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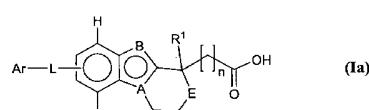
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(54) Title: MODULATORS OF THE SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO



(57) Abstract: The present invention relates to certain compounds 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 receptor-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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**MODULATORS OF THE SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR USEFUL  
FOR THE TREATMENT OF DISORDERS RELATED THERETO**

**FIELD OF THE INVENTION**

5       The present invention relates to certain compounds 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 receptor-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 15 associated diseases, 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 20 least immunosuppressive, anti-inflammatory, and/or hemostatic activities, *e.g.* by virtue of modulating leukocyte trafficking, sequestering lymphocytes in secondary lymphoid tissues, and/or enhancing vascular integrity.

The present application is in part focused on addressing an unmet need for immunosuppressive agents such as may be orally available which have therapeutic efficacy for 25 at least autoimmune diseases and disorders, inflammatory diseases and disorders (*e.g.*, acute and chronic inflammatory conditions), transplant rejection, cancer, and/or conditions that have an underlying defect in vascular integrity or that are associated with angiogenesis such as may be pathologic (*e.g.*, as may occur in inflammation, tumor development, and atherosclerosis) with fewer side effects such as the impairment of immune responses to systemic infection.

30       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 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 35 phosphorylation of sphingosine. S1P1, S1P4, and S1P5 receptors activate Gi but not Gq, whereas S1P2 and S1P3 receptors activate both Gi and Gq. The S1P3 receptor, but not the S1P1 receptor, responds to an agonist with an increase in intracellular calcium.

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  $\beta$ -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 $\alpha$ -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 remitting-relapsing 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).

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 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 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, 25 inflammation, and pathological conditions such as sepsis, hypoxia, and solid tumor growth (T Sanchez *et al.*, *J. Biol. Chem.*, 278(47), 47281-47290, 2003).

Cyclosporin A and FK506 (calcineurin inhibitors) are drugs used to prevent rejection of transplanted organs. Although they are effective in delaying or suppressing transplant rejection, classical immunosuppressants such as cyclosporin A and FK506 are known to cause several 30 undesirable side effects including nephrotoxicity, neurotoxicity,  $\beta$ -cell toxicity and gastrointestinal discomfort. There is an unmet need in organ transplantation for an immunosuppressant without these side effects which is effective as a monotherapy or in combination with a classical immunosuppressant for inhibiting migration of, e.g., alloantigen-reactive T-cells to the grafted tissue, thereby prolonging graft survival.

FTY720 has been shown to have therapeutic efficacy in transplant rejection both as a monotherapy and in synergistic combination with a classical immunosuppressant, including cyclosporin A, FK506 and RAD (an mTOR inhibitor). It has been shown that, unlike the

classical immunosuppressants cyclosporin A, FK506 and RAD, FTY720 has efficacy for prolonging graft survival without inducing general immunosuppression, and this difference in drug action is believed to be relevant to the synergism observed for the combination (Brinkmann *et al.*, *Transplant Proc.*, 33:530-531, 2001; Brinkmann *et al.*, *Transplantation*, 72:764-769, 2001).

Agonism of the 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 5 gravis (EAMG) in C57BL/6 mice (T. Kohono *et al.*, *Biological & Pharmaceutical Bulletin*, 28(4), 736-739, 2005).

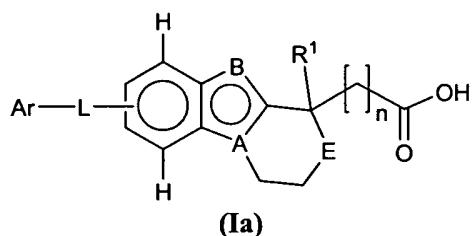
In one embodiment, the present invention encompasses compounds which are agonists of the S1P1 receptor having selectivity over the S1P3 receptor. The S1P3 receptor, and not the S1P1 receptor, has been directly implicated in bradycardia (Sanna *et al.*, *J. Biol. Chem.*, 10 279:13839-13848, 2004). An 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.

15 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.

20 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:

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NR<sup>3</sup> or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

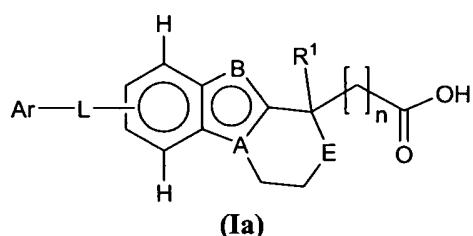
R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

$R^2$  is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen;

$R^3$  is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

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



wherein:

$n$  is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

$R^2$  is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

One aspect of the present invention pertains to compounds of Formula (Ia) provided that when  $n$  is 0, E is NH, and L is -CH<sub>2</sub>-O-, then Ar is substituted with 2 substituents.

One aspect of the present invention pertains to compounds of Formula (Ia) provided that when  $n$  is 0, A is C, B is NH, E is NH, and L is -CH<sub>2</sub>-O-, then Ar is substituted with 2 substituents.

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 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, tumor development and atherosclerosis). Such conditions where suppression of the immune

10 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; arthritis, including psoriatic arthritis, and rheumatoid arthritis; diabetes, including type I  
15 diabetes; demyelinating disease, including multiple sclerosis; ischemia-reperfusion injury, including renal and cardiac ischemia-reperfusion injury; inflammatory skin disease, including psoriasis, atopic dermatitis, and acne; hyperproliferative skin disease, including acne; inflammatory bowel disease, including Crohn's disease, and ulcerative colitis; systemic lupus erythematosus; asthma; uveitis; myocarditis; allergy; atherosclerosis; brain inflammation,  
20 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; acute lung injury; acute respiratory disease syndrome; sepsis; and the like.

25 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 therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.  
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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.

35 One aspect of the present invention pertains to methods for treating an autoimmune disease or disorder in an individual comprising administering to the individual in need thereof a

therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

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

One aspect of the present invention pertains to methods for treating 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.

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 a disease or disorder mediated by lymphocytes.

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 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.

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 a microbial 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 a viral infection or disease.

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 cancer.

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

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 Crohn's disease.

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

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

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 systemic lupus erythematosus.

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

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 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.

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 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.

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 glomerulosclerosis.

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.

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 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.

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 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.

10 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.

15 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.

20 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.

25 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.

30 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.

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

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

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

5 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.

10 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.

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

15 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.

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

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

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

25 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.

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

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

**BRIEF DESCRIPTION OF THE DRAWINGS**

**Figure 1** shows the results of an experiment which measured the ability of Compound 41 to lower the absolute count of peripheral lymphocytes in mice compared to vehicle. Values are presented as Mean ± SD; n = 4 per treatment group.

5       **Figure 2** shows the results of an experiment which measured the ability of Compound 25 to lower the absolute count of peripheral lymphocytes in mice compared to vehicle. Values are presented as Mean ± SD; n = 4 per treatment group.

10      **Figure 3** shows the results of an experiment which measured the ability of Compound 31 to lower the absolute count of peripheral lymphocytes in mice compared to vehicle. Values are presented as Mean ± SD; n = 4 per treatment group.

15      **Figure 4** shows the results of an experiment which measured the ability of the 1<sup>st</sup> enantiomer of Compound 4 (as described in **Example 1.5**) to lower the absolute count of peripheral lymphocytes in rats compared to vehicle. Values are presented as Mean ± SD; n = 4 per treatment group.

20      **Figure 5** shows the results of an experiment which measured the ability of the 2<sup>nd</sup> enantiomer of Compound 4 (as described in **Example 1.5**) to lower the absolute count of peripheral lymphocytes in rats compared to vehicle. Values are presented as Mean ± SD; n = 4 per treatment group.

25      **Figure 6** shows a general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is N, B is CR<sup>2</sup>, E is O, and L is -CH<sub>2</sub>-O-.

30      **Figure 7** shows a general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is N, B is CR<sup>2</sup>, E is NH, and L is -CH<sub>2</sub>-O-.

35      **Figure 8** shows a general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is N, B is CR<sup>2</sup>, and L is 1,2,4-oxadiazole-3,5-diyl.

40      **Figure 9** shows general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is C, B is NH, E is O, and L is -CH<sub>2</sub>-O-.

45      **Figure 10** shows general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is C, B is NH, E is NH, and L is -CH<sub>2</sub>-O-.

50      **Figure 11** shows a general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is C, B is NH, E is NH, n = 0, and L is -CH<sub>2</sub>-O-.

55      **Figure 12** shows a general synthetic scheme for the preparation of compounds of Formula **(Ia)** wherein A is C, B is NH, E is O, and L is 1,2,4-oxadiazole-3,5-diyl.

**DETAILED DESCRIPTION OF THE INVENTION****35    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 5 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).

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 10 activate the intracellular response initiated by the active form of the receptor and can thereby inhibit the intracellular responses by an agonist or partial agonist. An antagonist does not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term “**hydrate**” as used herein means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non- 15 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.

20 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 25 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.

30 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.

35 The term “**inverse agonist**” is intended to mean a moiety that binds to the endogenous form of the receptor or to the constitutively activated form of the receptor and which inhibits the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of an agonist or partial agonist, or decreases GTP binding to a membrane. In some embodiments, the baseline intracellular response is inhibited in the

presence of the inverse agonist by at least 30%. In some embodiments, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 50%. In some embodiments, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

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

The term “**pharmaceutical composition**” is intended to mean a composition comprising at least one active ingredient; including but not limited to, salts, solvates, and hydrates of compounds of the present invention, whereby the composition is amenable to investigation for a 10 specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term “**therapeutically effective amount**” is intended to mean the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, 15 system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, caregiver or by an individual, which includes one or more of the following:

(1) Preventing the disease, for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet 20 experience or display the pathology or symptomatology of the disease;

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

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

## CHEMICAL GROUP, MOIETY OR RADICAL

30 The term “**C<sub>1</sub>-C<sub>6</sub> alkoxy**” is intended to mean a C<sub>1</sub>-C<sub>6</sub> 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 “**C<sub>1</sub>-C<sub>6</sub> 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(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>], 2-methylbutyl [*i.e.*, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>], *n*-hexyl and the like.

The term "**C<sub>1</sub>-C<sub>6</sub> alkylamino**" is intended to mean one alkyl radical attached to an -NH- radical wherein the alkyl radical has the same meaning as described herein. Some examples include, but are not limited to, methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, *sec*-butylamino, isobutylamino, *tert*-butylamino and the like.

The term "**C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl**" is intended to mean a C<sub>1</sub>-C<sub>6</sub> alkyl radical attached to the sulfur of a sulfone radical having the formula: -S(O)<sub>2</sub>- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, *iso*-propylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, *iso*-butylsulfonyl, *tert*-butylsulfonyl and the like.

The term "**carboxy**" or "**carboxyl**" is intended to mean the group -CO<sub>2</sub>H; also referred to as a carboxylic acid group.

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

The term "**C<sub>3</sub>-C<sub>7</sub> 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 "**C<sub>3</sub>-C<sub>7</sub> 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 "**C<sub>2</sub>-C<sub>8</sub> dialkylamino**" denotes an amino substituted with two of the same or different C<sub>1-4</sub> alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but are not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like. Some embodiments are "**C<sub>2-4</sub> dialkylamino**."

The term "**C<sub>1</sub>-C<sub>6</sub> haloalkoxy**" is intended to mean a C<sub>1</sub>-C<sub>6</sub> 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 "**C<sub>1</sub>-C<sub>6</sub> haloalkyl**" is intended to mean an C<sub>1</sub>-C<sub>6</sub> alkyl group, defined herein, wherein the alkyl is substituted with between one halogen up to fully substituted wherein a fully substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl can be represented by the formula C<sub>z</sub>L<sub>2z+1</sub> 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,

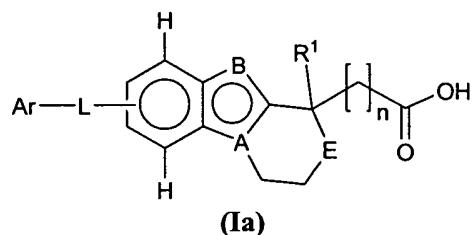
some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

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

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

## COMPOUNDS OF THE INVENTION:

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



25

wherein:

n, A, B, E, L, R<sup>1</sup>, and Ar have the same definitions as described herein, *supra* and *infra*.

One aspect of the invention pertains to compounds of Formula (Ia) provided that when n is 0, E is NH, and L is -CH<sub>2</sub>-O-, then Ar is substituted with 2 substituents. In another embodiment, the present invention pertains to compounds of Formula (Ia) provided that when n is 0, A is C, B is NH, E is NH, and L is -CH<sub>2</sub>-O-, then Ar is substituted with 2 substituents. It is understood that when the Ar group is substituted with 2 substituents, the 2 substituents are selected independently from one or more substituents from the group consisting of C<sub>1</sub>-C<sub>6</sub>

alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

5 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.

It is appreciated that certain features of the invention, which are, for clarity, described in  
10 the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., n, A, B, E, L, R<sup>1</sup>, R<sup>2</sup>, and Ar) contained within the generic  
15 chemical formulae described herein, for example, (Ia), (Ic), (Ie), (Ig), (Ii), (Ik), (Im), (Io), (Iq), (Is), (Iu), (Iw), (Iy), (IIa), (IIc), (IIe), (IIg), (III), (IIk), (IIIa), 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 and tested for biological activity). In addition, all subcombinations of the  
20 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,  
35 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 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.

5       The present disclosure includes all isotopes of atoms occurring in the present compounds, intermediates, salts and crystalline forms thereof. Isotopes include those atoms 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  
10      but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as <sup>1</sup>H or <sup>12</sup>C, found in one the present compounds, intermediates, salts, and crystalline forms thereof, with a different atom that is not the most naturally abundant isotope, such as <sup>2</sup>H or <sup>3</sup>H (replacing <sup>1</sup>H), or <sup>11</sup>C, <sup>13</sup>C, or <sup>14</sup>C (replacing <sup>12</sup>C). A compound wherein such a replacement has taken place is commonly referred to as being an  
15      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 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 <sup>2</sup>H (deuterium) and <sup>3</sup>H (tritium). Isotopes of carbon include <sup>11</sup>C, <sup>13</sup>C, and <sup>14</sup>C. Isotopes of nitrogen include <sup>13</sup>N and <sup>15</sup>N. Isotopes of oxygen include <sup>15</sup>O, <sup>17</sup>O, and <sup>18</sup>O. An isotope of fluorine includes <sup>18</sup>F. An isotope of sulfur includes <sup>35</sup>S. An isotope of chlorine includes <sup>36</sup>Cl. Isotopes of bromine include <sup>75</sup>Br, <sup>76</sup>Br, <sup>77</sup>Br, and <sup>82</sup>Br. Isotopes of iodine include <sup>123</sup>I, <sup>124</sup>I, <sup>125</sup>I, and <sup>131</sup>I.  
20      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 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  
25      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 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.  
30

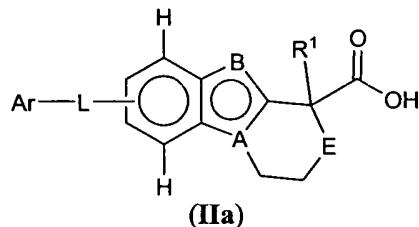
35      It is understood and appreciated that compounds of Formula (Ia) and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers,

diastereomers and mixtures thereof, including but not limited to racemates. It is understood that Formula (Ia) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

5    **The Variable “n”**

In some embodiments, n is 0.

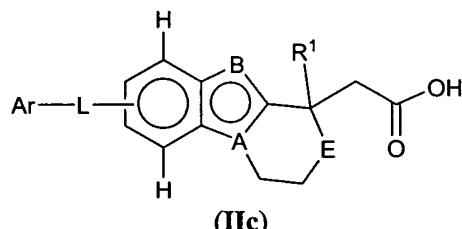
In some embodiments, compounds of the present invention are represented by Formula (IIa) as illustrated below:



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

In some embodiments, n is 1.

In some embodiments, compounds of the present invention are represented by Formula (IIc) as illustrated below:

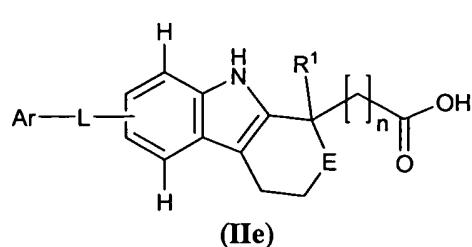


15    wherein each variable in Formula (IIc) has the same meaning as described herein, *supra* and *infra*.

**The Variables “A” and “B”**

20    In some embodiments, A is C (i.e., carbon), and B is NH.

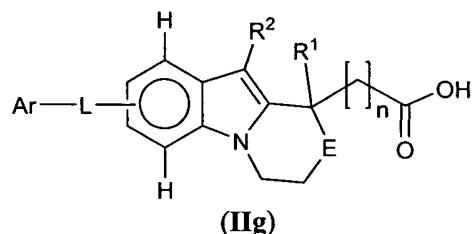
In some embodiments, compounds of the present invention are represented by Formula (IIe) as illustrated below:



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

In some embodiments, A is N, and B is CR<sup>2</sup>.

In some embodiments, compounds of the present invention are represented by Formula (IIg) as illustrated below:

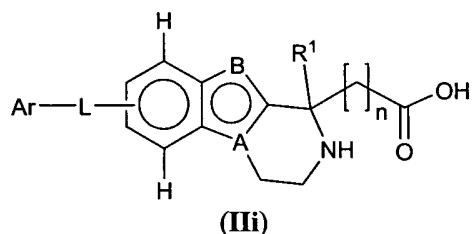


- 5 wherein each variable in Formula (IIg) has the same meaning as described herein, *supra* and *infra*.

#### The Variable “E”

In some embodiments, E is NH.

- 10 In some embodiments, compounds of the present invention are represented by Formula (III) as illustrated below:



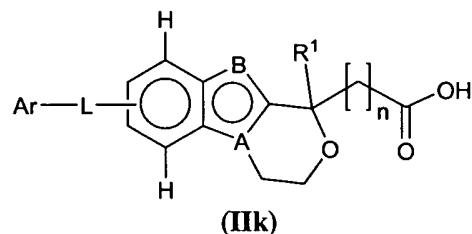
wherein each variable in Formula (III) has the same meaning as described herein, *supra* and *infra*.

- 15 In some embodiments, E is NR<sup>3</sup>, wherein R<sup>3</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, E is NCH<sub>3</sub>.

In some embodiments, E is O.

- In some embodiments, compounds of the present invention are represented by Formula (IIIk) as illustrated below:

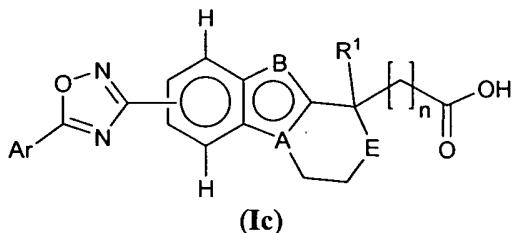


- 20 wherein each variable in Formula (IIIk) has the same meaning as described herein, *supra* and *infra*.

#### The Variable “L”

- 25 In some embodiments, L is 1,2,4-oxadiazole-3,5-diyl.

In some embodiments, compounds of the present invention are represented by Formula (Ic) as illustrated below:

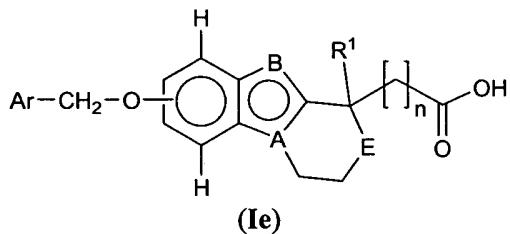


wherein each variable in Formula (Ic) has the same meaning as described herein, *supra* and

5 *infra*.

In some embodiments, L is -CH<sub>2</sub>-O-.

In some embodiments, compounds of the present invention are represented by Formula (Ie) as illustrated below:



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

#### The Variable R<sup>1</sup>

In some embodiments, R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl.

15 In some embodiments, R<sup>1</sup> is H.

In some embodiments, R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl.

In some embodiments, R<sup>1</sup> is methyl.

#### The Group R<sup>2</sup>

20 In some embodiments, R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen.

In some embodiments, R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl.

25 The Group Ar

In some embodiments, Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub>

alkylamino, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

In some embodiments, Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

In some embodiments, Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, cyclopropylmethoxy, diethylamino, 1,3-difluoropropan-2-yloxy, fluoro, fluoromethoxy, isobutyl, isopropoxy, methoxy, methylsulfonyl, pyrrolidin-1-yl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, cyclopropylmethoxy, diethylamino, 1,3-difluoropropan-2-yloxy, fluoro, fluoromethoxy, isobutyl, isopropoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.

In some embodiments, Ar is pyridinyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, methoxy, pyrrolidin-1-yl, and trifluoromethyl.

In some embodiments, Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl, and 4-isobutyl-2-methoxyphenyl.

In some embodiments, Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-

*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, and 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl.

In some embodiments, Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl, and 4-isobutyl-2-methoxyphenyl.

In some embodiments, Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, and 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl.

In some embodiments, Ar is selected from the group consisting of 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, and 2-chloro-6-methoxypyridin-4-yl.

In some embodiments, Ar is 3-cyano-4-isopropoxyphenyl.

In some embodiments, Ar is 3-cyano-5-(trifluoromethoxy)phenyl.

In some embodiments, Ar is 4-cyclopentyl-3-(trifluoromethyl)phenyl.

In some embodiments, Ar is 4-chloro-3-(trifluoromethyl)phenyl.

In some embodiments, Ar is 4-isobutyl-3-(trifluoromethyl)phenyl.

In some embodiments, Ar is 6-methoxy-5-(trifluoromethyl)pyridin-3-yl.

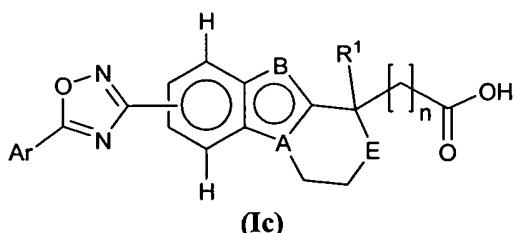
In some embodiments, Ar is 3-chloro-4-(trifluoromethoxy)phenyl.

- In some embodiments, Ar is 2,4-bis(trifluoromethyl)phenyl.
- In some embodiments, Ar is 4-fluoro-2-(trifluoromethyl)phenyl.
- In some embodiments, Ar is 4-*tert*-butylphenyl.
- In some embodiments, Ar is 4-(methylsulfonyl)phenyl.
- 5 In some embodiments, Ar is 4-(trifluoromethyl)phenyl.
- In some embodiments, Ar is 3,4-dichlorophenyl.
- In some embodiments, Ar is 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl.
- In some embodiments, Ar is 3-(trifluoromethoxy)phenyl.
- In some embodiments, Ar is 3,5-bis(trifluoromethyl)phenyl.
- 10 In some embodiments, Ar is 3-cyano-4-cyclohexylphenylphenyl.
- In some embodiments, Ar is 2-chloro-6-methoxypyridin-4-yl.
- In some embodiments, Ar is 3-cyano-5-(cyclopentyloxy)phenyl.
- In some embodiments, Ar is 4-(diethylamino)phenyl.
- In some embodiments, Ar is phenyl.
- 15 In some embodiments, Ar is 4-isopropoxy-3-(trifluoromethyl)phenyl.
- In some embodiments, Ar is 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl.
- In some embodiments, Ar is 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl.
- In some embodiments, Ar is 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl.
- In some embodiments, Ar is 4-isobutyl-2-methoxyphenyl.

20

### Certain Combinations

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



25

wherein:

n is 1;

A is N, and B is CH; or A is C, and B is NH;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

E is NH or O; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, C<sub>3</sub>-C<sub>7</sub>

30

cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and halogen.

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

n is 1;

A is N, and B is CH; or A is C, and B is NH;

R<sup>1</sup> is H or methyl;

E is NH or O; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, diethylamino, isopropoxy, methoxy, trifluoromethoxy, and trifluoromethyl.

15

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

n is 1;

A is N, and B is CH; or A is C, and B is NH;

R<sup>1</sup> is H or methyl;

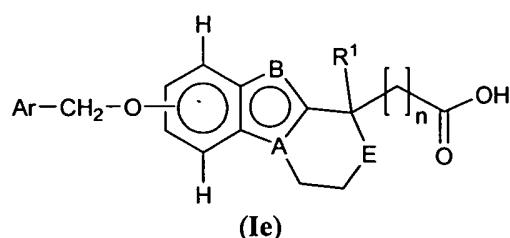
E is NH or O; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, and 4-(diethylamino)phenyl.

25

30

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



wherein:

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NR<sup>3</sup> or O;

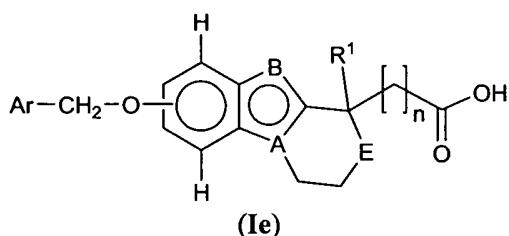
R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen;

5 R<sup>3</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

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:

n is 0 or 1;

20 A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NH or O;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen; and

25 Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

30

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

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

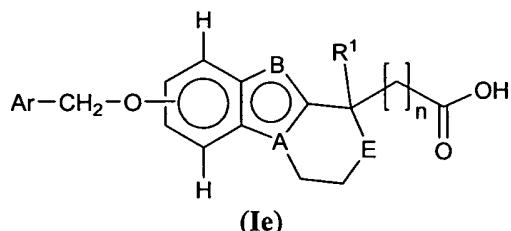
E is NH or O;

R<sup>1</sup> is H or methyl;

5 R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, chloro, cyano, cyclopentyl, cyclopropylmethoxy, 1,3-difluoropropan-2-yloxy, fluoro, fluoromethoxy, 10 isobutyl, isopropoxy, methoxy, methylsulfonyl, pyrrolidin-1-yl, trifluoromethoxy, and trifluoromethyl.

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



wherein:

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

20 E is NH or O;

R<sup>1</sup> is H or methyl;

R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl;

and

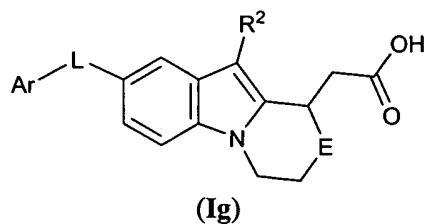
Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl, and 4-isobutyl-2-methoxyphenyl.

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

5           n is 0 or 1;  
              A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;  
              E is NH or O;  
              R<sup>1</sup> is H or methyl;  
              R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl;

10          and  
              Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, and 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl.

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



25          wherein:  
              E is NH, NCH<sub>3</sub>, or O;  
              L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;  
              R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen; and  
              Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, C<sub>3</sub>-C<sub>7</sub>

cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and halogen, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

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

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and  
10 halogen; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and halogen, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

15

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

E is NH, NCH<sub>3</sub>, or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro;  
and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, cyano, cyclopentyl, cyclopropylmethoxy,  
25 1,3-difluoropropan-2-yloxy, fluoromethoxy, isobutyl, isopropoxy, trifluoromethoxy, and trifluoromethyl.

30

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

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro;  
and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, cyano, cyclopentyl, cyclopropylmethoxy,

1,3-difluoropropan-2-yloxy, fluoromethoxy, isobutyl, isopropoxy, trifluoromethoxy, and trifluoromethyl.

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

E is NH or O;

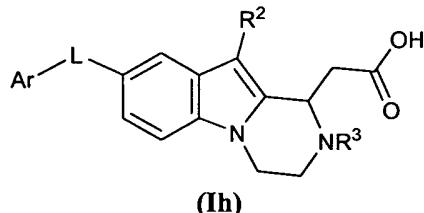
L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro;

10 and

Ar is selected from the group consisting of 3-cyano-4-isopropoxypyhenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, and 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl.

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



(Ih)

wherein:

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

25 R<sup>3</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, and C<sub>1</sub>-C<sub>6</sub> haloalkyl.

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

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl;

R<sup>3</sup> is H or CH<sub>3</sub>; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently

selected from the group consisting of cyano, cyclopentyl, isobutyl, isopropoxy,

5 trifluoromethoxy, and trifluoromethyl.

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

10 L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

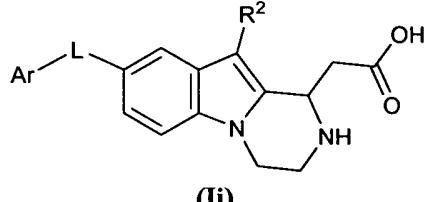
R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro;

R<sup>3</sup> is H or CH<sub>3</sub>; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, phenyl,

15 and 4-isopropoxy-3-(trifluoromethyl)phenyl, and 3-cyano-5-(trifluoromethoxy)phenyl.

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



20

wherein:

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>3</sub>-C<sub>7</sub>

cycloalkyl; and

25 Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and C<sub>1</sub>-C<sub>6</sub> haloalkyl.

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

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of cyano, cyclopentyl, isobutyl, isopropoxy, and trifluoromethyl.

5

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

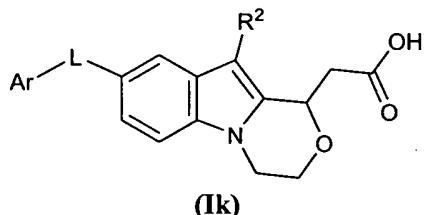
10 L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, phenyl, and 4-isopropoxy-3-(trifluoromethyl)phenyl.

15

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



20

wherein:

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is H or halogen; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and halogen, wherein the C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

25

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

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is H or chloro; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, cyano, cyclopentyl, cyclopropylmethoxy, 1,3-difluoropropan-2-yloxy, fluoromethoxy, isopropoxy, trifluoromethoxy, and trifluoromethyl.

5

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

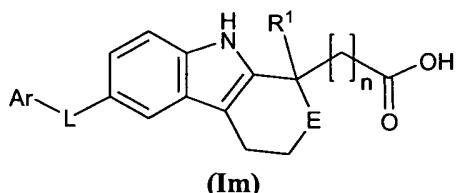
L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

10 R<sup>2</sup> is H or chloro; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, and 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl.

15

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



20

wherein:

n is 0 or 1;

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

25 R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl.

30

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

n is 0 or 1;

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>1</sup> is H or methyl; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents

5 independently selected from the group consisting of *tert*-butyl, chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, diethylamino, fluoro, isobutyl, isopropoxy, methoxy, methylsulfonyl, pyrrolidin-1-yl, trifluoromethoxy, and trifluoromethyl.

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

n is 0 or 1;

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

15 R<sup>1</sup> is H or methyl; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, and 4-isobutyl-2-methoxyphenyl.

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

30 n is 0 or 1;

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

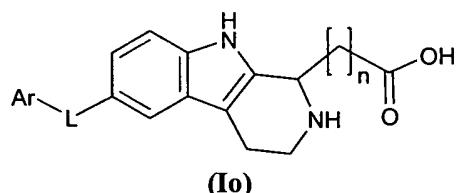
R<sup>1</sup> is H or methyl; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-

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bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, and 4-(diethylamino)phenyl.

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (I0) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



10

wherein:

n is 0 or 1;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl.

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Some embodiments of the present invention pertain to compounds selected from compounds of Formula (I0) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

n is 0 or 1;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-; and

25

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, diethylamino, fluoro, isobutyl, isopropoxy, methoxy, methylsulfonyl, pyrrolidin-1-yl, trifluoromethoxy, and trifluoromethyl.

30

Some embodiments of the present invention pertain to compounds selected from compounds of Formula (I0) and pharmaceutically acceptable salts, solvates, and hydrates thereof, wherein:

n is 0 or 1;

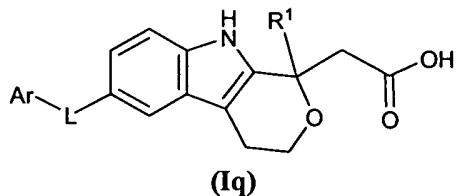
L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-; and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, and 4-isobutyl-2-methoxyphenyl.

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

n is 0 or 1;  
L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-; and  
Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, and 4-(diethylamino)phenyl.

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



30

wherein:

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;  
R¹ is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>3</sub>-C<sub>7</sub> cycloalkyl and C<sub>1</sub>-C<sub>6</sub> haloalkyl.

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

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>1</sup> is H or methyl; and

Ar is phenyl optionally substituted with 1 or 2 substituents independently  
10 selected from the group consisting of cyclopentyl and trifluoromethyl.

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

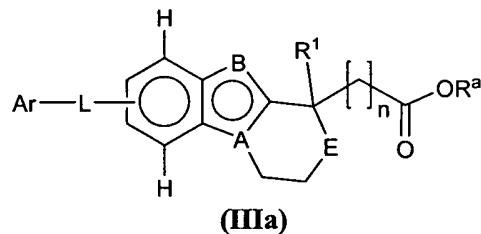
15 L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>1</sup> is H or methyl; and

Ar is 4-cyclopentyl-3-(trifluoromethyl)phenyl or 3,5-bis(trifluoromethyl)phenyl.

## 20 Esters and Prodrugs

One aspect of the present invention pertains to compounds of Formula (IIIa) as synthetic intermediates useful in the preparation of compounds of Formula (Ia) and/or prodrugs useful for the oral delivery of compounds of Formula (Ia):



25 wherein: n, A, B, E, L, R<sup>1</sup>, and Ar have the same definitions as described herein, *supra* and *infra*, and R<sup>a</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl.

One aspect of the present invention pertains to compounds of Formula (IIIa).

In some embodiments, R<sup>a</sup> is ethyl.

In some embodiments, R<sup>a</sup> is *tert*-butyl.

30 It is appreciated that all of the embodiments described herein, *supra* and *infra*, that relate to the common variables shared between Compounds of Formula (Ia) and (IIIa) namely, n, A, B, E, L, R<sup>1</sup>, R<sup>2</sup>, and Ar, apply to Compounds of Formula (IIIa) just as if they were each individually disclosed herewith with specific reference to Formula (IIIa).

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

One aspect of the present invention pertains to compounds of Formula (IIIa) as esters of compounds, described and shown herein, such as compounds in Table A, where R<sup>a</sup> is ethyl.

5 One aspect of the present invention pertains to compounds of Formula (IIIa) as esters of compounds, described and shown herein, such as compounds in Table A, where R<sup>a</sup> is *tert*-butyl.

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

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

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

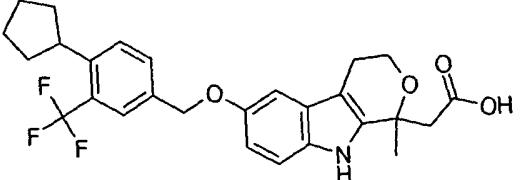
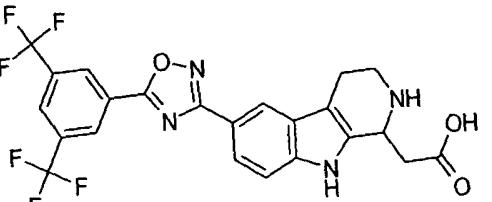
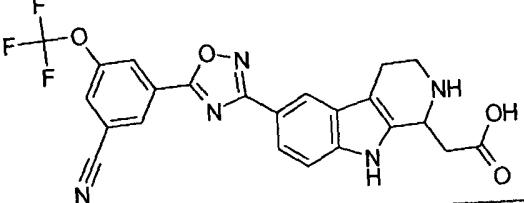
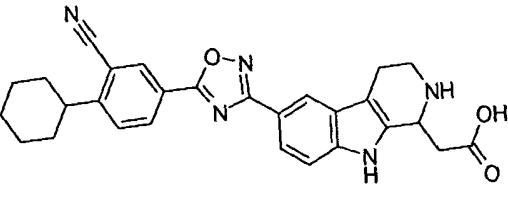
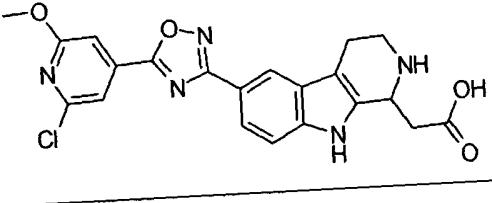
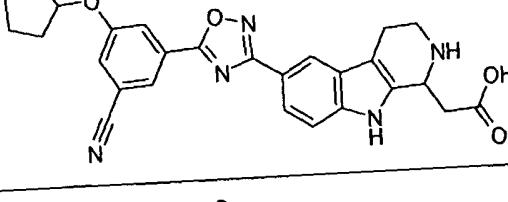
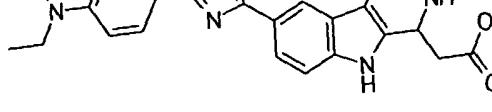
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**Table A**

Cmpd No.	Chemical Structure	Chemical Name
1		2-(6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
2		2-(6-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
3		6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indole-1-carboxylic acid

Cmpd No.	Chemical Structure	Chemical Name
4		2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
5		2-(6-(4-chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
6		2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid
7		2-(6-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
8		2-(6-((6-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
9		2-(6-(3-chloro-4-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
10		2-(6-(2,4-bis(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid

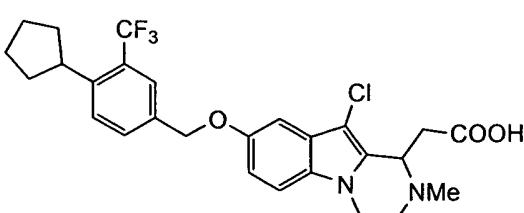
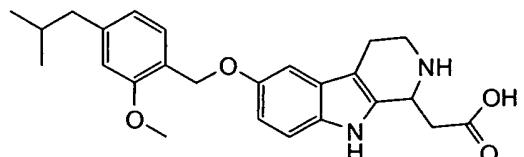
Cmpd No.	Chemical Structure	Chemical Name
11		2-(6-(4-fluoro-2-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
12		2-(6-(4- <i>tert</i> -butylbenzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
13		2-(6-(4-(methylsulfonyl)benzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
14		2-(6-(4-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
15		2-(6-(3,4-dichlorobenzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
16		2-(6-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid
17		2-(6-(3-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1 <i>H</i> -pyrido[3,4- <i>b</i> ]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
18		2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid
19		2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
20		2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
21		2-(6-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
22		2-(6-(5-(2-chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
23		2-(6-(5-(3-cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid
24		2-(6-(5-(diethylamino)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
25		2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid
26		2-(8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
27		2-(8-(benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid
28		2-(8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
29		2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
30		2-(8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
31		2-(8-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid
32		2-(10-chloro-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
33		2-(10-chloro-8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
34		2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid
35		2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-cyclopropyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid
36		2-(8-(4-(fluoromethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
37		2-(8-(3-chloro-4-(1,3-difluoropropyl)oxy)benzyloxy)-3,4-dihydro-1 <i>H</i> -[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
38		2-(10-chloro-8-(4-(cyclopropylmethoxy)trifluoromethyl)benzyloxy)-3,4-dihydro-1 <i>H</i> -[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
39		2-(8-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1 <i>H</i> -[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
40		2-(8-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid
41		2-(8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1 <i>H</i> -[1,4]oxazino[4,3-a]indol-1-yl)acetic acid
42		2-(10-chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid

Cmpd No.	Chemical Structure	Chemical Name
43		2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid
44		2-(6-(4-isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetic acid

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.

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### **C(1) Ring Carbon Stereochemistry**

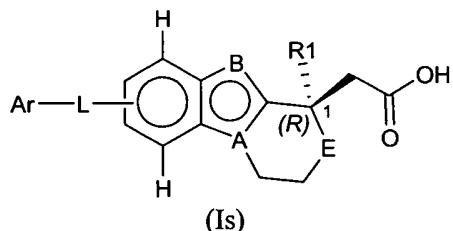
Compounds of the present invention contain a three ring fused system and present on one of the rings is either a carboxylic acid ( $-CO_2H$ ,  $n = 0$ ) or an acetic acid group ( $-CH_2CO_2H$ ,  $n = 1$ ). The ring carbon to which the carboxylic acid or acetic acid group is attached is referred to herein as the C(1) Ring Carbon. It is understood that the stereochemistry for the C(1) Ring Carbon contained in the three ring fused system can be either *R* or *S*.

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

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

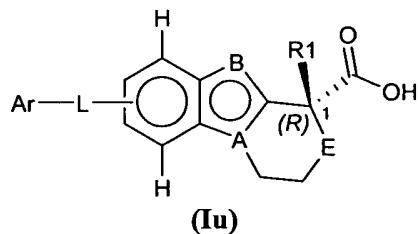
One aspect of the present invention pertains to compounds wherein the stereochemistry of the C(1) ring carbon of the compound is *R*.

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



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

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



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

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:

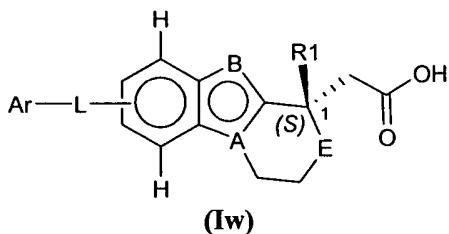
- (R)-2-(6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-1-carboxylic acid; (R)-2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-((6-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(3-chloro-4-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(2,4-bis(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-fluoro-2-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-*tert*-butylbenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-(methylsulfonyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(3,4-dichlorobenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(3-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (R)-2-(6-(5-(2-chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;

1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*R*)-2-(6-(5-(3-cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*R*)-2-(6-(4-(diethylamino)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*R*)-2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid; (*R*)-2-(8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(10-chloro-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-cyclopropyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(4-fluoromethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(3-chloro-4-(1,3-difluoropropan-2-yloxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(10-chloro-8-(4-(cyclopropylmethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-yl)acetic acid; (*R*)-2-(10-chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; (*R*)-2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-1-yl)acetic acid; and (*R*)-2-(6-(4-isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid.

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

One aspect of the present invention pertains to compounds wherein the stereochemistry of the C(1) ring carbon of the compound is *S*.

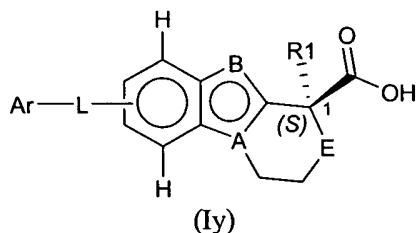
Some embodiments of the present invention pertain to compounds of Formula (Iw) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



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

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

5



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

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:

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(*S*)-2-(6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid; (*S*)-2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-((6-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(3-chloro-4-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(2,4-bis(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-fluoro-2-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-*tert*-butylbenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-(methylsulfonyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(4-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-(3,4-dichlorobenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic acid; (*S*)-2-(6-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-

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yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(3-trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(2-chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(3-cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(4-(diethylamino)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid; (*S*)-2-(8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(8-(benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(8-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(10-chloro-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(10-chloro-8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-cyclopropyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(8-(4-(fluoromethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(8-(3-chloro-4-(1,3-difluoropropan-2-yloxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(10-chloro-8-(4-(cyclopropylmethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(8-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(8-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid; (*S*)-2-(10-chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; (*S*)-2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-

tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; and (S)-2-(6-(4-isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid.

It is understood that the present invention embraces each diastereomer, each enantiomer  
5 and mixtures thereof of each compound and generic formulae disclosed herein just as if they  
were each individually disclosed with the specific stereochemical designation for each chiral  
carbon. Separation of the individual isomers (such as, by chiral HPLC, recrystallization of  
diastereomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective  
syntheses and the like) of the individual isomers is accomplished by application of various  
10 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,  
15 for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3<sup>rd</sup>  
Edition, 1999 [Wiley]).

## PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions  
20 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  
25 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,  
30 tabletting lubricants and disintegrants may be used in tablets and capsules for oral  
administration. Liquid preparations for oral administration may be in the form of solutions,  
emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be  
in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle  
before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles  
35 (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*, 20<sup>th</sup> 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.

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

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

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

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably

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

Compounds of the present invention or a salt, solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as 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  
5 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  
10 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  
15 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  
20 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.

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

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

The powders and tablets may contain varying percentage amounts of the active  
30 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.  
35 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, 5 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 10 an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising the active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and 15 acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient 20 administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols (*e.g.*, nasal aerosols, by inhalation), this can be 25 carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. Solutions or dispersions of the compounds of the present invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative thereof in water, 30 water/alcohol mixtures or suitable saline solutions, for example, can be employed using customary additives (*e.g.*, benzyl alcohol or other suitable preservatives), absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants (*e.g.*, carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and the like). The aerosol may conveniently 35 also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active 5 ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder (e.g., a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP)).

Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition 10 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 15 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.

20 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, 25 hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfiric, 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).

30 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.

35 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 companionship animals (*e.g.*, cats, dogs, *etc.*) and in livestock animals (*e.g.*, cows, chickens, fish, *etc.*). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

## 20 Hydrates and Solvates

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

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be apparent to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt or as a solvate or hydrate thereof. Moreover, various hydrates and solvates of the compounds of the invention and their salts will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of 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 the present invention 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 (PXRD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide  
5 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

10 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 in the solid state.

15 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, 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  
20 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 constituent of the atmosphere, hydrates of drugs may be formed rather easily.

25 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 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*  
30 (2007), 7(6), 1007-1026.)

## OTHER UTILITIES

Another object of the present invention relates to radiolabeled compounds of the present invention that are useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*,  
35 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 radiolabeled compounds.

The present invention embraces isotopically-labeled compounds of the present invention. Isotopically or radiolabeled compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Suitable radionuclides that may be incorporated in compounds of the present invention include, but are not limited, to  $^2\text{H}$  (also written as D for deuterium),  $^3\text{H}$  (also written as T for tritium),  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{N}$ ,  $^{15}\text{O}$ ,  $^{17}\text{O}$ ,  $^{18}\text{O}$ ,  $^{18}\text{F}$ ,  $^{35}\text{S}$ ,  $^{36}\text{Cl}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$ ,  $^{77}\text{Br}$ ,  $^{82}\text{Br}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$  and  $^{131}\text{I}$ . The radionuclide that is incorporated in the instant radiolabeled compounds will depend on the specific application of that radiolabeled compound. For example, for *in vitro* S1P1 receptor labeling and competition assays, compounds that incorporate  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{82}\text{Br}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$  or  $^{35}\text{S}$  will generally be most useful. For radio-imaging applications  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{131}\text{I}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$  or  $^{77}\text{Br}$  will generally be most useful.

It is understood that a "radiolabeled" or "labeled compound" is a compound of Formula (Ia), (Ic), (Ie), (Ig), (II), (Ik), (Im), (Io), (Iq), (Is), (Iu), (Iw), (Iy), (IIa), (IIc), (IIe), (IIf), (IIk), or (IIIa), etc. containing at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{125}\text{I}$ ,  $^{35}\text{S}$  and  $^{82}\text{Br}$ .

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide  $^3\text{H}$  and/or  $^{14}\text{C}$  isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (*i.e.*,  $^2\text{H}$ ) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in Figures 6 to 11 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 [<sup>3</sup>H]: This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

5 C. Reduction with Lithium Aluminum Hydride [<sup>3</sup>H]: This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

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

10 E. N-Methylation using Methyl Iodide [<sup>3</sup>H]: This procedure is usually employed to prepare O-methyl or N-methyl [<sup>3</sup>H] products by treating appropriate precursors with high specific activity methyl iodide [<sup>3</sup>H]. This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of <sup>125</sup>I into target molecules include:

15 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 <sup>125</sup>I labeled compound using Na<sup>125</sup>I. A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.

20 B. Ortho <sup>125</sup>Iodination of phenols: This procedure allows for the incorporation of <sup>125</sup>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.

25 C. Aryl and heteroaryl bromide exchange with <sup>125</sup>I: This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. Pd(Ph<sub>3</sub>P)<sub>4</sub>] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., (CH<sub>3</sub>)<sub>3</sub>SnSn(CH<sub>3</sub>)<sub>3</sub>]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

30 A radiolabeled S1P1 receptor compound of Formula (Ia) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the “radiolabeled compound of Formula (Ia)” to the S1P1 receptor. Accordingly, the ability of a test compound to compete with the “radiolabeled compound of Formula (Ia)” for the binding to the S1P1 receptor directly correlates to its binding affinity.

35 The labeled compounds of the present invention bind to the S1P1 receptor. In one embodiment the labeled compound has an IC<sub>50</sub> less than about 500 μM, in another embodiment the labeled compound has an IC<sub>50</sub> less than about 100 μM, in yet another embodiment the labeled compound has an IC<sub>50</sub> less than about 10 μM, in yet another embodiment the labeled

compound has an IC<sub>50</sub> less than about 1 μM and in still yet another embodiment the labeled inhibitor has an IC<sub>50</sub> less than about 0.1 μM.

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

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

10

## EXAMPLES

### Example 1: Syntheses of Compounds of the Present Invention.

Illustrated syntheses for compounds of the present invention are shown in Figures 6 through 11 where the variables have the same definitions as used throughout this disclosure.

15 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  
20 understood that these common names would be recognized by those skilled in the art.

**Chemistry:** Proton nuclear magnetic resonance (<sup>1</sup>H 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 (<sup>1</sup>H 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, td = triplet of doublets, q = quartet, m = multiplet, bs = broad singlet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer chromatography (TLC) was performed on silica gel 60 F<sub>254</sub> (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 Å 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.

35 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 6-(3-Cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-1-carboxylic Acid (Compound 3).**

5      **Step A: Preparation of *tert*-butyl 2-(5-hydroxy-1*H*-indol-3-yl)ethylcarbamate.**

To a suspension of serotonin hydrochloride (5.00 g, 22.8 mmol) in 1,4-dioxane (50 mL) was added triethylamine (6.4 mL, 45.6 mmol) and di-*tert*-butyl dicarbonate (5.53 g, 25.1 mmol). The reaction was stirred at room temperature overnight. The mixture was filtered to remove 10 triethylammonium chloride salt and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and water (20 mL) was added. The solution was acidified with 1 N aqueous hydrochloric acid solution to pH 4. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to provide the title compound as a beige foam (6.30 g). LCMS *m/z* = 277.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.44 (s, 9H), 2.87 (t, *J* = 6.82 Hz, 2H), 3.39-3.46 (m, 2H), 4.65 (bs, 1H), 5.20 (bs, 1H), 6.79 (dd, *J* = 8.72, 15 2.40 Hz, 1H), 6.98 (s, 1H), 7.01 (d, *J* = 2.27 Hz, 1H), 7.21 (d, *J* = 12.0 Hz 1H), 7.94 (bs, 1H).

15      **Step B: Preparation of *tert*-Butyl 2-(5-(3-cyano-4-isopropoxybenzyloxy)-1*H*-indol-3-yl)ethylcarbamate.**

To a solution of *tert*-butyl 2-(5-hydroxy-1*H*-indol-3-yl)ethylcarbamate (4.72 g, 17.1 mmol) in *N,N*-dimethylformamide (100 mL) was added 5-(chloromethyl)-2-isopropoxybenzonitrile (3.41 g, 16.3 mmol) and cesium carbonate (6.36 g, 19.5 mmol). The reaction was stirred at room temperature overnight. The mixture was filtered through Celite®, concentrated *in vacuo*. The residue was purified by column chromatography and triturated with methyl *tert*-butyl ether to provide the title compound as a white solid (5.04 g). LCMS *m/z* = 450.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31 (d, *J* = 6.06 Hz, 6H), 1.37 (s, 9H), 2.74 (t, *J* = 7.52 Hz, 2H), 3.13-3.20 (m, 2H), 4.74-4.82 (m, 1H), 5.03 (s, 2H), 6.77 (dd, *J* = 8.72, 2.40 Hz, 1H), 6.82 (bs, 1H), 7.08 (d, *J* = 2.27 Hz, 1H), 7.10 (bs, 1H), 7.22 (d, *J* = 8.72 Hz, 1H), 7.27 (d, *J* = 8.84 Hz, 1H), 7.72 (d, *J* = 8.72 Hz, 1H), 7.78 (d, *J* = 1.77 Hz, 1H), 10.62 (s, 1H).

20      **Step C: Preparation of 5-((3-(2-Aminoethyl)-1*H*-indol-5-yloxy)methyl)-2-isopropoxybenzonitrile**

To *tert*-butyl 2-(5-(3-cyano-4-isopropoxybenzyloxy)-1*H*-indol-3-yl)ethylcarbamate (4.26 g, 9.48 mmol) in a sealed tube was added 1.25 M hydrogen chloride solution in methanol (75.0 mL, 94.0 mmol). The reaction was stirred at 35 °C overnight. The mixture was cooled in a dry ice-bath, basified with 50% aqueous sodium hydroxide solution to pH 7 at 0 °C, and 25 concentrated *in vacuo*. The residue was triturated with acetone and sodium chloride salt was removed by vacuum filtration. The filtrate was concentrated *in vacuo* and dried under vacuum to provide the title compound as an off-white solid (3.66 g). LCMS *m/z* = 350.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR

(400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31 (d, *J* = 4.00 Hz, 6H), 2.04 (bs, 1H), 2.26 (bs, 1H), 2.91-2.97 (m, 1H), 2.99-3.07 (m, 2H), 4.73-4.84 (m, 1H), 5.04 (s, 2H), 6.78-6.83 (m, 1H), 7.18 (dd, *J* = 9.54, 2.34 Hz, 2H), 7.25 (t, *J* = 4.42 Hz, 1H), 7.27 (dd, *J* = 8.00, 4.00 Hz, 1H), 7.72 (dd, *J* = 8.65, 2.34 Hz, 1H), 7.79 (s, 1H), 7.85 (bs, 2H), 10.81 (bs, 1H).

5       **Step D: Preparation of 6-(3-Cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic Acid.**

To a solution of 5-((3-(2-aminoethyl)-1*H*-indol-5-yloxy)methyl)-2-isopropoxybenzonitrile (0.78 g, 2.23 mmol) in water (10 mL) was added glyoxalic acid hydrate (0.23 g, 2.46 mmol). The reaction mixture was added 50% aqueous sodium hydroxide solution dropwise to adjust pH to 4-5. It formed a solid right away and the reaction was complete in 30 min. The solid was filtered and purified by HPLC. The combined fractions were added saturated aqueous sodium bicarbonate solution to adjust pH to 3-4. The organic solvent was removed under reduced pressure and a precipitate was formed out of the aqueous media. The precipitate was collected to give the title compound as a light yellow solid (0.34 g). LCMS *m/z* = 406.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31 (d, *J* = 6.06 Hz, 6H), 2.72-2.81 (m, 1H), 2.84-2.93 (m, 1H), 3.22-3.32 (m, 1H), 3.36-3.44 (m, 1H), 4.62 (s, 1H), 4.73-4.83 (m, 1H), 5.01 (s, 2H), 6.75 (dd, *J* = 8.72, 2.40 Hz, 1H), 6.97 (d, *J* = 2.27 Hz, 1H), 7.27 (d, *J* = 8.97 Hz, 1H), 7.34 (d, *J* = 8.84 Hz, 1H), 7.70 (dd, *J* = 8.72, 2.15 Hz, 1H), 7.77 (d, *J* = 2.15 Hz, 1H), 8.91 (bs, 1H), 10.50 (s, 1H).

20

**Example 1.2: Preparation of 2-(6-(3-Cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic Acid (Compound 1).**

**Step A: Preparation of Methyl 2-(6-(Benzylxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate.**

25       To a suspension of 5-benzylxytryptamine hydrochloride (2.93 g, 9.48 mmol) in methanol (45 mL) was added methyl 3,3-dimethoxypropanoate (1.7 mL, 11.4 mmol), 2,2,2-trifluoroacetic acid (0.85 mL, 11.4 mmol), and water (0.20 mL, 11.4 mmol). The mixture was heated at 80 °C overnight and allowed to cool to room temperature to form a solid. The solid was filtered and washed with methyl *tert*-butyl ether. The solid was dissolved in ethyl acetate and triturated with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide the title compound as an off-white solid (2.61 g). LCMS *m/z* = 351.40 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.50-2.57 (m, 3H), 2.82-2.90 (m, 1H), 2.95 (dd, *J* = 15.28, 3.41 Hz, 1H), 3.01-3.08 (m, 1H), 3.64 (s, 3H), 4.32 (dd, *J* = 10.29, 3.09 Hz, 1H), 5.06 (s, 2H), 6.73 (dd, *J* = 8.65, 2.46 Hz, 1H), 6.95 (d, *J* = 2.40 Hz, 1H), 7.16 (d, *J* = 8.72 Hz, 1H), 7.27-7.32 (m, 1H), 7.37 (t, *J* = 7.39 Hz, 2H), 7.45 (d, *J* = 6.95 Hz, 2H), 10.49 (s, 1H).

**Step B: Preparation of Methyl 2-(6-Hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

To a solution of methyl 2-(6-(benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate (2.61 g, 7.45 mmol) in a mixed solvent of methanol (200 mL) and tetrahydrofuran (30.0 mL) was added palladium on charcoal. The reaction was charged with hydrogen gas and stirred at room temperature for 1 h. The mixture was filtered through Celite® and concentrated *in vacuo* to provide the title compound as an off-white solid (1.84 g) and used without further purification. LCMS *m/z* = 261.30 [M+H]<sup>+</sup>.

**Step C: Preparation of *tert*-Butyl 6-Hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

To a solution of methyl 2-(6-hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate (0.99 g, 3.80 mmol) in 1,4-dioxane (10 mL) was added triethylamine (1.6 mL, 11.4 mmol) and di-*tert*-butyl dicarbonate (1.26 g, 5.69 mmol). The mixture was stirred at room temperature for 2 h and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and acidified with 1 N aqueous hydrochloric acid solution. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to provide the title compound as an off-white foam (0.92 g). LCMS *m/z* = 361.50 [M+H]<sup>+</sup>.

**Step D: Preparation of *tert*-Butyl 6-Hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

To a solution of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.92 g, 2.55 mmol) and 5-(chloromethyl)-2-isopropoxybenzonitrile (0.54 g, 2.55 mmol) in *N,N*-dimethylformamide (30 mL) was added cesium carbonate (1.25 g, 3.83 mmol). The mixture was stirred at room temperature overnight. The reaction was filtered through Celite®, concentrated *in vacuo*, and purified by column chromatography to provide the title compound as a yellow foam (1.12 g). LCMS *m/z* = 534.50 [M+H]<sup>+</sup>.

**Step E: Preparation of Methyl 2-(6-(3-Cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate 2,2,2-trifluoroacetate.**

To a solution of *tert*-butyl 6-(3-cyano-4-isopropoxybenzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (244.4 mg, 0.458 mmol) in dichloromethane (5 mL) was added 2,2,2-trifluoroacetic acid (1.0 mL, 12.9 mmol). The mixture was stirred at 0 °C for 1 h and concentrated *in vacuo* to provide the title compound without further purification. LCMS *m/z* = 434.60 [M+H]<sup>+</sup>.

**Step F: Preparation of 2-(6-(3-Cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

To a solution of methyl 2-(6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate 2,2,2-trifluoroacetate (251.0 mg, 0.458 mmol) in methanol (4.5 mL), tetrahydrofuran (1.5 mL), and water (1.5 mL) was added lithium hydroxide hydrate (67.3 mg, 1.60 mmol). The mixture was stirred at room temperature for 2 h. The mixture was acidified 5 with 1 N aqueous hydrochloric acid solution to pH 4-5 to provide the title compound as a beige solid (139.4 mg). LCMS *m/z* = 420.40 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31 (d, *J* = 6.06 Hz, 6H), 2.56 (dd, *J* = 16.29, 8.97 Hz, 1H), 2.65-2.75 (m, 3H), 3.09-3.16 (m, 1H), 3.24-3.33 (m, 1H), 4.43-4.49 (m, 1H), 4.75-4.82 (m, 1H), 5.02 (s, 2H), 6.77 (dd, *J* = 8.72, 2.40 Hz, 10 1H), 7.01 (d, *J* = 2.40 Hz, 1H), 7.21 (d, *J* = 8.84 Hz, 1H), 7.27 (d, *J* = 8.84 Hz, 1H), 7.70 (dd, *J* = 8.78, 2.21 Hz, 1H), 7.77 (d, *J* = 2.15 Hz, 1H), 10.74 (s, 1H).

#### Resolution via Chiral HPLC

Column: normal phase preparative ChiralPak IC, 250 x 4.6 mm ID, 5 μm particle size

Eluent: carbon dioxide/methanol/diethylamine = 47/53/0.2%

Gradient: Isocratic

15 Flow: 3 mL/minute

Pressure: 100 bar

Detector: 230 nm

Retention Times: 1<sup>st</sup> enantiomer: 8.069 min.; 2<sup>nd</sup> enantiomer: 18.930 min.

20 **Example 1.3: Preparation of 2-(6-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic Acid (Compound 2).**

**Step A: Preparation of Methyl 2-(6-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate.**

To a mixture of methyl 2-(6-hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (103.9 mg, 0.399 mmol), 3-(hydroxymethyl)-5-(trifluoromethoxy)benzonitrile (125 mg, 0.576 mmol), and triphenylphosphine (157 mg, 0.599 mmol) in THF (5 mL) was added diisopropyl azodicarboxylate (DIAD, 116 μL, 0.599 mmol). After stirring at room temperature for 1 h, more DIAD (116 μL, 0.599 mmol) and triphenyl phosphine (100 mg, 0.38 mmol) were added. After stirring for another 1 h, the mixture was purified by HPLC to give the title compound as a tan solid (TFA salt, 34.1 mg). LCMS *m/z* = 460.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 3.04-3.09 (m, 3H), 3.32-3.38 (m, 1H), 3.50-3.57 (m, 1H), 3.71-3.77 (m, 1H), 3.84 (s, 3H), 5.11-5.14 (m, 1H), 5.24 (s, 2H), 6.98 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.75 (s, 1H), 7.87 (s, 1H).

**Step B: Preparation of 2-(6-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic Acid.**

To a solution of methyl 2-(6-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (32.0 mg, 0.070 mmol) in 1.5 mL of 3:1:1 mixture of

THF/MeOH/H<sub>2</sub>O, was added lithium hydroxide hydrate (2.92 mg, 0.070 mmol). After stirring at room temperature for 1 h, the mixture was purified by HPLC to give the title compound as a tan solid (TFA salt, 14.1 mg). LCMS *m/z* = 446.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 3.00-3.09 (m, 3H), 3.31-3.37 (m, 1H), 3.49-3.56 (m, 1H), 3.71-3.77 (m, 1H), 5.07-5.11 (m, 1H), 5.24 (s, 2H), 6.98 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.32-7.34 (m, 1H), 7.68 (s, 1H), 7.76 (d, *J* = 0.78 Hz, 1H), 7.87 (s, 1H).

**Example 1.4: Preparation of 2-(6-(4-Chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 5).**

10       **Step A: Preparation of 1-Chloro-4-(chloromethyl)-2-(trifluoromethyl)benzene.**

(4-Chloro-3-(trifluoromethyl)phenyl)methanol (5.1 g, 24.22 mmol) was added in small portions to SOCl<sub>2</sub> (20 mL, 275 mmol). The reaction was stirred at 50 °C for 18 h and then under reflux for 23 h. The mixture was concentrated and dried under high vacuum to give the title compound as a colorless liquid (5.41 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 4.58 (s, 2H), 7.50-7.51 (m, 2H), 7.71 (s, 1H).

15       **Step B: Preparation of tert-Butyl 6-(BenzylOxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of methyl 2-(6-(benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate (2.2 g, 6.28 mmol), BOC-anhydride (2.0 mL, 8.61 mmol), and triethylamine (2.625 mL, 18.83 mmol) in THF (60 mL) was stirred at room temperature. After 1 h, the mixture was concentrated and the residue was treated with EtOH. The solid was collected by filtration, washed with additional EtOH, and dried to give the title compound as a white solid (2.3 g). LCMS *m/z* = 451.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.49 (s, 9H), 2.64-3.09 (m, 5H), 3.76 (s, 3H), 4.34-4.51 (m, 1H), 5.10 (s, 2H), 5.48-5.64 (m, 1H), 6.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.01 (s, 1H), 7.21-7.30 (m, 1H). 7.30-7.40 (m, 3H), 7.46-7.48 (m, 2H), 8.61-8.76 (m, 1H).

20       **Step C: Preparation of tert-Butyl 6-Hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

To a solution of *tert*-butyl 6-(benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (2.18 g, 4.84 mmol) in EtOH (100 mL) and THF (10 mL) was added Pd/C (140 mg, 10% wet, Degussa Type). H<sub>2</sub> was bubbled through the solution for 1 min and then the mixture was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature. After stirring for 18 h, an additional amount of Pd/C (140 mg) was added and the reaction was stirred for an additional 2 h. Pd/C was filtered off through Celite®. The filtrate was concentrated to give the title compound as an off-white solid (1.75 g). LCMS *m/z* = 361.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.49 (s, 9H), 2.61-3.08 (m, 5H), 3.75 (s, 3H), 4.33-4.51 (m, 2H), 5.48-5.63 (m, 1H), 6.72-6.73 (d, *J* = 6.7 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 8.52-8.67 (m, 1H).

**Step D: Preparation of tert-Butyl 6-(4-Chloro-3-(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (697 mg, 1.934 mmol), 1-chloro-4-(chloromethyl)-2-(trifluoromethyl)benzene (445 mg, 1.94 mmol), and cesium carbonate (630 mg, 1.934 mmol) was stirred at room temperature for 3 d. The mixture was concentrated and the residue was extracted with water and CH<sub>2</sub>Cl<sub>2</sub>. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a white solid (786 mg). LCMS *m/z* = 553.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.49 (s, 9H), 2.64-3.09 (m, 5H), 3.76 (s, 3H), 4.34-4.51 (m, 1H), 5.10 (s, 2H), 5.48-5.64 (m, 1H), 6.88 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.98 (s, 1H), 7.22-7.26 (m, 1H), 7.49-7.59 (m, 2H), 7.80 (s, 1H), 8.61-8.76 (m, 1H).

**Step E: Preparation of Methyl 2-(6-(4-Chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

To a solution of *tert*-butyl 6-(4-chloro-3-(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (91.7 mg, 0.166 mmol) in dioxane (1 mL) was added 4 M HCl in dioxane (1 mL, 4.00 mmol). The reaction was stirred overnight at room temperature. The mixture was concentrated and dried under high vacuum to give the title compound as a white solid (HCl salt, 81 mg). LCMS *m/z* = 553.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.83-2.96 (m, 2H), 3.06-3.12 (m, 1H), 3.27-3.42 (m, 2H), 3.55-3.64 (m, 1H), 3.74 (s, 3H), 5.01-5.03 (m, 1H), 5.21 (s, 2H), 6.88 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.74-7.80 (m, 2H), 7.95 (s, 1H), 9.30-9.60 (m, 2H), 10.9 (s, 1H).

**Step F: Preparation of 2-(6-(4-Chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

To a solution of methyl 2-(6-(4-chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate (60 mg, 0.132 mmol) in 5 mL of THF/H<sub>2</sub>O/MeOH (3:1:1) was added lithium hydroxide hydrate (27.8 mg, 0.662 mmol). The reaction was stirred at room temperature for 3 h and was partly concentrated. The residue was treated with 1 M HCl (ca. 1 mL) and water. The solid was filtered off, washed with additional water and dried in vacuum oven to give the title compound as a white solid (HCl salt, 54.3 mg). LCMS *m/z* = 439.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.67-2.90 (m, 3H), 3.04-3.58 (m, 3H), 4.81-4.83 (m, 1H), 5.20 (s, 2H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.74-7.80 (m, 2H), 7.94 (s, 1H), 10.8 (s, 1H).

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**Example 1.5: Preparation of 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 4).**

**Step A: Preparation of tert-Butyl 6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (134 mg, 0.372 mmol), 4-(chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (98 mg, 0.372 mmol), and cesium carbonate (121 mg, 0.372 mmol) in DMF (5 mL) was stirred at room temperature for 3 d. The mixture was purified by preparative HPLC. The combined fractions were partly concentrated and the residue was diluted with 1 M NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound as a white solid (105 mg). LCMS *m/z* = 587.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.59 (s, 9H), 1.54-1.64 (m, 2H), 1.67-1.78 (m, 2H), 1.79-1.91 (m, 2H), 2.05-2.12 (m, 2H), 2.62-3.15 (m, 5H), 3.33-3.42 (m, 1H), 3.76 (s, 3H), 4.34-4.51 (m, 1H), 5.08 (s, 2H), 5.50-5.64 (m, 1H), 6.90 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.01 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.70 (s, 1H), 8.58-8.73 (m, 1H).

**Step B: Preparation of Methyl 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

To a solution of *tert*-butyl 6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (105 mg, 0.179 mmol) in dioxane (2 mL), was added 4 M HCl in dioxane (0.045 mL, 0.179 mmol). After stirring at room temperature for 3 h, the mixture was concentrated and dried under high vacuum to give the title compound as a white solid (HCl salt, 94.0 mg). LCMS *m/z* = 587.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.58-1.75 (m, 4H), 1.82-1.92 (m, 2H), 1.99-2.07 (m, 2H), 2.85-2.99 (m, 2H), 3.07-3.14 (m, 1H), 3.24-3.35 (m, 2H), 3.39-3.47 (m, 1H), 3.56-3.62 (m, 1H), 3.77 (s, 3H), 5.04-5.06 (m, 1H), 5.18 (s, 2H), 6.88-6.91 (m, *J* = 8.8, 2.4 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.65-7.76 (m, 3H), 9.29-9.57 (m, 2H), 10.9 (s, 1H).

**Step C: Preparation of 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

To a solution of methyl 2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate hydrochloride (51.0 mg, 0.098 mmol) in 5 mL of THF/H<sub>2</sub>O/MeOH (3:1:1) was added lithium hydroxide hydrate (22.1 mg, 0.527 mmol). After 1 h, the solution was acidified with 1 M HCl and partly concentrated whereupon a solid precipitated. Additional water was added. The solid was filtered off, washed with additional water, and dried under high vacuum to give the title compound as a white solid (HCl salt, 49 mg). LCMS *m/z* = 473.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.59-1.79 (m, 4H), 1.82-1.92 (m, 2H), 1.99-2.07 (m, 2H), 2.85-3.02 (m, 3H), 3.18-3.43 (m, 5H), 3.54-3.60 (m, 1H), 4.95-4.97 (m, 1H), 5.18 (s, 2H), 6.89 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.30-7.33 (d, *J* = 8.8 Hz, 1H), 7.65-7.76 (m, 3H), 10.9 (s, 1H).

**Resolution via Chiral HPLC**

Column: normal phase preparative ChiralPak IC, 250x10 mm ID, 5 µm particle size

Eluent: 35%CO<sub>2</sub>/65%MeOH/0.2%TEA

Gradient: Isocratic

5      Temperature: 35 °C

Flow: 10 mL/minute

Pressure: 300 bar inlet, 100 bar outlet

Detector: 220 nm

Retention Times: 1<sup>st</sup> enantiomer: 2.9 min.; 2<sup>nd</sup> enantiomer: 4.5 min.

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**Example 1.6: Preparation of 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic Acid (Compound 6).****Step A: Preparation of 2-(5-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1*H*-indol-3-yl)ethanol.**

15      3-(2-Hydroxyethyl)-1*H*-indol-5-ol (0.2 g, 1.129 mmol) was dissolved in DMF (10 mL) and 4-(chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (0.296 g, 1.127 mmol) and cesium carbonate (0.367 g, 1.127 mmol) were added. The reaction mixture was stirred at room temperature for 16 h, then filtered through Celite® and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide the title compound (378 mg). LCMS *m/z* = 404.3 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic Acid.**

To a solution of 2-(5-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1*H*-indol-3-yl)ethanol (0.1 g, 0.248 mmol) in DCM (1.0 mL) were added methyl 3-methoxyacrylate (0.086 g, 0.744 mmol) and boron trifluoride etherate (2.324 µL, 0.018 mmol). The reaction was stirred for 1 d at room temperature, warmed to 50 °C and stirred an additional 24 h, and then warmed to 75 °C and stirred 24 h. The mixture was concentrated to an oil, dissolved in dioxane (3 mL) and added 1.0 M LiOH (600 µL). The mixture was stirred for 2 h and then acidified to pH 4 with 1 M HCl. The mixture was diluted with water and extracted twice with EtOAc. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by HPLC to provide the title compound (1.0 mg). LCMS *m/z* = 474.43 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.54-1.65 (m, 2H), 1.67-1.78 (m, 2H), 1.81-2.16 (m, 4H), 2.68-2.76 (m, 1H), 2.86-2.98 (m, 2H), 3.04 (dd, *J* = 16.9, 5.2 Hz, 1H), 3.33-3.43 (m, 1H), 3.84-3.93 (m, 1H), 4.19-4.27 (m, 1H), 5.09 (s, 2H), 5.19-5.24 (m, 1H), 6.91 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.70 (s, 1H), 8.33 (bs, 1H).

**Example 1.7: Preparation of 2-(6-(4-Isobutyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 7).**

**Step A: Preparation of *tert*-Butyl 6-(4-Isobutyl-3-(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

5       *tert*-Butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.1 g, 0.277 mmol), 4-(chloromethyl)-1-isobutyl-2-(trifluoromethyl)benzene (0.070 g, 0.277 mmol), and cesium carbonate (0.108 g, 0.333 mmol) were dissolved in DMF (2 mL) and stirred at room temperature for 16 h. The solids were removed by filtration and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give 10 the title compound (83 mg). LCMS *m/z* = 575.7 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(6-(4-Isobutyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

15       *tert*-Butyl 6-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.083 g, 0.144 mmol) was dissolved in THF (1.0 mL) and 4.0 M HCl in dioxane (1.0 mL, 4.0 mmol) was added. The reaction was stirred at room temperature for 16 h and then concentrated under reduced pressure. The concentrate was dissolved in THF (3.6 mL) and 1 M LiOH (720  $\mu$ L) was added. The reaction was stirred at room temperature for 2 h and then acidified to pH 3 with 1.0 M aqueous HCl. The reaction mixture was concentrated to an oil, and the residue was purified by HPLC to give the 20 title compound (TFA salt, 2.5 mg). LCMS *m/z* = 461.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.89 (d, *J* = 6.6 Hz, 6H), 1.93 (septet, *J* = 6.9 Hz, 1H), 2.59-2.66 (m, 2H), 2.82-3.01 (m, 3H), 3.15-3.30 (m, 1H), 3.34-3.46 (m, 1H), 3.53-3.63 (m, 1H), 4.94-5.03 (m, 1H), 5.16 (s, 2H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.76 (s, 1H), 10.9 (s, 1H).

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**Example 1.8: Preparation of 2-(6-((6-Methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 8).**

30       *tert*-Butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.1 g, 0.277 mmol), 5-(chloromethyl)-2-methoxy-3-(trifluoromethyl)pyridine (0.063 g, 0.277 mmol), and cesium carbonate (0.108 g, 0.333 mmol) were suspended in DMF (2.0 mL) and stirred at room temperature for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in dioxane (4.0 mL) and 1.0 M aqueous LiOH (0.83 mL) was added. The reaction was stirred at room temperature for 16 h. 4.0 M HCl in dioxane (4.0 mL) was then added, and the 35 reaction was stirred at room temperature for 20 min. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in methanol (1.0 mL). The methanol solution was diluted with water (15 mL) generating a turbid solution with formation of an

observable precipitate. The precipitate was collected by filtration to give the title compound (HCl salt, 9.0 mg). LCMS  $m/z$  = 436.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 2.63 (dd,  $J$  = 16.4, 9.0 Hz, 1H), 2.73-2.84 (m, 3H), 3.16-3.24 (m, 1H), 3.31-3.40 (m, 1H), 4.02 (s, 3H), 4.52-4.58 (m, 1H), 5.15 (s, 2H), 6.83 (dd,  $J$  = 8.8, 2.5 Hz, 1H), 7.10 (d,  $J$  = 2.3 Hz, 1H), 5 7.26 (d,  $J$  = 8.8 Hz, 1H), 8.22 (d,  $J$  = 2.0 Hz, 1H), 8.58 (d,  $J$  = 1.4 Hz, 1H), 10.8 (s, 1H).

**Example 1.9: Preparation of 2-(6-(3-Chloro-4-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 9).**

*tert*-Butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-10 2(9*H*)-carboxylate (0.1 g, 0.277 mmol), 4-(bromomethyl)-2-chloro-1-(trifluoromethoxy)benzene (0.080 g, 0.277 mmol), and cesium carbonate (0.108 g, 0.333 mmol) were suspended in DMF (2.0 mL) and stirred at room temperature for 16 h. The solids were removed by filtration and the filtrate was concentrated under reduced pressure. The concentrate was dissolved in dioxane (4.0 mL) and 1.0 M aqueous LiOH (0.83 mL) was added. The reaction was stirred at room 15 temperature for 16 h. 4.0 M HCl in dioxane (4.0 mL) was added and the reaction was stirred for 20 min and then concentrated under reduced pressure. The residue was dissolved in MeOH (1.0 mL) and water (15.0 mL) was added. The turbid mixture was stirred for 16 h and then filtered to give a tan solid. The tan solid was triturated with methanol to give the title compound (HCl salt, 23.0 mg). LCMS  $m/z$  = 455.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.57 (dd,  $J$  = 16.2, 9.0 20 Hz, 1H), 2.68-2.76 (m, 3H), 3.10-3.18 (m, 1H), 3.25-3.33 (m, 1H), 4.45-4.51 (m, 1H), 5.14 (m, 2H), 6.81 (dd,  $J$  = 8.7, 2.3 Hz, 1H), 7.03 (d,  $J$  = 2.3 Hz, 1H), 7.23 (d,  $J$  = 8.7 Hz, 1H), 7.54-7.60 (m, 2H), 7.78 (d,  $J$  = 1.1 Hz, 1H), 10.8 (s, 1H).

**Example 1.10: Preparation of 2-(6-(4-*tert*-Butylbenzyloxy)-2,3,4,9-tetrahydro-1*H*-25 pyrido[3,4-b]indol-1-yl)acetic acid (Compound 26).**

*tert*-Butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.1 g, 0.277 mmol), 1-(bromomethyl)-4-*tert*-butylbenzene (0.063 g, 0.277 mmol), and cesium carbonate (0.108 g, 0.333 mmol) were suspended in DMF (2.0 mL) and stirred at room temperature for 24 h. The solids were removed by filtration, and the filtrate was taken up in dioxane (4.0 mL) and 1.0 M aqueous LiOH (0.83 mL) was added. The reaction was 30 stirred at room temperature for 16 h and 4.0 M HCl in dioxane (6.0 mL) was added. After stirring at room temperature for 30 min, the reaction was concentrated under reduced pressure. The residue was purified by HPLC to give the title compound (TFA salt, 32 mg). LCMS  $m/z$  = 393.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 1.28 (s, 9H), 2.82-3.30 (m, 3H), 3.20 (dd, 35  $J$  = 17.9, 3.4 Hz, 1H), 3.34-3.45 (m, 1H), 3.52-3.62 (m, 1H), 4.94-5.02 (m, 1H), 5.05 (s, 2H), 6.84 (dd,  $J$  = 8.7, 2.4 Hz, 1H), 7.08 (d,  $J$  = 2.3 Hz, 1H), 7.28 (d,  $J$  = 8.8 Hz, 1H), 7.36-7.42 (m, 4H), 9.00 (bs, 1H), 9.31 (bs, 1H), 10.8 (s, 1H), 13.1 (bs, 1H).

**Example 1.11: Preparation of 2-(6-(4-(Methylsulfonyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid (Compound 13).**

5     *tert*-Butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-  
2(9*H*)-carboxylate (0.1 g, 0.277 mmol), 1-(bromomethyl)-4-(methylsulfonyl)benzene (0.069 g,  
0.277 mmol), and cesium carbonate (0.108 g, 0.333 mmol) were suspended in DMF (2.0 mL)  
and stirred at room temperature for 24 h. The solids were removed by filtration and the filtrate  
was concentrated under reduced pressure. The concentrate was dissolved in dioxane (4.0 mL)  
and 1.0 M aqueous LiOH (0.83 mL) was added. The mixture was stirred at room temperature for  
10 16 h and 4.0 M HCl in dioxane (6 mL) was added. After 30 min, the reaction was concentrated  
under reduced pressure and the concentrate was purified by HPLC to give the title compound  
(TFA salt, 21 mg). LCMS *m/z* = 415.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.82-  
3.01 (m, 3H), 3.16-3.26 (m, 4H), 3.35-3.46 (m, 1H), 3.52-3.61 (m, 1H), 4.96-5.03 (m, 1H), 5.25  
(s, 2H), 6.88 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.73  
15 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H), 9.14 (bs, 1H), 9.44 (bs, 1H), 10.9 (s, 1H).

**Example 1.12: Preparation of 2-(6-(3-(Trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 17).**

To a solution of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-  
20 pyrido[3,4-b]indole-2(9*H*)-carboxylate (50 mg, 0.139 mmol) in DMF (1.0 mL) was added  
cesium carbonate (0.166 mmol) and 1-(bromomethyl)-3-(trifluoromethoxy)benzene (0.139  
mmol). The reaction was stirred overnight at 60 °C. The solids were removed by filtration and  
the filtrate was concentrated. The residue was diluted with dioxanes (4.0 mL) and 1 N LiOH  
(0.417 mL) was added. The reaction was stirred overnight and acidified with 4 mL of 4.0 M HCl  
25 in dioxanes. After 1 h, the solvent was removed under reduced pressure and the residue was  
purified by preparative HPLC to give the title compound as a solid. LCMS *m/z* = 421.5 [M+H]<sup>+</sup>;  
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.83-3.00 (m, 3H), 3.20 (dd, *J* = 17.94, 3.41 Hz, 1H),  
3.36-3.46 (m, 1H), 3.52-3.63 (m, 1H), 4.98 (d, *J* = 7.58 Hz, 1H), 5.17 (s, 2H), 6.87 (dd, *J* = 8.78,  
2.46 Hz, 1H), 7.09 (d, *J* = 2.40 Hz, 1H), 7.26-7.36 (m, 2H), 7.43-7.59 (m, 3H), 9.16 (bs, 1H),  
30 10.87 (s, 1H).

**Example 1.13: Preparation of 2-(6-(4-(Trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 14).**

**Step A: Preparation of *tert*-Butyl 1-(2-Methoxy-2-oxoethyl)-6-(4-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-  
pyrido[3,4-b]indole-2(9*H*)-carboxylate (100.4 mg, 0.279 mmol), 1-(bromomethyl)-4-

(trifluoromethyl)benzene (66.6 mg, 0.279 mmol), and cesium carbonate (109 mg, 0.334 mmol) was stirred at room temperature for 2 days. The mixture was purified by preparative HPLC to give the title compound as a tan, sticky solid (67.1 mg). LCMS  $m/z$  = 519.4 [M+H]<sup>+</sup>.

5 **Step B: Preparation of Methyl 2-(6-(4-(Trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

A mixture of *tert*-butyl 1-(2-methoxy-2-oxoethyl)-6-(4-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (67.7 mg, 0.131 mmol) and 4 M hydrogen chloride solution in dioxane (1 mL, 4.00 mmol) was stirred at room temperature for 1 h. The mixture was concentrated and dried under high vacuum to give the title compound as an off-white solid (HCl salt, 54.5 mg). LCMS  $m/z$  = 419.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.86-2.91 (m, 2H), 3.05-3.12 (m, 1H), 3.27-3.41 (m, 2H), 3.54-3.58 (m, 1H), 3.74 (s, 3H), 5.00-5.04 (m, 1H), 5.22 (s, 2H), 6.87-6.89 (m, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 9.28-9.58 (m, 2H), 10.9 (s, 1H).

10 **Step C: Preparation of 2-(6-(4-(Trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

A mixture of methyl 2-(6-(4-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate hydrochloride (50.8 mg, 0.112 mmol) and lithium hydroxide hydrate (30 mg, 0.715 mmol) in 1.5 mL of 3:1:1 mixture of THF/MeOH/H<sub>2</sub>O was stirred at room temperature for 1 h. The reaction was acidified with 2 M HCl and partly concentrated. The 20 solid was filtered off, washed with additional water, and dried under high vacuum to give the title compound as an off-white solid (HCl salt, 42 mg). LCMS  $m/z$  = 405.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.62-2.85 (m, 4H), 3.16-3.58 (m, 5H), 4.58-4.59 (m, 1H), 5.21 (s, 2H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.2, 2H), 7.75 (d, *J* = 8.2, 2H), 10.8 (s, 1H).

25 **Example 1.14: Preparation of 2-(6-(3,4-Dichlorobenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 15).**

**Step A: Preparation of *tert*-Butyl 6-(3,4-Dichlorobenzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

30 A mixture of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (103.4 mg, 0.287 mmol), 4-(bromomethyl)-1,2-dichlorobenzene (50 μL, 0.294 mmol), and cesium carbonate (112 mg, 0.344 mmol) was stirred at room temperature for 2 days. The mixture was purified by preparative HPLC to give the title compound as a tan, sticky solid (TFA salt, 66.9 mg). LCMS  $m/z$  = 519.2 [M+H]<sup>+</sup>.

35 **Step B: Preparation of *tert*-Butyl 6-(3,4-Dichlorobenzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-(3,4-dichlorobenzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (65.7mg, 0.126 mmol) and 4 M HCl in dioxane (1 mL, 4.00 mmol) was stirred at room temperature for 1 h. The mixture was concentrated and the residue was dried under high vacuum to give the title compound as an off-white solid (HCl salt, 57.4 mg). LCMS *m/z* = 419.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.85-2.91 (m, 2H), 3.05-3.12 (m, 1H), 3.27-3.57 (m, 3H), 3.74 (s, 3H), 4.99-5.03 (m, 1H), 5.12 (s, 2H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 9.30-9.60 (m, 2H), 10.9 (s, 1H).

10           **Step C: Preparation of 2-(6-(3,4-Dichlorobenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic Acid.**

A mixture of methyl 2-(6-(3,4-dichlorobenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate hydrochloride (45.4 mg, 0.100 mmol) and lithium hydroxide hydrate (30 mg, 0.715 mmol) in 1.5 mL of 3:1:1 mixture of THF/MeOH/H<sub>2</sub>O was stirred at room 15 temperature for 1 h. The reaction was acidified with 2 M HCl and partly concentrated. The solid was filtered off, washed with additional water, and dried under high vacuum to give the title compound as an off-white solid (HCl salt, 38 mg). LCMS *m/z* = 405.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.78-2.85 (m, 3H), 2.99-3.04 (m, 1H), 3.25-3.60 (m, 4H), 4.76-4.78 (m, 1H), 5.12 (s, 2H), 6.83 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 20 1H), 7.45 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.65 (d, *J* = 8.3, 1H), 7.72 (d, *J* = 1.8, 1H), 10.8 (s, 1H).

**Example 1.15: Preparation of 2-(6-(2,4-Bis(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic Acid (Compound 10).**

25           **Step A: Preparation of *tert*-Butyl 6-(2,4-Bis(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate.**

A heterogeneous mixture of *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (100 mg, 0.27 mmol), 1-(bromomethyl)-2,4-bis(trifluoromethyl)benzene (85 mg, 0.27 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (140 mg, 0.41 mmol) in DMF (2 mL) was stirred overnight at room temperature. The reaction was diluted with H<sub>2</sub>O (10 mL), and 30 then extracted with DCM (2 x 10 mL). The combined organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and concentrated to give the title compound (95 mg) and used without further purification. LCMS *m/z* = 587.4 [M+H]<sup>+</sup>.

35           **Step B: Preparation of 2-(6-(2,4-Bis(trifluoromethyl)benzyloxy)-2-(*tert*-butoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetic Acid.**

*tert*-Butyl 6-(2,4-bis(trifluoromethyl)benzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate in dioxane (2 mL) was treated with 1 N LiOH (0.83 mL) for 4 h at room temperature. The reaction was acidified with 4 N HCl and

extracted with DCM (twice). The combined organic layer was washed with H<sub>2</sub>O, dried, and concentrated to give the title compound. LCMS *m/z* = 573.6 [M+H]<sup>+</sup>.

**Step C: Preparation of 2-(6-(2,4-Bis(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

5 A solution of 2-(6-(2,4-bis(trifluoromethyl)benzyloxy)-2-(*tert*-butoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid in DCM/TFA (4:1) was stirred for 1 h at room temperature. The reaction mixture was purified by passing through a SCX resin using 0.5 N NH<sub>3</sub> in MeOH as an eluting solvent to give the title compound as a white powder (25 mg). LCMS *m/z* = 473.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.84-2.96 (m, 3H), 3.18 (dd, *J* = 17.6 and 3.5 Hz, 1H), 3.34-3.42 (m, 1H), 3.51-3.59 (m, 1H), 4.94-4.99 (m, 1H), 5.34 (s, 2H), 6.88 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 8.09 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 9.16 (bs, 1H), 10.9 (s, 1H), 13.07 (bs, 1H).

10

15 **Example 1.16: Preparation of 2-(6-(4-Fluoro-2-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 11).**

From *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate and 1-(bromomethyl)-4-fluoro-2-(trifluoromethyl)benzene, using a similar method to the one described in **Example 1.15**, the title compound was obtained. LCMS *m/z* = 423.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.64-2.72 (m, 3H), 3.07-3.14 (m, 1H), 3.22-3.28 (m, 1H), 3.34-3.42 (m, 1H), 4.40-4.46 (m, 1H), 5.19 (s, 2H), 6.77 (dd, *J* = 8.8 and 2.5 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.58 (td, *J* = 8.4 and 2.8 Hz, 1H), 7.68 (dd, *J* = 9.2 and 2.5 Hz, 1H), 7.84 (dd, *J* = 8.6 and 6.0 Hz, 1H), 9.76 (bs, 1H), 10.8 (s, 1H).

20

25 **Example 1.17: Preparation of 2-(6-((6-(Pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 16).**

**Step A: Preparation of *tert*-Butyl 6-((6-chloro-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

30 The title compound was obtained from *tert*-butyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate and 2-chloro-5-(chloromethyl)-3-(trifluoromethyl)pyridine using a similar method to the one described in **Example 1.15, Step A**. LCMS *m/z* = 554.6 [M+H]<sup>+</sup>.

35 **Step B: Preparation of *tert*-Butyl 1-(2-methoxy-2-oxoethyl)-6-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate**

A solution of *tert*-butyl 6-((6-chloro-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (60 mg, 0.10 mmol) and pyrrolidine (31 mg, 0.40 mmol) in IPA (1 mL) was heated under microwave irradiation for 1 h at 140 °C. The mixture was purified by preparative HPLC to give the title compound (22 mg). LCMS *m/z* = 589.6 [M+H]<sup>+</sup>.

**Step C: Preparation of 2-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

The title compound was obtained from *tert*-butyl 1-(2-methoxy-2-oxoethyl)-6-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate using a similar method to the one described in **Example 1.15, Step B & C**. LCMS *m/z* = 475.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.86-1.92 (m, 4H), 2.65-2.73 (m, 4H), 3.07-3.16 (m, 1H), 3.35-3.41 (m, 1H), 3.48-3.54 (m, 4H), 4.42-4.47 (m, 1H), 5.01 (s, 2H), 6.76 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 1.9 Hz, 1H), 10.7 (s, 1H).

**Example 1.18: Preparation of 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic Acid (Compound 18).**

**Step A: Preparation of Methyl 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate.**

To a stirred solution of 2-(5-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1*H*-indol-3-yl)ethanol (50 mg, 0.12 mmol) and methyl 3-oxobutanoate (17 μL, 0.16 mmol) in toluene (1 mL) was added *p*-toluenesulfonic acid monohydrate (2.4 mg, 0.012 mmol). The reaction mixture was heated at 80 °C for 5 h. The resulting mixture was cooled and ethyl acetate was added. The organic layer was washed with saturated NaHCO<sub>3</sub> solution, dried, filtered, and concentrated. The residue was purified using a preparative TLC plate to give the title compound (35 mg). LCMS *m/z* = 502.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.56-1.65 (m, 2H), 1.68 (s, 3H), 1.67-1.78 (m, 2H), 1.81-1.90 (m, 2H), 2.06-2.14 (m, 2H), 2.76 (t, *J* = 5.4 Hz, 2H), 2.88 (d, *J* = 16.5 Hz, 1H), 3.01 (d, *J* = 16.5 Hz, 1H), 3.35-3.41 (m, 1H), 3.73 (s, 3H), 4.00-4.04 (m, 2H), 5.09 (s, 2H), 6.90 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 8.95 (s, 1H).

**Step B: Preparation of 2-(6-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic Acid.**

Methyl 2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (27 mg, 0.054 mmol) was dissolved in dioxane (0.5 mL), then 1 M LiOH aqueous solution (0.27 mL, 0.27 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. Part of the solvent was removed. The residue was acidified with an aqueous HCl solution and extracted with ethyl acetate. The organics were dried

and concentrated to give the title compound (25 mg) as a yellow solid. LCMS  $m/z$  = 488.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.55-1.65 (m, 2H), 1.69 (s, 3H), 1.67-1.78 (m, 2H), 1.81-1.88 (m, 2H), 2.06-2.14 (m, 2H), 2.75-2.85 (m, 2H), 2.95 (d,  $J$  = 16.4 Hz, 1H), 3.04 (d,  $J$  = 16.4 Hz, 1H), 3.35-3.41 (m, 1H), 4.05-4.15 (m, 2H), 5.09 (s, 2H), 6.91 (dd,  $J$  = 8.7 and 2.4 Hz, 1H), 7.03 (d,  $J$  = 2.3 Hz, 1H), 7.26 (d,  $J$  = 8.7 Hz, 1H), 7.48 (d,  $J$  = 8.0 Hz, 1H), 7.60 (d,  $J$  = 8.2 Hz, 1H), 7.70 (s, 1H), 8.38 (s, 1H).

### Resolution via Chiral HPLC

Column: normal phase Chiralcel OD column, 5cm ID x 50cm L

10 Eluent: 20% IPA/hexanes

Gradient: Isocratic

Flow: 60 mL/min

Detector: 280 nm

Retention time: 1<sup>st</sup> enantiomer: 21.1 min, 2<sup>nd</sup> enantiomer: 30.8 min

15

### Example 1.19: Preparation of 2-(8-(3-Cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 26).

#### Step A: Preparation of Ethyl 3-(5-(Benzylloxy)-1*H*-indol-2-yl)acrylate.

20 To a solution of ethyl 3-(5-(benzylloxy)-1*H*-indol-2-yl)acrylate (1.46 g, 4.54 mmol) in DMF (6.0 mL) was added NaH (60% dispersion in mineral oil, 2.0 equivalent). (2-Bromoethoxy)(*tert*-butyl)dimethylsilane (2.72 g, 11.36 mmol) was added and the mixture was stirred and heated under microwave irradiation at 80 °C for 3 h. The mixture was diluted with MTBE and washed with saturated NH<sub>4</sub>Cl and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (1.64 g) as a yellow oil. LCMS  $m/z$  = 480.3 [M+H]<sup>+</sup>.

#### Step B: Preparation of Ethyl 3-(5-(Benzylloxy)-1-(2-hydroxyethyl)-1*H*-indol-2-yl)acrylate.

30 Ethyl 3-(5-(benzylloxy)-1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1*H*-indol-2-yl)acrylate was dissolved in THF (10 mL). TBAF (1.0 M in THF) (5.13 mL, 5.13 mmol) was added. The reaction was stirred overnight at room temperature. The mixture was diluted with MTBE and washed with saturated NH<sub>4</sub>Cl (2 times) and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (461 mg) as a yellow solid. LCMS  $m/z$  = 366.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.34 (t,  $J$  = 7.1 Hz, 3H), 1.56-1.63 (m, 1H), 1.63 (t,  $J$  = 6.0 Hz, 1H), 3.90-3.96 (m, 2H), 4.26 (q,  $J$  = 7.1 Hz, 2H), 4.36 (t,  $J$  = 5.5 Hz, 2H), 5.10 (s, 2H), 6.46 (d,  $J$  = 15.7 Hz,

1H), 6.89 (s, 1H), 7.00 (dd,  $J = 9.0, 2.4$  Hz, 1H), 7.10 (d,  $J = 2.4$  Hz, 1H), 7.25-7.34 (m, 2H), 7.35-7.41 (m, 2H), 7.44-7.48 (m, 2H), 7.76 (d,  $J = 15.7$  Hz, 1H).

**Step C: Preparation of Ethyl 2-(Benzylxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of ethyl 3-(5-(benzyloxy)-1-(2-hydroxyethyl)-1*H*-indol-2-yl)acrylate (103 mg, 0.282 mmol) in PhCH<sub>3</sub>/THF (2:1, 4 mL) was added KOtBu (1.0 M in THF) (352  $\mu$ L, 0.352 mmol). The reaction was stirred under microwave heating at 60 °C for 1.5 h. The mixture was diluted with MTBE and washed with 1 N HCl and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (72 mg) as a white solid. LCMS *m/z* = 366.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.31 (t,  $J = 7.1$  Hz, 3H), 2.85 (dd,  $J = 15.7, 8.9$  Hz, 1H), 2.98 (dd,  $J = 15.7, 4.0$  Hz, 1H), 4.01-4.10 (m, 3H), 4.25 (q,  $J = 7.1$  Hz, 2H), 4.33-4.38 (m, 1H), 5.10 (s, 2H), 5.34 (dd,  $J = 8.8, 4.0$  Hz, 1H), 6.13 (s, 1H), 6.94 (dd,  $J = 8.8, 2.4$  Hz, 1H), 7.12 (d,  $J = 2.4$  Hz, 1H), 7.18 (d,  $J = 8.8$  Hz, 1H), 7.28-7.34 (m, 1H), 7.35-7.41 (m, 2H), 7.45-7.49 (m, 2H).

**Step D: Preparation of Ethyl 2-(8-Hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of ethyl 2-(8-(benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (72 mg, 0.197 mmol) in EtOAc (5.0 mL) was added 20% Pd hydroxide/C (150 mg). The reaction was placed in a Parr™ shaker at 40 psi H<sub>2</sub> for 2 h. The mixture was filtered through Celite® and concentrated to give the title compound as a white solid. LCMS *m/z* = 276.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.30 (t,  $J = 7.1$  Hz, 3H), 2.85 (dd,  $J = 15.8, 9.0$  Hz, 1H), 2.98 (dd,  $J = 15.8, 4.0$  Hz, 1H), 4.00-4.05 (m, 3H), 4.24 (q,  $J = 7.1$  Hz, 2H), 4.32-4.36 (m, 1H), 4.62 (bs, 1H), 5.33 (dd,  $J = 9.0, 4.0$  Hz, 1H), 6.09 (s, 1H), 6.78 (dd,  $J = 8.7, 2.4$  Hz, 1H), 6.98 (d,  $J = 2.4$  Hz, 1H), 7.12 (d,  $J = 8.7$  Hz, 1H).

**Step E: Preparation of Ethyl 2-(8-(3-Cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of ethyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (50 mg, 0.18 mmol) in DMA (2.0 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (89 mg, 0.272 mmol) followed by 5-(chloromethyl)-2-isopropoxybenzonitrile (42 mg, 0.20 mmol). The reaction was stirred under microwave irradiation at 60 °C for 3.0 h. The mixture was diluted with MTBE and washed with 1 N HCl (twice), and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (67 mg) as a white solid. LCMS *m/z* = 449.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.30 (t,  $J = 7.1$  Hz, 3H), 1.40 (d,  $J = 6.0$  Hz, 6H), 2.85 (dd,  $J = 15.7, 8.9$  Hz, 1H), 2.98 (dd,  $J = 15.7, 4.0$  Hz, 1H), 4.01-4.10(m, 3H), 4.24 (q,  $J = 7.1$  Hz, 2H), 4.32-4.38 (m, 1H), 4.64 (septet,  $J = 6.0$  Hz, 1H), 5.01 (s, 2H), 5.34 (dd,  $J = 8.9, 4.0$  Hz, 1H), 6.13 (s, 1H), 6.90 (dd,  $J = 8.8, 2.4$  Hz, 1H),

6.96 (d,  $J$  = 8.7 Hz, 1H), 7.08 (d,  $J$  = 2.4 Hz, 1H), 7.18 (d,  $J$  = 8.7 Hz, 1H), 7.58 (dd,  $J$  = 8.7, 2.1 Hz, 1H), 7.64 (d,  $J$  = 2.1 Hz, 1H).

**Step F: Preparation of 2-(8-(3-Cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid.**

To a solution of ethyl 2-(8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (10 mg, 0.022 mmol) in THF/MeOH/H<sub>2</sub>O (3:1:1, 3.0 mL) was added LiOH monohydrate (10.0 equiv.). The reaction was stirred at room temperature for 2 h, acidified with 1 N HCl, and purified directly by preparative HPLC. The combined fractions collected were concentrated and extracted with EtOAc. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound (8.0 mg) as a white solid. LCMS *m/z* = 421.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.40 (d,  $J$  = 6.1 Hz, 6H), 2.93 (dd,  $J$  = 16.0, 8.7 Hz, 1H), 3.07 (dd,  $J$  = 16.0, 3.9 Hz, 1H), 4.04–4.15 (m, 3H), 4.37–4.41 (m, 1H), 4.65 (septet,  $J$  = 6.1 Hz, 1H), 5.01 (s, 2H), 5.32 (dd,  $J$  = 8.7, 3.9 Hz, 1H), 6.18 (s, 1H), 6.91 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 6.96 (d,  $J$  = 8.7 Hz, 1H), 7.08 (d,  $J$  = 2.4 Hz, 1H), 7.19 (d,  $J$  = 8.8 Hz, 1H), 7.58 (dd,  $J$  = 8.7, 2.2 Hz, 1H), 7.64 (d,  $J$  = 2.2 Hz, 1H).

**Example 1.20: Preparation of 2-(10-Chloro-8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 33).**

To a solution of ethyl 2-(8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (54 mg, 0.120 mmol) in DCM (3.0 mL) at 0 °C was added NCS (32.2 mg, 0.241 mmol). The reaction was stirred for 20 min and then Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% aqueous solution) was added. The layers were separated and the aqueous phase was back-extracted with DCM. The organics were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% aqueous solution) and saturated NaHCO<sub>3</sub>. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was dissolved in THF/MeOH/H<sub>2</sub>O (3:1:1, 4.0 mL) and added LiOH monohydrate (5.0 equiv.). The reaction was stirred at room temperature for 1.5 h, acidified with 1 N HCl and purified by preparative HPLC. The combined HPLC fractions collected were concentrated and extracted with EtOAc. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound (16 mg) as a white solid. LCMS *m/z* = 455.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.41 (d,  $J$  = 6.1 Hz, 6H), 2.97 (dd,  $J$  = 16.0, 9.8 Hz, 1H), 3.50 (dd,  $J$  = 16.0, 2.9 Hz, 1H), 4.03 (m, 3H), 4.32 (m, 1H), 4.66 (septet,  $J$  = 6.1 Hz, 1H), 5.04 (s, 2H), 5.48 (dd,  $J$  = 9.8, 2.9 Hz, 1H), 6.95 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 6.98 (d,  $J$  = 8.9 Hz, 1H), 7.08 (d,  $J$  = 2.4 Hz, 1H), 7.07 (d,  $J$  = 2.4 Hz, 1H), 7.20 (d,  $J$  = 8.9 Hz, 1H), 7.59 (dd,  $J$  = 8.7, 2.2 Hz, 1H), 7.64 (d,  $J$  = 2.2 Hz, 1H).

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**Example 1.21: Preparation of 2-(6-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 19).**

**Step A: Preparation of Methyl 2-(6-Bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

A mixture of 2-(5-bromo-1*H*-indol-3-yl)ethanamine hydrochloride (2.03 g, 7.37 mmol), 2,2,2-trifluoroacetic acid (0.680 mL, 8.83 mmol), methyl 3,3-dimethoxypropanoate (1.253 mL, 8.84 mmol), and water (5 mL) in CH<sub>3</sub>CN (40 mL) was stirred at 80 °C (oil bath). After 4 h, the suspension was allowed to cool to room temperature. The solid was collected by filtration, washed with additional CH<sub>3</sub>CN, and dried under high vacuum to give the title compound as a white solid (HCl salt, 1.61 g). LCMS *m/z* = 323.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 2.91-3.03 (m, 2H), 3.15-3.22 (m, 1H), 3.35-3.45 (m, 1H), 3.54-3.60 (m, 1H), 3.95 (s, 3H), 5.06-5.08 (m, 1H), 7.26 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 1.7 Hz, 1H), 9.62-9.86 (m, 2H), 11.40 (s, 1H).

**Step B: Preparation of *tert*-Butyl 6-Bromo-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of methyl 2-(6-bromo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate hydrochloride (1.35 g, 3.75 mmol), di-*tert*-butyl dicarbonate (1.044 mL, 4.50 mmol), and triethylamine (2.615 mL, 18.76 mmol) in THF (70 mL) was stirred at room temperature for 6 h. The mixture was concentrated and the residue was extracted with water and CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was treated with EtOAc and hexane. The solid precipitate was filtered off, washed with additional hexane, and dried under high vacuum to give the title compound as a white solid (1.51 g). LCMS *m/z* = 423.2 [M+H]<sup>+</sup>.

**Step C: Preparation of *tert*-Butyl 6-Cyano-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-bromo-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (1.403 g, 3.31 mmol), dicyanozinc (0.395 g, 3.36 mmol), zinc dust (0.062 g, 0.948 mmol), bis(2,2,2-trifluoroacetoxy)palladium (0.077 g, 0.232 mmol), and 1,1'-binaphthyl-2-yldi-*tert*-butylphosphine (0.127 g, 0.319 mmol) in DMA (50 mL) was stirred at 100 °C (oil bath) for 16 h. The mixture was concentrated and the residue was purified by silica gel column chromatography. Fractions containing product were concentrated and treated with hexane and EtOAc. The solid was filtered off, washed with additional hexane, and dried to give the title compound as a white solid (1.1 g). LCMS *m/z* = 370.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.50 (s, 9H), 2.72-3.08 (m, 5H), 3.78 (s, 3H), 4.36-4.57 (m, 1H), 5.47-5.65 (m, 1H), 7.36-7.41 (m, 2H), 7.82 (s, 1H), 9.18-9.33 (m, 1H).

**Step D: Preparation of *tert*-Butyl 6-(N'-Hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A solution of *tert*-butyl 6-cyano-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (943 mg, 2.55 mmol) in EtOH (50 mL) was heated to 70 °C (oil bath) and hydroxylamine (50% water, 2.0 mL, 32.6 mmol) was added. After stirring at 70 °C for

5 h, the mixture was concentrated and the residue was purified by silica gel column chromatography to give the title compound as a white solid (1.0 g). LCMS  $m/z$  = 403.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.50 (s, 9H), 2.70-3.10 (m, 5H), 4.13 (s, 3H), 4.34-4.55 (m, 1H), 4.90 (s, 2H), 5.50-5.65 (m, 1H), 7.31 (dd,  $J$  = 8.5, 0.4 Hz, 1H), 7.45 (d,  $J$  = 8.4 Hz, 1H), 7.76 (s, 1H), 8.86-9.01 (m, 1H).

**Step E: Preparation of *tert*-Butyl 6-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-(N'-hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (105 mg, 0.261 mmol), 3,5-bis(trifluoromethyl)benzoyl chloride (47.0  $\mu$ L, 0.261 mmol), and triethylamine (182  $\mu$ L, 1.306 mmol) in dioxane (5 mL) was stirred under reflux for 0.5 h. The mixture was extracted with water and CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by column chromatography to give the title compound as a white solid (136 mg). LCMS  $m/z$  = 625.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.51 (s, 9H), 2.85-3.13 (m, 5H), 3.79 (s, 3H), 4.37-4.57 (m, 1H), 5.30-5.67 (m, 1H), 7.45 (dd,  $J$  = 8.5, 1.6 Hz, 1H), 8.00 (dd,  $J$  = 8.5, 1.6 Hz, 1H), 8.11 (s, 1H), 8.35 (s, 1H), 8.70 (s, 1H), 9.03 (s, 1H), 9.15-9.30 (m, 1H).

**Step F: Preparation of Methyl 2-(6-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

A mixture of *tert*-butyl 6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (134 mg, 0.215 mmol) and 4 M HCl in dioxane (2 mL, 8.00 mmol) was stirred at room temperature for 30 min. Et<sub>2</sub>O (4 mL) was added and the mixture was kept stirring at room temperature for 1.5 h. The solid was collected by filtration, washed with additional Et<sub>2</sub>O, and dried under high vacuum to give the title compound as a white solid (HCl salt, 102 mg). LCMS  $m/z$  = 525.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 3.15-3.3.64 (m, 6H), 3.79 (s, 3H), 5.13-5.16 (m, 1H), 7.63 (d,  $J$  = 8.5 Hz, 1H), 7.96 (d,  $J$  = 8.4 Hz, 1H), 8.37 (s, 1H), 8.58 (s, 1H), 8.78-8.82 (m, 2H), 9.42-9.71 (m, 2H), 11.60 (s, 1H).

**Step G: Preparation of 2-(6-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

To a solution of methyl 2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate hydrochloride (100 mg, 0.178 mmol) in 5 mL of THF/MeOH/H<sub>2</sub>O (3:1:1), lithium hydroxide hydrate (120 mg, 2.86 mmol) was added. After stirring at room temperature overnight, the mixture was purified by preparative HPLC. To the collected HPLC fractions were added 2M HCl (ca. 5 mL). The mixture was concentrated and dried under high vacuum to give the title compound as a white solid (HCl salt, 58.7 mg). LCMS

*m/z* = 511.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 3.07-3.3.54 (m, 6H), 4.96-4.99 (m, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 8.26 (s, 1H), 8.48 (s, 1H), 8.69-8.73 (m, 2H), 9.32-9.61 (m, 2H), 11.51 (s, 1H).

5   **Example 1.22: Preparation of 2-(6-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 20).**

Step A: Preparation of *tert*-Butyl 6-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.

10   A mixture of *tert*-butyl 6-(*N*<sup>’</sup>-hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (101.2 mg, 0.251 mmol) and CDI (42.0 mg, 0.259 mmol) in DMA (2 mL) was stirred at 60 °C. After 30 min, the mixture was allowed to cool to room temperature. 3-Cyano-5-(trifluoromethoxy)benzoic acid (60.9 mg, 0.263 mmol) and pyridin-2-ol (1 mg, 10.52  $\mu$ mol) were added. After stirring at 90 °C for 3 h, the mixture was concentrated and the residue was purified by silica gel column chromatography to give the title compound as a white solid (84 mg). LCMS *m/z* = 598.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.51 (s, 9H), 2.84-3.13 (m, 5H), 3.79 (s, 3H), 4.38-4.58 (m, 1H), 5.67-5.87 (m, 1H), 7.456 (d, *J* = 8.5 Hz, 1H), 7.73 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 8.32 (s, 2H), 8.48 (s, 1H), 9.03-9.14 (m, 1H).

20   **Step B: Preparation of Methyl 2-(6-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

A mixture of *tert*-butyl 6-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (81.7 mg, 0.137 mmol) and 4 M HCl in dioxane (4 mL, 16.00 mmol) was stirred at room temperature. After 15 min, the mixture was concentrated and the residue was purified by HPLC to give the title compound as a white solid (7.2 mg). LCMS *m/z* = 498.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 2.82-2.90 (m, 4H), 3.14-3.30 (m, 2H), 3.80 (s, 3H), 4.50-4.53 (m, 1H), 7.44 (dd, *J* = 8.5, 0.55 Hz, 1H), 7.72 (s, 1H), 7.96 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.32-8.34 (m, 2H), 8.48 (s, 1H), 8.93 (s, 1H).

30   **Step C: Preparation of 2-(6-(3-Cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

To a solution of methyl 2-(6-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate (6.0 mg, 0.012 mmol) in 1 mL of CH<sub>3</sub>CN/H<sub>2</sub>O (100:2), LiBr (10.4 mg, 0.120 mmol) and triethylamine (5  $\mu$ L, 0.036 mmol) were added. After stirring at 75 °C for 3 h, more LiBr (50 mg, 0.57 mmol) was added. After stirring at 75 °C for 2 h, the mixture was allowed to cool to room temperature and concentrated. The residue was treated with water and 2 M HCl. The solid was collected by filtration, washed with

additional water, and dried under high vacuum to give the title compound as a white solid (HCl salt, 5.8 mg). LCMS  $m/z$  = 484.2 [M+H]<sup>+</sup>.

**Example 1.23: Preparation of 2-(6-(5-(3-Cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-5-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 21).**

3-Cyano-4-cyclohexylbenzoic acid (0.057 g, 0.248 mmol) and CDI (0.040 g, 0.248 mmol) in DMA (2.0 mL) were heated to 60 °C for 30 min and then cooled to room temperature. *tert*-Butyl 6-(*N*'-hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.1 g, 0.248 mmol) was added and the reaction was warmed to 90 °C and stirred for 1 h and then cooled to 60 °C and stirred for 16 h. The reaction mixture was cooled to room temperature and then diluted with water (20 mL) resulting in the formation of a white precipitate. The solid was collected by filtration and dissolved in THF (5 mL). 4 M HCl in dioxane (6 mL) was added and the reaction was stirred at room temperature for 1 h and then concentrated to a yellow solid (128 mg). The solid (50 mg, 0.101 mmol) was dissolved in dioxane (2.5 mL) and 1.0 M aqueous LiOH (0.504 mL, 0.504 mmol) was added. The reaction was stirred at room temperature for 1 h and then acidified to pH 3 (aqueous 1.0 M HCl). The reaction mixture was diluted with water and then concentrated to dryness to give a light orange solid. The solid was sequentially triturated with water and methanol to give the title compound (29.0 mg). LCMS  $m/z$  = 482.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.20-1.65 (m, 5H), 1.70-1.94 (m, 5H), 2.62-2.74 (m, 1H), 2.78-3.03 (m, 4H), 3.12-3.51 (m, 2H), 4.56-4.66 (m, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.80-7.87 (m, 2H), 8.23 (s, 1H), 8.43 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.54 (d, *J* = 1.6 Hz, 1H), 11.4 (s, 1H).

**Example 1.24: Preparation of 2-(6-(5-(4-(Diethylamino)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 24).**

4-(Diethylamino)benzoic acid (0.019 g, 0.099 mmol) and CDI (0.016 g, 0.099 mmol) were stirred in DMA (1.0 mL) at 60 °C for 30 min. *tert*-Butyl 6-(*N*'-hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.04 g, 0.099 mmol) was added and the mixture was warmed to 90 °C and stirred for 2 h. 4-(Diethylamino)benzoic acid (40 mg) and CDI (32 mg) were stirred in DMA (1.0 mL) for 5 minutes at 90 °C and transferred to the reaction. The reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was concentrated to an oil and diluted with dioxane (1.5 mL). 1.0 M aqueous LiOH (0.6 mL) was then added and the mixture was stirred at room temperature for 16 h. 4.0 M HCL in dioxane (6.0 mL) was added and the reaction mixture was stirred for 30 min. The reaction was concentrated under reduced pressure. The crude product was purified by HPLC to give the title compound (17 mg). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.15 (t, *J* = 7.2 Hz, 6H), 2.97-3.08 (m, 3H), 3.25 (dd, *J* = 17.9, 3.4 Hz, 1H), 3.42-3.51 (m, 5H), 3.58-3.67 (m, 1H),

5.03-5.11 (m, 1H), 6.84 (d,  $J$  = 9.1 Hz, 2H), 7.56 (d,  $J$  = 8.7 Hz, 1H), 7.86 (dd,  $J$  = 8.5, 1.5 Hz, 1H), 7.95 (d,  $J$  = 9.1 Hz, 2H), 8.23 (s, 1H), 9.1 (bs, 1H), 9.4 (bs, 1H), 11.4 (s, 1H).

**Example 1.25: Preparation of 2-(6-(5-(2-Chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 22).**

**Step A: Preparation of *tert*-Butyl 6-(5-(2-Chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of *tert*-butyl 6-(*N*<sup>+</sup>-hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (50.7 mg, 0.126 mmol), 2-chloro-6-methoxyisonicotinoyl chloride (30 mg, 0.146 mmol), and triethylamine (12.75 mg, 0.126 mmol) in dioxane (2 mL) was heated at 100 °C (oil bath) for 4 h. The mixture was purified by preparative HPLC. The combined fractions collected were concentrated to give the title compound (41.5 mg) as an off-white solid. LCMS *m/z* = 554.3 [M+H]<sup>+</sup>;

**Step B: Preparation of Methyl 2-(6-(5-(2-Chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

A mixture of *tert*-butyl 6-(5-(2-chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (41.0 mg, 0.074 mmol) and hydrogen chloride (1 mL, 4.00 mmol) was stirred at room temperature for 30 min. The mixture was concentrated and dried under high vacuum to give the title compound (HCl salt, 36.3 mg) as a tan solid. LCMS *m/z* = 454.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 3.05-3.18 (m, 3H), 3.32-3.64 (m, 3H), 3.76 (s, 3H), 3.98 (s, 3H), 5.09-5.13 (m, 1H), 7.53 (s, 1H), 7.60 (d,  $J$  = 8.5 Hz, 1H), 7.77 (d,  $J$  = 0.8 Hz, 1H), 7.90 (dd,  $J$  = 8.5, 1.6 Hz, 1H), 8.29 (d,  $J$  = 0.96 Hz, 1H), 9.35-8.63 (m, 2H), 11.5 (s, 1H).

**Step C: Preparation of 2-(6-(5-(2-Chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

A mixture of methyl 2-(6-(5-(2-chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate hydrochloride (27.7 mg, 0.056 mmol) and lithium bromide (60 mg, 0.691 mmol) in CH<sub>3</sub>CN/H<sub>2</sub>O (100:2, 1 mL) was stirred at 75 °C (oil bath) for 2 h. To the solution was added water (2 mL) and 2 M HCl (0.2 mL). The solid was filtered off, washed with water, and dried under high vacuum to give the title compound (HCl salt, 18.9 mg). LCMS *m/z* = 440.4 [M+H]<sup>+</sup>.

**Example 1.26: Preparation of 2-(6-(3-Cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 23).**

**Step A: Preparation of *tert*-Butyl 6-(5-(2-Chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

A mixture of 3-cyano-5-(cyclopentyloxy)benzoic acid (28.0 mg, 0.121 mmol) and di(*1H*-imidazol-1-yl)methanone (19.8 mg, 0.122 mmol) in DMA (1 mL) was stirred at 70 °C for 30 min. *tert*-Butyl 6-(*N'*-hydroxycarbamimidoyl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (45.6 mg, 0.113 mmol) was added and the mixture was stirred at 90 °C for 1 h. The mixture was purified by preparative HPLC. The combined fractions collected were concentrated to give the title compound (11.5 mg) as a brownish solid. LCMS 10 *m/z* = 598.3 [M+H]<sup>+</sup>.

**Step B: Preparation of Methyl 2-(6-(3-Cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

A mixture of *tert*-butyl 6-(5-(3-cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (10.5 mg, 0.018 mmol) and 4.0 M hydrogen chloride in dioxane (1.0 mL) was stirred at room temperature for 1 h. The mixture was concentrated and dried under high vacuum to give the title compound (HCl salt, 9.3 mg) as an off-white solid. LCMS *m/z* = 498.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.68-1.79 (m, 6H), 1.96-2.04 (m, 2H), 3.05-3.17 (m, 3H), 3.46-3.71 (m, 3H), 3.76 (s, 3H), 5.07-5.10 (m, 2H), 7.58-7.60 (d, *J* = 8.5 Hz, 1H), 7.79-7.80 (m, 1H), 7.89-7.91 (m, 2H), 8.14-8.15 (m, 1H), 8.30 (s, 1H), 9.29-9.59 (m, 2H), 11.4 (s, 1H).

**Step C: Preparation of 2-(6-(3-Cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid.**

A mixture of methyl 2-(6-(3-cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate hydrochloride (6.6 mg, 0.012 mmol) and lithium bromide (50 mg, 0.576 mmol) in CH<sub>3</sub>CN/H<sub>2</sub>O (100:1, 1 mL) was stirred at 70 °C for 3 h. 2 M HCl and H<sub>2</sub>O was added. The precipitate was filtered off, washed with additional water, and dried under high vacuum to give the title compound (HCl salt, 4.5 mg) as an off-white solid. LCMS *m/z* = 484.3 [M+H]<sup>+</sup>.

**30 Example 1.27: Preparation of 2-(10-Chloro-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 32).**

The title compound was prepared from ethyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate and 4-(chloromethyl)-1-isopropoxy-2-(trifluoromethyl)benzene, using a similar method to the one described in **Example 1.19, Step E, And Example 1.20**. Exact mass calculated for C<sub>24</sub>H<sub>23</sub>ClF<sub>3</sub>NO<sub>5</sub>: 497.9, found: LCMS *m/z* = 498.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.38 (d, *J* = 6.1 Hz, 6H), 2.96 (dd, *J* = 16.0,

9.8 Hz, 1H), 3.51 (dd,  $J$  = 16.0, 2.9 Hz, 1H), 3.90-4.10 (m, 3H), 4.32 (m, 1H), 4.66 (septet,  $J$  = 6.1 Hz, 1H), 5.06 (s, 2H), 5.48 (dd,  $J$  = 9.8, 2.9 Hz, 1H), 6.97 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 7.02 (d,  $J$  = 8.5 Hz, 1H), 7.10 (d,  $J$  = 2.3 Hz, 1H), 7.20 (d,  $J$  = 8.9 Hz, 1H), 7.56 (dd,  $J$  = 8.5, 1.9 Hz, 1H), 7.67 (d,  $J$  = 1.9 Hz, 1H).

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**Example 1.28: Preparation of 2-(8-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 28).**

**Step A: Preparation of *tert*-Butyl 2-(BenzylOxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of *tert*-butyl 3-(5-(benzyloxy)-1-(2-hydroxyethyl)-1*H*-indol-2-yl)acrylate (3.68 g, 9.36 mmol) in THF (90 mL) was added CsF (2.84 g, 18.7 mmol). The reaction was heated in a sealed tube at 100 °C overnight. The mixture was cooled to ambient temperature, diluted with MTBE, and washed with saturated NH<sub>4</sub>Cl (twice) and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (1.70 g) as a white solid. LCMS *m/z* = 394.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.51 (s, 9H), 2.77 (dd,  $J$  = 15.8, 8.7 Hz, 1H), 2.91 (dd,  $J$  = 15.8, 4.2 Hz, 1H), 4.01-4.07 (m, 3H), 4.32-4.37 (m, 1H), 5.10 (s, 2H), 5.29 (dd,  $J$  = 8.7, 4.2 Hz, 1H), 6.13 (s, 1H), 6.93 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 7.12 (d,  $J$  = 2.4 Hz, 1H), 7.18 (d,  $J$  = 8.8 Hz, 1H), 7.28-7.33 (m, 1H), 7.35-7.40 (m, 2H), 7.46-7.48 (m, 2H).

**Step B: Preparation of *tert*-Butyl 2-(8-Hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

A mixture of *tert*-butyl 2-(8-(benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (0.1 g, 0.254 mmol), 20% palladium hydroxide on carbon (50 mg) and ammonium formate (0.064 g, 1.017 mmol) in methanol (5 mL) was heated under microwave irradiation for 30 min at 60 °C. After cooling, the mixture was filtered through Celite® and the solvent was removed under reduced pressure. Water (10 mL) and DCM (10 mL) were added and the layers separated. The aqueous layer was back-extracted with DCM. The combined organics were dried by passing through a phase separator cartridge. The solvent was removed under reduced pressure to give the title compound (72 mg) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.50 (s, 9H), 2.76 (dd,  $J$  = 15.8, 8.7 Hz, 1H), 2.90 (dd,  $J$  = 15.8, 4.2 Hz, 1H), 3.99-4.09 (m, 3H), 4.31-4.38 (m, 1H), 4.44 (s, 1H), 5.28 (dd,  $J$  = 8.7, 4.2 Hz, 1H), 6.09 (s, 1H), 6.76 (dd,  $J$  = 8.7, 2.4 Hz, 1H), 6.98 (d,  $J$  = 2.4 Hz, 1H), 7.13 (d,  $J$  = 8.7 Hz, 1H).

**Step C: Preparation of *tert*-Butyl 2-(8-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

4-(Chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (68.6 mg, 0.261 mmol), *tert*-butyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (72 mg, 0.237 mmol) and K<sub>2</sub>CO<sub>3</sub> (49.2 mg, 0.356 mmol) were taken up in DMF (1.0 mL) and heated to 60 °C

for 16 h in a sealed scintillation vial. The reaction was cooled down to room temperature, filtered through Celite®, and concentrated. The residue was purified by HPLC to give the title compound (25 mg) as a white solid. LCMS  $m/z$  = 530.6 [M+H]<sup>+</sup>.

5      **Step D: Preparation of 2-(8-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid.**

To a solution of 2-amino-3-mercaptopropanoic acid (17.16 mg, 0.142 mmol) in TFA (236  $\mu$ L) was added *tert*-butyl 2-(8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (25 mg, 0.047 mmol). The reaction was stirred at 23 °C for 15 min. The mixture was poured into water and stirred for 30 minutes. The precipitate 10 was collected by filtration to give the title compound (11.5 mg) as a white solid. LCMS  $m/z$  = 474.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.54-1.65 (m, 2H), 1.68-1.78 (m, 2H), 1.86-1.89 (m, 2H), 2.05-2.14 (m, 2H), 2.94 (dd,  $J$  = 16.0, 8.8 Hz, 1H), 3.08 (dd,  $J$  = 16.0, 3.8 Hz, 1H), 3.33-3.43 (m, 1H), 4.06-4.14 (m, 3H), 4.37-4.47 (m, 1H), 5.09 (s, 2H), 5.34 (dd,  $J$  = 8.8, 3.8 Hz, 1H), 6.19 (s, 1H), 6.95 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 7.12 (d,  $J$  = 2.4 Hz, 1H), 7.20 (d,  $J$  = 8.8 Hz, 1H), 7.48 (d,  $J$  = 8.1 Hz, 1H), 7.57-7.61 (m, 1H), 7.69 (d,  $J$  = 1.8 Hz, 1H).

Example 1.29: Preparation of 2-(10-Chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 29).

20      2-(8-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid (10 mg, 0.021 mmol) was dissolved in DCM (211  $\mu$ L) and cooled to 0 °C. NCS (2.8 mg, 0.021 mmol) was added and the reaction was stirred at 0 °C for 15 min in a 20 mL sealed scintillation vial. The mixture was diluted with DCM and washed with water (2 x 10 mL) and saturated sodium thiosulfate (aq) (2 x 10 mL). The organics were dried over MgSO<sub>4</sub> 25 and filtered by vacuum filtration through a glass fiber paper. The solvent was removed under reduced pressure to give the title compound (3.0mg). LCMS  $m/z$  = 508.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.55-1.65 (m, 2H), 1.70-1.77 (m, 2H), 1.81-1.90 (m, 2H), 2.05-2.14 (m, 2H), 2.96 (dd,  $J$  = 16.1, 9.8 Hz, 1H), 3.34-3.42 (m, 1H), 3.51 (dd,  $J$  = 16.1, 2.8 Hz, 1H), 3.98-4.13 (m, 3H), 4.29-4.35 (m, 1H), 5.11 (s, 2H), 5.48 (dd,  $J$  = 9.8, 2.8 Hz, 1H), 6.98 (dd,  $J$  = 8.8, 30 2.2 Hz, 1H), 7.10 (d,  $J$  = 2.2 Hz, 1H), 7.20 (d,  $J$  = 8.9 Hz, 1H), 7.49 (d,  $J$  = 8.1 Hz, 1H), 7.60 (d,  $J$  = 8.1 Hz, 1H), 7.71 (s, 1H).

Example 1.30: Preparation of 2-(10-Chloro-8-(4-(cyclopropylmethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 38).

The title compound was prepared from *tert*-butyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate and 4-(chloromethyl)-1-(cyclopropylmethoxy)-2-

(trifluoromethyl)benzene using a similar method to the one described in **Example 1.28, Step C**, followed by a similar method to the one described in **Example 1.29** followed by a deprotection method as described in **Example 1.28, Step D**. LCMS  $m/z$  = 510.4 [M+H]<sup>+</sup>.

**5 Example 1.31: Preparation of 2-(8-(4-(Fluoromethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 36).**

The title compound was prepared from *tert*-butyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate and 4-(chloromethyl)-1-(fluoromethoxy)-2-(trifluoromethyl)benzene using a similar method to the one described in **Example 1.28, Steps C & D**. LCMS  $m/z$  = 454.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm, 2.95 (dd,  $J$  = 16.0, 8.7 Hz, 1H), 3.08 (dd,  $J$  = 16.0, 3.9 Hz, 1H), 4.04-4.13 (m, 3H), 4.40 (m, 1H), 5.09 (s, 2H), 5.34 (dd,  $J$  = 8.7, 3.8 Hz, 1H), 5.75 (d,  $J$  = 53.9 Hz, 2H), 6.18 (s, 1H), 6.94 (dd,  $J$  = 8.8, 1.6 Hz, 1H), 7.10 (d,  $J$  = 1.8 Hz, 1H), 7.20 (d,  $J$  = 8.7 Hz, 1H), 7.29 (d,  $J$  = 8.6 Hz, 1H), 7.63 (d,  $J$  = 8.5 Hz, 1H), 7.73 (s, 1H).

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**Example 1.32: Preparation of 2-(8-(3-Chloro-4-(1,3-difluoropropan-2-yloxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 37).**

The title compound was prepared from *tert*-butyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate and 2-chloro-4-(chloromethyl)-1-(1,3-difluoropropan-2-yloxy)benzene using a similar method to the one described in **Example 1.31**. LCMS  $m/z$  = 466.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 2.93 (dd,  $J$  = 16.0, 8.7 Hz, 1H), 3.08 (dd,  $J$  = 16.0, 3.9 Hz, 1H), 4.01-4.12 (m, 3H), 4.37-4.42 (m, 1H), 4.56-4.70 (m, 3H), 4.75-4.78 (m, 2H), 5.02 (s, 2H), 5.30-5.38 (m, 1H), 6.18 (s, 1H), 6.93 (dd,  $J$  = 8.9, 2.3 Hz, 1H), 7.06-7.11 (m, 2H), 7.19 (d,  $J$  = 8.8 Hz, 1H), 7.31 (dd,  $J$  = 8.4, 2.0 Hz, 1H), 7.52 (d,  $J$  = 1.9 Hz, 1H).

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**Example 1.33: Preparation of 2-(8-(Benzylxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 27).**

**Step A: Preparation of *tert*-Butyl 3-(5-(Benzylxy)-1*H*-indol-2-yl)acrylate.**

To a solution of *tert*-butyl 3-(5-(benzylxy)-1*H*-indol-2-yl)acrylate (4.00 g, 11.45 mmol) in DMF (30 mL) was added NaH (60% dispersion in mineral oil, 2.0 equiv.) at 0 °C. (2-Bromoethoxy)(*tert*-butyl)dimethylsilane (5.48 g, 22.89 mmol) was added and the reaction was stirred in a sealed tube at 80 °C overnight. The mixture was diluted with MTBE and washed with 1 N HCl, water, and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (4.26 g) as a yellow oil. LCMS  $m/z$  = 508.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm -0.16 (s, 6H), 0.79 (s, 9H), 1.49 (s, 9H), 3.86 (t,  $J$  = 5.7 Hz, 2H), 4.30 (t,  $J$  = 5.7 Hz, 2H), 5.10 (s, 2H),

6.39 (d,  $J = 15.7$  Hz, 1H), 6.83 (s, 1H), 6.97 (dd,  $J = 9.0, 2.4$  Hz, 1H), 7.10 (d,  $J = 2.4$  Hz, 1H), 7.23 (d,  $J = 9.0$  Hz, 1H), 7.32 (m, 1H), 7.39 (m, 2H), 7.47 (m, 2H), 7.68 (d,  $J = 15.7$  Hz, 1H).

**Step B: Preparation of *tert*-Butyl 3-(BenzylOxy)-1-(2-hydroxyethyl)-1*H*-indol-2-yl)acrylate.**

To a solution of *tert*-butyl 3-(benzyloxy)-1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1*H*-indol-2-yl)acrylate (4.23 g, 8.33 mmol) in THF (25 mL) was added TBAF (1.0 M in THF) (16.66 mL, 16.66 mmol). The reaction was stirred for 3 h at room temperature. The mixture was diluted with MTBE and washed with saturated NH<sub>4</sub>Cl (twice) and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (2.64 g) as a yellow solid. LCMS *m/z* = 394.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.54 (s, 9H), 1.63 (t,  $J = 6.0$  Hz, 1H), 3.89-3.95 (m, 2H), 4.35 (t,  $J = 5.6$  Hz, 2H), 5.09 (s, 2H), 6.40 (d,  $J = 15.7$  Hz, 1H), 6.86 (s, 1H), 6.99 (dd,  $J = 8.9, 2.3$  Hz, 1H), 7.10 (d,  $J = 2.4$  Hz, 1H), 7.25-7.34 (m, 2H), 7.35-7.41 (m, 2H), 7.44-7.48 (m, 2H), 7.68 (d,  $J = 15.7$  Hz, 1H).

**Step C: Preparation of *tert*-Butyl 3-(BenzylOxy)-1-(2-(methylsulfonyloxy)ethyl)-1*H*-indol-2-yl)acrylate.**

To a solution of *tert*-butyl 3-(benzyloxy)-1-(2-hydroxyethyl)-1*H*-indol-2-yl)acrylate (525 mg, 1.334 mmol) in DCM (4.0 mL) at 0 °C was added MsCl (156 μL, 2.001 mmol) followed by DMAP (652 mg, 5.34 mmol). The reaction was stirred for 0.5 h. The mixture was diluted with MTBE and washed with 1 N HCl (twice), saturated NaHCO<sub>3</sub>, and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound as a white solid. LCMS *m/z* = 472.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.55 (s, 9H), 2.68 (s, 3H), 4.46 (t,  $J = 5.0$  Hz, 2H), 4.54 (t,  $J = 5.0$  Hz, 2H), 5.10 (s, 2H), 6.41 (d,  $J = 15.6$  Hz, 1H), 6.88 (s, 1H), 7.02 (dd,  $J = 9.0, 2.4$  Hz, 1H), 7.10 (d,  $J = 2.3$  Hz, 1H), 7.25 (d,  $J = 9.0$  Hz, 1H), 7.29-7.33 (m, 1H), 7.35-7.40 (m, 2H), 7.44-7.48 (m, 2H), 7.62 (d,  $J = 15.6$  Hz, 1H).

**Step D: Preparation of *tert*-Butyl 2-(BenzylOxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

To a solution of *tert*-butyl 3-(benzyloxy)-1-(2-(methylsulfonyloxy)ethyl)-1*H*-indol-2-yl)acrylate (620 mg, 1.33 mmol) in dioxane (10 mL) was added 7 N ammonia in MeOH (20 mL). The reaction was heated in a sealed tube at 80 °C for 18 h, cooled to room temperature, and concentrated *in vacuo*. The residue was extracted with DCM and H<sub>2</sub>O. The layers were separated and the aqueous phase was extracted with DCM. The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (330 mg) as a white solid. LCMS *m/z* = 393.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 2.70 (dd,  $J = 16.6, 9.2$  Hz, 1H), 2.95 (dd,  $J = 15.7, 3.5$  Hz, 1H), 3.27 (ddd,  $J = 15.3, 10.9, 4.4$  Hz, 1H), 3.46 (ddd,  $J = 12.7, 4.7, 2.3$  Hz, 1H), 3.91 (ddd,  $J = 15.8, 11.0, 4.8$  Hz, 1H), 4.07 (ddd,  $J = 11.2, 4.3, 2.3$  Hz, 1H), 4.47 (dd,  $J = 9.1, 3.5$  Hz, 1H),

5.10 (s, 2H), 6.12 (s, 1H), 6.91 (dd,  $J = 8.8, 2.4$  Hz, 1H), 7.12 (d,  $J = 2.4$  Hz, 1H), 7.18 (d,  $J = 8.8$  Hz, 1H), 7.29-7.33 (m, 1H), 7.35-7.40 (m, 2H), 7.44-7.48 (m, 2H).

**Step E: Preparation of 2-(Benzylloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid.**

5 A solution of *tert*-butyl 2-(benzylloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate (15 mg, 0.038 mmol) in TFA was stirred at room temperature for 0.5 h. The mixture was concentrated *in vacuo* to give the title compound. LCMS  $m/z = 337.6$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 3.22-3.27 (m, 2H), 3.41-3.50 (m, 1H), 3.79-3.89 (m, 2H), 4.05-4.12 (m, 1H), 4.82-4.89 (m, 1H), 5.10 (s, 2H), 6.31 (s, 1H), 7.03 (m, 2H), 7.12 (s, 1H), 7.29-7.33 (m, 1H), 7.35-7.40 (m, 2H), 7.44-7.48 (m, 2H).

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**Example 1.34: Preparation of 2-(3-Cyano-4-isopropoxybenzylloxy)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 34).**

15 **Step A: Preparation of *tert*-Butyl 8-(Benzylloxy)-1-(2-*tert*-butoxy-2-oxoethyl)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

A solution of *tert*-butyl 2-(benzylloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate (770 mg, 1.962 mmol) and di-*tert*-butyl dicarbonate (642 mg, 2.94 mmol) in THF (10 mL) was stirred at room temperature for 3 h and concentrated. The residue was purified by silica gel chromatography to give the title compound (795 mg) as a yellow solid. LCMS  $m/z = 493.5$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 1.50 (s, 9H), 2.76 (d,  $J = 7.1$ , Hz, 2H), 3.35-3.60 (m, 1H), 3.91 (td,  $J = 11.4, 4.3$  Hz, 1H), 4.09 (m, 1H), 4.32-4.54 (m, 1H), 5.09 (s, 2H), 5.79-5.97 (m, 1H), 6.23 (s, 1H), 6.92 (dd,  $J = 8.8, 2.3$  Hz, 1H), 7.10 (d,  $J = 2.3$  Hz, 1H), 7.17 (d,  $J = 8.8$  Hz, 1H), 7.28-7.33 (m, 1H), 7.35-7.40 (m, 2H), 7.40-7.59 (m, 2H).

25 **Step B: Preparation of *tert*-Butyl 1-(2-*tert*-Butoxy-2-oxoethyl)-8-hydroxy-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

To a solution of *tert*-butyl 8-(benzylloxy)-1-(2-*tert*-butoxy-2-oxoethyl)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate (785 mg, 1.594 mmol) in MeOH/THF (2:1, 25 mL) was added ammonium formate (630 mg, 7.97 mmol) followed by 20% Pd(OH)<sub>2</sub>/C (250 mg). The reaction was stirred at 60 °C overnight in a sealed tube and cooled down. The mixture was filtered through Celite® and concentrated. The residue was added EtOAc/H<sub>2</sub>O and extracted. The organic layer was separated and washed with brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound (615 mg) as an off-white solid. LCMS  $m/z = 403.5$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 1.50 (s, 9H), 2.76 (d,  $J = 7.1$ , Hz, 2H), 3.37-3.58 (m, 1H), 3.91 (td,  $J = 11.5, 4.4$  Hz, 1H), 4.04-4.12 (m, 1H), 4.29-4.62 (m, 2H), 5.78-5.98 (m, 1H), 6.19 (s, 1H), 6.75 (dd,  $J = 8.7, 2.4$  Hz, 1H), 6.96 (d,  $J = 2.4$  Hz, 1H), 7.11 (d,  $J = 8.6$  Hz, 1H).

**Step C: Preparation of *tert*-Butyl 1-(2-*tert*-Butoxy-2-oxoethyl)-8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

To a solution of *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-hydroxy-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate (400 mg, 0.994 mmol) in DMA (6.0 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (486 mg, 1.491 mmol) followed by 5-(chloromethyl)-2-isopropoxybenzonitrile (229 mg, 1.093 mmol). The reaction was stirred at 65 °C for 2.5 h under microwave irradiation. The mixture was diluted with MTBE and washed with 1 N HCl (twice) and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (419 mg) as a white solid. LCMS *m/z* = 576.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.40 (d, *J* = 6.1 Hz, 6H), 1.47 (s, 9H), 1.50 (s, 9H), 2.76 (d, *J* = 7.1 Hz, 2H), 3.35-3.65 (m, 1H), 3.92 (td, *J* = 11.8, 4.2 Hz, 1H), 4.09 (m, 1H), 4.30-4.59 (m, 1H), 4.65 (septet, *J* = 6.1 Hz, 1H), 5.00 (s, 2H), 5.78-5.97 (m, 1H), 6.24 (s, 1H), 6.88 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.58 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.64 (d, *J* = 2.2 Hz, 1H).

**Step D: Preparation of *tert*-Butyl 1-(2-*tert*-Butoxy-2-oxoethyl)-8-(3-cyano-4-isopropoxybenzyloxy)-10-iodo-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

To a solution of *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate (220 mg, 0.382 mmol) in DCM (5.0 mL) was added NIS (95 mg, 0.420 mmol). The reaction was stirred at room temperature for 0.5 h and washed with saturated sodium thiosulfate. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (183 mg) as a white solid. LCMS *m/z* = 702.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.41 (d, *J* = 6.1 Hz, 6H), 1.45 (s, 9H), 1.48 (s, 9H), 2.60-2.305 (m, 2H), 3.49-3.71 (m, 1H), 3.82-3.98 (m, 1H), 4.07-4.13 (m, 1H), 4.30-4.59 (m, 1H), 4.66 (septet, *J* = 6.1 Hz, 1H), 5.04 (s, 2H), 5.72-5.96 (m, 1H), 6.92 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 1H), 7.17 (m, 1H), 7.60 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.67 (d, *J* = 2.2 Hz, 1H).

**Step E: Preparation of 2-(8-(3-Cyano-4-isopropoxybenzyloxy)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid Hydrochloride.**

To *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(3-cyano-4-isopropoxybenzyloxy)-10-iodo-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate (60 mg, 0.086 mmol) in THF (1.0 mL) was added methylzinc chloride (2.0 M in THF, 214 μL, 0.428 mmol) followed by Pd(Ph<sub>3</sub>P)<sub>4</sub> (7.41 mg, 6.41 μmol). The reaction was heated to 80 °C for 3 h under microwave irradiation. The mixture was diluted with EtOAc and washed with saturated NaHCO<sub>3</sub> and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was treated with 4 N HCl/dioxane overnight at room temperature. The mixture was concentrated *in vacuo*. The residue was purified by HPLC. The combined fractions were added 2 N HCl and concentrated to give the title compound (3.1 mg) as a brown solid. LCMS *m/z* = 434.5 [M+H]<sup>+</sup>.

**Example 1.35: Preparation of 2-(8-(3-Cyano-4-isopropoxybenzyloxy)-10-cyclopropyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 35).**

The title compound was prepared from *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(3-cyano-4-isopropoxybenzyloxy)-10-iodo-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate (59 mg, 0.084 mmol) and cyclopropylzinc(**II**) chloride (0.5 M in Et<sub>2</sub>O, 1.00 mL, 0.50 mmol) using a similar method to the one described in Example 1.34, Step E. LCMS *m/z* = 460.4 [M+H]<sup>+</sup>.

**10 Example 1.36: Preparation of 2-(8-(4-Isopropoxy-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 30).**

**Step A: Preparation of *tert*-Butyl 1-(2-*tert*-Butoxy-2-oxoethyl)-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

The title compound was prepared from *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-hydroxy-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate and 4-(chloromethyl)-1-isopropoxy-2-(trifluoromethyl)benzene using a similar method to the one described in Example 1.34, Step C. LCMS *m/z* = 619.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.37 (d, *J* = 6.1 Hz, 6H), 1.47 (s, 9H), 1.50 (s, 9H), 2.76 (d, *J* = 7.1 Hz, 2H), 3.38-3.60 (m, 1H), 3.92 (td, *J* = 11.8, 4.2 Hz, 1H), 4.09 (m, 1H), 4.30-4.52 (m, 1H), 4.65 (septet, *J* = 6.1 Hz, 1H), 5.02 (s, 2H), 5.80-5.97 (m, 1H), 6.24 (s, 1H), 6.90 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H).

**Step B: Preparation of 2-(8-(4-Isopropoxy-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid.**

To a solution of *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate (15 mg, 0.024 mmol) in dioxane (1.0 mL) was added 4 N HCl dioxane (1.0 mL). The reaction was stirred at room temperature overnight. The mixture was purified by HPLC to give the title compound as a light brown solid. LCMS *m/z* = 463.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ ppm 1.32 (d, *J* = 6.0, Hz, 6H), 3.21 (m, 2H), 3.58 (m, 1H), 3.80 (td, *J* = 13.1, 3.9 Hz, 1H), 4.18 (dd, *J* = 5.6, 2.5 Hz, 1H), 4.34 (m, 1H), 4.74 (septet, *J* = 6.0 Hz, 1H), 4.91 (m, 1H), 5.07 (s, 2H), 6.36 (s, 1H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.62 (m, 1H), 7.68 (s, 1H).

**35 Example 1.37: Preparation of 2-(8-(4-Isobutyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 31).**

**Step A: Preparation of *tert*-Butyl 1-(2-*tert*-Butoxy-2-oxoethyl)-8-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-3,4-dihdropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

The title compound was prepared from *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-hydroxy-3,4-dihdropyrazino[1,2-a]indole-2(1*H*)-carboxylate and 4-(chloromethyl)-1-isobutyl-2-(trifluoromethyl)benzene using a similar method to the one described in Example 1.34, Step C. LCMS *m/z* = 617.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 0.93 (d, *J* = 6.6 Hz, 6H), 1.47 (s, 9H), 1.50 (s, 9H), 1.96 (m, 1H), 2.66 (d, *J* = 7.1 Hz, 2H), 2.76 (d, *J* = 7.1 Hz, 2H), 3.38-3.59 (m, 1H), 3.92 (td, *J* = 11.4, 4.3 Hz, 1H), 4.10 (m, 1H), 4.28-4.55 (m, 1H), 5.09 (s, 2H), 5.78-6.00 (m, 1H), 6.24 (s, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.72 (s, 1H).

**Step B: Preparation of 2-(8-(4-Isobutyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid Hydrochloride.**

A mixture of *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-3,4-dihdropyrazino[1,2-a]indole-2(1*H*)-carboxylate (50 mg, 0.081 mmol) in 4 N HCl dioxane was stirred at room temperature for 18 h. The mixture was concentrated *in vacuo* to give the title compound (37 mg) as a brown solid. LCMS *m/z* = 461.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.89 (d, *J* = 6.6 Hz, 6H), 1.92 (m, 1H), 2.63 (d, *J* = 7.4 Hz, 2H), 3.07 (dd, *J* = 17.4, 6.5 Hz, 1H), 3.22 (dd, *J* = 17.4, 5.6 Hz, 1H), 3.48 (m, 1H), 3.69 (m, 1H), 4.10 (m, 1H), 4.39 (m, 1H), 5.03 (m, 1H), 45.16 (s, 2H), 6.39 (s, 1H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.68 (m, 1H), 7.76 (s, 1H), 9.5 (bs, 1H).

**Example 1.38: Preparation of 2-(8-(5-(3-Cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 39).**

**Step A: Preparation of *tert*-Butyl 2-(8-(Trifluoromethylsulfonyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of *tert*-butyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (750 mg, 2.472 mmol) in DCM/MeCN (1:1, 40 mL) and triethylamine (1.251 g, 12.36 mmol) at 0 °C was added 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (972 mg, 2.72 mmol). The reaction was slowly warmed to room temperature over 1 h. Additional 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (417 mg, 4.12 mmol) was added and the reaction was stirred for an additional 2 h. The mixture was concentrated and the residue purified by silica gel column chromatography to give the title compound (969 mg) as a white solid. LCMS *m/z* = 436.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.50 (s, 9H), 2.79 (dd, *J* = 15.9, 8.3 Hz, 1H), 2.92 (dd, *J* = 15.9, 4.5 Hz, 1H), 4.08 (m, 3H), 4.38 (m, 1H), 5.38 (dd, *J* = 8.3, 4.5 Hz, 1H), 6.27 (s, 1H), 7.09 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H).

**Step B: Preparation of *tert*-Butyl 2-(8-Cyano-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

A mixture of *tert*-butyl 2-(8-(trifluoromethylsulfonyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (100 mg, 0.230 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (39.8 mg, 0.034 mmol) and sodium cyanide (33.8 mg, 0.689 mmol) in acetonitrile was heated at 130 °C for 2 h under microwave irradiation. The mixture was extracted with EtOAc and H<sub>2</sub>O. The organics were separated and purified by silica gel column chromatography to give the title compound (29 mg) as a white solid. LCMS *m/z* = 313.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.50 (s, 9H), 2.80 (dd, *J* = 15.9, 8.3 Hz, 1H), 2.92 (dd, *J* = 15.9, 4.5 Hz, 1H), 4.09 (m, 3H), 4.39 (m, 1H), 5.30 (m, 1H), 6.29 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.42 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H).

**Step C: Preparation of *tert*-Butyl 2-(8-(*N*'-Hydroxycarbamimidoyl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of *tert*-butyl 2-(8-cyano-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (90 mg, 0.288 mmol) in EtOH (1.5 mL) was added hydroxylamine (50% in H<sub>2</sub>O, 15.0 equiv.) The reaction was stirred at 70 °C for 3 h under microwave irradiation. The mixture was diluted with EtOAc and washed with H<sub>2</sub>O and brine. The organics were dried over MgSO<sub>4</sub>, filtered and concentrated to give the title compound (65 mg). LCMS *m/z* = 346.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.50 (s, 9H), 2.79 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.92 (dd, *J* = 15.8, 4.3 Hz, 1H), 4.06 (m, 3H), 4.36 (m, 1H), 4.91 (bs, 2H), 5.30 (dd, *J* = 8.5, 4.3 Hz, 1H), 6.24 (s, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.83 (d, *J* = 1.5 Hz, 1H).

**Step D: Preparation of *tert*-Butyl 2-(8-(5-(3-Cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

To a solution of *tert*-butyl 2-(8-(*N*'-hydroxycarbamimidoyl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (55 mg, 0.159 mmol) and 3-cyano-4-isopropoxybenzoic acid (49.0 mg, 0.239 mmol) in dioxane (1.5 mL) was added triethylamine (166 μL, 1.194 mmol) followed by propyl phosphonic acid cyclic anhydride (50% in EtOAc) (0.239 mmol). The reaction was heated at 100 °C for 1.5 h under microwave irradiation. The mixture was diluted with EtOAc and washed sequentially with 1*N* HCl, saturated NaHCO<sub>3</sub>, and brine. The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (35 mg) as a white solid. LCMS *m/z* = 515.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.49 (d, *J* = 6.1 Hz, 6H), 1.51 (s, 9H), 2.82 (dd, *J* = 15.8, 8.4 Hz, 1H), 2.96 (dd, *J* = 15.8, 4.4 Hz, 1H), 4.10 (m, 3H), 4.40 (m, 1H), 4.79 (septet, *J* = 6.1 Hz, 1H), 5.33 (m, 1H), 6.33 (s, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 8.0 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.35 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.41 (d, *J* = 1.5 Hz, 1H), 8.46 (d, *J* = 2.2 Hz, 1H).

**Step E: Preparation of 2-(8-(5-(3-Cyano-4-isopropoxypyhenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid.**

*tert*-Butyl 2-(8-(5-(3-cyano-4-isopropoxypyhenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (35 mg, 0.068 mmol) was stirred in TFA (3.0 mL) for 30 min. The mixture was concentrated *in vacuo* and purified by reverse phase HPLC to give the title compound (6.0 mg) as a white solid. LCMS *m/z* = 459.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.39 (d, *J* = 6.0 Hz, 6H), 2.68 (dd, *J* = 15.8, 9.0 Hz, 1H), 3.14 (dd, *J* = 15.8, 3.7 Hz, 1H), 4.04 (m, 2H), 4.25 (m, 1H), 4.34 (m, 1H), 4.98 (septet, *J* = 6.0 Hz, 1H), 5.26 (dd, *J* = 9.0, 3.7 Hz, 1H), 6.51 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.87 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.31 (d, *J* = 1.5 Hz, 1H), 8.41 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.50 (d, *J* = 2.2 Hz, 1H), 12.40 (bs, 1H).

**Example 1.39: Preparation of 2-(8-(5-(4-Cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 40).**

**Step A: Preparation of *tert*-Butyl 1-(2-*tert*-Butoxy-2-oxoethyl)-8-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate.**

The title compound was prepared as a white solid from *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(*N'*-hydroxycarbamimidoyl)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate and 4-cyclopentyl-3-(trifluoromethyl)benzoic acid using a similar method to the one described in **Example 1.38, Step D**. LCMS *m/z* = 515.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.44 (s, 9H), 1.51 (s, 9H), 1.63 (m, 2H), 1.75 (m, 2H), 1.91 (m, 2H), 2.1 (m, 2H), 2.82 (dd, *J* = 15.8, 8.4 Hz, 1H), 2.96 (dd, *J* = 15.8, 4.4 Hz, 1H), 4.10 (m, 3H), 4.40 (m, 1H), 4.79 (septet, *J* = 6.1 Hz, 1H), 5.33 (m, 1H), 6.33 (s, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 8.0 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.35 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.41 (d, *J* = 1.5 Hz, 1H), 8.46 (d, *J* = 2.2 Hz, 1H).

**Step B: Preparation of 2-(8-(5-(4-Cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid.**

The title compound was prepared as a white solid from *tert*-butyl 1-(2-*tert*-butoxy-2-oxoethyl)-8-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydropyrazino[1,2-a]indole-2(1*H*)-carboxylate using a similar method to the one described in **Example 1.38, Step D**. LCMS *m/z* = 511.4

**Example 1.40: Preparation of 2-(6-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic Acid (Compound 25).**

**Step A: Preparation of Methyl 2-(6-Bromo-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate.**

To a mixture of 2-(5-bromo-1*H*-indol-3-yl)ethanol (400 mg, 1.666 mmol) and methyl 3-oxobutanoate (234  $\mu$ L, 2.166 mmol) in toluene (5 mL) was added *p*-toluenesulfonic acid monohydrate (31.7 mg, 0.167 mmol). The reaction mixture was stirred at 80 °C for 15 min, cooled, and diluted with ethyl acetate. The organics were washed with saturated NaHCO<sub>3</sub>, brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated, and the residue was purified by column chromatography to give the title compound (452 mg). LCMS *m/z* = 338.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.71 (s, 3H), 2.77-2.82 (m, 2H), 2.92 (d, *J* = 16.6 Hz, 1H), 3.05 (d, *J* = 16.6 Hz, 1H), 3.78 (s, 3H), 4.05 (t, *J* = 5.5 Hz, 1H), 7.24-7.30 (m, 2H), 7.64-7.66 (m, 1H), 9.23 (s, 1H).

**Step B: Preparation of Methyl 2-(6-Cyano-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate.**

The reaction mixture of methyl 2-(6-bromo-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (250 mg, 0.739 mmol) and copper(I) cyanide (166 mg, 1.848 mmol) in NMP (5 mL) was heated at 200 °C under microwave irradiation for 3.5 h, poured into water, and extracted with ethyl acetate. The combined organics were washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated, and the residue was purified by column chromatography to give the title compound (150 mg). LCMS *m/z* = 285.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.68 (s, 3H), 2.76-2.82 (m, 2H), 2.92 (d, *J* = 16.7 Hz, 1H), 3.03 (d, *J* = 16.7 Hz, 1H), 3.76 (s, 3H), 4.03 (t, *J* = 5.5 Hz, 1H), 7.37-7.42 (m, 2H), 7.82-7.85 (m, 1H), 9.61 (s, 1H).

**Step C: Preparation of Methyl 2-(6-(*N*'-Hydroxycarbamimidoyl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate.**

To a stirred solution of methyl 2-(6-cyano-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (150 mg, 0.528 mmol) in EtOH (5 mL) was added hydroxylamine (50 wt % solution in water) (323  $\mu$ L, 5.28 mmol). The reaction mixture was stirred at 70 °C for 4 h. The solvent was evaporated to give the title compound (160 mg) without further purification. LCMS *m/z* = 318.2 [M+H]<sup>+</sup>.

**Step D: Preparation of Methyl 2-(6-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate.**

To a stirred solution of 3,5-bis(trifluoromethyl)benzoic acid (89 mg, 0.347 mmol), HATU (180 mg, 0.473 mmol) in DMF (2 mL) was added DIEA (110  $\mu$ L, 0.630 mmol). The reaction mixture was stirred for 10 min, methyl 2-(6-(*N*'-hydroxycarbamimidoyl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (100 mg, 0.315 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, then heated at 70 °C for 1 h. The solvent was evaporated, and the residue was purified by column chromatography to give the title compound (100 mg). LCMS *m/z* = 540.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.71 (s, 3H), 2.88-2.92 (m, 2H), 2.94 (d, *J* = 16.8 Hz, 1H), 3.06 (d, *J* = 16.8 Hz, 1H), 3.76 (s, 3H), 4.04-

4.10 (m, 2H), 7.48 (d,  $J$  = 8.5 Hz, 1H), 8.00 (dd,  $J$  = 8.5, 1.6 Hz, 1H), 8.11 (s, 1H), 8.37 (m, 1H), 8.70 (s, 2H), 9.40 (s, 1H).

**Step E: Preparation of 2-(6-(5-(3,5-Bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic Acid.**

To a stirred solution of methyl 2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (70 mg, 0.148 mmol) in dioxane (1 mL) was added a 1 M LiOH aqueous solution (593  $\mu$ L, 0.593 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with water, acidified with 0.5 M citric acid aqueous solution, extracted with ethyl acetate. The combined organics were washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated to give the title compound (58 mg) as a white solid. LCMS  $m/z$  = 526.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.74 (s, 3H), 2.88-3.00 (m, 2H), 3.04 (d,  $J$  = 16.6 Hz, 1H), 3.10 (d,  $J$  = 16.6 Hz, 1H), 4.07-4.20 (m, 2H), 7.42 (d,  $J$  = 8.5 Hz, 1H), 7.98 (dd,  $J$  = 8.5, 1.5 Hz, 1H), 8.11 (s, 1H), 8.37 (m, 1H), 8.69 (s, 2H), 8.95 (s, 1H).

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**Example 1.41: Preparation of 2-(8-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid (Compound 41).**

**Step A: Preparation of *tert*-Butyl 2-(8-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate.**

3-(Chloromethyl)-5-(trifluoromethoxy)benzonitrile (58.2 mg, 0.247 mmol), *tert*-butyl 2-(8-hydroxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (50.0 mg, 0.165 mmol) and  $\text{Cs}_2\text{CO}_3$  (81 mg, 0.247 mmol) were taken up in DMA (2 mL) and heated to 70 °C for 3 h in a 20 mL sealed scintillation vial. The mixture was cooled down to room temperature and filtered by vacuum filtration through Celite® and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (61.2 mg) as a white solid. LCMS  $m/z$  = 503.5 [M+H]<sup>+</sup>.

**Step B: Preparation 2-(8-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic Acid.**

A solution of 2-amino-3-mercaptopropanoic acid (21.70 mg, 0.179 mmol) in TFA (1 mL) was added to *tert*-butyl 2-(8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetate (30 mg, 0.060 mmol) in dioxane (1 mL) and stirred at 23 °C for 3 h in a 20 mL sealed scintillation vial. The reaction mixture was poured into water and stirred for 30 minutes. The resulting precipitate was collected by vacuum filtration and washed with *n*-hexanes (3 x 10 mL) and dried (vacuum oven) to give the title compound (9.7 mg) as a pink solid. LCMS  $m/z$  = 447.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 2.61 (dd,  $J$  = 15.79, 9.09 Hz, 1H), 3.07 (dd,  $J$  = 15.85, 3.85 Hz, 1H), 3.86-4.02 (m, 2H), 4.08-4.15 (m, 1H), 4.25-4.32 (m, 1H), 5.18 (dd,  $J$  = 8.91, 3.73 Hz, 1H), 5.22 (s, 2H), 6.23 (s, 1H), 6.89 (dd,  $J$  =

8.78, 2.34 Hz, 1H), 7.12 (d,  $J$  = 2.40 Hz, 1H), 7.32 (d,  $J$  = 8.84 Hz, 1H), 7.83 (s, 1H), 7.94-8.00 (m, 2H), 12.41 (s, 1H).

**Example 1.42: Preparation of 2-(10-Chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 42).**

**Step A: Preparation of *tert*-Butyl 2-(3-Cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

The title compound was prepared in a similar manner as described in **Example 1.1 Step C** using *tert*-butyl 2-(8-hydroxy-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate and 3-(chloromethyl)-5-(trifluoromethoxy)benzonitrile. LCMS  $m/z$  = 516.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 2.48 (s, 3H), 2.70-2.82 (m, 2H), 2.97-3.05 (m, 1H), 3.25-3.32 (m, 1H), 3.95-4.10 (m, 2H), 4.25 (t,  $J$  = 6.3 Hz, 1H), 5.13 (s, 2H), 6.18 (s, 1H), 6.88 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 7.05 (d,  $J$  = 2.4 Hz, 1H), 7.19 (d,  $J$  = 8.8 Hz, 1H), 7.44 (s, 1H), 7.58 (s, 1H), 7.71 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(10-Chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

The title compound was prepared in a similar manner as described in **Example 1.1 Step D** using *tert*-butyl 2-(3-cyano-5-(trifluoromethoxy)benzyloxy-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate and NCS. LCMS  $m/z$  = 550.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.48 (s, 9H), 2.56 (s, 3H), 2.75 (dd,  $J$  = 15.3, 5.3 Hz, 1H), 2.84 (dd,  $J$  = 15.3, 4.1 Hz, 1H), 3.05 (dt,  $J$  = 13.8, 3.7 Hz, 1H), 3.40-3.48 (m, 1H), 3.91-3.98 (m, 1H), 4.02-4.09 (m, 1H), 4.45 (dd,  $J$  = 9.3, 4.1 Hz, 1H), 5.19 (s, 2H), 6.96 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 7.07 (d,  $J$  = 2.4 Hz, 1H), 7.25 (d,  $J$  = 8.8 Hz, 1H), 7.47 (s, 1H), 7.62 (s, 1H), 7.75 (s, 1H).

**Step C Preparation of 2-(10-Chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 42).**

The title compound was prepared in a similar manner as described in **Example 1.1 Step E** using *tert*-butyl 2-(10-chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate. LCMS  $m/z$  = 494.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.72 (s, 3H), 2.90 (dd,  $J$  = 17.2, 10.1 Hz, 1H), 2.98 (dd,  $J$  = 17.2, 4.5 Hz, 1H), 3.23 (dt,  $J$  = 14.1, 3.7 Hz, 1H), 3.58-3.66 (m, 1H), 4.11-4.16 (m, 2H), 4.35 (dd,  $J$  = 10.1, 4.5 Hz, 1H), 5.17 (s, 2H), 7.01 (dd,  $J$  = 8.8, 2.4 Hz, 1H), 7.07 (d,  $J$  = 2.4 Hz, 1H), 7.25 (d,  $J$  = 8.8 Hz, 1H), 7.47 (s, 1H), 7.59 (s, 1H), 7.73 (s, 1H).

**Example 1.43: Preparation of 2-(10-Chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 43).**

**Step A: Preparation of *tert*-Butyl 2-(8-Benzyl-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

*tert*-Butyl 3-(5-(benzyloxy)-1-(2-(methylsulfonyloxy)ethyl)-1*H*-indol-2-yl)acrylate (750 mg, 1.590 mmol; prepared as described in Example 1.33 Step C) in a 2 M solution of methylamine in THF (40 mL) was heated at 120 °C for 2.5 h under microwave irradiation, and then diluted with ethyl acetate. The organic layer was washed with saturated NaHCO<sub>3</sub> and water, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and then concentrated. The residue was purified by column chromatography with 60% ethyl acetate/hexanes to give the title compound (394 mg) as white solid. LCMS *m/z* = 407.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 2.48 (s, 3H), 2.70-2.80 (m, 2H), 2.97-3.05 (m, 1H), 3.25-3.32 (m, 1H), 3.95-4.07 (m, 2H), 4.25 (t, *J* = 6.3 Hz, 1H), 5.10 (s, 2H), 6.16 (s, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.27-7.33 (m, 1H), 7.35-7.40 (m, 2H), 7.44-7.48 (m, 2H).

**Step B: Preparation of *tert*-Butyl 2-(8-Hydroxy-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

The reaction mixture of *tert*-butyl 2-(8-(benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate (400 mg, 0.984 mmol) and 10% Pd on carbon (150 mg, 0.984 mmol) in THF/MeOH solution (1:2, total 12 mL) was degassed and charged with hydrogen, then stirred overnight at room temperature. The solid was filtered off and washed with ethyl acetate. The filtrate was concentrated to give the title compound (320 mg) as an orange solid. LCMS *m/z* = 317.0 [M+H]<sup>+</sup>.

**Step C: Preparation of *tert*-Butyl 2-(8-(4-Cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

To a stirred solution of *tert*-butyl 2-(8-hydroxy-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate (70 mg, 0.221 mmol) in DMF (2 mL) was added 4-(chloromethyl)-1-cyclopentyl-2-(trifluoromethyl)benzene (92 mg, 0.288 mmol) and cesium carbonate (108 mg, 0.332 mmol). The reaction mixture was heated at 65 °C for 8 h. The solid was filtered off, and washed with ethyl acetate. The filtrate was concentrated, and the residue was purified by column chromatography with 60% ethyl acetate/hexanes to give the title compound. LCMS *m/z* = 543.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 1.55-1.65 (m, 2H), 1.65-1.78 (2H), 1.80-1.88 (m, 2H), 2.05-2.15 (m, 2H), 2.48 (s, 3H), 2.72-2.82 (m, 2H), 2.97-3.05 (m, 1H), 3.25-3.32 (m, 1H), 3.34-3.42 (m, 1H), 3.95-4.07 (m, 2H), 4.25 (t, *J* = 6.3 Hz, 1H), 5.08 (s, 2H), 6.18 (s, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.70 (d, *J* = 1.2 Hz, 1H).

**Step D: Preparation of *tert*-Butyl 2-(10-Chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate.**

To a stirred solution of *tert*-butyl 2-(8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate (30 mg, 0.055 mmol) in DCM (1 mL) was added NCS (8.86 mg, 0.066 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 1 h, and then diluted with DCM. The organic layer was washed with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and water, and then dried. The solvent was evaporated, and the residue was purified by column chromatography, eluting with 40% ethyl acetate/hexanes, to give the title compound (22 mg). LCMS *m/z* = 577.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.47 (s, 9H), 1.55-1.65 (m, 2H), 1.70-1.78 (2H), 1.80-1.88 (m, 2H), 2.05-2.15 (m, 2H), 2.53 (s, 3H), 2.72 (dd, *J* = 15.3, 9.4 Hz, 1H), 2.82 (dd, *J* = 15.3, 4.1 Hz, 1H), 3.02 (dt, *J* = 13.8, 3.7 Hz, 1H), 3.34-3.46 (m, 2H), 3.86-3.93 (m, 1H), 3.98-4.07 (m, 1H), 4.45 (dd, *J* = 9.4, 4.0 Hz, 1H), 5.11 (s, 2H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.71 (s, 1H).

**Step E: Preparation of 2-(10-Chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic Acid (Compound 43).**

DL-cysteine (23.09 mg, 0.191 mmol) was dissolved in TFA (1 mL) and cooled down to 0 °C. The solution was added to a solution of *tert*-butyl 2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetate (22 mg, 0.038 mmol) in DCM (1 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 hr, water was added, then ethyl acetate was added. The organic layer was separated, washed with water, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and the residue was lyophilized to give the title compound (17 mg). LCMS *m/z* = 521.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.55-1.65 (m, 2H), 1.65-1.78 (2H), 1.80-1.88 (m, 2H), 2.05-2.15 (m, 2H), 2.70 (s, 3H), 2.88 (dd, *J* = 17.2, 10.2 Hz, 1H), 2.96 (dd, *J* = 17.2, 4.4 Hz, 1H), 3.20 (dt, *J* = 14.0, 3.7 Hz, 1H), 3.34-3.42 (m, 1H), 3.57-3.65 (m, 1H), 4.09-4.15 (m, 2H), 4.35 (dd, *J* = 10.4, 4.3 Hz, 1H), 5.11 (s, 2H), 7.01 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.71 (s, 1H).

**Example 1.44: Preparation of 2-(6-(4-Isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 44).**

**Step A: Preparation of 2-(Trimethylsilyl)ethyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

Methyl 2-(6-hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate (0.130 g, 0.499 mmol, see Example 1.2, Steps A and B) was suspended in dichloromethane (4.99 mL), DIEA (0.113 mL, 0.649 mmol), then TMSCl (0.160 mL, 1.249 mmol) were added at 24 °C to give an amber solution. Additional DIEA (0.113 mL, 0.649 mmol) was added, the reaction

mixture was stirred for 2 h after which 2-(trimethylsilyl)ethyl *p*-nitrophenyl carbonate (0.149 g, 0.524 mmol) was added at 24 °C. After 18 h DMF (4.99 mL, 0.499 mmol) was added to the reaction mixture, DCM was removed *in vacuo*, and the reaction mixture was stirred at 24 °C for 16 h. The solvent was concentrated at 24 °C to give an oil which was partitioned between

- 5 EtOAc (50 mL) and water/brine (10 mL/10 mL). The organic layer was washed with brine (20 mL), dried with MgSO<sub>4</sub>, concentrated, and purified by silica gel flash chromatography to give an oil. This oil was dissolved in DCM (3 mL) and coevaporated *in vacuo* with hexane (10 mL) to give the title compound as a solid (0.057 g). LCMS *m/z* = 405.4 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.03 (s, 9 H), 0.90 - 1.05 (m, 2 H), 2.53 - 2.62 (m, 3 H), 2.70 - 2.82 (m, 1 H), 10.28 - 2.90 (m, 1 H), 3.60 (s, 3 H), 4.14 (t, *J* = 8.27 Hz, 2 H), 4.18 - 4.24 (m, 1 H), 6.57 (dd, *J* = 8.59, 2.40 Hz, 1 H), 6.69 (d, *J* = 2.15 Hz, 1 H), 7.09 (d, *J* = 8.59 Hz, 1 H), 8.58 (s, 1 H), 10.48 (s, 1 H).

**Step B: Preparation of 2-(Trimethylsilyl)ethyl 6-(4-isobutyl-2-methoxybenzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate.**

- 15 2-(Trimethylsilyl)ethyl 6-hydroxy-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate (0.0534 g, 0.132 mmol) was dissolved in anhydrous DMF (1.320 ml), cesium carbonate (0.056 g, 0.172 mmol) was added, and after stirring for 10 min at 24 °C, 1-(chloromethyl)-4-isobutyl-2-methoxybenzene (0.033 ml, 0.145 mmol) was added. The reaction mixture was heated at 50 °C for 2 h after which the solvent was evaporated 20 to give an oil which was dissolved in EtOAc (50 mL). The solution was washed with water-brine (20 mL) and brine (20 mL), dried with MgSO<sub>4</sub>, and the organic phase was concentrated to give an oil which was purified by silica gel flash chromatography to give the titled compound as a resin (0.011 g, 0.019 mmol, 14.35 % yield). LCMS *m/z* = 581.3 [M+H]<sup>+</sup>.

25 **Step C: Preparation of Methyl 2-(6-(4-isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate.**

- 2-(Trimethylsilyl)ethyl 6-(4-isobutyl-2-methoxybenzyloxy)-1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indole-2(9*H*)-carboxylate was dissolved in THF (1.0 ml) 1.0 M TBAF in THF (0.038 ml, 0.038 mmol) was added and the reaction was stirred at 24 °C for 3 h after which additional 1.0 M TBAF in THF (0.038 mL, 0.038 mmol) was added. After stirring at 30 24 °C for 16 h the solvent was evaporated to give the crude product as an oil contaminated with NBu<sub>4</sub>F. LCMS *m/z* = 437.4 [M+H]<sup>+</sup>. This crude product was used without further purification for the next step.

**Step D: Preparation of 2-(6-(4-Isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic Acid (Compound 44).**

- 35 Methyl 2-(6-(4-isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetate as a crude mixture was dissolved in 1,4-dioxane (0.760 mL), 1.0 M lithium hydroxide (0.076 mL, 0.076 mmol) was added at 24 °C, and after 17 h 0.5 M citric acid (0.304

mL, 0.15 mmol) was added to pH 4-5. The reaction mixture was diluted with EtOAc (25 mL), washed with brine (5 mL), and the organic layer was concentrated to give an oil which was purified by preparative HPLC. Appropriate fractions were collected, the pH was adjusted to pH 7 with aqueous saturated NaHCO<sub>3</sub> (200 µL), and the mixture was concentrated to a small volume of water (3 mL) to give a white precipitate. The water was decanted and the product was dried *in vacuo* to give the title compound as a white solid (0.0034 g). LCMS *m/z* = 423.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.88 (d, *J* = 6.57 Hz, 6 H), 1.80 - 1.94 (m, 1 H), 2.21 - 2.36 (m, 1 H), 2.36 - 2.36 (m, 1 H), 2.37 - 2.42 (m, 1 H), 2.45 (d, *J* = 7.20 Hz, 2 H), 2.64 - 2.70 (m, 2 H), 2.80 - 2.92 (m, 1 H), 3.82 (s, 3 H), 4.09 - 4.21 (m, 1 H), 4.98 (s, 2 H), 6.66 (dd, *J* = 8.65, 2.21 Hz, 1 H), 6.74 (d, *J* = 7.33 Hz, 1 H), 6.83 (s, 1 H), 6.90 (d, *J* = 1.89 Hz, 1 H), 7.13 (d, *J* = 8.72 Hz, 1 H), 7.31 (d, *J* = 7.58 Hz, 1 H), 7.68 (br. s., 1 H), 11.15 (bs, 1 H).

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

Compounds 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 receptors. 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 EC<sub>50</sub> 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  $\mu$ M) and rolipram (20  $\mu$ M) (phosphodiesterase inhibitors; Sigma-Aldrich, St. Louis, MO; catalog # I5879 and catalog # R6520, respectively), followed by test compound in 5  $\mu$ L compound buffer (PBS+ supplemented with 10  $\mu$ L NKH477 (water-soluble forskolin derivative; SigmaGen Laboratories, 5 Gaithersburg, MD; catalog # PKI-NKH477-010)) or 5  $\mu$ L compound buffer. The plate was then incubated at room temperature for 1 h. To each well was then added 5  $\mu$ L cAMP-d2 conjugate in lysis buffer and 5  $\mu$ 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.

10 **Assay readout:** HTRF<sup>®</sup> readout was accomplished using a PHERAstar (BMG LABTECH Inc., Durham, NC) or EnVision<sup>TM</sup> (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 <sub>50</sub> S1P1 (HTRF <sup>®</sup> )
1	0.06 nM
3	0.05 nM
6	0.41 nM
20	0.54 nM
26	1.65 nM

15

Certain other compounds of the invention had activity values ranging from about 15 pm to about 10  $\mu$ M in this assay.

**Example 3: Cellular/Functional Ca<sup>2+</sup> Assay for Agonist Activity on S1P3 Receptor.**

20 A compound of the 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).

25 **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

5   **Example 4: Effect of Compounds in Peripheral Lymphocyte Lowering (PLL) Assay.**

A compound of the invention were shown to induce peripheral lymphocyte lowering (PLL) or lymphopenia in Female B1/6 mice and Male Sprague-Dawley rats as described herein below. Immunosuppression by sequestering lymphocytes into secondary lymphoid tissues [i.e. lymphopenia] and away from graft sites and inflammatory lesions plays a role in the treatment 10 of a number of diseases, such as, rheumatoid arthritis, ulcerative colitis, type I diabetes, multiple sclerosis, and the like.

A.   **Mouse PLL Assay.**

15   **Animals:** Female B1/6 mice (Charles River Laboratories, Wilmington, MA) were 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 were allowed one week of habituation to the animal facility before testing.

20   **PLL Assay:** Mice were given a 1.00 mg/kg intravenous dose of Compound 41, Compound 25, Compound 31, or dosing vehicle (20 % hydroxypropyl cyclodextrin in 0.9% NaCl) in a total volume of 10 mL/kg. Peripheral blood samples were collected at 5 hours post-dose. The mice were anesthetized with isoflurane and blood was collected *via* cardiac puncture. 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 Figures 1, 2, and 3, in which peripheral blood lymphocyte (PBL) count is shown for the 5 hour group. 25 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 Figures 1, 2, and 3 that Compound 41, Compound 25, and Compound 31 exhibited activity for inducing PBL lowering (lymphopenia) in the mouse.

B.   **Rat PLL Assay.**

30   **Animals:** Male Sprague-Dawley rats (Charles River Laboratories) were 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 6:30 am) with free access to food (Harlan Teklad, Orange, CA, Rodent Diet 8604) and water. Rats were allowed one week of habituation to the animal facility before testing.

35   **PLL Assay:** Rats were given a 1.00 mg/kg intravenous dose of either the 1<sup>st</sup> or the 2<sup>nd</sup> enantiomer of compound 4 (as described in Example 1.5) or dosing vehicle (40% hydroxypropyl-cyclo-dextrin in water) via indwelling catheter in a total volume of 2.00 mL/kg.

Peripheral blood samples were collected at 5 hours 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 4** and **Figure 5** in which peripheral blood lymphocyte (PBL) 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 exhibited activity or induced peripheral lymphocyte lowering. It is apparent from inspection of **Figure 4** and **Figure 5** that the 1<sup>st</sup> and the 2<sup>nd</sup> enantiomer of compound **4** exhibited activities for inducing PBL lowering (lymphopenia) in the rat.

10

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

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

**A. MOG-induced EAE in Mice.**

**Animals:** Female C57BL/6 mice (8 to 10 weeks of age at start of study) (Jackson Laboratory, Bar Harbor, ME) are housed four per cage and maintained in a humidity-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 MOG<sub>35-55</sub> 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 the test compound once a day from day 3 until day 21. Dosing volume is 5 mL/kg. The test compound is dosed at 0.3 mg/kg, 1 mg/kg and 3 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 PLP<sub>139-151</sub> peptide emulsified 1:1 with Complete Freund's adjuvant containing 4 mg/mL heat-killed *Mycobacterium tuberculosis*. Mice also receive 200 ng pertussis toxin intravenously on the day of immunization.

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

**Drug treatment:** Mice are dosed orally, with vehicle or a test compound, once a day from day 3 until day 21. Dosing volume is 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.

**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 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 paws of each rat, for a total injected volume of 100 µL per rat and a total dose of 50 µg of MBP per rat.

**Clinical scoring:** Severity of disease symptoms is scored daily after body weighing and before drug dosing. Severity of disease symptoms is scored as follows (in increasing order of severity): 0 = normal; 1 = tail OR limb weakness; 2 = tail AND limb weakness; 3 = severe hind limb weakness or single limb paralysis; 4 = loss of tail tone and paralysis of 2 or more limbs; 5 = death.

**Drug treatment:** Rats are dosed orally, with vehicle or a test compound, 1 hour prior to MBP injection on day 0 and daily thereafter, after clinical scoring, for the duration of the study. Dosing volume is 5 mL/kg. The test compound is dosed at, e.g., 1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg. Reduction of the severity of disease symptoms by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in EAE.

5  
**Example 6: Effect of Compounds on Type I Diabetes.**

A compound of the invention can be shown to have therapeutic efficacy in type I diabetes using an animal model for type I diabetes, such as cyclophosphamide-induced type I diabetes in 10 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).

15  
**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.

20  
**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 25 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.

30  
**Example 7: Allograft Survival.**

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

35  
**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 (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.

**Skin allograft:** Balbc/J and C57BL/6 mice are used as donors and recipients, respectively, in a model of skin allograft transplantation. Donor Balbc/J mice are anesthetized, and 0.5 cm - diameter full thickness areas of abdominal skin are surgically removed. Skin grafts harvested from the Balbc/J mice are sutured onto the dorsum of anesthetized recipient C57BL/6 mice. Sutured allografts are covered with Vaseline gauze and Bolster dressing for 7 days. The allografted mice are divided into 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 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 µL) 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 CO<sub>2</sub> and colon is removed from anus to cecum. Excised colon is measured for entire length, length from anus to end of inflamed area and length of inflamed (affected) area. After measurements, colon is cleared of excrement by flushing with saline and then cut open to clear more thoroughly. Colon is then weighed and preserved in neutral buffered formalin (NBF; 10% formalin, pH 6.7-7.0). The colon tissue is embedded in paraffin and processed for hematoxylin and eosin (H & E)-stained sections. Severity of disease symptoms is scored histologically from the stained sections as follows: 0 = no evidence of inflammation; 1 = low level of leukocyte infiltration with infiltration seen in <10% of high-power fields AND no structural changes; 2 = moderate leukocyte infiltration with infiltration seen in 10% to 25% of high-power fields AND crypt elongation AND bowel wall thickening that does not extend beyond the mucosal layer AND no ulcerations; 3 = high level of leukocyte infiltration seen in 25% to 50% of high-power fields AND crypt elongation AND infiltration beyond the mucosal layer AND thickening of the bowel wall AND superficial ulcerations; 4 = marked degree of transmural leukocyte infiltration seen in >50% of high-power fields AND

elongated and distorted crypts AND bowel wall thickening AND extensive ulcerations.

Reduction of the severity of the disease symptoms by the test compound in comparison with vehicle is indicative of the test compound exhibiting therapeutic efficacy in colitis.

**B. Rat Model for Colitis.**

5 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.

10 **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 µL) 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.

20 **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.

25 **Clinical scoring:** Upon conclusion of the experiment, colons are extracted and measured. Rats are euthanized with CO<sub>2</sub> 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.

5      **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 10 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 15 transmitted 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 binned the data into 1 min averages using DataSciences ART software. Telemetry recording occurs over a 21-h period, starting at noon and continuing until 9:00 am the following day. A maximum of eight rats are 20 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 (PEG400) and the test 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 25 are divided into four treatment groups such that each group comprised 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 had received all treatments in a pseudo-random order, and each group comprised N = 8.

**Exemplary bradycardia assay:** The rats could be used to show that a compound of the 30 invention had no or substantially no activity for bradycardia. By way of illustration and not limitation, the rats are administered vehicle (PEG 400) and the test compound and heart rate is then measured over a 120 min period. Results of no reduction of heart or substantially no reduction of heart rate is indicative of the test compound exhibiting no or substantially no activity for bradycardia.

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**Example 10: Effect of Compounds on Arthritis.**

Female Lewis rats are used in this study. Acclimated animals are anesthetized with isoflurane and given the first collagen injection (day 0). On day 6, they 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 held its form when placed in water. Each animal receives 5 300 µL of the mixture each time, spread over 3 subcutaneous sites on the back.

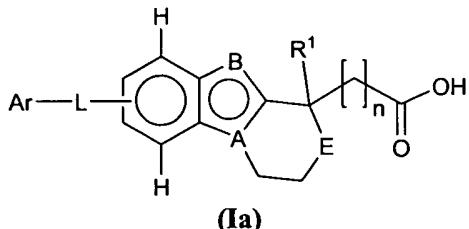
Treatment (*p.o.*, *q.d.*, 5 mL/kg dosing volume) begins on day 0 and continues through day 16 with vehicle or compounds given at 24 h intervals. Rats are weighed on days 0, 3, 6 and 9 through 17 and caliper measurements of the ankles taken on days 9 through 17. The test 10 compound is dosed at 0.3, 1 and 3 mg/kg. A reduction in mean ankle diameter in the treated animal compared to vehicle only treated animals is an indication that the test compound exhibits therapeutic efficacy in the collagen-induced arthritis assay.

Those skilled in the art will recognize that various modifications, additions, 15 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:

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NR<sup>3</sup> or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen;

R<sup>3</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkylamino, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group;

provided that when n is 0, A is C, B is NH, E is NH, and L is -CH<sub>2</sub>-O-, then Ar is substituted with 2 substituents.

- 25 2. The compound according to claim 1, wherein E is NH.
3. The compound according to claim 1, wherein E is NCH<sub>3</sub>.
4. The compound according to claim 1, wherein E is O.
- 30 5. The compound according to any one of claims 1 to 4, wherein n is 1.
6. The compound according to any one of claims 1 to 5, wherein A is C, and B is NH.

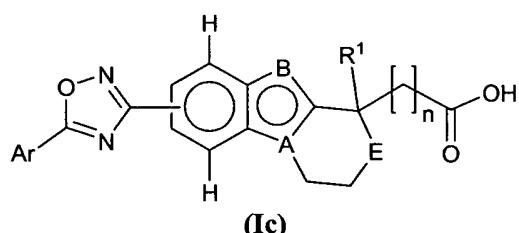
7. The compound according to any one of claims 1 to 5, wherein A is N, and B is CR<sup>2</sup>.
8. The compound according to claim 7, wherein R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl.
9. The compound according to any one of claims 1 to 8, wherein L is 1,2,4-oxadiazole-3,5-diyli.
10. The compound according to any one of claims 1 to 8, wherein L is -CH<sub>2</sub>-O-.
11. The compound according to any one of claims 1 to 10, wherein R<sup>1</sup> is H.
12. The compound according to any one of claims 1 to 11, wherein Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.
13. The compound according to any one of claims 1 to 11, wherein Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, isobutyl, chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, cyclopropylmethoxy, diethylamino, 1,3-difluoropropan-2-yloxy, fluoro, fluoromethoxy, isobutyl, isopropoxy, methoxy, methylsulfonyl, pyrrolidin-1-yl, trifluoromethoxy, and trifluoromethyl.
14. The compound according to any one of claims 1 to 11, wherein Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, isobutyl, chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, cyclopropylmethoxy, diethylamino, 1,3-difluoropropan-2-yloxy, fluoro, fluoromethoxy, isobutyl, isopropoxy, methylsulfonyl, trifluoromethoxy, and trifluoromethyl.
15. The compound according to any one of claims 1 to 11, wherein Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-

chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, 4-(diethylamino)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl, and 4-isobutyl-2-methoxyphenyl.

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



wherein:

15

*n* is 1;

A is N, and B is CH; or A is C, and B is NH;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

E is NH or O; and

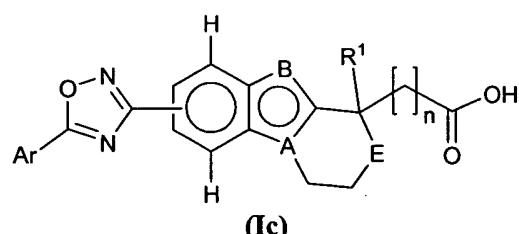
Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents

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independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>2</sub>-C<sub>8</sub> dialkylamino, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and halogen.

25

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



wherein:

*n* is 1;

A is N, and B is CH; or A is C, and B is NH;

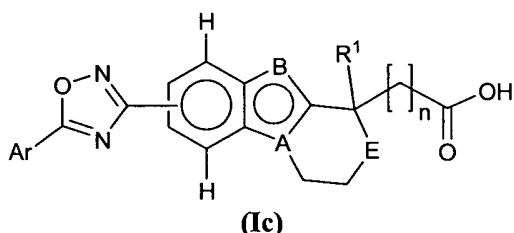
R<sup>1</sup> is H or methyl;

E is NH or O; and

Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents

5 independently selected from the group consisting of chloro, cyano, cyclohexyl, cyclopentyloxy, cyclopentyl, diethylamino, isopropoxy, methoxy, trifluoromethoxy, and trifluoromethyl.

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



10

wherein:

n is 1;

A is N, and B is CH; or A is C, and B is NH;

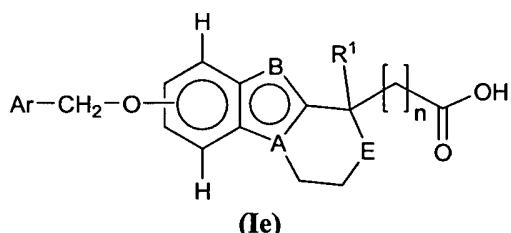
R<sup>1</sup> is H or methyl;

E is NH or O; and

15 Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 3-cyano-4-cyclohexylphenylphenyl, 2-chloro-6-methoxypyridin-4-yl, 3-cyano-5-(cyclopentyloxy)phenyl, and 4-(diethylamino)phenyl.

20

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



wherein:

25

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NR<sup>3</sup> or O;

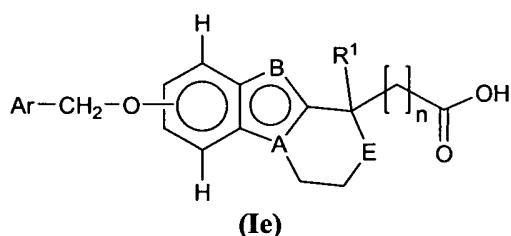
R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

$R^2$  is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and halogen;

$R^3$  is H or C<sub>1</sub>-C<sub>4</sub> alkyl; and

5 Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen, and heterocyclyl, wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

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



wherein:

n is 0 or 1;

15 A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NH, NCH<sub>3</sub>, or O;

R<sup>1</sup> is H or methyl;

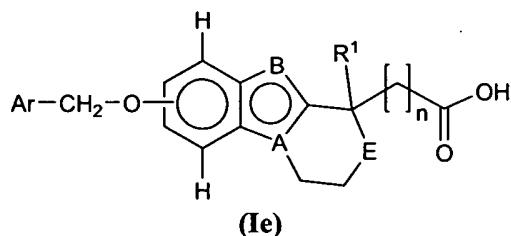
R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl;

and

- 20 Ar is phenyl or pyridinyl, each optionally substituted with 1 or 2 substituents independently selected from the group consisting of *tert*-butyl, isobutyl, chloro, cyano, cyclopentyl, cyclopropylmethoxy, 1,3-difluoropropan-2-yloxy, fluoro, fluoromethoxy, isobutyl, isopropoxy, methoxy, methylsulfonyl, pyrrolidin-1-yl, trifluoromethoxy, and trifluoromethyl.

25

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



wherein:

n is 0 or 1;

A is N, and B is CR<sup>2</sup>; or A is C, and B is NH;

E is NH or O;

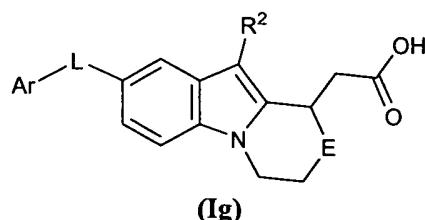
R<sup>1</sup> is H or methyl;

5 R<sup>2</sup> is selected from the group consisting of H, methyl, chloro, and cyclopropyl;

and

Ar is selected from the group consisting of 3-cyano-4-isopropoxyphenyl, 3-cyano-5-(trifluoromethoxy)phenyl, 4-cyclopentyl-3-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 4-isobutyl-3-(trifluoromethyl)phenyl, 6-methoxy-5-(trifluoromethyl)pyridin-3-yl, 3-chloro-4-(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethyl)phenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-*tert*-butylphenyl, 4-(methylsulfonyl)phenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl, 3-(trifluoromethoxy)phenyl, phenyl, 4-isopropoxy-3-(trifluoromethyl)phenyl, 4-(fluoromethoxy)-3-(trifluoromethyl)phenyl, 3-chloro-4-(1,3-difluoropropan-2-yloxy)phenyl, 4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl, and 4-isobutyl-2-methoxyphenyl.

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



wherein:

E is NH, NCH<sub>3</sub>, or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

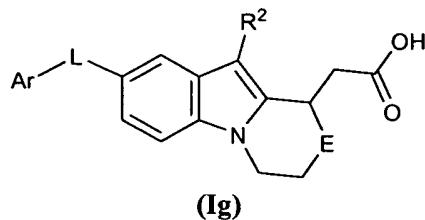
R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, and

halogen; and

25 Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and halogen, wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with one C<sub>3</sub>-C<sub>7</sub> cycloalkyl group.

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



wherein:

E is NH, NCH<sub>3</sub>, or O;

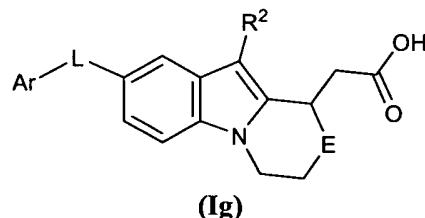
L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro;

and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, cyano, cyclopentyl, cyclopropylmethoxy, 1,3-difluoropropan-2-yloxy, fluoromethoxy, isobutyl, isopropoxy, trifluoromethoxy, and trifluoromethyl.

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



wherein:

E is NH or O;

L is 1,2,4-oxadiazole-3,5-diyl or -CH<sub>2</sub>-O-;

R<sup>2</sup> is selected from the group consisting of H, methyl, cyclopropyl, and chloro;

and

Ar is phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of chloro, cyano, cyclopentyl, cyclopropylmethoxy, 1,3-difluoropropan-2-yloxy, fluoromethoxy, isobutyl, isopropoxy, trifluoromethoxy, and trifluoromethyl.

25. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

2-(6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;

2-(6-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-

pyrido[3,4-b]indol-1-yl)acetic acid;

- 6-(3-cyano-4-isopropoxybenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-1-carboxylic acid;
- 2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 5 2-(6-(4-chloro-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid;
- 10 2-(6-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-((6-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 15 2-(6-(3-chloro-4-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(2,4-bis(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(4-fluoro-2-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 20 2-(6-(4-*tert*-butylbenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(4-(methylsulfonyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(4-(trifluoromethyl)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 25 2-(6-(3,4-dichlorobenzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-((6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methoxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 30 2-(6-(3-(trifluoromethoxy)benzyloxy)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid;
- 2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;
- 35 2-(6-(5-(3-cyano-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;

2-(6-(5-(3-cyano-4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-  
1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;

2-(6-(5-(2-chloro-6-methoxypyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-  
tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;

5        2-(6-(5-(3-cyano-5-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-  
tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)acetic acid;

2-(6-(5-(4-(diethylamino)phenyl)-1,2,4-oxadiazol-3-yl)-2,3,4,9-tetrahydro-1*H*-  
pyrido[3,4-b]indol-1-yl)acetic acid;

2-(6-(5-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1-methyl-  
10      1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetic acid;

2-(8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(8-(benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;

2-(8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-  
15      [1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;

20      2-(8-(4-isobutyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;

2-(10-chloro-8-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(10-chloro-8-(3-cyano-4-isopropoxybenzyloxy)-3,4-dihydro-1*H*-  
25      [1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;

2-(8-(3-cyano-4-isopropoxybenzyloxy)-10-cyclopropyl-1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;

30      2-(8-(4-(fluoromethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(8-(3-chloro-4-(1,3-difluoropropan-2-yloxy)benzyloxy)-3,4-dihydro-1*H*-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

35      2-(10-chloro-8-(4-(cyclopropylmethoxy)-3-(trifluoromethyl)benzyloxy)-3,4-dihydro-1*H*-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

2-(8-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3,4-dihydro-1*H*-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;

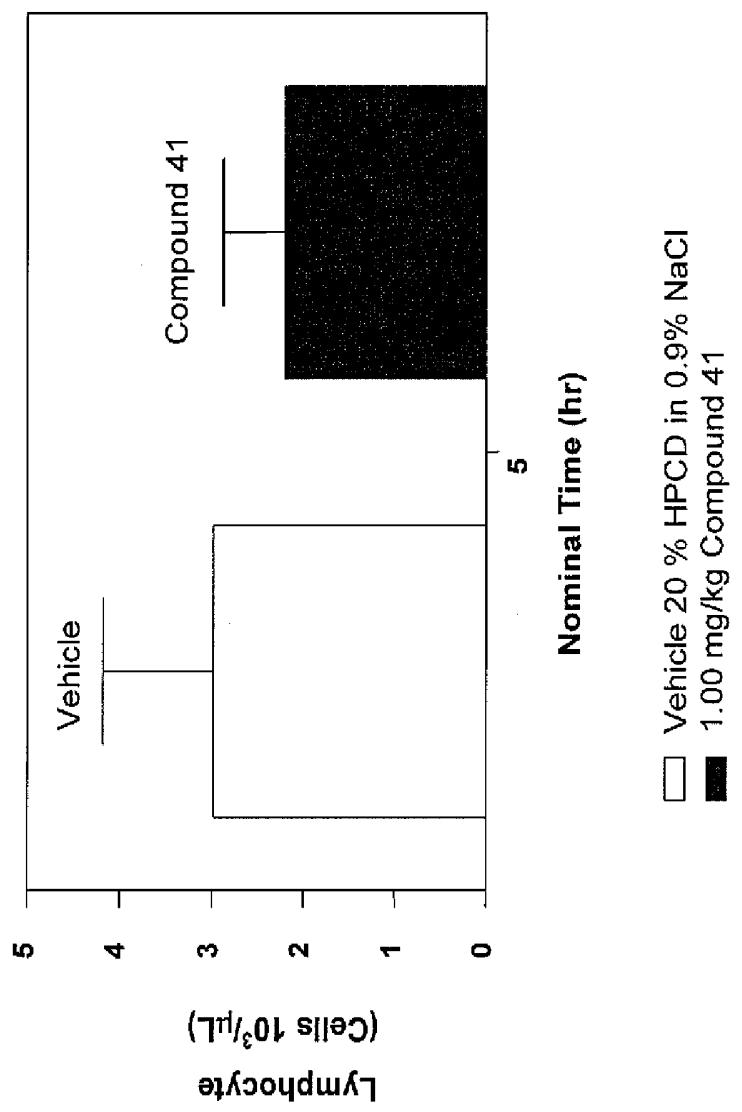
2-(8-(5-(4-cyclopentyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-  
1,2,3,4-tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;  
5           2-(8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-3,4-dihydro-1H-  
[1,4]oxazino[4,3-a]indol-1-yl)acetic acid;  
             2-(10-chloro-8-(3-cyano-5-(trifluoromethoxy)benzyloxy)-2-methyl-1,2,3,4-  
tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid;  
             2-(10-chloro-8-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-  
tetrahydropyrazino[1,2-a]indol-1-yl)acetic acid; and  
10           2-(6-(4-isobutyl-2-methoxybenzyloxy)-2,3,4,9-tetrahydro-1H-pyrido[3,4-  
b]indol-1-yl)acetic acid.

26. The compound according to any one of claims 1 to 25, wherein the stereochemistry of  
the C(1) ring carbon of said compound is *R*.
- 15 27. The compound according to any one of claims 1 to 25, wherein the stereochemistry of  
the C(1) ring carbon of said compound is *S*.
28. A pharmaceutical composition comprising a compound according to any one of claims  
1 to 27 and a pharmaceutically acceptable carrier.
- 20 29. 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 27, or a pharmaceutical composition  
according to claim 28.
- 25 30. 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 27, or a pharmaceutical composition according to claim 28,  
wherein said disorder is selected from the group consisting of psoriasis, rheumatoid  
30 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 31. 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 27, or a pharmaceutical composition according to claim 28.

32. 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 27, or a pharmaceutical composition according to  
5 claim 28.
33. Use of a compound according to any one of claims 1 to 27 in the manufacture of a medicament for the treatment of an S1P1 receptor-associated disorder.
- 10 34. Use of a compound according to any one of claims 1 to 27 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, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.  
15
35. Use of a compound according to any one of claims 1 to 27 in the manufacture of a medicament for the treatment of psoriasis.  
20
36. Use of a compound according to any one of claims 1 to 27 in the manufacture of a medicament for the treatment of multiple sclerosis.
- 25 37. A compound according to any one of claims 1 to 27 for use in a method for the treatment of the human or animal body by therapy.
38. A compound according to any one of claims 1 to 27 for use in a method for the treatment of an S1P1 receptor-associated disorder.
- 30 39. A compound according to any one of claims 1 to 27 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,  
35 polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

40. A compound according to any one of claims 1 to 27 for use in a method for the treatment of psoriasis.
41. A compound according to any one of claims 1 to 27 for use in a method for the treatment of multiple sclerosis.
42. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 27 and a pharmaceutically acceptable carrier.

**Mouse Blood Lymphocyte Levels after an Intravenous Dose of Compound 41  
or Vehicle at 5 Hours Post-Dose**



**FIGURE 1**

Mouse Blood Lymphocyte Levels after an Intravenous Dose of Compound 25  
or Vehicle at 5 Hours Post-Dose

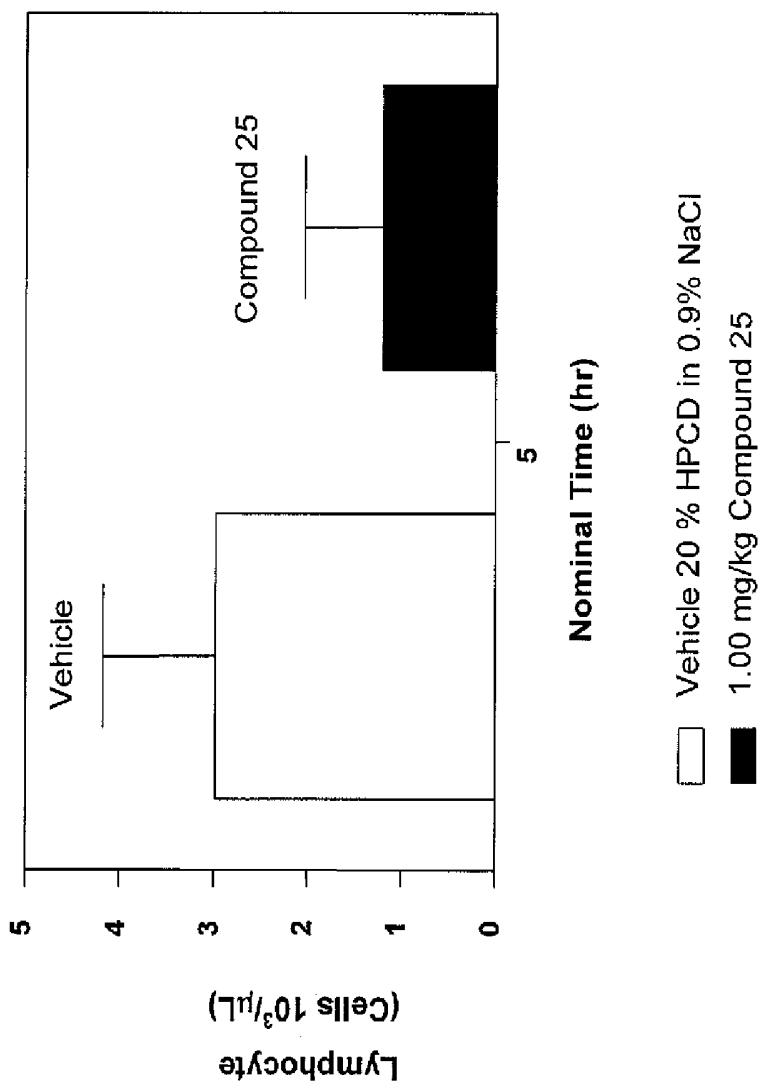


FIGURE 2

Mouse Blood Lymphocyte Levels after an intravenous Dose of Compound 31  
or Vehicle at 5 Hours Post-Dose

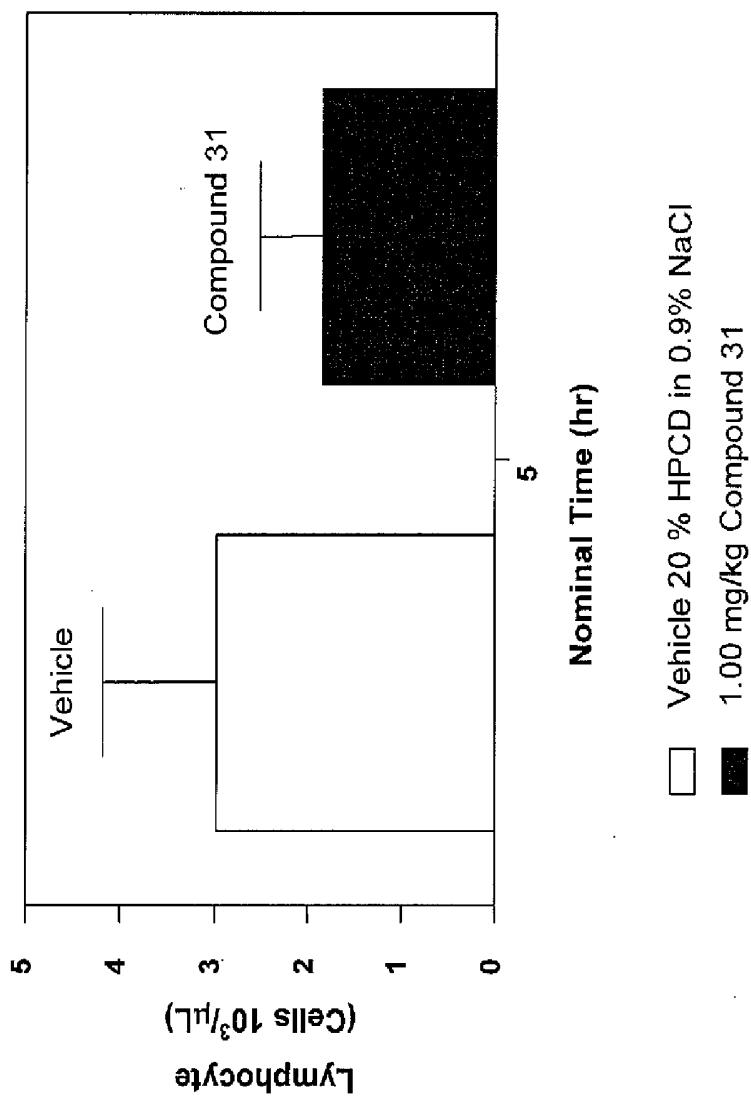


FIGURE 3

Rat Blood Lymphocyte Levels after an Intravenous Dose of the 1<sup>st</sup> Enantiomer of Compound 4 or Vehicle at 5 Hours Post-Dose

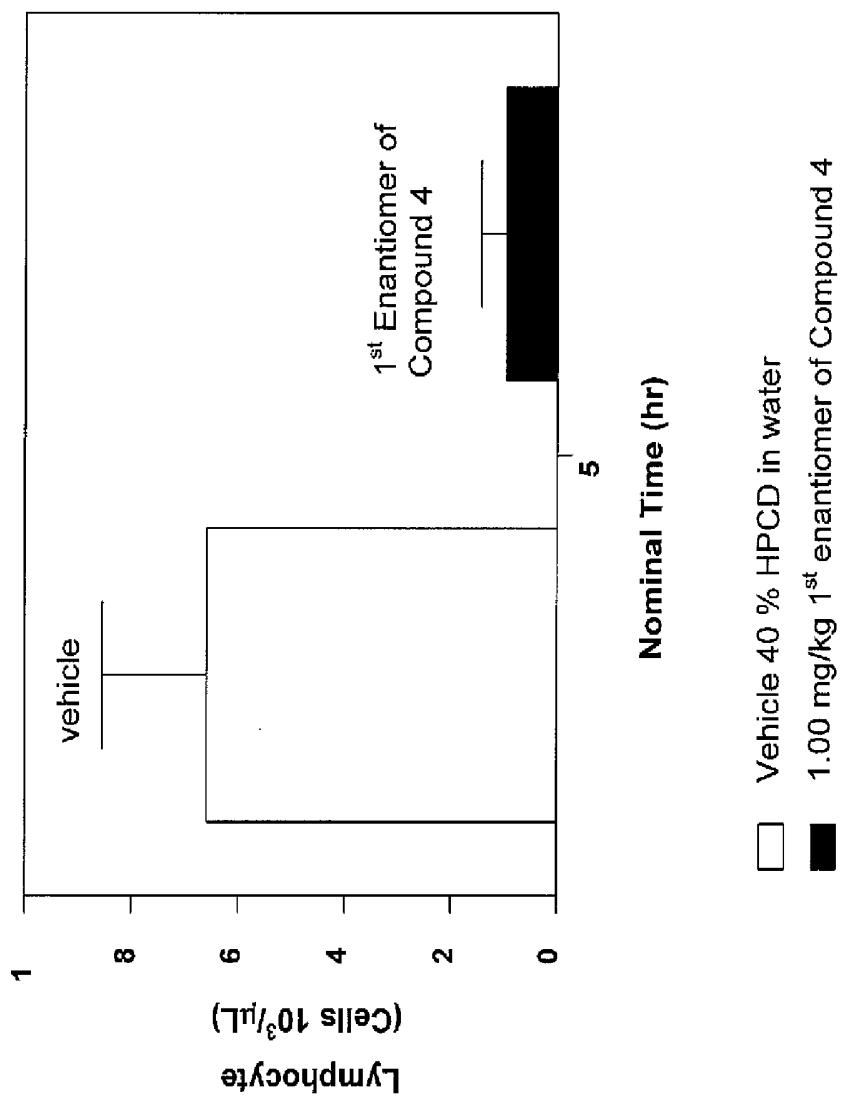


FIGURE 4

Rat Blood Lymphocyte Levels after an Intravenous Dose of the 2<sup>nd</sup> Enantiomer of Compound 4 or Vehicle at 5 Hours Post-Dose

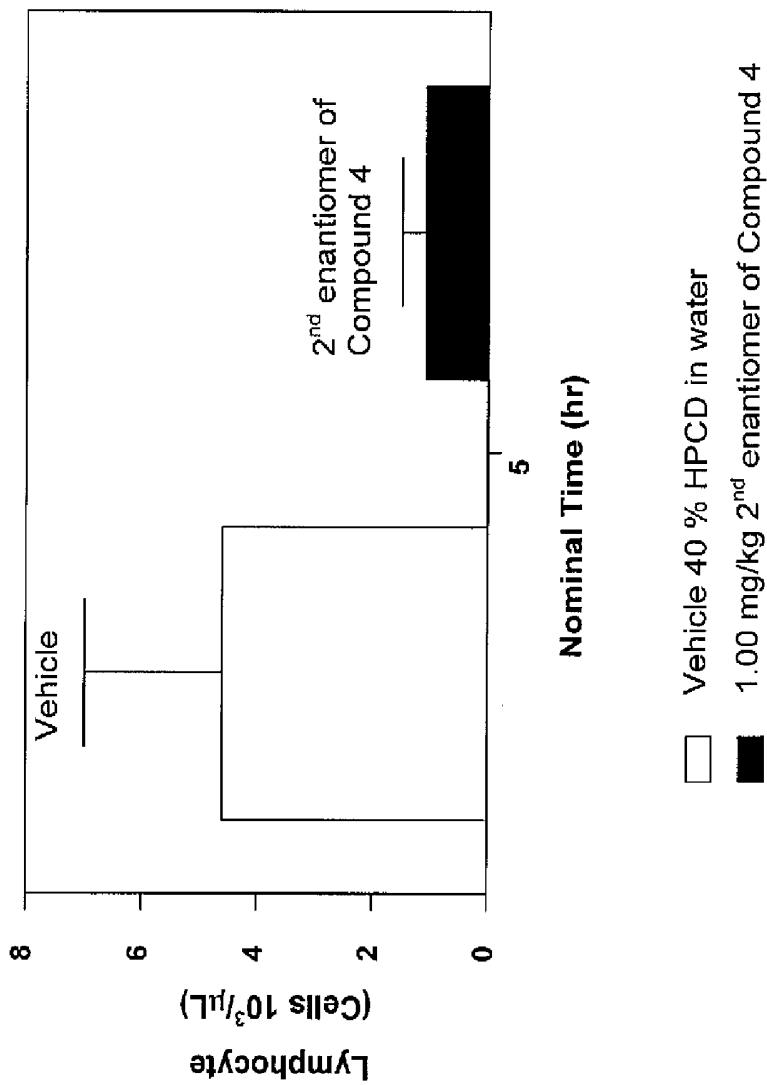


FIGURE 5

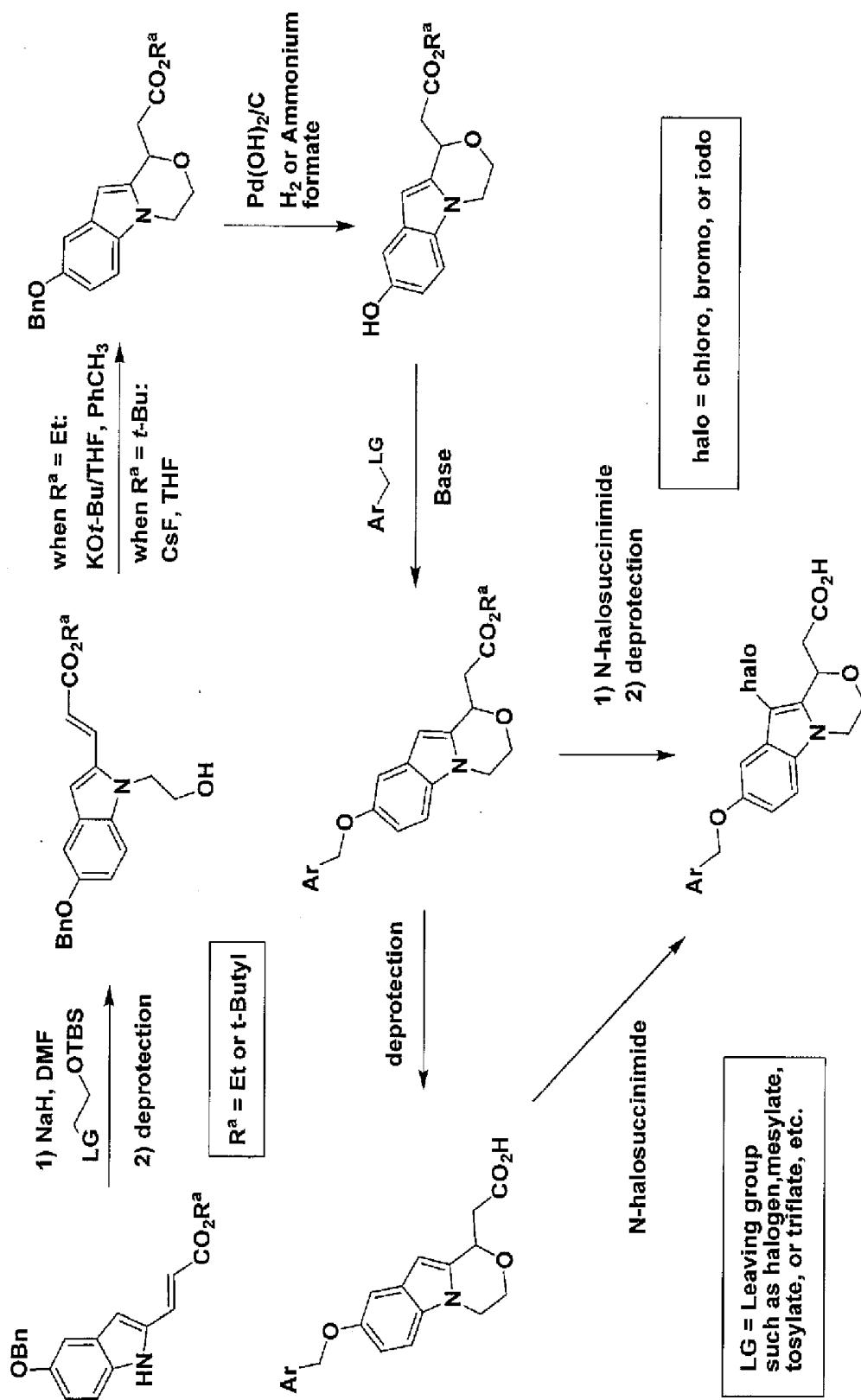


FIGURE 6

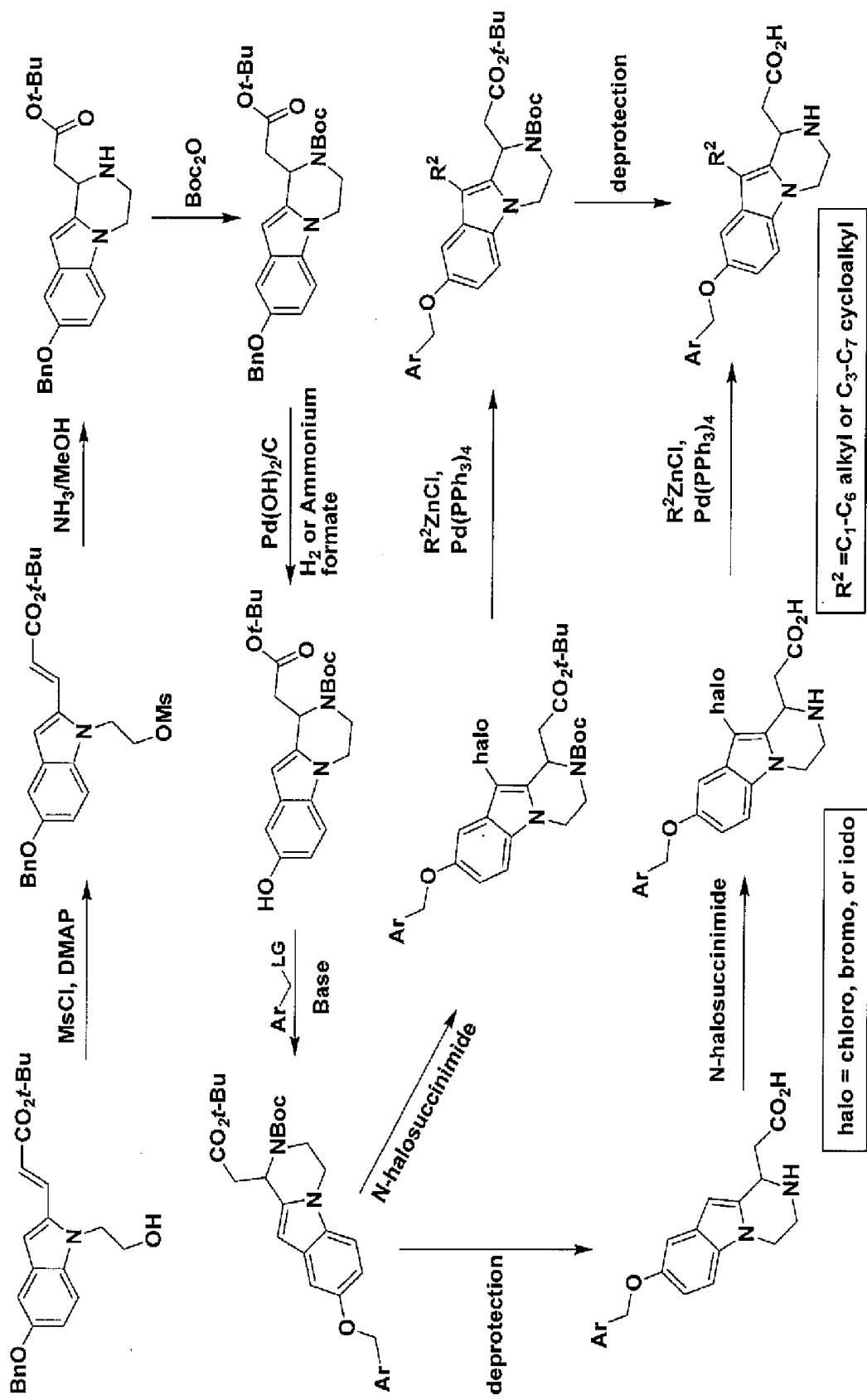


FIGURE 7

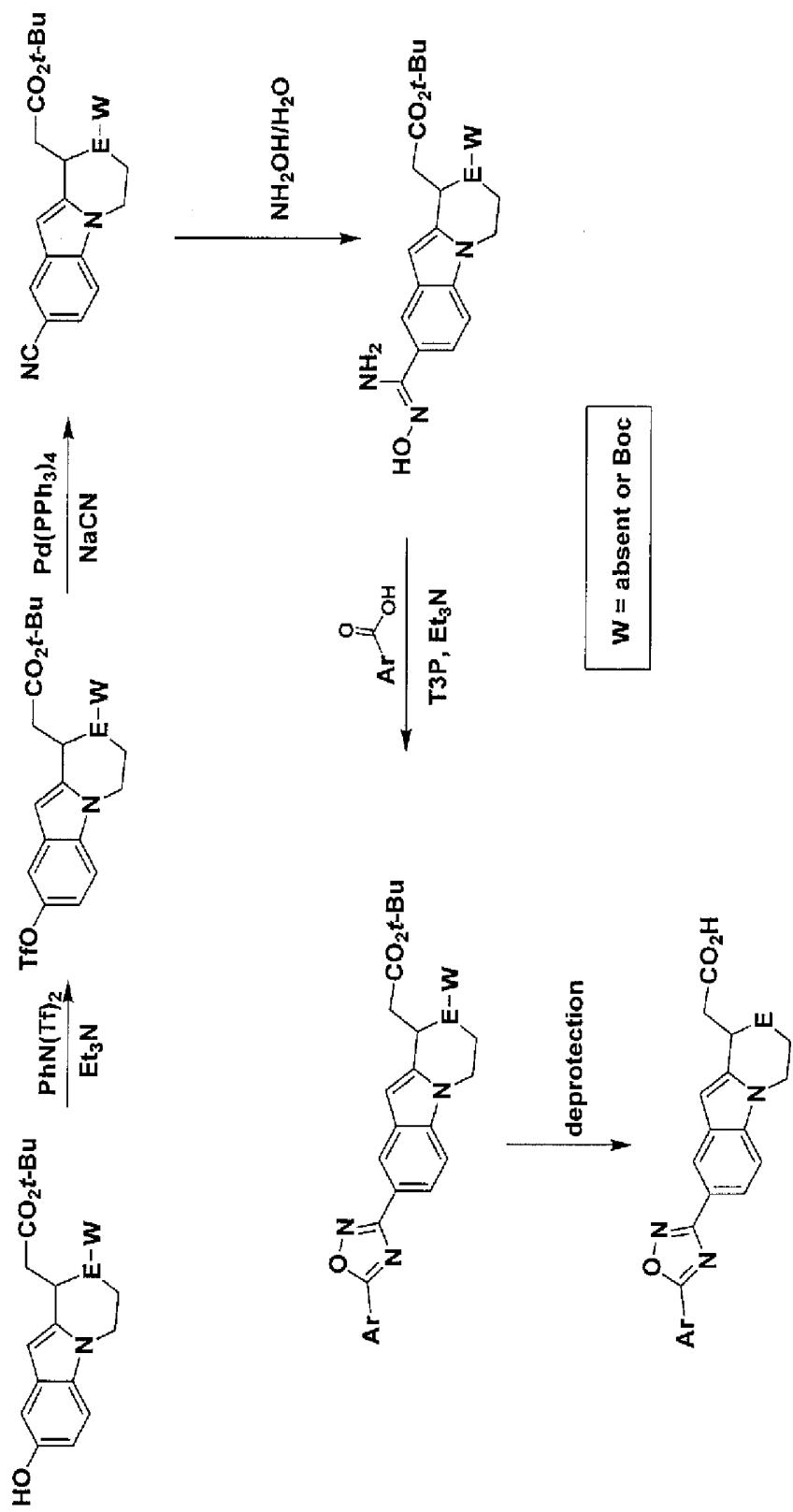


FIGURE 8

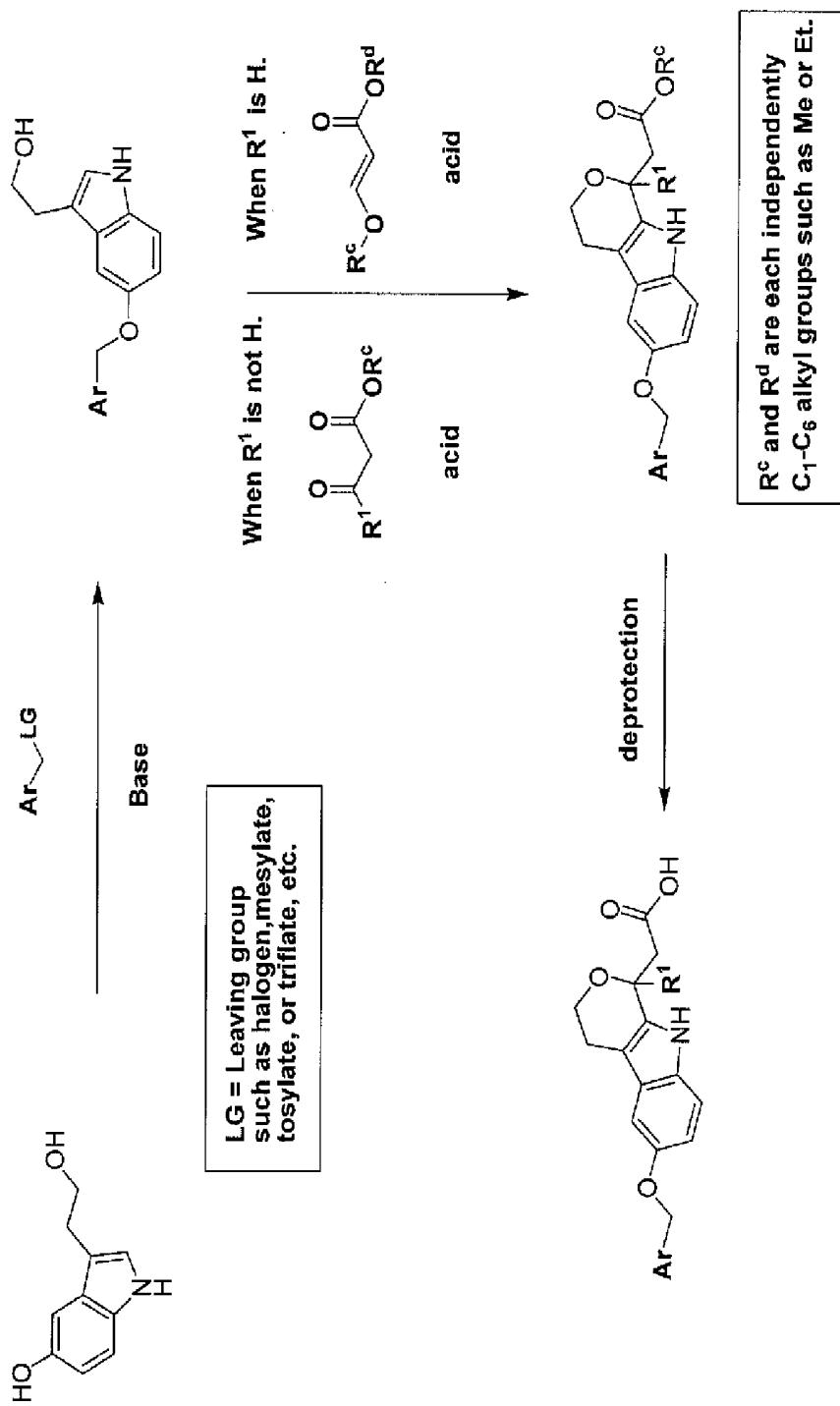


FIGURE 9

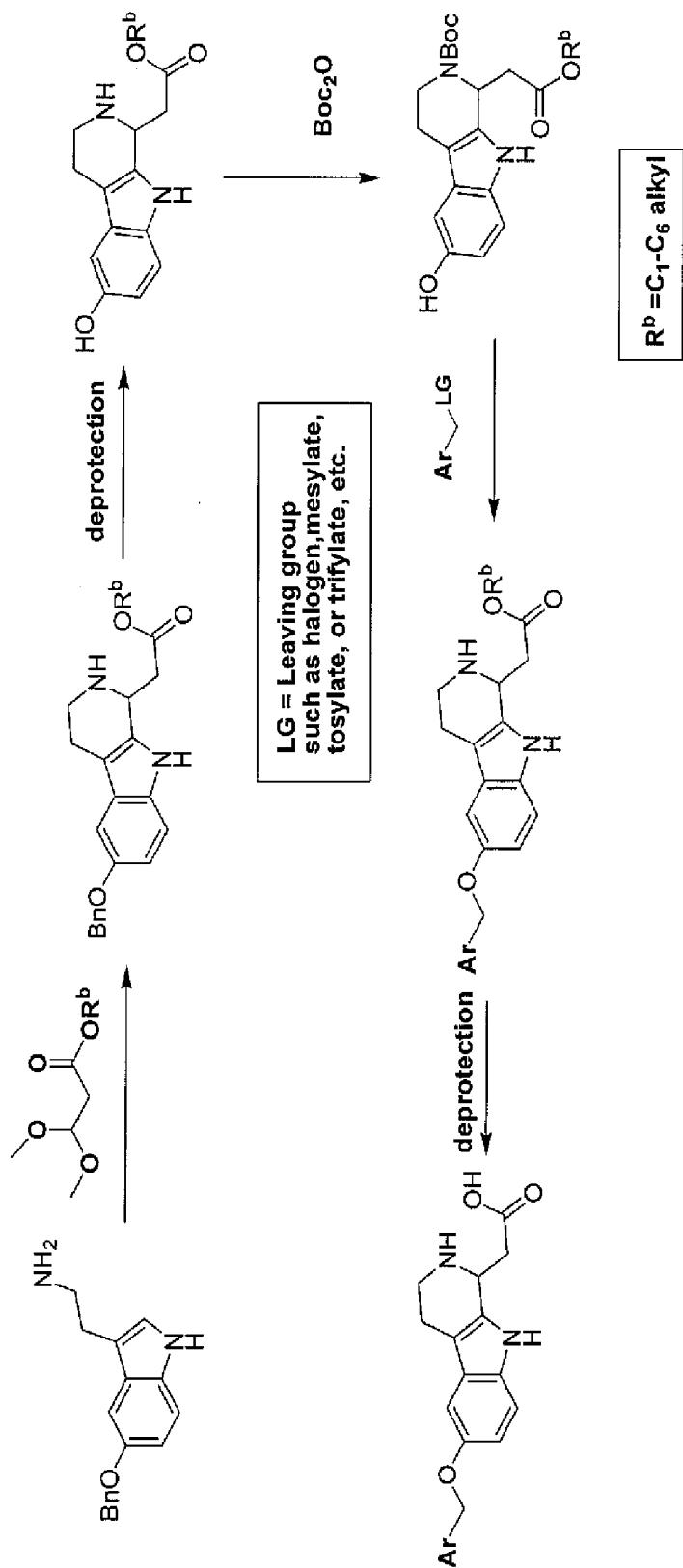
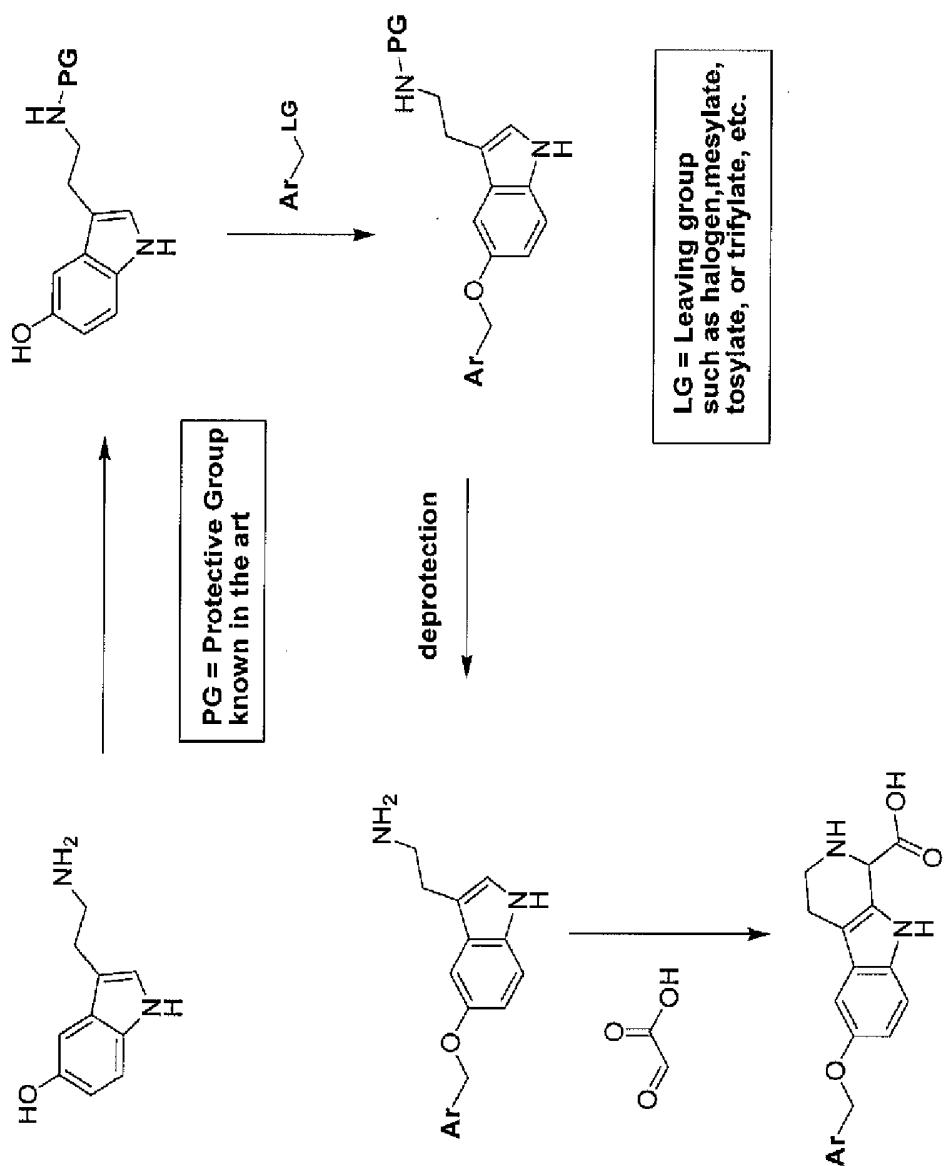


FIGURE 10

**FIGURE 11**

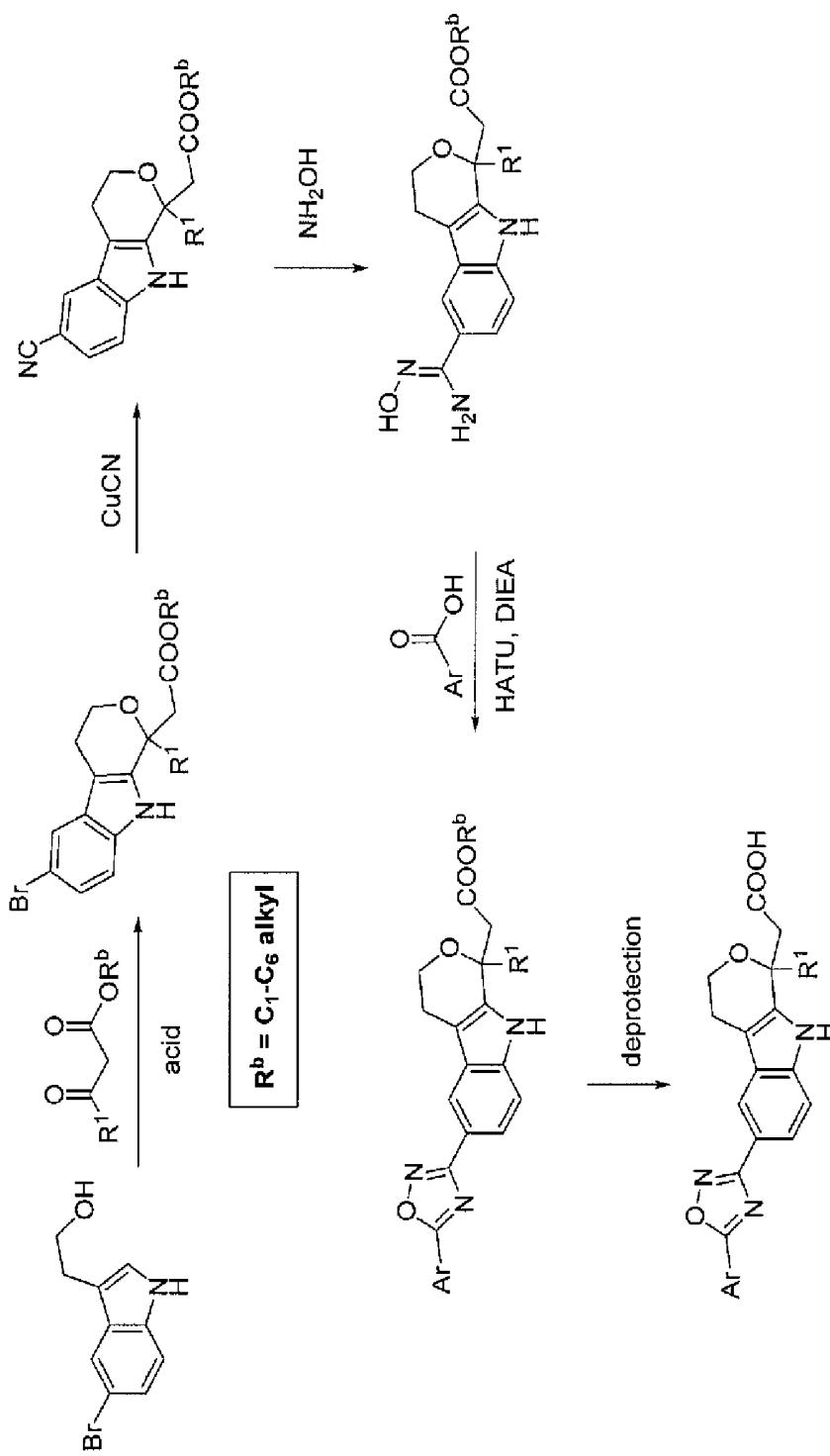


FIGURE 12

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2010/001803

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>
INV. C07D471/04 C07D487/04 C07D491/04 C07D498/04 A61K31/407
A61K31/437 A61P29/00 A61P31/12 A61P37/00

**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.
Y, P	WO 2010/027431 A1 (ARENA PHARM INC [US]; JONES ROBERT M [US]; BUZARD DANIEL J [US]; KAWAS) 11 March 2010 (2010-03-11) claim 1 -----	1-42
Y	EP 1 826 197 A1 (ONO PHARMACEUTICAL CO [JP]) 29 August 2007 (2007-08-29) claims 1,6; example 14 -----	1-42
Y	WO 2008/074821 A1 (GLAXO GROUP LTD [GB]; AHMED MAHMOOD [SG]; MYATT JAMES [GB]; NORTON DAV) 26 June 2008 (2008-06-26) claim 1 -----	1-42



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

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- \*P\* document published prior to the international filing date but later than the priority date claimed

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

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

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\*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2010	29/10/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Bareyt, Sébastien

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/001803

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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EP 1826197	A1	29-08-2007	AU 2005314938 A1 BR PI0519012 A2 CA 2591399 A1 WO 2006064757 A1 JP 4318087 B2 JP 2009137969 A KR 20070091013 A US 2009275554 A1		22-06-2006 23-12-2008 22-06-2006 22-06-2006 19-08-2009 25-06-2009 06-09-2007 05-11-2009
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