), 2.55 (dd, *J* = 15.8 and 8.2 Hz, 1H), 2.78 (dd, *J* = 15.9 and 6.6 Hz, 1H), 2.88-2.96 (m, 1H), 3.72-3.80 (m, 1H), 4.02-4.10 (m, 1H), 4.15-4.23 (m, 1H), 6.26 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.94 (dd, *J* = 8.5 and 1.5 Hz, 1H), 8.09 (s, 1H), 8.40 (s, 1H), 8.67 (s, 2H).

5 **Step B: Preparation of *tert*-Butyl 2-(7-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.**

To a stirred solution of *tert*-butyl 2-(7-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (53 mg, 0.096 mmol) in DCM (2 mL) was added NCS (13.5 mg, 0.1 mmol) at 0 °C. The reaction mixture was stirred at this
10 temperature for 30 min, diluted with ethyl acetate, washed with aqueous Na₂S₂O₃ solution and water, and dried over anhydrous Na₂SO₄. The solvent was evaporated to give the title compound (40 mg). LCMS *m/z* = 586.3 [M+H]⁺.

Step C: Preparation of 2-(7-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

15 D/L-Cysteine (41.4 mg, 0.341 mmol) was dissolved in TFA (1 mL) then cooled to 0 °C. The solution was added to a solution of *tert*-butyl 2-(7-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (40 mg, 0.068 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. Water was added, then ethyl acetate was added. The organic layer was
20 separated, washed with water, brine and dried over anhydrous Na₂SO₄. The solvent was evaporated, and the residue was passed through a silica gel column with 10% MeOH/DCM to give the title compound as light yellow solid (23 mg). LCMS *m/z* = 530.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.30-2.41 (m, 1H), 2.63 (dd, *J* = 16.4 and 9.6 Hz, 1H), 2.84-2.94 (m, 1H), 3.00 (dd, *J* = 16.4 and 4.2 Hz, 1H), 3.72-3.80 (m, 1H), 4.10-4.18 (m, 1H), 4.25-4.32 (m, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 8.5 and 1.5 Hz, 1H), 8.20 (s, 1H), 8.54 (s, 1H),
25 8.76 (s, 2H), 12.3 (br, 1H).

Example 1.16: Preparation of 2-(6-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-3-yl)acetic Acid (Compound 15).

30 **Step A: Preparation of Ethyl 2-(1-(4-Cyano-2-nitrophenyl)-2-oxopyrrolidin-3-yl)acetate.**

Ethyl 2-(2-oxopyrrolidin-3-yl)acetate (0.792 g, 4.63 mmol) was taken up in DMA (15 mL) and the resulting mixture was cooled to 0 °C. Sodium hydride (0.185 g, 4.63 mmol) was
35 added and the reaction was warmed to room temperature and stirred for 1 h. 4-Fluoro-3-nitrobenzonitrile (0.768 g, 4.63 mmol) was added and the reaction was stirred at room temperature for 2 days. The reaction was diluted with water and extracted with EtOAc. The

organic extract was dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (620 mg). LCMS m/z = 318.2 $[H+M]^+$.

**Step B: Preparation of Ethyl 2-(6-Cyano-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-
5 a]imidazol-3-yl)acetate.**

Ethyl 2-(1-(4-cyano-2-nitrophenyl)-2-oxopyrrolidin-3-yl)acetate (0.62 g, 1.954 mmol) was taken up in THF (10 mL) and palladium on carbon (0.042 g, 0.391 mmol) was added. The reaction vessel was purged with nitrogen followed by hydrogen. A hydrogen balloon was attached and the reaction was stirred at room temperature for 5 h. The reaction mixture was
10 filtered through Celite[®], and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetic acid (5 mL, 87 mmol) and the solution was warmed to 75 °C. After stirring for 16 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (426 mg). LCMS m/z = 270.2 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.25 (t, J = 7.2 Hz, 3H), 2.45-2.55 (m, 1H),
15 2.73 (dd, J = 16.8, 9.0 Hz, 1H), 3.04-3.19 (m, 2H), 3.70-3.80 (m, 1H), 4.07-4.28 (m, 4H), 7.37 (d, J = 8.3 Hz, 1H), 7.49 (dd, J = 8.3, 1.4 Hz, 1H), 8.02 (s, 1H).

Step C: Preparation of Ethyl 2-(6-(*N'*-Hydroxycarbamimidoyl)-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-a]imidazol-3-yl)acetate.

Ethyl 2-(6-cyano-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-a]imidazol-3-yl)acetate (0.213 g,
20 0.791 mmol) was dissolved in ethanol (10 mL) and 50% hydroxylamine in water (0.261 g, 7.91 mmol) was added. The reaction was warmed to 60 °C and stirred for 16 h. The mixture was concentrated under reduced pressure to give the title compound (213 mg) as a tan solid. LCMS m/z = 303.4 $[M+H]^+$.

Step D: Preparation of Ethyl 2-(6-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-a]imidazol-3-yl)acetate.

3-Cyano-5-(trifluoromethoxy)benzoic acid (0.163 g, 0.705 mmol) was dissolved in DMA (3 mL). HATU (0.348 g, 0.916 mmol) and triethylamine (0.196 mL, 1.409 mmol) were added. The reaction was stirred for 30 min at room temperature. Ethyl 2-(6-(*N'*-hydroxycarbamimidoyl)-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-a]imidazol-3-yl)acetate (0.213 g,
30 0.705 mmol) was added. The reaction was stirred for 1 h, warmed to 90 °C, and stirred for an additional hour. The mixture was extracted with EtOAc and water. The EtOAc layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (82 mg). LCMS m/z = 498.5 $[M+H]^+$.

Step E: Preparation of 2-(6-(5-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-a]imidazol-3-yl)acetic Acid.

Ethyl 2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-*a*]imidazol-3-yl)acetate (82 mg, 0.165 mmol) was dissolved in 2% water in acetonitrile solution (1.0 mL). LiBr (12.0 mg, 1.65 mmol) and triethylamine (69 μ L, 0.495 mmol) were added. The reaction was warmed to 70 °C and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and purified by preparatory TLC to give the title compound. LCMS m/z = 470.1 [M+H]⁺.

Example 1.17: Preparation of 2-(9-Chloro-7-(5-(3-chloro-5-(trifluoromethoxy) phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid (Compound 16).

Step A: Preparation of *tert*-Butyl 2-(7-(5-(3-Chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a stirred solution of 3-chloro-5-(trifluoromethoxy)benzoic acid (51 mg, 0.213 mmol) and HATU (105 mg, 0.276 mmol) in DMF (1 mL) was added DIEA (74.0 μ L, 0.425 mmol). After 15 min, *tert*-butyl 2-(7-(*N*-hydroxycarbamimidoyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (70 mg, 0.213 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, then heated at 70 °C for 1 h, and cooled down. The solvent was evaporated, and the residue was purified by silica gel column chromatography to give the title compound as a white solid (80 mg). LCMS m/z = 534.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) 1.51 (s, 9H), 2.28-2.38 (m, 1H), 2.55 (dd, *J* = 15.8 and 8.2 Hz, 1H), 2.78 (dd, *J* = 15.8 and 6.6 Hz, 1H), 2.88-2.96 (m, 1H), 3.72-3.80 (m, 1H), 4.02-4.11 (m, 1H), 4.15-4.23 (m, 1H), 6.28 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.45 (s, 1H), 7.93 (dd, *J* = 8.5 and 1.5 Hz, 1H), 7.99 (s, 1H), 8.17 (t, *J* = 1.3 Hz, 1H), 8.39 (d, *J* = 1.3 Hz, 1H).

Step B: Preparation of *tert*-Butyl 2-(9-Chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate.

To a stirred solution of *tert*-butyl 2-(7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (80 mg, 0.150 mmol) in DCM (1 mL) was added NCS (21 mg, 0.157 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, diluted with ethyl acetate, washed with aqueous Na₂S₂O₃ solution and water, dried over anhydrous Na₂SO₄. The solvent was evaporated and the residue was purified by silica gel column chromatography to give the title compound as a yellowish white solid (62 mg). LCMS m/z = 568.3 [M+H]⁺.

Step C: Preparation of 2-(9-Chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic Acid.

D/L-Cysteine (66 mg, 0.545 mmol) was dissolved in TFA (1.5 mL) then cooled to 0 °C. The solution was added to a solution of *tert*-butyl 2-(9-chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-

yl)acetate (62 mg, 0.109 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 30 min, and water was added, followed by ethyl acetate. The organic layer was separated, washed with water and brine, and dried over anhydrous Na₂SO₄. The solvent was evaporated, and the residue was passed through a silica gel column with 10% MeOH/DCM to give the title compound as a solid (48 mg). LCMS *m/z* = 512.2 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) 2.38-2.48 (m, 1H), 2.66 (dd, *J* = 16.8, 10.2 Hz, 1H), 2.98-3.08 (m, 1H), 3.35 (dd, *J* = 16.8 and 3.9 Hz, 1H), 3.82-3.92 (m, 1H), 4.06-4.15 (m, 1H), 4.21-4.28 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.48 (s, 1H), 7.98-8.03 (m, 2H), 8.20 (t, *J* = 1.6 Hz, 1H), 8.41 (d, *J* = 1.3 Hz, 1H).

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Example 1.18: Preparation of 2-(9-Chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 17).

Step A: Preparation of *tert*-Butyl 2-(7-(5-(3-Fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

15 3-Fluoro-4-methoxybenzoyl chloride (42.9 mg, 0.228 mmol) was added to a solution of *tert*-butyl 2-(7-(*N*-hydroxycarbamimidoyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (50.0 mg, 0.152 mmol) and TEA (0.032 mL, 0.228 mmol) in THF (1.0 mL) in a 20 mL sealed scintillation vial. The reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in DMA (1.0 mL) and heated to 70 °C for 16 h. The solvent was again removed under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound (35.6 mg) as a white solid. LCMS *m/z* = 464.3 [M+H]⁺.

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Step B: Preparation of *tert*-Butyl 2-(9-Chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

25 To a solution of *tert*-butyl 2-(7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (35.6 mg, 0.077 mmol) in DCM (1.00 mL) at 0 °C in a 20 mL sealed scintillation vial. NCS (10.26 mg, 0.077 mmol) was added and the reaction was stirred at 0 °C for 1 h. The mixture was taken up in DCM (5 mL) and washed with water (3 x 5 mL), then saturated sodium thiosulfate (aq) (1 x 5 mL), dried over MgSO₄, and filtered by vacuum filtration through a glass fiber paper. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (22.9 mg) as a light yellow solid. LCMS *m/z* = 498.4 [M+H]⁺.

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Step C: Preparation of 2-(9-Chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid.

35 A solution of 2-amino-3-mercaptopropanoic acid (16.72 mg, 0.138 mmol) in TFA (1 mL) was made and cooled down to 0 °C. The cold solution was added to *tert*-butyl 2-(9-chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-

yl)acetate (22.9 mg, 0.046 mmol) in a 20 mL sealed scintillation vial at 0 °C and stirred at 0 °C for 5 min. The reaction mixture was warmed up to room temperature and stirred at 23 °C for 15 min. The mixture was poured into ice water and stirred for 30 min. The resulting precipitate was collected by vacuum filtration, washed with water (2 x 5 mL), *n*-hexanes (3 x 5 mL) and dried (vacuum oven) to give the title compound as a tan solid (18.6 mg). LCMS m/z = 442.6 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.31-2.42 (m, 1H), 2.63 (dd, *J* = 16.42, 9.60 Hz, 1H), 2.82-2.93 (m, 1H), 2.99 (dd, *J* = 16.42, 4.17 Hz, 1H), 3.72-3.81 (m, 1H), 3.98 (s, 3H), 4.08-4.17 (m, 1H), 4.23-4.32 (m, 1H), 7.44 (t, *J* = 8.59 Hz, 1H), 7.57 (d, *J* = 8.46 Hz, 1H), 7.88 (dd, *J* = 8.59, 1.52 Hz, 1H), 7.98-8.08 (m, 2H), 8.17 (d, *J* = 1.26 Hz, 1H), 12.40 (s, 1H).

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Example 1.19: Preparation of 2-(9-Chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 18).

Step A: Preparation of *tert*-Butyl 2-(9-Chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate.

tert-Butyl 2-(7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.049 g, 0.097 mmol) was dissolved in anhydrous dichloromethane (1.95 mL) to give a solution which was cooled to 5 °C after which 1-chloropyrrolidine-2,5-dione (0.014 g, 0.107 mmol) was added. After stirring at 0 °C for 1.5 h the reaction mixture was allowed to warm to 24 °C for about 15 min, then the reaction was quenched with 2 M sodium sulfathioate (2.4 mL, 4.9 mmol). The reaction mixture was extracted with MTBE (50 mL), the organic layer was washed with 2 M sodium sulfathioate (10 mL), water (10 mL), brine (10 mL), dried with MgSO₄, and the solvent was concentrated to give a yellow solid which was purified by silica gel flash chromatography to give the title compound as a beige solid (0.035 g). LCMS m/z = 538.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.33 (d, *J* = 6.06 Hz, 6H), 1.39 (s, 9H), 2.29 - 2.43 (m, 1H), 2.61 - 2.70 (m, 1H), 2.81 - 2.90 (m, 1H), 2.93 (dd, *J* = 16.04, 4.29 Hz, 1H), 3.68 - 3.84 (m, 1H), 3.91 (s, 3H), 4.05 - 4.19 (m, 1H), 4.21 - 4.32 (m, 1H), 4.66 - 4.84 (m, 1H), 7.23 (d, *J* = 8.72 Hz, 1H), 7.57 (d, *J* = 8.46 Hz, 1H), 7.67 (d, *J* = 2.02 Hz, 1H), 7.79 (dd, *J* = 8.34, 2.02 Hz, 1H), 7.89 (dd, *J* = 8.59, 1.52 Hz, 1H), 8.17 (d, *J* = 1.39 Hz, 1H).

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Step B: Preparation of 2-(9-Chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic Acid (Compound 18).

L(+)-Cysteine (0.037 g, 0.307 mmol) was dissolved in TFA (0.613 mL) to give a solution which was cooled to 0 °C. This solution was added to *tert*-butyl 2-(9-chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (0.033 g, 0.061 mmol) which was contained in a flask pre-cooled to 0 °C. The reaction was stirred at 0 °C for 45 min then at 24 °C for 10 min. Cold water (20 mL) was added to the reaction mixture while stirring to give a suspension to which Et₂O (50 mL) was added to give

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dissolution of the suspension. The mixture was shaken, the organic layer was washed with water (3 x 20 mL), brine (20 mL), dried with MgSO₄, and the solvent was evaporated in the presence of toluene under reduced pressure at 25 °C to afford the title compound as a grey solid (17 mg). LCMS m/z = 482.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.33 (d, J = 6.06 Hz, 6H), 2.31 - 2.42 (m, 1H), 2.63 (dd, J = 16.42, 9.73 Hz, 1H), 2.81 - 2.92 (m, 1H), 2.99 (dd, J = 16.48, 4.23 Hz, 1H), 3.70 - 3.82 (m, 1H), 3.91 (s, 3H), 4.07 - 4.18 (m, 1H), 4.23 - 4.33 (m, 1H), 4.69 - 4.82 (m, 1H), 7.23 (d, J = 8.72 Hz, 1H), 7.57 (d, J = 8.59 Hz, 1H), 7.67 (d, J = 2.02 Hz, 1H), 7.79 (dd, J = 8.46, 2.02 Hz, 1H), 7.89 (dd, J = 8.59, 1.52 Hz, 1H), 8.17 (d, J = 1.39 Hz, 1H), 12.39 (bs, 1H).

Example 2: Homogeneous Time-Resolved Fluorescence (HTRF[®]) Assay for Direct cAMP Measurement.

Compounds of the present invention were screened for agonists of the S1P1 receptor (*e.g.*, human S1P1 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 S1P1. CHO-K1 cells were obtained from ATCC[®] (Manassas, VA; Catalog # CCL-61). An agonist of the S1P1 receptor was detected in the HTRF[®] assay for direct cAMP measurement as a compound which decreased cAMP concentration. HTRF[®] assay also was used to determine EC₅₀ values for S1P1 receptor agonists.

Principle of the assay: 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 # I5879 and catalog #

R6520, respectively), followed by test compound in 5 μ L compound buffer (PBS+ supplemented with 10 μ L NKH477 (water-soluble forskolin derivative; SigmaGen Laboratories, Gaithersburg, MD; catalog # PKI-NKH477-010)) or 5 μ L compound buffer. The plate was then incubated at room temperature for 1 h. To each well was then added 5 μ L cAMP-d2 conjugate in lysis buffer and 5 μ L 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 PHERAstar (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 B

Compound No.	EC ₅₀ S1P1 (HTRF) [®]
2	0.60 nM
6	0.20 nM
7	0.13 nM

Certain other compounds of the invention had EC₅₀ S1P1 (HTRF[®]) values ranging from about 5 nM to about 0.1 nM in this assay.

Example 3: Cellular/Functional Ca²⁺ Assay for Agonist Activity on S1P3 Receptor.

A compound of the present invention can be shown to have no or substantially no agonist activity on the S1P3 receptor by using in assay a human neuroblastoma cell line which endogenously expresses S1P3 (predominantly), S1P2 and S1P5 receptors, but not S1P1 or S1P4 receptors, based on mRNA analysis (Villullas *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 present invention can be shown to induce peripheral lymphocyte lowering (PLL).

A. Mouse PLL Assay.

5 **Animals:** Male BALB/c mice (Charles River Laboratories, Wilmington, MA) are housed four per cage and maintained in a humidity-controlled (40 to 60%) and temperature-controlled (68 to 72 °F) 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.

10 **PLL Assay:** Mice are given an oral dose of a compound of the present invention or dosing vehicle (0.5% methylcellulose) in a total volume of 10 mL/kg. Peripheral blood samples are collected at 5 hours post-dose. The mice are anesthetized with isoflurane and blood is collected *via* cardiac puncture. A complete cell count (CBC), including lymphocyte count, is obtained using a CELL-DYN® 3700 (Abbott Laboratories, Abbott Park, IL) instrument.

15 Reduction of the PBL count by the test compounds in comparison with vehicle is indicative of the test compounds exhibiting activity or inducing peripheral lymphocyte lowering.

B. Rat PLL Assay.

20 **Animals:** Male Sprague-Dawley rats (Charles River Laboratories, Hollister, CA) were housed and maintained in humidity (40 to 60%) and temperature (68 to 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 were allowed (approximately) one week of habituation to the animal facility before testing.

25 **PLL Assay:** Rats were given a 1 mg/kg intravenous dose of the enantiomer of compound 4 (as reported in Example 1.3), or dosing vehicle (20% hydroxypropyl-cyclodextrin (HPCD)) in a total volume of 1.00 mL/kg. Peripheral blood samples were collected at 5 h post-dose. Blood was collected *via* indwelling catheter. A complete cell count (CBC), including lymphocyte count, was obtained using a CELL-DYN® 3700 (Abbott Laboratories, Abbott Park, IL) instrument. Results are presented in Figure 1, in which peripheral blood lymphocyte (PBL)

30 count is shown for the 5 hour group. Reduction of the PBL count by the test compound in comparison with vehicle is indicative of the test compound exhibiting activity or inducing peripheral lymphocyte lowering. It is apparent from inspection of Figure 1 that the exemplified enantiomer of compound 4 (as reported in Example 1.3) exhibited activity for inducing PBL lowering (lymphopenia) in the rat.

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

A compound of the present 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-controlled (40-60%) and temperature-controlled (68-72 °F) 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 MOG₃₅₋₅₅ 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 h 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 5 mL/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-controlled (40-60%) and temperature-controlled (68-72 °F) facility on a 12 h:12 h light/dark cycle (lights on at 6:30 am) with free access to food (Harlan-Teklad Western Res, 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.

- 5 **Drug treatment:** Mice are dosed orally, with vehicle or a test compound, once a day from day 3 until day 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. 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.

10 **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-controlled (30-70%) and temperature-controlled (20-22 °C) 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
15 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 (1 mg/mL). 50 µL of this emulsion is administered by intraplantar (ipl) injection into both hind
20 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
25 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 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 present invention can be shown to have therapeutic efficacy in type I
35 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).

- 5 **Cyclophosphamide induction of type I diabetes:** On day 0 and day 14, normoglycemic NOD mice are injected intraperitoneally with 4 mg 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.

- 10 **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
15 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.

- 20 A compound of the present 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-controlled
25 (40-60%) and temperature-controlled (68-72 °F) 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.

- 30 **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
35 allografted mice are divided into 8 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.

A compound of the present invention can be shown to have therapeutic efficacy in colitis using an animal model for colitis. Suitable animal models are known in the art (Boismenu *et al.*, *J. Leukoc. Biol.*, 67:267-278, 2000). A first exemplary animal model for colitis is trinitrobenzenesulfonic acid (TNBS)-induced colitis, which presents clinical and histopathological findings that resemble those in Crohn's disease (Neurath *et al.*, *J. Exp. Med.*, 182:1281-1290, 1995; Boismenu *et al.*, *J. Leukoc. Biol.*, 67:267-278, 2000). A second exemplary animal model for colitis is dextran sulfate sodium (DSS)-induced colitis, which presents clinical and histopathological findings that resemble those in ulcerative colitis (Okayasu *et al.*, *Gastroenterology*, 98:694-702, 1990; Boismenu *et al.*, *J. Leukoc. Biol.*, 67:267-278, 2000). 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-controlled (40-60%) and temperature-controlled (68-72 °F) 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 μ L) using an intubation needle (22 g, 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.

30 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-controlled (40-60%) and temperature-controlled (68-72 °F) 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 habituation 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 anesthetized 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 μ L) using a fabricated intubation needle (7.5 Fr umbilical catheter and 14 g hub) inserted 8 cm into the anus with the rat held by the tail in a vertical position. The rat is held vertically for 30 additional s 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-controlled (30-70%) and temperature-controlled (20-22 °C) 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 min averages using DataSciences ART software. Telemetry recording takes place 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 1:00 pm. 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 min 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.

Example 10: Effect of Compounds on Arthritis.

Female Lewis rats can be used in this study to determine that a compound of the invention has an effect on arthritis. Acclimated animals are anesthetized with isoflurane and given the first collagen injection (day 0). On day 6, the animals are anesthetized again for the second collagen injection. Collagen is prepared by making a 4 mg/mL solution in 0.01 N acetic acid. Equal volumes of collagen and incomplete Freund's adjuvant are emulsified by hand mixing until a bead of this material holds its form when placed in water. Each animal receives 300 μ L of the mixture each time, spread over 3 subcutaneous sites on the back.

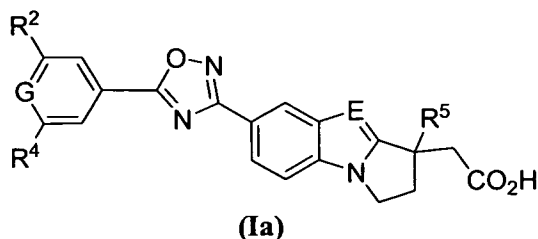
Treatment (*p.o.*, *q.d.*, 5 mL/kg dosing volume) begins on day 0 and continued through day 16 with vehicle or compounds given at 24 h intervals. Rats are weighed on days 0, 3, 6 and 9 through 17 and caliper measurements of the ankles taken on days 9 through 17. A reduction of mean ankle diameter in the treated animals compared to untreated animals is indicative of the compound exhibiting a positive effect on arthritis as described by this animal model.

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.

CLAIMS

What is claimed is:

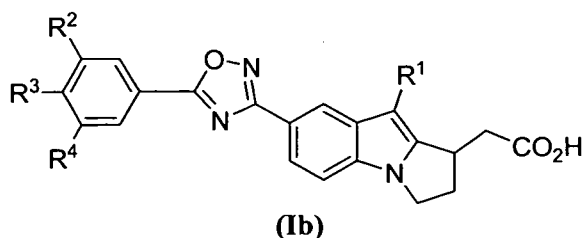
1. A compound selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

- E is N or CR¹;
 G is N or CR³;
- 10 R¹ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, cyano, C₁-C₆ haloalkyl, C₁-C₆ haloacyl, and halogen;
- R², R³, and R⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyloxy, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, and halogen; and
- 15 R⁵ is H or halogen.
2. The compound according to claim 1, wherein E is N.
3. The compound according to claim 1, wherein E is CR¹.
- 20 4. The compound according to claim 3, wherein R¹ is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl.
5. The compound according to claim 3, wherein R¹ is chloro or fluoro.
- 25 6. The compound according to any one of claims 1 to 5, wherein G is CR³.
7. The compound according to any one of claims 1 to 6, wherein R², R³, and R⁴ are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, fluoro, iodo, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.
- 30

8. The compound according to any one of claims 1 to 7, wherein R² is selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.
- 5 9. The compound according to any one of claims 1 to 8, wherein R³ is selected from the group consisting of H, cyclohexyl, cyclopentyl, and isopropoxy.
- 10 10. The compound according to any one of claims 1 to 9, wherein R⁴ is selected from the group consisting of H, chloro, cyano, methoxy, methyl, trifluoromethoxy, and trifluoromethyl.
11. The compound according to any one of claims 1 to 5, wherein G is N.
12. The compound according to claim 11, wherein R² and R⁴ are each independently C₁-C₆ alkyl or halogen.
- 15 13. The compound according to claim 11 or 12, wherein R² and R⁴ are each independently chloro or methyl.
- 20 14. The compound according to any one of claims 1 to 13, wherein R⁵ is H or F.
15. The compound according to any one of claims 1 to 13, wherein R⁵ is H.
- 25 16. The compound according to claim 1, wherein:
R¹ is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl;
R², R³, and R⁴ are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, fluoro, iodo, isopropoxy, methoxy, methyl, trifluoromethoxy, and trifluoromethyl; and
30 R⁵ is H or F.
17. The compound according to claim 1, selected from compounds of Formula (Ib) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

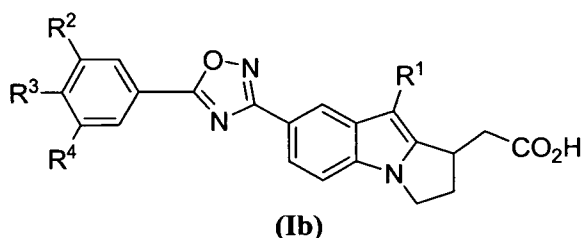


wherein:

R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloacyl, cyano, and halogen; and

R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, C_1 - C_6 alkoxy, cyano, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

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

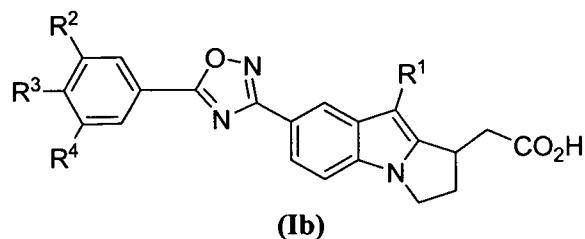


wherein:

R^1 is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl; and

R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, chloro, cyano, cyclohexyl, cyclopentyl, fluoro, iodo, isopropoxy, methoxy, trifluoromethoxy, and trifluoromethyl.

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



wherein:

R^1 is selected from the group consisting of chloro, cyano, fluoro, iodo, methyl, methylsulfonyl, trifluoroacetyl, and trifluoromethyl;

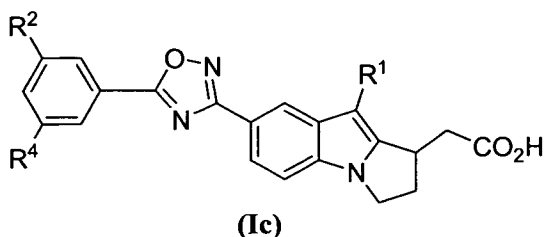
R^2 is selected from the group consisting of H, chloro, cyano, fluoro, methoxy, trifluoromethoxy, and trifluoromethyl;

R^3 is selected from the group consisting of H, cyclohexyl, cyclopentyl, and isopropoxy; and

R^4 is selected from the group consisting of H, chloro, cyano, fluoro, methoxy, trifluoromethoxy, and trifluoromethyl.

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

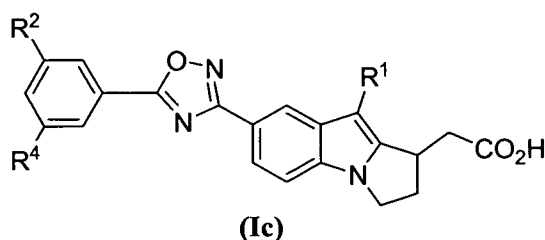


wherein:

- 10 R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 haloalkyl, cyano, and halogen; and

R^2 and R^4 are each independently selected from the group consisting of cyano, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, and halogen.

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

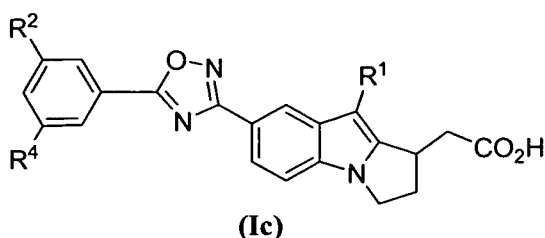


wherein:

- 20 R^1 is selected from the group consisting of methyl, trifluoromethyl, chloro, cyano, methylsulfonyl, chloro, iodo, and fluoro; and

R^2 and R^4 are each independently from the group consisting of cyano, methoxy, trifluoromethoxy, and trifluoromethyl.

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



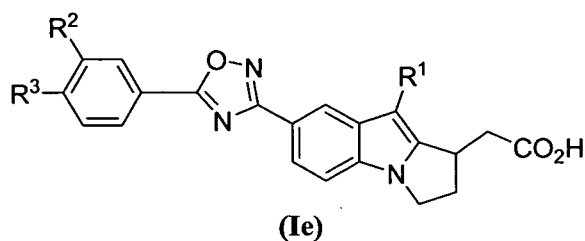
wherein:

R¹ is selected from the group consisting of methyl, trifluoromethyl, cyano, methylsulfonyl, chloro, iodo, and fluoro;

5 R² is cyano; and

R⁴ is trifluoromethoxy.

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



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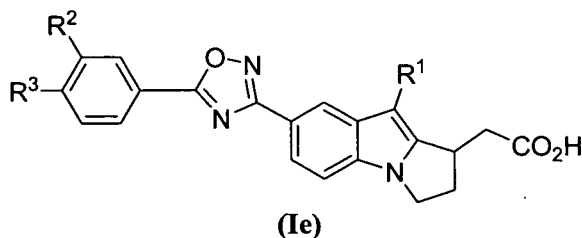
wherein:

R¹ is C₁-C₆ haloacyl or halogen; and

R² and R³ are each independently selected from the group consisting of C₁-C₆ alkoxy, cyano, C₃-C₇ cycloalkyl, and halogen.

15

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



wherein:

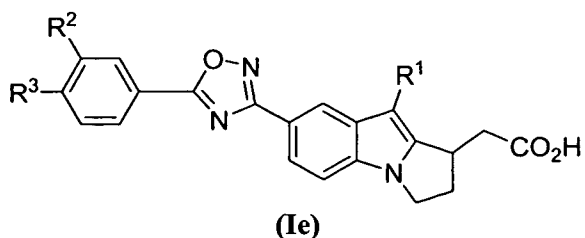
20 R¹ is C₁-C₆ haloacyl or halogen;

R² is cyano, C₁-C₆ haloalkyl, or halogen; and

R³ is C₁-C₆ alkoxy or C₃-C₇ cycloalkyl.

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

25



wherein:

R^1 is chloro or trifluoroacetyl;

R^2 is cyano, fluoro, or trifluoromethyl; and

5 R^3 is cyclohexyl, cyclopentyl, isopropoxy, or methoxy.

26. A compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:
- 10 2-(7-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-9-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-fluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1,9-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 15 2-(9-chloro-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(9-chloro-7-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 20 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-iodo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 25 2-(9-cyano-7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(7-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-9-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 30 2-(7-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-9-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;
- 2-(9-chloro-7-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;

2-(9-chloro-7-(5-(2-chloro-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;

2-(9-chloro-7-(5-(3-cyano-5-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;

5 2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-3-yl)acetic acid;

2-(9-chloro-7-(5-(3-chloro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid;

10 2-(9-chloro-7-(5-(3-fluoro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid; and

2-(9-chloro-7-(5-(4-isopropoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetic acid.

15 27. The compound according to any one of claims 1 to 26, wherein the stereochemistry of the C(1) ring carbon of said compound is *R*.

28. The compound according to any one of claims 1 to 26, wherein the stereochemistry of the C(1) ring carbon of said compound is *S*.

20 29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 28 and a pharmaceutically acceptable carrier.

25 30. A method for treating an S1P1 receptor-associated 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 28, or a pharmaceutical composition according to claim 29.

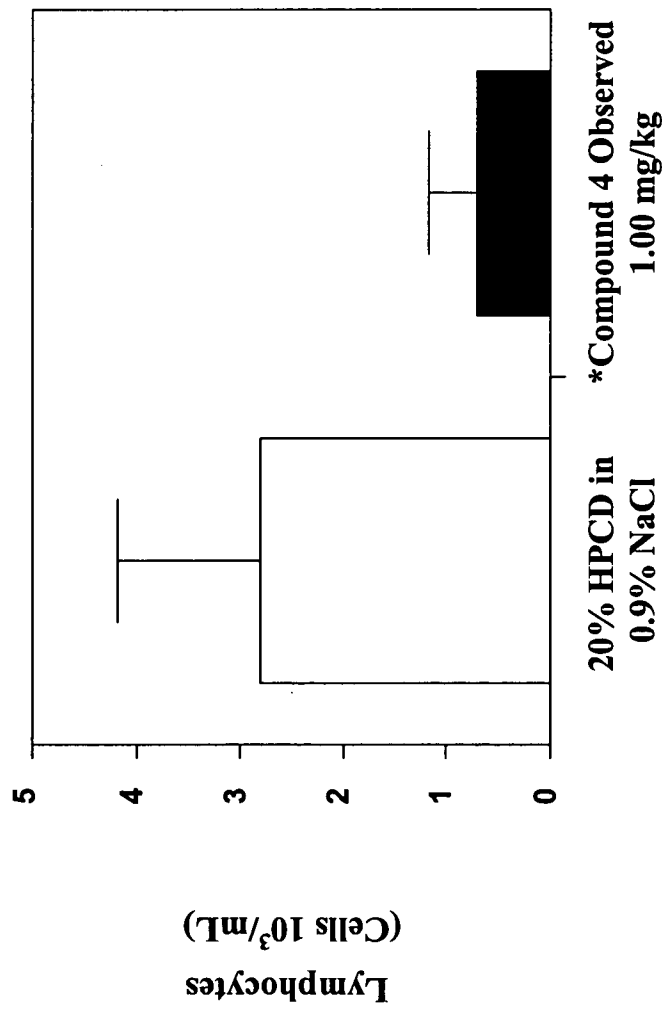
30 31. A method for treating a disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 28, or a pharmaceutical composition according to claim 29, wherein said disorder is selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, 35 thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

32. 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 28, or a pharmaceutical composition according to claim 29.
- 5 33. 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 28, or a pharmaceutical composition according to claim 29.
- 10 34. Use of a compound according to any one of claims 1 to 28 in the manufacture of a medicament for the treatment of an S1P1 receptor-associated disorder.
35. Use of a compound according to any one of claims 1 to 28 in the manufacture of a medicament for the treatment of an S1P1 receptor-associated disorder selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, 15 acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.
- 20 36. Use of a compound according to any one of claims 1 to 28 in the manufacture of a medicament for the treatment of psoriasis.
37. Use of a compound according to any one of claims 1 to 28 in the manufacture of a medicament for the treatment of multiple sclerosis. 25
38. A compound according to any one of claims 1 to 28 for use in a method for the treatment of the human or animal body by therapy.
- 30 39. A compound according to any one of claims 1 to 28 for use in a method for the treatment of an S1P1 receptor-associated disorder.
40. A compound according to any one of claims 1 to 28 for use in a method for the treatment of an S1P1 receptor-associated disorder selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, 35 systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial

ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

- 5 41. A compound according to any one of claims 1 to 28 for use in a method for the treatment of psoriasis.
42. A compound according to any one of claims 1 to 28 for use in a method for the treatment of multiple sclerosis.
- 10 43. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 28 and a pharmaceutically acceptable carrier.

Rat peripheral lymphocytes lowering (PLL) assay (*P. O.* 5 h)



* The enantiomer as described in Example 1.3

FIGURE 1

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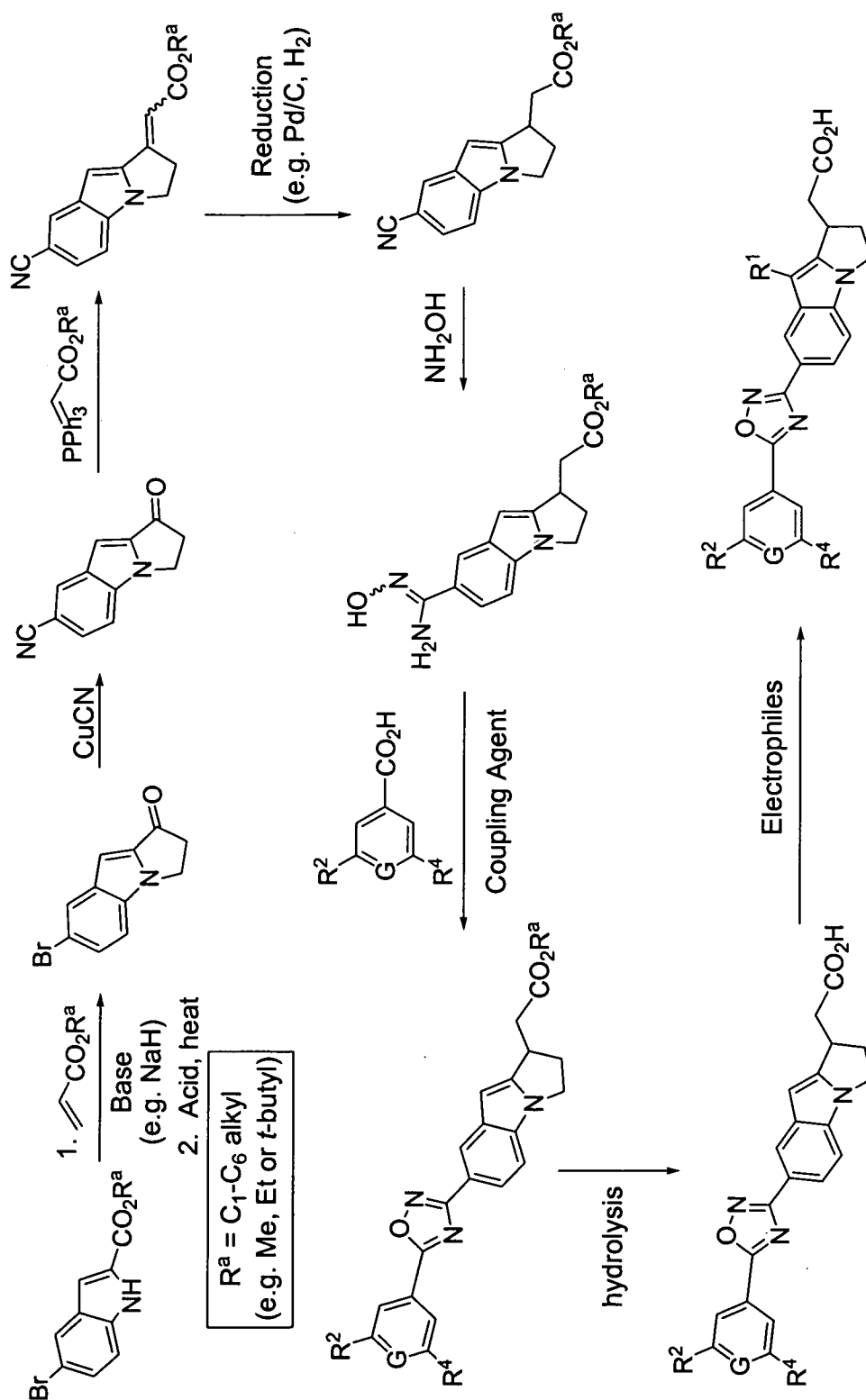


FIGURE 2

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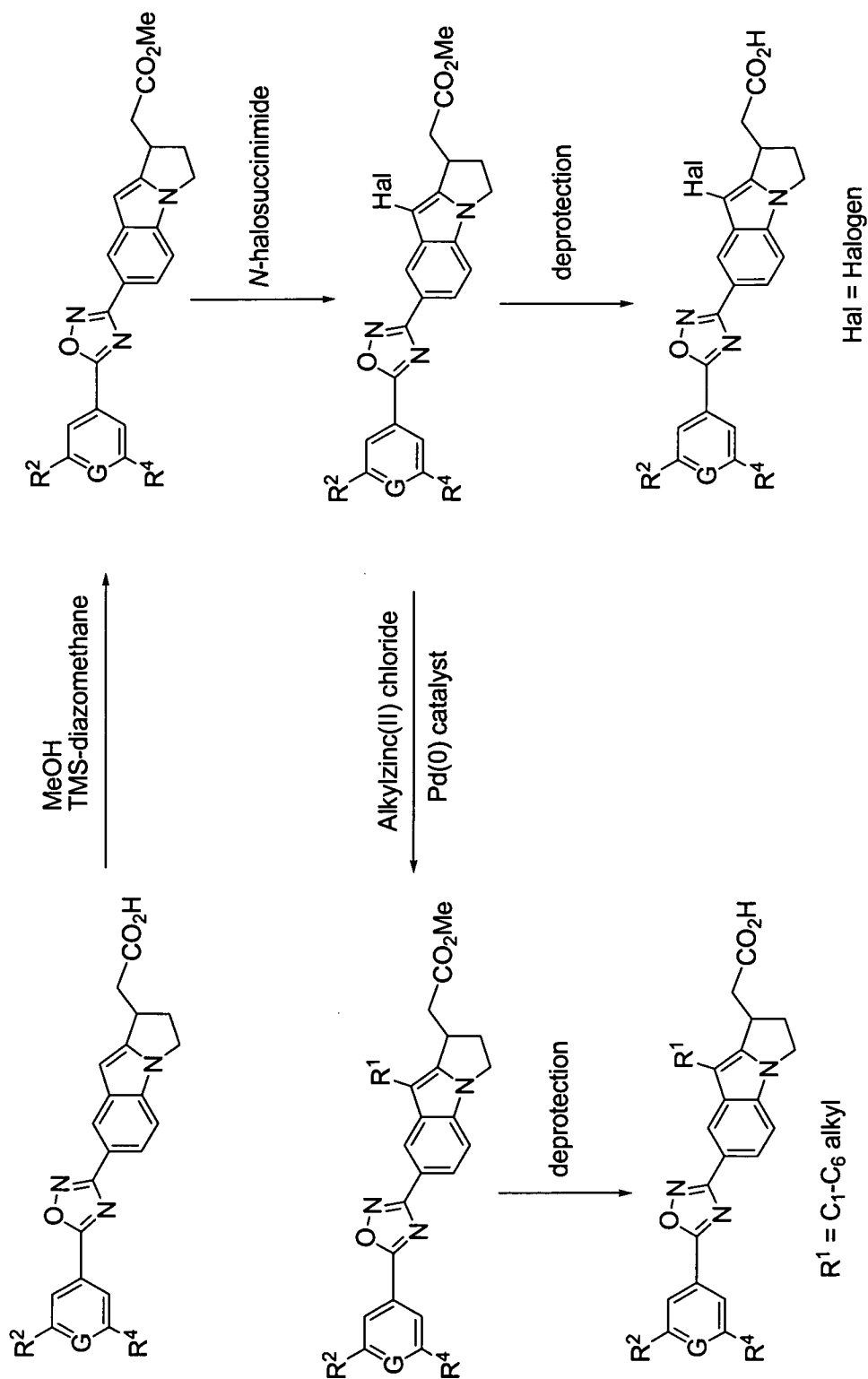


FIGURE 3

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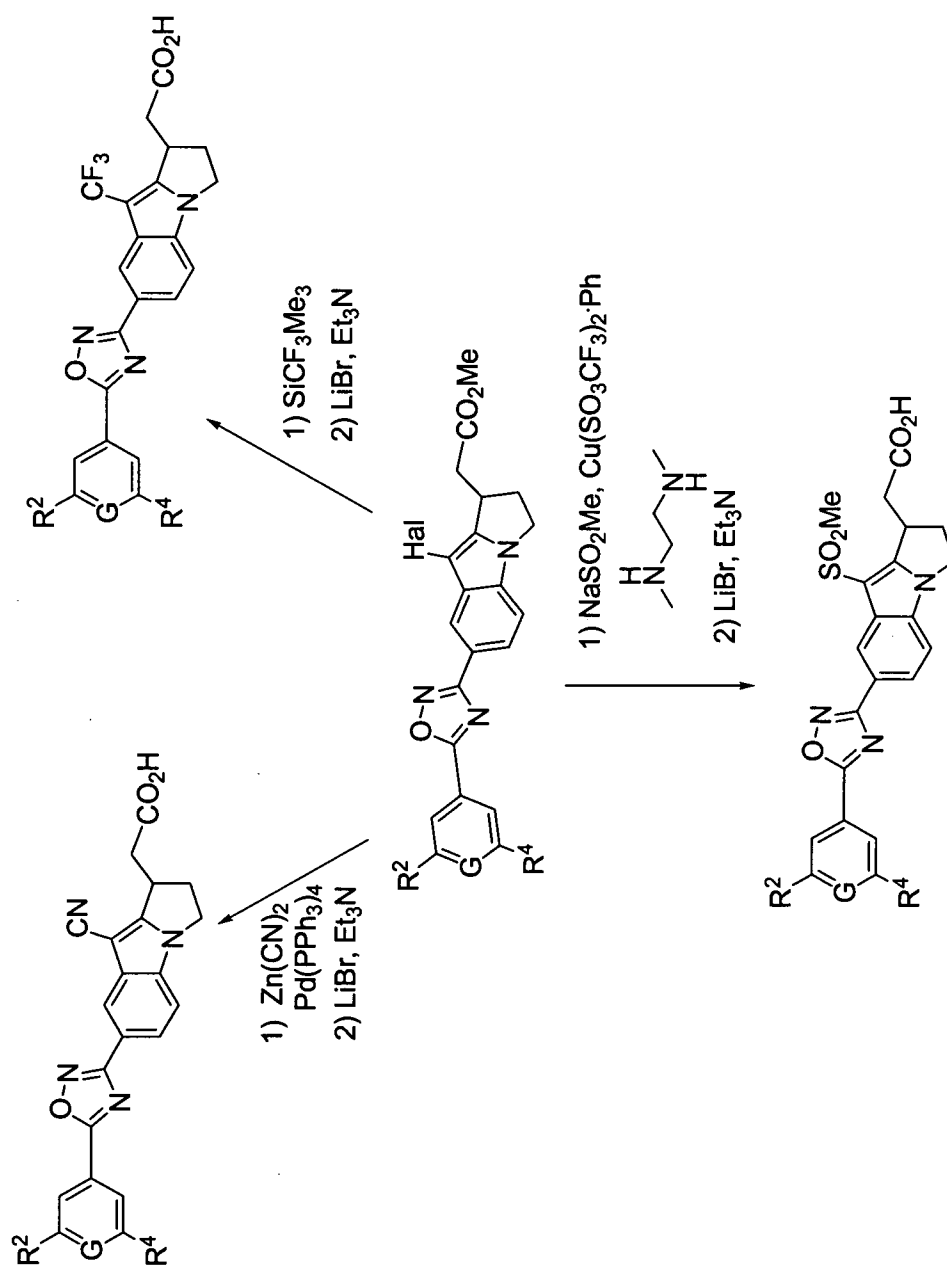


FIGURE 4

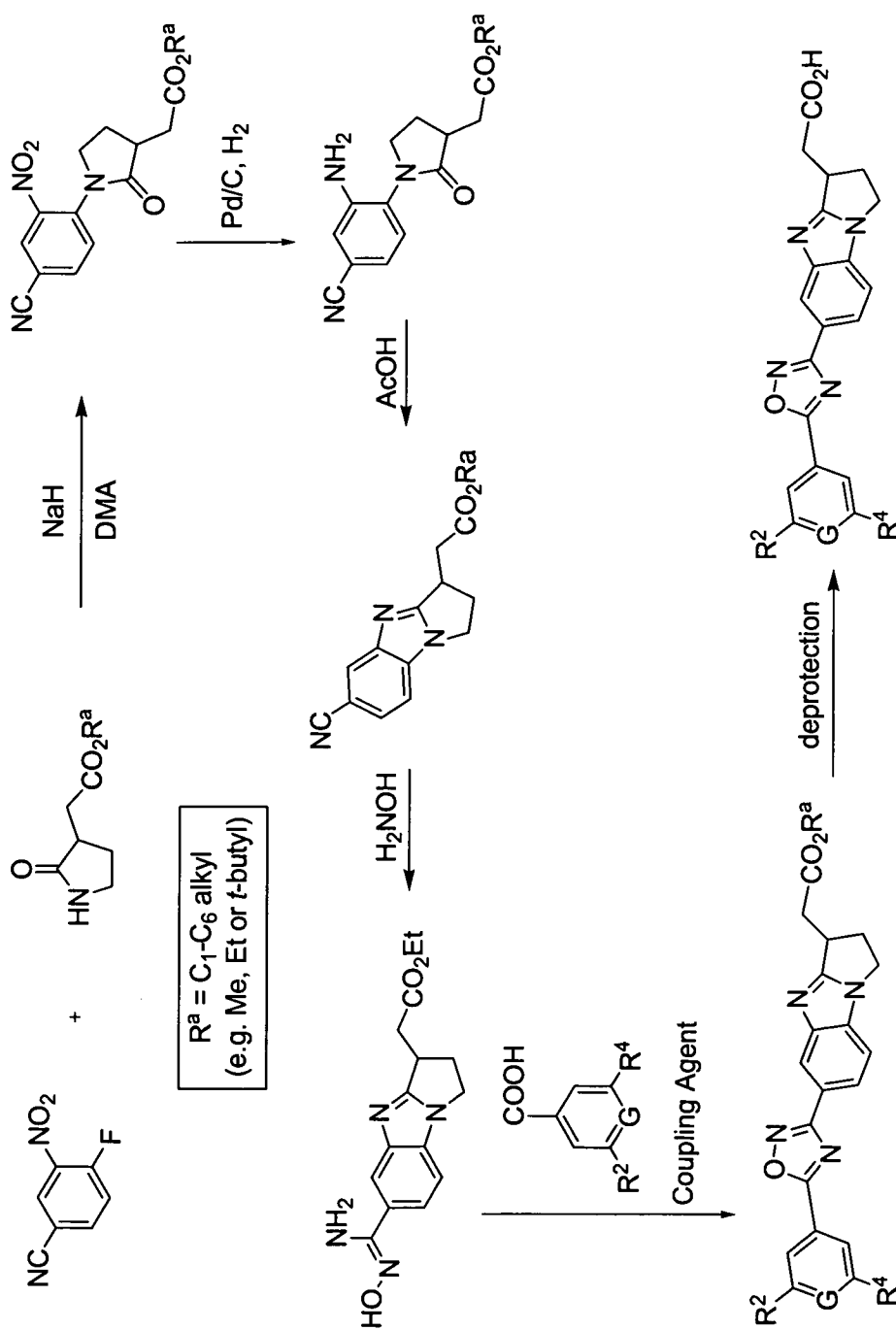


FIGURE 5

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/001787

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/4245 A61P17/06 A61P17/10 A61P19/02
A61P29/00 A61P31/04 A61P31/12 A61P43/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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, BEILSTEIN Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, FSTA, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/094157 A1 (ARENA PHARM INC [US]; JONES ROBERT M [US]; BUZARD DANIEL J [US]; KAWAS) 30 July 2009 (2009-07-30) claim all	1-43
A	WO 2008/076356 A1 (ABBOTT LAB [US]; HOBSON ADRIAN D [US]; FIX-STENZEL SHANNON [US]; CUSAC) 26 June 2008 (2008-06-26) claim 1	1-43
A	EP 2 003 132 A1 (ASTELLAS PHARMA INC [JP]) 17 December 2008 (2008-12-17) claim 1	1-43

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

☒ See patent family annex.

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

"&" document member of the same patent family

Date of the actual completion of the international search

13 October 2010

Date of mailing of the international search report

21/10/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/001787

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