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(54) Title: METHODS FOR TREATING SPINAL CORD INJURY WITH LPA RECEPTOR ANTAGONISTS

(57) Abstract: The invention is directed to methods for treating spinal cord injury and other neurological conditions by administering an LPA1 receptor antagonist or an autotaxin inhibiting compound.

METHODS FOR TREATING SPINAL CORD INJURY WITH LPA RECEPTOR ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application Serial No. 61/558,230, filed November 10, 2011, the entire disclosure of said application being incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates to methods for treating central nervous system injury, such as spinal cord injury, brain injury or stroke with LPA receptor antagonists. Additionally, the present invention is directed to methods for ameliorating or inflammation and/or demyelination in a neural condition, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or neuropathic pain by administering LPA receptor antagonists.

BACKGROUND OF THE INVENTION

[0003] Injury to the spinal cord (SCI) results in immediate (primary) damage followed by a secondary phase of tissue damage that occurs over a period of several weeks. The mechanisms of the secondary injury are multiple and not fully defined. However, a large number of studies suggest that the inflammatory response occurring after SCI is one of the main contributors to secondary damage.

[0004] Endogenous glial cells (microglia and astrocytes) and macrophages play a key role during the course of the inflammatory response after SCI. Although these cells are needed for efficient clearance of cellular and myelin debris and tissue healing, they also release several factors such as cytokines, free radicals, proteases, as well as eicosanoids that cause damage to neurons, glia, axons and myelin. In addition, these toxic mediators can further activate glial cells and macrophages, thus increasing secondary damage.

[0005] Apart from secondary injury, reactive glia and macrophages contribute to the failure of axon regeneration in the CNS. Reactive astrocytes, for instance, synthesize proteoglycans which have potent effects in inhibiting axonal outgrowth in the CNS. Microglia and macrophages also contribute to inhibit axonal outgrowth. A recent study

from Jerry Silver's lab showed that activated microglia/macrophages trigger retraction of growing axons by cell-cell interaction.

[0006] Importantly, inflammation also contributes to the development of neuropathic pain after SCI. This is of special interest, since pain severely compromises the quality of life in nearly 70% of the SCI patients. Therefore, reactive glia and macrophages not only contribute to functional loss after SCI by inducing secondary damage and axon repulsion, but also trigger the development of neuropathic pain. These lines of evidence suggest that targeting inflammation could be a useful approach to reduce tissue loss, axon repulsion, functional impairments and neuropathic pain after SCI.

[0007] Chemokines, cytokines and some lipids mediators, such as prostaglandins, are mainly involved in triggering the recruitment and activation of glial cells and leukocytes into the injured SCI. Although the chemokines, cytokines, and immune cells involved in neuroinflammation have been well characterized in the context of injury, little is known regarding the molecules that trigger the induction of these mediators. This is important since blocking the molecules or receptors that regulate the expression of these inflammatory triggers could be a more effective approach to alleviate inflammation after SCI, and other injuries and diseases in the CNS, than blocking one of these molecules alone, such as COX-2, iNOS, cell adhesion molecules, integrins or cytokines.

[0008] Lysophosphatidic acid (LPA) is implicated in certain human diseases such as atherosclerosis, cancer and pulmonary fibrosis, and also in triggering neuropathic pain after nerve injury. Recent evidence suggests that LPA is involved in the development of immune responses, and modulating immune cell activities and functions. For instance, LPA is able to induce the expression of certain cytokines and chemokines, such as IL-1, IL-6, IL-8 and MCP-1, and increase COX-2 and prostaglandin levels. Moreover, LPA is a potent chemoattractive molecule and promotes the migration and recruitment of several cell types, such as macrophages and induces proliferation of several cell types, including immune cells. Therefore, the presence of LPA, which may promote the synthesis and release of several biologically active molecules, such as cytokines/chemokines and arachidonic acid metabolites, among others, may contribute to initiation and progression of the inflammatory response, and thus contribute to secondary injury after SCI.

[0009] It has been shown that LPA treatment induces neurite retraction. Recent *in vitro* studies have shown that LPA activates microglia and astrocytes, and induces

neuronal cell death. *In vivo* studies have also shown that LPA is involved in the condition of neuropathic pain. Injury to the sciatic nerve causes allodynia and hyperalgesia. Intrathecal injection of LPA mimics nerve injury and produces thermal hyperalgesia and mechanical allodynia. Furthermore, both LPA and nerve injury cause a transient demyelination of the dorsal root. Mice lacking LPA1 receptor do not show nerve injury-induced hyperalgesia and allodynia or demyelination of the dorsal root, indicating this receptor may be involved in the pain response and demyelination that occurs as a consequence of nerve injury.

[0010] These prior *in vitro* and *in vivo* studies suggest that an increase in LPA levels after SCI could have a potential role in initiating the inflammatory response, but may also contribute to axonal retraction, demyelination and neuronal cell death after SCI, which leads to functional loss and neuropathic pain. Despite the potential role for LPA in triggering these detrimental responses after injury, no studies have so far addressed the role of LPA in SCI, or in other disorders of the CNS. There is therefore a need to know if LPA is involved in secondary injury, functional impairments and neuropathic pain, and if so, to find new therapies for treating spinal cord injury and other central nervous system disorders where inflammation or demyelination contributes to the course of pathology. For example, new therapies are needed for treating multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and neuropathic pain.

SUMMARY

[0011] The present invention is directed to methods for treating central nervous system injury, especially spinal cord injury (SCI), brain trauma, and stroke, by administering to a patient in need of such treatment an effective amount of an LPA receptor antagonist. Preferably, the LPA receptor antagonist is an LPA1, LPA2 or LPA3 receptor antagonist, or a dual or triple LPA1/2/3 antagonist. In one preferred embodiment, the LPA receptor antagonist is an LPA1 receptor antagonist. Additionally, the present invention is directed to methods for ameliorating the inflammation and/or demyelination that occurs in diseases of the central nervous system, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and neuropathic pain.

DETAILED DESCRIPTION

Definitions

[0012] The terms "effective amount" or "therapeutically effective amount" as used herein, refer to a sufficient amount of at least one agent being administered which achieve a desired result, *e.g.*, to relieve to some extent one or more symptoms of a disease or condition being treated. In certain instances, the result is a reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In certain instances, an "effective amount" for therapeutic uses is the amount of the ***composition*** comprising an agent as set forth herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

[0013] The terms "administer", "administering", "administration", and the like, as used herein, refer to the methods that are used to enable delivery of agents or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Administration techniques that are optionally employed with the agents and methods described herein, include *e.g.*, as discussed in Goodman et al., *The Pharmacological Basis of Therapeutics* (Current Edition), Pergamon; and *Remington's, Pharmaceutical Sciences* (Current Edition), Mack Publishing Co., Easton, Pa. In certain embodiments, the agents and compositions described herein are administered orally.

[0014] The term "pharmaceutically acceptable" as used herein, refers to a material that does not abrogate the biological activity or properties of the agents described herein, and is relatively nontoxic (*i.e.*, the toxicity of the material significantly outweighs the benefit of the material). In some instances, a pharmaceutically acceptable material is administered to an individual without causing significant undesirable biological effects or significantly interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0015] The terms "treat", "treating" or "treatment", and other grammatical equivalents as used herein, include alleviating, inhibiting or reducing symptoms, reducing or inhibiting severity of, reducing incidence of, prophylactic treatment of reducing or inhibiting recurrence of, preventing, delaying onset of, delaying recurrence of, abating or

ameliorating a disease or condition symptoms, ameliorating the underlying metabolic causes of symptoms, inhibiting the disease or condition, *e.g.*, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition. The terms further include achieving a therapeutic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated, and/or the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the individual.

[0016] The term "neural condition" as used herein, refers to multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or neuropathic pain.

[0017] The present invention is directed to methods for treating central nervous system injury, especially spinal cord injury (SCI), brain trauma, and stroke, by administering to a patient in need of such treatment a therapeutically effective amount of an LPA receptor antagonist.

[0018] Additionally, the present invention is directed to methods for ameliorating the inflammation and/or demyelination that occurs in diseases of the central nervous system, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and neuropathic pain comprising administering to a patient in need of such treatment, a therapeutically effective amount of an LPA receptor antagonist.

[0019] The present invention is also directed to methods for treating central nervous system injury, especially spinal cord injury (SCI), brain trauma, and stroke, by administering to a patient in need of such treatment a therapeutically effective amount of an autotaxin inhibiting substance.

[0020] Additionally, the present invention is directed to methods for ameliorating the inflammation and/or demyelination that occurs in diseases of the central nervous system, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and neuropathic pain comprising administering to a patient in need of such treatment, a therapeutically effective amount of an autotaxin inhibiting substance.

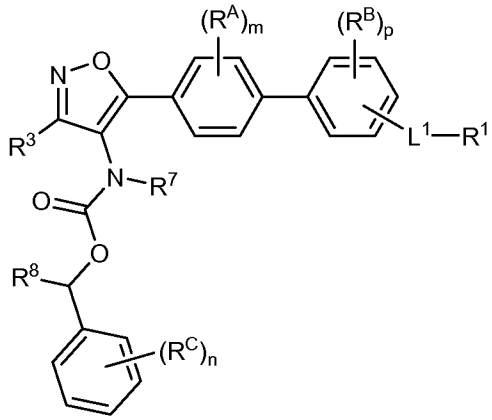
[0021] According to one embodiment of the present invention, the LPA receptor antagonist is selected from the group consisting of antisense nucleic acids, siRNAs and

antagonist antibodies against LPA, such as those disclosed in soluble LPA1 and small molecule inhibitors that bind to LPA to inhibit signaling.

[0022] Antibodies binding LPA include those disclosed by Fleming et al., *J. Mol. Biol.*, 408:462-476 (2011).

[0023] Preferred LPA receptor antagonists of the present invention include those disclosed in US 2006/194850, US 2003/114505, US 2006/194850, U.S. Patent No. 6,964,945, US 2005/0256160, US 2006/148830, US 2007/0149595, US 2008/0293764, US 2010/0249157, WO 2011/053948, US 2004/122236, WO 2009/135590, WO 2008/014286, WO 2010/077883, US 2010/50786, WO 2010/141768, WO 2011/041461, the disclosures of which are all incorporated herein by reference.

[0024] In one preferred embodiment of the present invention, LPA receptor antagonists have the following Formula (I):



Formula (I)

wherein

R^1 is $-CO_2H$, $-CO_2R^D$, -CN, tetrazolyl, $-C(=O)NH_2$, $-C(=O)NHR^{10}$, $-C(=O)NHSO_2R^{10}$ or $-C(=O)NHCH_2CH_2SO_3H$; R^D is H or C_1-C_4alkyl;

L^1 is absent or C_1-C_6alkylene;

R^3 is H, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_1-C_4fluoroalkyl;

R^7 is H or C_1-C_4alkyl;

R^8 is H, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

R^{10} is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, or a substituted or unsubstituted phenyl;

each of R^A, R^B, and R^C are independently selected from H, F, Cl, Br, I, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl;

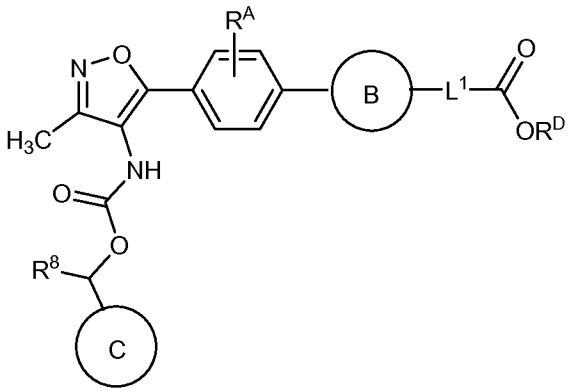
m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0, 1, or 2.

[0025] In some preferred embodiments, compounds of the present invention are selected from the following Tables:

Table 1



Formula Ia

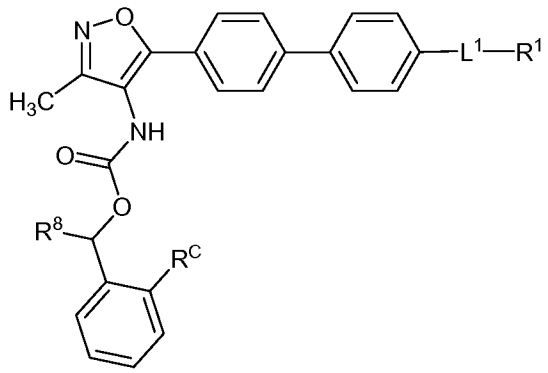
R^A	B	-L^1-	R^D	C	R^8	M+H*
H	Phen-1,4-ylene	-CH_2-	H	2-Trifluoromethyl-phenyl	CH_3	525
H	Phen-1,4-ylene	-CH_2-	H	3-Trifluoromethyl-phenyl	CH_3	525
H	Phen-1,4-ylene	-CH_2-	H	2,4-Dichloro-phenyl	CH_3	525
H	Phen-1,4-ylene	-CH_2-	H	2-Fluoro-phenyl	CH_3	475
H	Phen-1,4-ylene	-CH_2-	H	3-Bromo-phenyl	CH_3	535
H	Phen-1,4-ylene	-CH_2-	H	2-Methoxy-phenyl	CH_3	487
H	2-Methoxyphen-1,5-ylene	-CH_2-	H	2-Chloro-phenyl	CH_3	521
H	Phen-1,4-ylene	-	H	2-Chloro-phenyl	CH_3	477

R^A	B	$-L^1-$	R^D	C	R^8	M+H*
H	Phen-1,2-ylene	-	H	2-Chloro-phenyl	CH_3	477
H	Phen-1,2-ylene	$-CH_2-$	H	2-Chloro-phenyl	CH_3	491
H	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	CH_3	491
H	Phen-1,3-ylene	$-CH_2-$	H	2-Chloro-phenyl	CH_3	491
H	Phen-1,4-ylene	$-CH_2CH_2-$	H	2-Chloro-phenyl	CH_3	505
H	2-Fluorophen-1,5-ylene	$-CH_2-$	H	2-Chloro-phenyl	CH_3	509
H	4-Fluorophen-1,5-ylene	$-CH_2-$	H	2-Chloro-phenyl	CH_3	509
H	Phen-1,4-ylene	$-CH_2-$	$-CH_3$	2-Chloro-phenyl	CH_3	505
H	Phen-1,4-ylene	$-CH(CH_3)-$	$-CH_2CH_3$	2-Chloro-phenyl	CH_3	533
H	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Chloro-phenyl	CH_3	505
H	Phen-1,4-ylene	$-C(CH_3)_2-$	H	2-Chloro-phenyl	CH_3	519
H	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Fluoro-phenyl	CH_3	489
H	Phen-1,4-ylene	$-CH_2CH_2CH_2-$	H	2-Chloro-phenyl	CH_3	519
H	Phen-1,3-ylene	-	H	2-Chloro-phenyl	CH_3	477
H	Phen-1,4-ylene	$-CH_2-$	H	2-Fluoro-4-chloro-phenyl	CH_3	509
H	Phen-1,4-ylene	$-CH_2-$	H	2-Fluoro-phenyl	(R)-CH_3	475
$-CH_3$	Phen-1,4-ylene	$-CH_2-$	H	2-Fluoro-phenyl	(R)-CH_3	489
H	Phen-1,4-ylene	$-C(CH_3)_2-$	H	2-Fluoro-phenyl	CH_3	503
H	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	(R)-CH_3	491
H	Phen-1,4-ylene	$-C(CH_3)_2-$	H	2-Chloro-phenyl	(R)-CH_3	519
H	Phen-1,4-ylene	$-C(CH_3)_2$	H	2-Fluoro-phenyl	(R)-CH_3	503
H	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Fluoro-phenyl	(R)-CH_3	489
H	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Chloro-phenyl	(R)-CH_3	505
H	Phen-1,4-ylene	$-CH_2-$	H	2,6-Dichloro-phenyl	CH_3	525
$-CH_3$	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Fluoro-phenyl	(R)-CH_3	503
H	Phen-1,4-ylene	$-CH_2-$	H	2-Fluoro-phenyl	(S)-CH_3	475
H	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	(S)-CH_3	491

R^A	B	$-L^1-$	R^D	C	R^8	M+H*
H	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	H	477
H	Phen-1,4-ylene	$-CH_2-$	H	Phenyl	(R)-CH_3	457
H	Phen-1,4-ylene	$-CH_2-$	H	2,3-Difluoro-phenyl	CH_3	493
H	Phen-1,4-ylene	$-CH_2-$	H	2,4-Difluoro-phenyl	CH_3	493
H	Phen-1,4-ylene	$-CH_2-$	H	2-Fluoro-4-methoxy-phenyl	CH_3	505
H	Phen-1,4-ylene	$-CH_2-$	H	2,5-Difluoro-phenyl	CH_3	493
H	Phen-1,4-ylene	$-CH_2-$	H	2,6-Difluoro-phenyl	CH_3	493
H	Phen-1,3-ylene	$-CH_2-$	H	Phenyl	(R)-CH_3	457
H	Phen-1,4-ylene	-	H	Phenyl	(R)-CH_3	443
H	Phen-1,2-ylene	$-CH_2-$	H	Phenyl	(R)-CH_3	457
H	Phen-1,4-ylene	$-CH_2-$	H	2-Methyl-phenyl	(R)-CH_3	471
H	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Chloro-phenyl	(R)-CH_3	505
H	Phen-1,4-ylene	$-CH(CH_3)-$	H	2-Chloro-phenyl	(R)-CH_3	505
H	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	(R)-CH_3	525
H	Phen-1,4-ylene	$-CH(CH_2CH_3)-$	H	2-Chloro-phenyl	(R)-CH_3	519
Cl	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	(R)-CH_3	526
F	Phen-1,4-ylene	$-CH_2-$	H	2-Chloro-phenyl	(R)-CH_3	509
H	Phen-1,4-ylene	-	H	2-Chloro-phenyl	(R)-CH_3	477
H	Phen-1,4-ylene	$-CH_2-$	H	3,5-Dibromo-phenyl	(R)-CH_3	615
H	Phen-1,4-ylene	$-CH_2-$	H	Phenyl	(S)-CH_3	457
H	Phen-1,4-ylene	$-CH_2-$	H	3-Hydroxy-phenyl	(R)-CH_3	473
H	Phen-1,4-ylene	$-CH_2-$	H	Phenyl	$-CH_3$	457
H	Phen-1,4-ylene	$-CH_2-$	H	Phenyl-d5	$-CD_3$	466

* mass spectrometric data

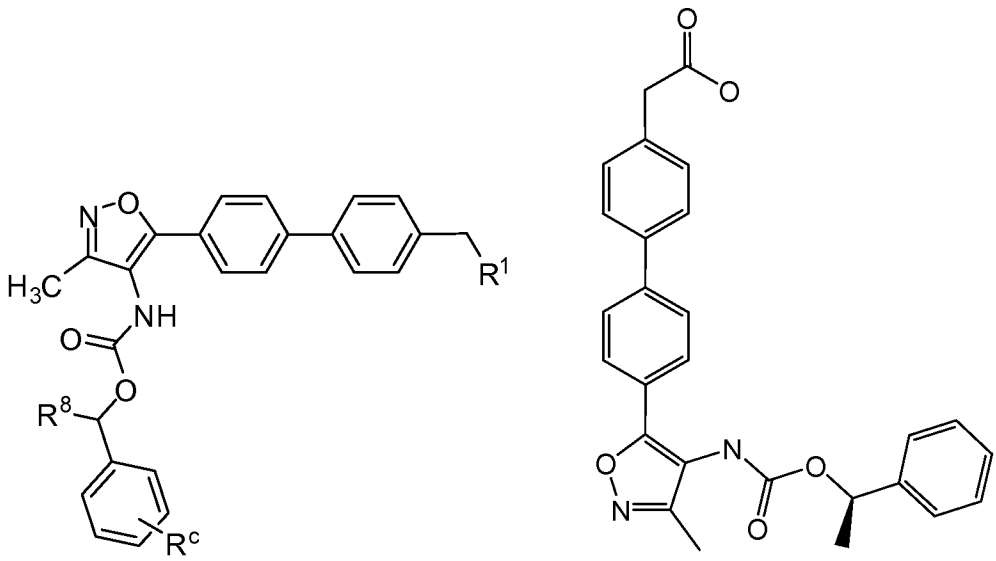
Table 2



L^1	R^1	R^C	R^8	M+H*
$-CH_2-$	-CN	Cl	(R)-CH_3	472
$-CH_2-$	-CN	F	(R)-CH_3	456
$-CH_2-$	2H-Tetrazol-5-yl	F	(R)-CH_3	499
$-CH_2-$	2H-Tetrazol-5-yl	Cl	(R)-CH_3	515
$-CH_2-$	$-C(=NH)-NH_2$	F	(R)-CH_3	473
$-CH_2-$	-C(=NH)-NH-Ac	F	(R)-CH_3	515
$-CH_2-$	$-C(=O)-NHCH_2CH_2\ SO_3H$	H	(R)-CH_3	564

* mass spectrometric data

Table 3



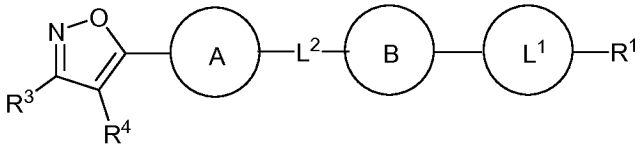
R^1	R^C	R^8

R^1	R^C	R^8
-C(=O)NHSO$_2$Me	H	(R)-CH$_3$
-C(=O)NHSO$_2$Me	H	H
-C(=O)NHSO$_2$Me	2-F	(R)-CH$_3$
-C(=O)NHSO$_2$Me	2-F	H
-C(=O)NHSO$_2$Me	2-Cl	(R)-CH$_3$
-C(=O)NHSO$_2$Me	2-Cl	H
-C(=O)NHSO$_2$Me	2-CH$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Me	2-CH$_3$	H
-C(=O)NHSO$_2$Me	2-CF$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Me	2-CF$_3$	H
-C(=O)NHSO$_2$Me	3-F	(R)-CH$_3$
-C(=O)NHSO$_2$Me	3-F	H
-C(=O)NHSO$_2$Me	3-Cl	(R)-CH$_3$
-C(=O)NHSO$_2$Me	3-Cl	H
-C(=O)NHSO$_2$Me	3-CH$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Me	3-CH$_3$	H
-C(=O)NHSO$_2$Me	3-CF$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Me	3-CF$_3$	H
-C(=O)NHSO$_2$Ph	H	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	H	H
-C(=O)NHSO$_2$Ph	2-F	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	2-F	H
-C(=O)NHSO$_2$Ph	2-Cl	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	2-Cl	H
-C(=O)NHSO$_2$Ph	2-CH$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	2-CH$_3$	H
-C(=O)NHSO$_2$Ph	2-CF$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	2-CF$_3$	H
-C(=O)NHSO$_2$Ph	3-F	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	3-F	H

R^1	R^C	R^8
-C(=O)NHSO$_2$Ph	3-Cl	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	3-Cl	H
-C(=O)NHSO$_2$Ph	3-CH$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	3-CH$_3$	H
-C(=O)NHSO$_2$Ph	3-CF$_3$	(R)-CH$_3$
-C(=O)NHSO$_2$Ph	3-CF$_3$	H

[0026] Methods for preparing the preceding compounds can be found in WO 2010/077883, the disclosure of which is incorporated by reference in its entirety.

[0027] In some embodiments of the present invention, LPA receptor antagonists have the following Formula II:



Formula (II)

wherein

R^1 is -CO$_2$H, -CO$_2R^D$, -C(=O)NHSO$_2R^{10}$, -C(=O)N(R^9)$_2$, -C(=O)NH-OH, -C(=O)NH-CN, -P(=O)(OH)$_2$, -P(=O)(OR^D)$_2$, -OPO$_3$H$_2$, -SO$_2$NHC(=O)R^{10}, -CN, -C(=NH)-NH$_2$, -C(=NH)-NHC(=O)R^D, -C(=O)NHCH$_2$CH$_2$SO$_3$H, tetrazolyl, 5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl, or carboxylic acid bioisostere; R^D is H or C$_1$-C$_6$alkyl;

L^1 is a substituted or unsubstituted cycloalkylene, a substituted or unsubstituted -alkylene-cycloalkylene, or a substituted or unsubstituted -cycloalkylene-alkylene-;

ring A is a substituted or unsubstituted cycloalkylene, a substituted or unsubstituted heterocycloalkylene, a substituted or unsubstituted arylene, or a substituted or unsubstituted heteroarylene, where if ring A is substituted then ring A is substituted with 1, 2, 3, or 4 R^A;

ring B is a substituted or unsubstituted cycloalkylene, a substituted or unsubstituted heterocycloalkylene, a substituted or unsubstituted arylene, or a substituted

or unsubstituted heteroarylene, where if ring B is substituted then ring B is substituted with 1, 2, 3, or 4 R^B;

L^2 is absent, a substituted or unsubstituted alkylene, a substituted or unsubstituted fluoroalkylene, a substituted or unsubstituted heteroalkylene, -O-, -S-, -SO-, $-SO_2$-, $-NR^2$-, or -C(=O)-;

R^2 is H, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

R^3 is H, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl or a substituted or unsubstituted phenyl;

R^4 is $-NR^7C(=O)OC(R^8)(R^{8a})$-CY, or $-NR^7C(=O)O$-CY;

R^7 is H or C_1-C_4alkyl;

R^8 is H, C_1-C_4alkyl, C_3-C_7cycloalkyl or C_1-C_4fluoroalkyl;

R^{8a} is H or C_1-C_4alkyl;

CY is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, or a substituted or unsubstituted heteroaryl, wherein if CY is substituted then CY is substituted with 1, 2, 3, or 4 R^C; or

R^8 and CY are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle;

each of R^A, R^B, and R^C are independently selected from halogen, -CN, $-NO_2$, -OH, $-OR^{10}$, $-SR^{10}$, $-S(=O)R^{10}$, $-S(=O)_2R^{10}$, $-N(R^9)S(=O)_2R^{10}$, $-S(=O)_2N(R^9)_2$, $-C(=O)R^{10}$, $-OC(=O)R^{10}$, $-CO_2R^9$, $-OCO_2R^{10}$, $-N(R^9)_2$, $-C(=O)N(R^9)_2$, $-OC(=O)N(R^9)_2$, $-NR^9C(=O)N(R^9)_2$, $-NR^9C(=O)R^{10}$, $-NR^9C(=O)OR^{10}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl;

each R^9 is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkylene-C_3-C_{10}cycloalkyl, a substituted or unsubstituted -C_1-C_4alkylene-C_2-C_{10}heterocycloalkyl, a substituted or

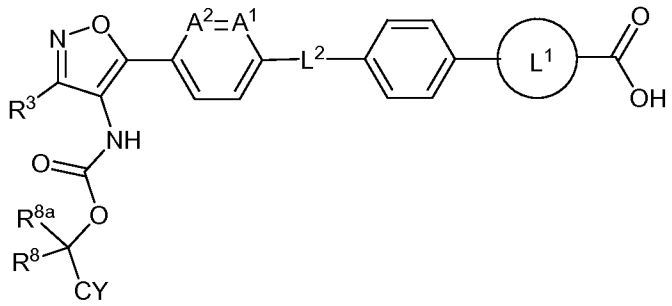
unsubstituted -C_1-C_4alkylene-aryl, or a substituted or unsubstituted -C_1-C_4alkylene-heteroaryl; or

two R^9 groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle; and

R^{10} is selected from C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkylene-C_3-C_{10}cycloalkyl, a substituted or unsubstituted -C_1-C_4alkylene-C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkylene-aryl, and a substituted or unsubstituted -C_1-C_4alkylene-heteroaryl.

[0028] According to some embodiments, the LPA receptor antagonists of the present invention are selected from the compounds listed in the following Tables:

Table 2



R^3	A^1	A^2	-L^2-	-L^1-	CY	R^8	R^{8a}	M+H*
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	(R)-CH_3	H	483
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	CH_3	CH_3	H	421
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Cyclohexyl	CH_3	H	489
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Methyl-phenyl	(R)-CH_3	H	497

R^3	A^1	A^2	$-L^2-$	$-L^1-$	CY	R^8	R^{8a}	M+H*
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	H	H	469
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	CH_3	H	H	407
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	H	H	H	393
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	CH_3	CH_3	497
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Cyclopropyl	CH_3	H	447
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Cyclopropyl	CH_3	H	447
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Cyclopropyl	H	H	433
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Chloro-phenyl	(R)-CH_3	H	517
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	CH_3	CH_3	CH_3	434
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Trifluoromethyl-phenyl	(R)-CH_3	H	551
CH_3	CH	CH	-	Cyclobutyl-1,1-diyl	Phenyl	(R)-CH_3	H	497
CH_3	CH	CH	-	Cyclopentyl-1,1-diyl	Phenyl	(R)-CH_3	H	511
CH_3	CH	CH	-	Cyclobutyl-1,1-diyl	CH_3	CH_3	CH_3	449
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Methoxy-phenyl	CH_3	H	513
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	4-Trifluoromethyl-phenyl	CH_3	H	551

R^3	A^1	A^2	$-L^2-$	$-L^1-$	CY	R^8	R^{8a}	M+H*
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	4-Trifluoromethyl-phenyl	CH_3	H	551
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Pyrazin-2-yl	CH_3	H	485
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Cyano-phenyl	CH_3	H	508
CH_3	CH	CH	-O-	Cyclopropyl-1,1-diyl	2-Chloro-phenyl	(R)-CH_3	H	533
CH_3	CH	CH	-O-	Cyclopropyl-1,1-diyl	Phenyl	CH_3	H	499
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	4-Methyl-phenyl	(R)-CH_3	H	497
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Methyl-phenyl	(R)-CH_3	H	497
CH_3	CH	CH	-O-	Cyclopropyl-1,1-diyl	Phenyl	(R)-CH_3	H	499
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	4-Cyano-phenyl	(R)-CH_3	H	508
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Cyano-phenyl	(R)-CH_3	H	508
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Methyl-prop-2-yl	(R)-CH_3	H	463
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Cyclobutyl	(R)-CH_3	H	461
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Prop-2-yl	(R)-CH_3	H	449
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Ethyl	Ethyl	H	449
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	2-Chloro-cyclohexenyl	CH_3	H	496

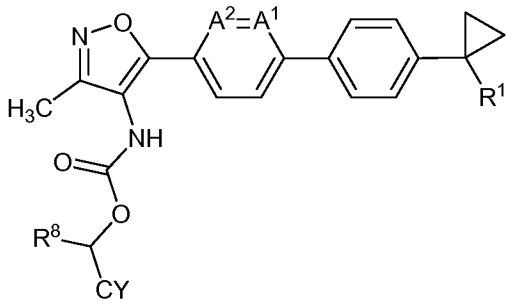
R^3	A^1	A^2	$-L^2-$	$-L^1-$	CY	R^8	R^{8a}	M+H*
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Trifluoromethyl-phenyl	(R)-CH_3	H	551
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Methoxy-phenyl	(R)-CH_3	H	513
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	4-Methoxy-phenyl	(R)-CH_3	H	513
CH_3	CH	CH	-	Cycloprop-2-enyl-1,1-diyl	Cyclopropyl	(R)-CH_3	H	445
CH_3	CH	CH	-	Cyclopropyl-1,2-diyl	Phenyl	(R)-CH_3	H	483
CH_3	N	CH	-	Cyclopropyl-1,1-diyl	Phenyl	(R)-CH_3	H	484
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Bromo-phenyl	CH_3	H	561
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Chloro-phenyl	CH_3	H	517
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	(S)-CH_3	H	483
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Hydroxy-phenyl	CH_3	H	499
CH_3	CH	CH	-	(Cyclopropyl-1,1-diyl)-CH_2-	3-Trifluoromethyl-phenyl	(R)-CH_3	H	565
CH_2CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	(R)-CH_3	H	497
Phenyl	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	(R)-CH_3	H	545
CH_3	CH	CH	-	-CH_2-(Cyclopropyl-1,1-diyl)	Phenyl	(R)-CH_3	H	497

R^3	A^1	A^2	$-L^2-$	$-L^1-$	CY	R^8	R^{8a}	M+H*
CH_3	CH	CH	-	$-CH_2-$ (Cyclopropyl-1,1-diyl)	3-Trifluoromethyl-phenyl	(R)-CH_3	H	565
CH_2CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Trifluoromethyl-phenyl	(R)-CH_3	H	565
Phenyl	CH	CH	-	Cyclopropyl-1,1-diyl	3-Trifluoromethyl-phenyl	(R)-CH_3	H	613
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl-d5	CD_3	D	492
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3-Trifluoromethyl-phenyl	CH_3	CH_3	565
CH_3	CH	C(OCH_3)	-	Cyclopropyl-1,1-diyl	3-Trifluoromethyl-phenyl	(R)-CH_3	H	581
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	3,5-Dibromo-phenyl	(R)-CH_3	H	614
H	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	(R)-CH_3	H	469
CH_3	CH	CH	-	Cyclopropyl-1,1-diyl	Phenyl	-CH_3	H	483

represent individual stereoisomers; absolute configuration not determined

* mass spectrometric data

Table 3



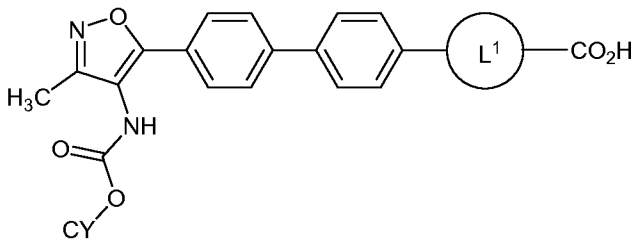
A^1	A^2	R^1	CY	R^8	M+H*

A^1	A^2	R^1	CY	R^8	M+H*
CH	CH	NH-S(=O)$_2$-CH_3	Phenyl	(R)-CH_3	560
CH	CH	NH-S(=O)$_2$-Phenyl	Phenyl	(R)-CH_3	622
CH	CH	CN	Phenyl	(R)-CH_3	464
CH	CH	(5-Oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl	Phenyl	(R)-CH_3	523
CH	CH	1*H*-Tetrazol-5-yl	Phenyl	(R)-CH_3	507
CH	CH	NH-S(=O)$_2$-CH_3	3-Trifluoromethyl-phenyl	(R)-CH_3	628
CH	C(OCH_3)	NH-S(=O)$_2$-CH_3	3-Trifluoromethyl-phenyl	(R)-CH_3	658

* mass spectrometric data

[0029] Additional non-limiting examples of compounds include those described in Tables 4 to 6.

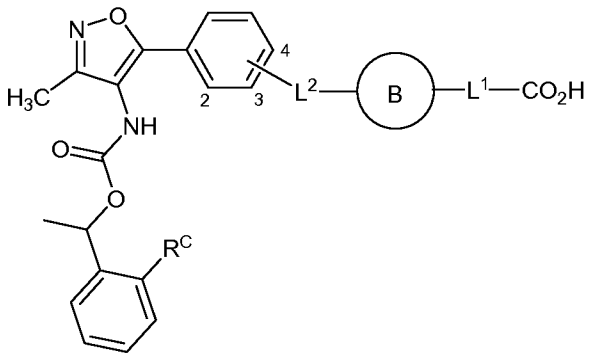
Table 4



B	-L^1-	CY	M+H*
Phen-1,4-ylene	Cyclopropyl-1,1-diyl	1-Methyl-cyclopent-1-yl	461
Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cyclobutyl	433

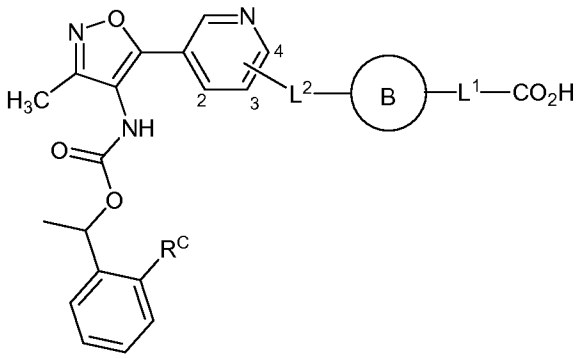
* mass spectrometric data

Table 5



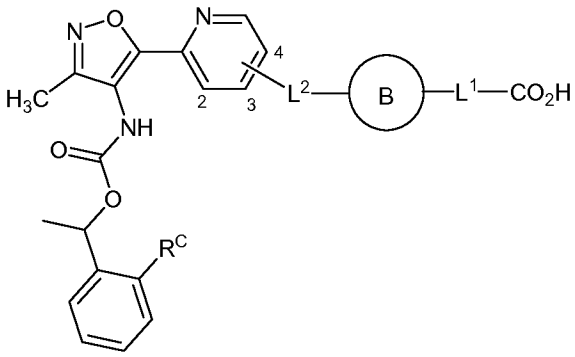
Position of L^2	$-L^2-$	B	$-L^1-$	R^C
3	-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-O-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-O-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-S-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-S-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-NH-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-NH-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2O-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2O-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-OCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-OCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2S-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2S-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2NH-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2NH-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-NHCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-NHCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl

Table 6



Position of L^2	$-L^2-$	B	$-L^1-$	R^C
3	-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-O-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-O-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-S-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-S-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-NH-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-NH-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2O-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2O-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-OCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-OCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2S-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2S-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2NH-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2NH-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-NHCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-NHCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl

Table 7



Position of L^2	$-L^2-$	B	$-L^1-$	R^C
3	-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-O-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-O-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-S-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-S-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	-NH-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	-NH-	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2O-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2O-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-OCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-OCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2S-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2S-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-CH_2NH-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-CH_2NH-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
3	$-NHCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl
4	$-NHCH_2-$	Phen-1,4-ylene	Cyclopropyl-1,1-diyl	Cl

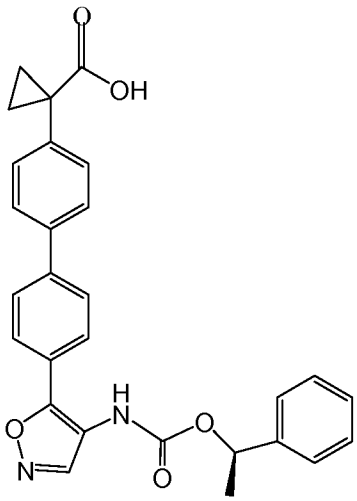
[0030] In one aspect, Phen-1,4-ylene (*i.e.*, ring B) in Tables 4 through 6 is replaced with a group selected from Phen-1,2-ylene, Phen-1,3-ylene, Pyridin-2,3-ylene, Pyridin-2,4-ylene, Pyridin-2,5-ylene, Pyridin-2,6-ylene, Pyridin-3,4-ylene, Pyridin-3,5-ylene, Pyridin-3,6-ylene, Pyridin-4,5-ylene, Pyridin-4,6-ylene, Pyridin-5,6-ylene, Pyrimidin-2,4-ylene, Pyrimidin-2,5-ylene, Pyrimidin-4,5-ylene, Pyrimidin-4,6-ylene, Pyrazin-2,3-ylene, Pyrazin-2,5-ylene, Pyrazin-2,6-ylene, Pyridazin-3,4-ylene, Pyridazin-3,5-ylene, Pyridazin-3,6-ylene, Pyridazin-4,5-ylene, 1*H*-Imidazol-1,2-ylene, 1*H*-Imidazol-1,4-ylene, 1*H*-Imidazol-1,5-ylene, 1*H*-Pyrazol-1,3-ylene, 1*H*-Pyrazol-1,4-ylene, 1*H*-Pyrazol-1,5-ylene, 1*H*-[1,2,3]Triazol-1,4-ylene, 1*H*-[1,2,3]Triazol-1,5-ylene, 1*H*-[1,2,4]Triazol-1,3-ylene, and 1*H*-[1,2,4]Triazol-1,5-ylene.

[0031] In one aspect, Phen-1,4-ylene (*i.e.*, ring B) in Tables 4 through 6 is replaced with a group selected from Phen-1,2-ylene, Phen-1,3-ylene, Pyridin-2,3-ylene, Pyridin-2,4-ylene, Pyridin-2,5-ylene, Pyridin-2,6-ylene, Pyridin-3,4-ylene, Pyridin-3,5-ylene, Pyridin-3,6-ylene, Pyridin-4,5-ylene, Pyridin-4,6-ylene, Pyridin-5,6-ylene, Pyrimidin-2,4-ylene, Pyrimidin-2,5-ylene, Pyrimidin-4,5-ylene, Pyrimidin-4,6-ylene, Pyrazin-2,3-ylene, Pyrazin-2,5-ylene, Pyrazin-2,6-ylene, Pyridazin-3,4-ylene, Pyridazin-3,5-ylene, Pyridazin-3,6-ylene, Pyridazin-4,5-ylene, 1*H*-Imidazol-1,2-ylene, 1*H*-Imidazol-1,4-ylene, 1*H*-Imidazol-1,5-ylene, 1*H*-Pyrazol-1,3-ylene, 1*H*-Pyrazol-1,4-ylene, 1*H*-Pyrazol-1,5-ylene, 1*H*-[1,2,3]Triazol-1,4-ylene, 1*H*-[1,2,3]Triazol-1,5-ylene, 1*H*-[1,2,4]Triazol-1,3-ylene, and 1*H*-[1,2,4]Triazol-1,5-ylene; and Cl (*i.e.*, R^C) is replaced with F.

[0032] In one aspect, Cl (*i.e.*, R^C) in Tables 4 through 6 is replaced with F. In one aspect, Cl (*i.e.*, R^C) in Tables 4 through 6 is replaced with H. In one aspect, Cl (*i.e.*, R^C) in Tables 4 through 6 is replaced with $-CH_3$. In one aspect, Cl (*i.e.*, R^C) in Tables 4 through 6 is replaced with $-CF_3$.

[0033] The compounds described above in Tables 2 to 7 can be prepared by the methods disclosed in PCT/US2010/037309, the disclosure of which is herein incorporated by reference in its entirety.

[0034] In one preferred embodiment of the present invention, the compound is :



or a pharmaceutically acceptable salt thereof.

[0035] According to some embodiments of the present invention, compounds described in WO 2011/041461 are preferred.

[0036] Preferred autotaxin inhibiting substances or compounds of the present invention include those disclosed by Prestwich et al., *Biochimica et Biophysica Acta*, 1781:588-594 (2009); Albers et al., *J. Med. Chem.*, 54(13):4619-4626 (Jul. 14, 2011), Epub. Jun. 9, 2011; Gierse, J. et al., *J. Pharmacol. Exp. Ther.*, 334(1):310-317 (Jul. 2010), Epub, Apr. 14, 2010, as well as found in the following patent applications by WO 2012/138797, WO 2009/046841, WO 2010/115491, PCT/US2012/038853 and WO 2010/060532, the disclosures of which are all incorporated by reference in their entirety.

[0037] The LPA receptor antagonists and autotaxin inhibiting compounds of the present invention are optionally administered to an individual by multiple administration routes, including but not limited to, oral, parenteral (*e.g.*, intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical compositions or formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

EXAMPLES

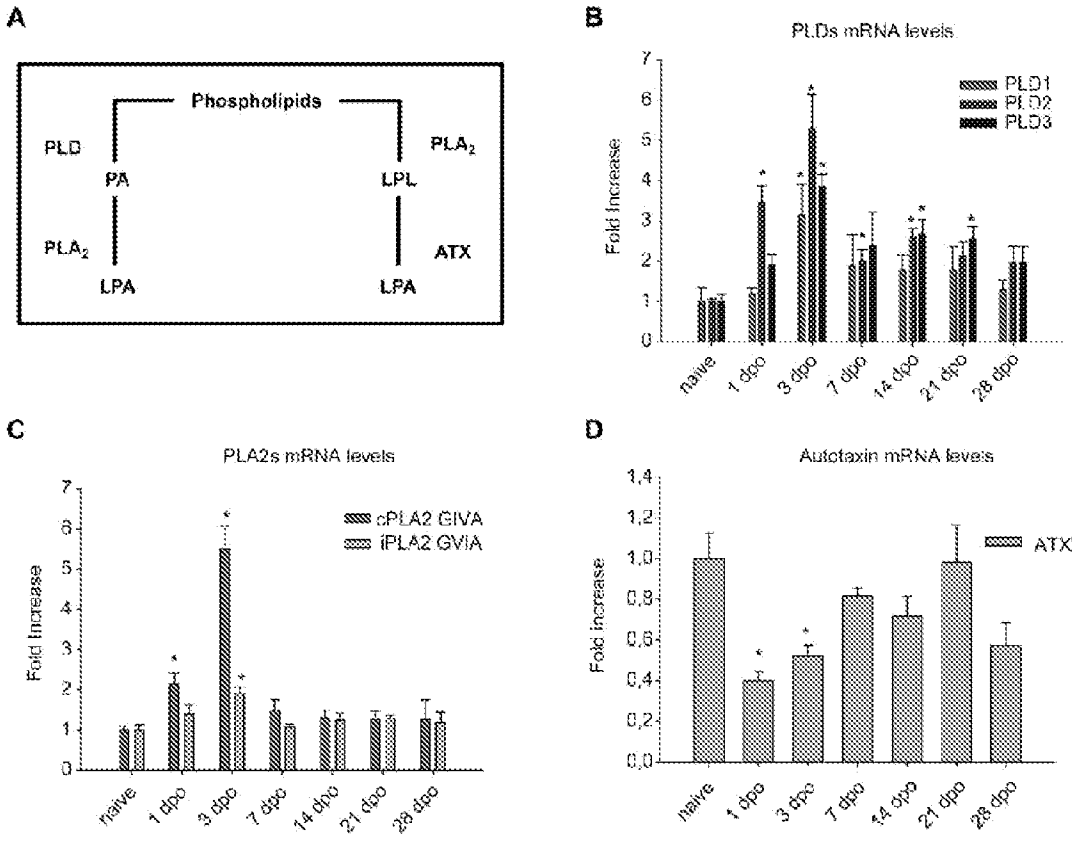
LPA Synthesis After SCI in Adult Mice

[0038] LPA is found in high concentrations in plasma, which extravasates into the spinal cord parenchyma after lesion. However, LPA might be also synthesized by glial cells or neurons in the spinal cord parenchyma, and thus, increase LPA levels. Expression of the enzymes involved in the synthesis of LPA after SCI was analyzed. LPA is synthesized *in vivo* from phospholipids by 2 pathways, as shown in Figure 1A. In the first pathway, phosphatidic acid (PA) generated by the action of the phospholipase D (PLD), is deacylated by phospholipase A_2 (PLA_2) to generate LPA. This is the main synthesis route for LPA in host tissues. In the second pathway, lysophospholipids (LPLs) generated by PLA_2, are subsequently converted to LPA by autotaxin (ATX).

[0039] As is shown in Figure 1B, mRNA levels for the three forms of the PLD family (PLD1-3) are significantly up-regulated after SCI ($p<0.05$). The two main forms of the intracellular PLA_2 family ($cPLA_2$ GIVA and $iPLA_2$ GVIA) are also up-regulated at 1 and 3 dpi ($p<0.05$) (Fig. 1C). However, mRNA levels for ATX are down-regulated at day 1 and 3 after injury ($p<0.05$) (Fig. 1D). These results suggest that LPA levels may increase in the injured spinal cord not only as a consequence of plasma extravasation, but also due to its *de novo* synthesis via PLD-PLA pathway. However, LPA synthesis via PLA2-ATX pathway cannot be discarded.

Figure 1

(A) Scheme showing the 2 pathways of LPA synthesis from phospholipids. (B-D) mRNA levels of enzymes involved in LPA synthesis assessed by Real Time PCR.



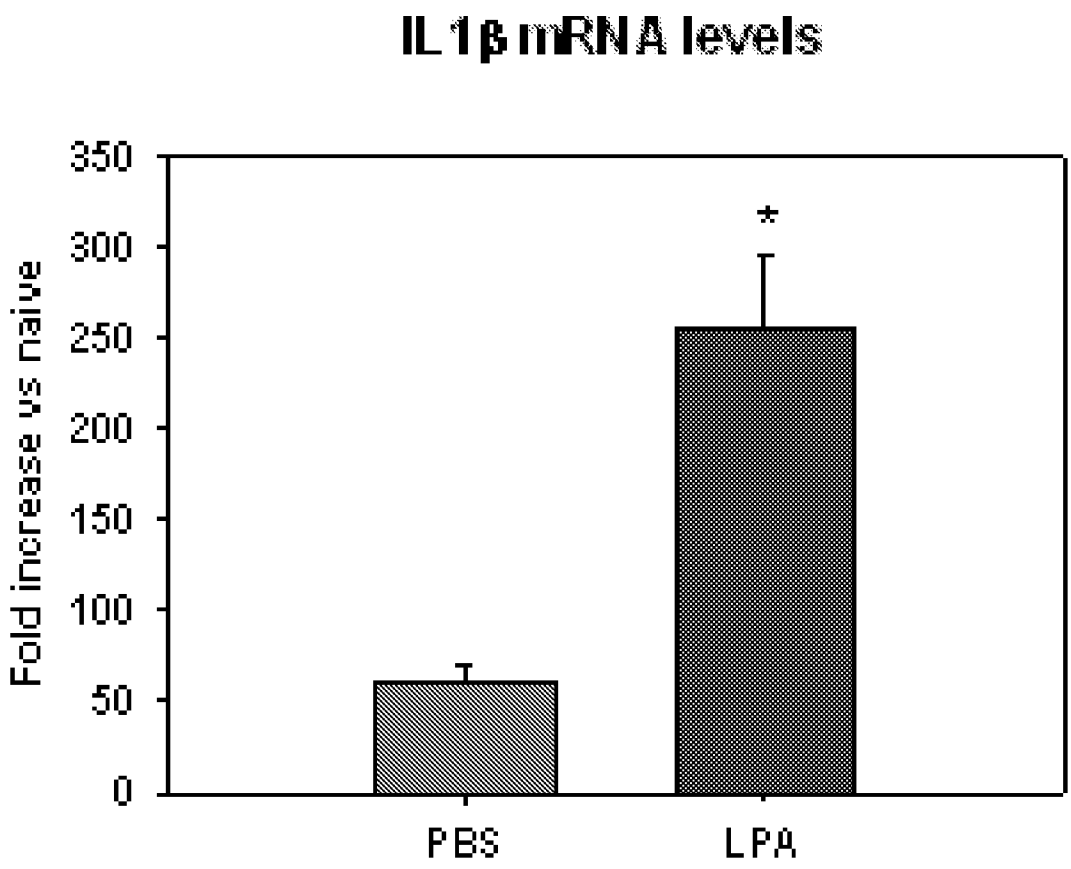
* $p<0.05$

Effects of Intraspinal Injection of LPA on Neuroinflammation

[0040] As shown in Figure 2, LPA levels increase after SCI. The potential contribution of LPA in the spinal cord parenchyma was assessed. 1µl of solution containing 5 nmoles of LPA or PBS was injected into the dorsal column of naïve spinal cord. Six hours after injection, the expression of IL-1β mRNA was 5 times higher in spinal cords injected with LPA as compared to those injected with PBS (Fig. 2).This result suggests that LPA triggers cytokine production in the spinal cord.

Figure 2

Quantification of IL-1β mRNA levels in the spinal cord after intraspinal injection of LPA or PBS at 6 hours post-injections.

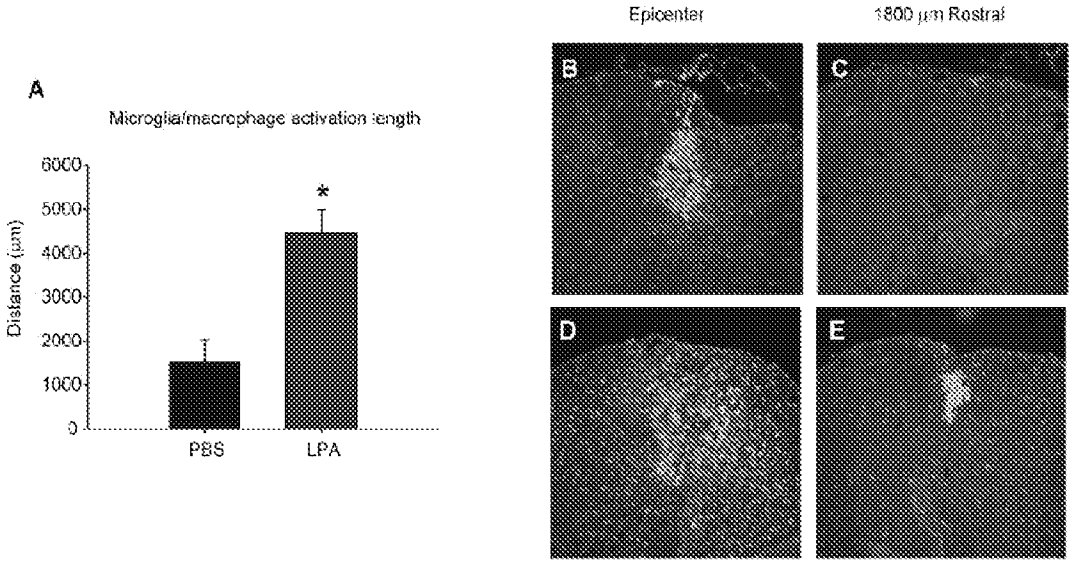


*p<0.001

[0041] It was then contemplated whether the increase in cytokine production induced by intraspinal injection of LPA into the uninjured spinal cord could trigger an inflammatory response. Microglia/macrophage recruitment in the spinal cord parenchyma at 4 days after injection was studied by measuring the presence of Iba1 positive cells. It was observed that microglia/macrophage activation in PBS injected mice was restricted to the injection area, probably due to the mechanical injury caused by the needle insertion (Fig. 3B), which spread a few microns along the rostro-caudal axis of the spinal cord. Interestingly, spinal cord sections from mice injected with LPA showed a marked recruitment and activation of microglia/macrophage at 4 dpi (Fig. 3D, E). The presence of these inflammatory cells was not limited to the injection site, since they were also observed in the grey matter (Fig. 3D). In addition, the spread of Iba1+ cells along the spinal cord was 3 times increased in LPA as compared to PBS injected mice (Fig. 3A, D, E).

Figure 3

(A) Quantification of microglia/macrophage activation length at 4 days after intraspinal injection of PBS or LPA. (B-E) Representative images of spinal cords stained against Iba1 at the epicenter (B, D) and 1800 µm rostral to the injection site (C, E) of PBS (B, C) and LPA (D, E) injected mice.



* p=0.006.

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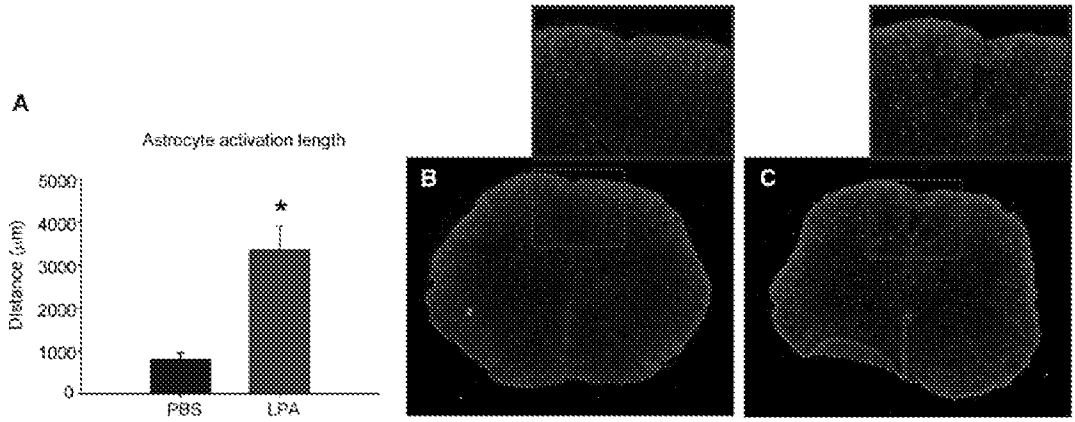
[0042] Apart from activated microglia/macrophages, astrocytes also contribute to the 15 neuroinflammatory response that occurs after spinal cord injury. For this reason, it was also assessed whether LPA injection triggered astrocyte activation in the spinal cord.

[0043] GFAP staining revealed astrocyte activation at the injection site in both, PBS and LPA injected mice. Reactive astrocytes surrounded an area of the dorsal column that was devoid of GFAP+ cells, suggesting that there was a lesion in the tissue (data not 25 shown). Similarly to Iba1+ cells, astrocyte activation was restricted to the needle tract in PBS injected mice, and extended a few microns along the rostro-caudal axis. Astrocyte activation along the spinal cord was significantly increased in LPA injected spinal cord (P=0.007) (Fig. 4). Therefore, these results suggest that LPA leads to microglia and astrocyte activation in the spinal cord.

Figure 4

(A) Quantification of astrocyte activation length at 4 days after intraspinal injection of PBS (B) or LPA (C). (B-C) Representative images of spinal cords stained against GFAP taken at 1800 µm rostral to the injection site in PBS (B) and LPA (C) injected mice. Inserts show a higher magnification of the dorsal column. Note that in spinal cord injected with LPA show more astrogliosis.



* p=0.007

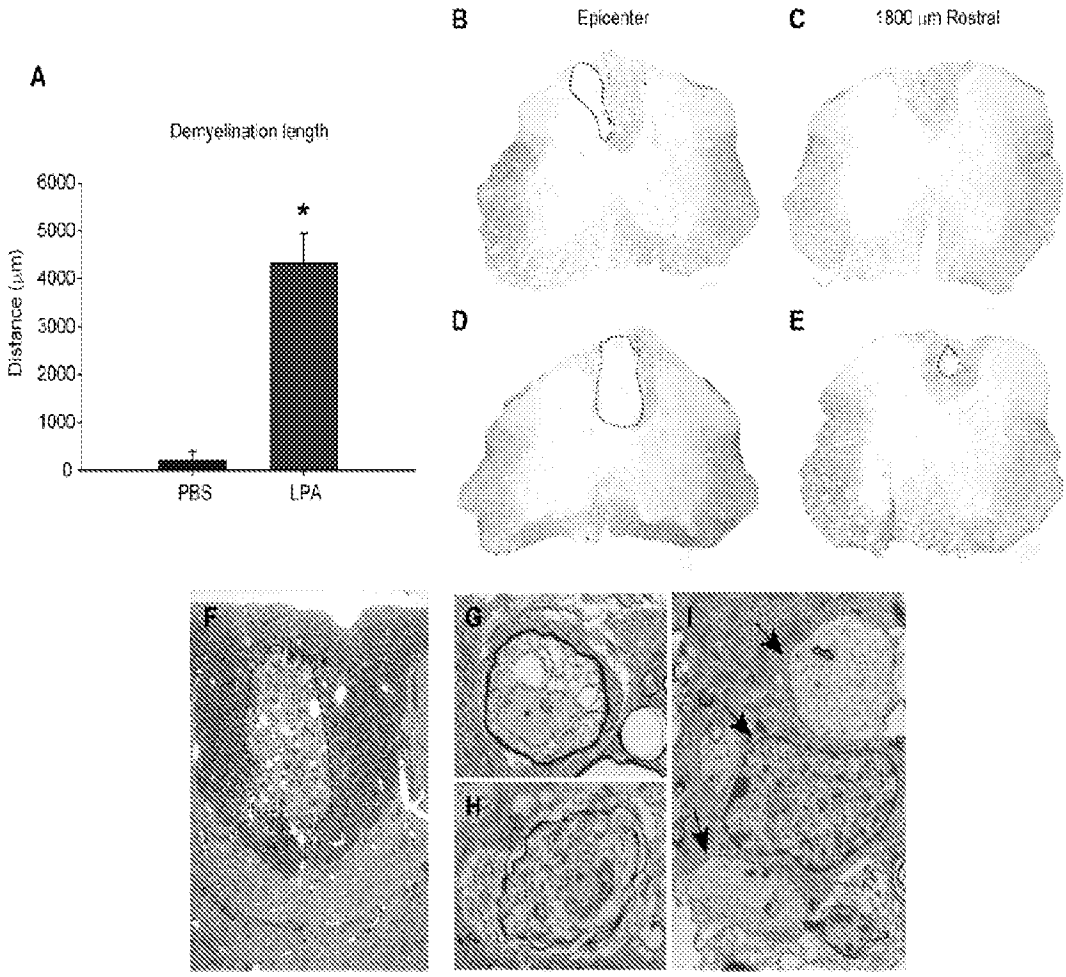
[0044] It was then assessed whether the inflammatory response triggered by LPA led to demyelination. At 4 dpi, LFB staining revealed the presence of a small demyelinating lesion in the dorsal column of PBS injected spinal cords. This lesion was restricted to the area of the needle insertion (Fig. 5B). We also observed a demyelinating lesion in the spinal cords injected with LPA (Fig. 5D). However, the area of this lesion was significantly larger in LPA as compared to PBS injected mice (p=0,003) (Fig. 5B-E) and its extension along the spinal cord was almost 10 times higher (p=0.001) (Fig. 5A, B-E).

[0045] To confirm whether the demyelinating lesion triggered by LPA was due to axon demyelination or axonal damage electron microscopy images were obtained (Fig. 5 F-I). This technique confirmed the presence of fibers with degenerating myelin (Fig. 5G, H) and naked axons (Fig. 5I) in the demyelinating lesion. The presence of damaged axons, however, was scarce. These results suggest that LPA mediates demyelination without causing axonal damage.

[0046] It was then assessed whether demyelination triggered by LPA was due to oligodendrocyte loss or to myelin damage caused by the inflammatory response by counting the number of oligodendrocytes in the dorsal columns at 4 dpi.

Figure 5

(A) Quantification of demyelination length injury at 4 days after intraspinal injection of PBS or LPA. (B-E) Representative images of spinal cords stained with LUXOL® fast blue at the epicenter (B, D) and 1800 µm rostral to the injection site (C, E) in PBS (B,C) and LPA (D, E) injected mice. (F) Toluidin Blue stained section from spinal cord at 4 days after intraspinal injection of LPA. (G-I) Electron microscopy images taken from the demyelinating area showing fibers with myelin breakdown (G, H) as well as demyelinated axons (I) (see arrows).



* p=0.001

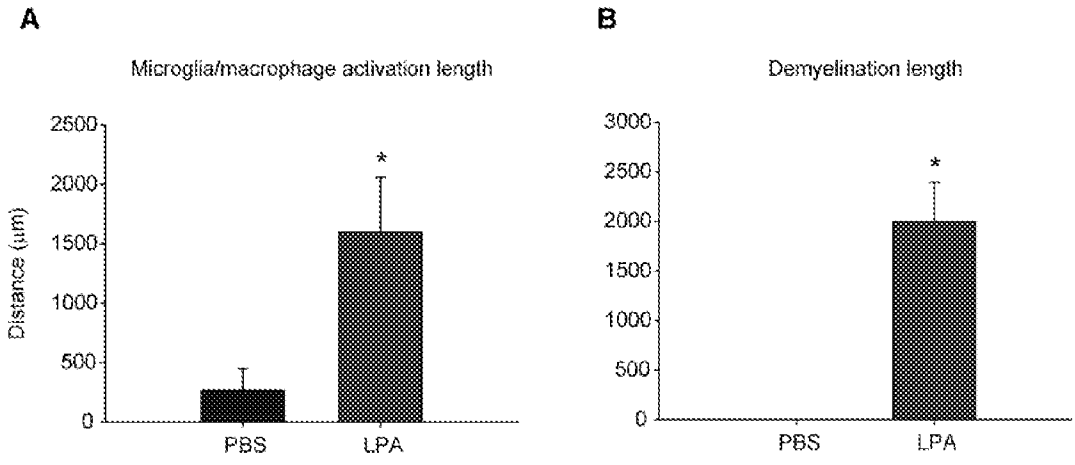
[0047] The results revealed that there was a significant reduction in the number of oligodendrocytes in LPA as compared to PBS injected spinal cord, but only at the

injection site ($p = 0.008$) and not at further distances (data not shown). The fact that most of the demyelinating lesion was present in areas with no oligodendrocyte loss suggests that the inflammatory response rather than oligodendrocyte death is the main inducer of the demyelination.

[0048] It was then assessed whether inflammation induced by LPA remits with time, or contrary, remains chronic as it happens in SCI. Microglia/macrophage and astrocyte activation was studied at 21 days following intraspinal injection of LPA. At this time point, there was a great reduction in the immunoreactivity for Iba1 and GFAP. The activation length of microglia/macrophages was reduced by 3 times as compared to day 4 (p=0,009). GFAP immunoreactivity decreased to naïve levels (data not shown). These results therefore suggest that inflammatory response triggered by intraspinal injection of LPA remits with time. However, the activation of microglia/macrophage in the spinal cords injected with LPA was still significantly increased as compared to those injected with PBS ($p = 0.006$) (Fig. 6A).

Figure 6

(A,B) Quantification of microglia/macrophages activation (A) and demyelination (B) length injury at 21 days after intraspinal injection of PBS or LPA.



[0049] It was then assessed whether remyelination occurred after intraspinal injection of LPA. At 21 days post-injection the extension of the demyelinating lesion along the spinal cord was significantly reduced as compared to day 4 (p = 0.001). Similarly, the area of the demyelinating lesion was reduced to over a half as compared to day 4 ($p =$

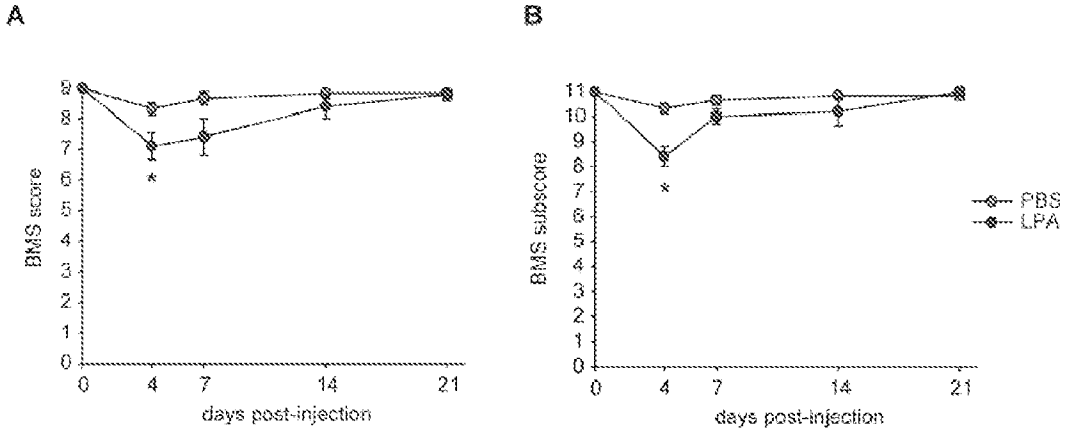
0.001). However, a small demyelinating lesion was still present in areas close to the injection site in mice receiving LPA but not PBS (Fig. 6B).

Effects of Intraspinal Injection of LPA on Locomotor Performance

[0050] Since intraspinal injection of LPA in the naïve spinal cord leads to inflammation and demyelination, it was proposed that LPA may also cause locomotor deficits. Motor skills were evaluated using the Basso Mouse Scale (BMS) test. BMS scores revealed that LPA led to functional impairments as compared to those mice injected with PBS ($p = 0.049$) (Fig. 7A). *Post-hoc* Bonferroni paired comparations revealed that differences were only statistically significant ($p = 0.023$) at 4 days after the injection (Fig. 7A) but not later on. At this time point, PBS injected mice displayed perfect locomotion (9 points score) or showed just a mild instability of the trunk (8 points score). However, most of the mice that received intraspinal injection of LPA showed mild trunk instability and paw rotation at initial contact and lift off (7 points score). One mouse injected with LPA also underwent failure in the coordination (5 points score). In addition, BMS subscores, which analyze finer aspects of locomotion, were also significantly lower in mice receiving intraspinal injection of LPA than to those receiving PBS (Fig. 7B). Similarly to the BMS scores, BMS subscores were significantly different only at day 4 after injection ($p = 0.001$) (Fig. 7B). These results suggest that intraspinal injection of LPA leads to transient functional deficits.

Figure 7

(A,B) Assessment of locomotor performance after intraspinal injection of PBS or LPA using the BMS score (A) and the BMS subscore (B).



* p = 0.023 in A and 0.001 in B

Effects of Intraspinal Injection of LPA on Neuropathic Pain

[0051] LPA has been recently shown to play a crucial role in the development of neuropathic pain after sciatic nerve injury. It was assessed whether intraspinal injection of LPA led to allodynia. In order to evaluate pain responses, an Electronic von Frey Aesthesiometer was used. These experiments revealed that neither intraspinal injection of LPA nor PBS injected mice induced pain response (data not shown).

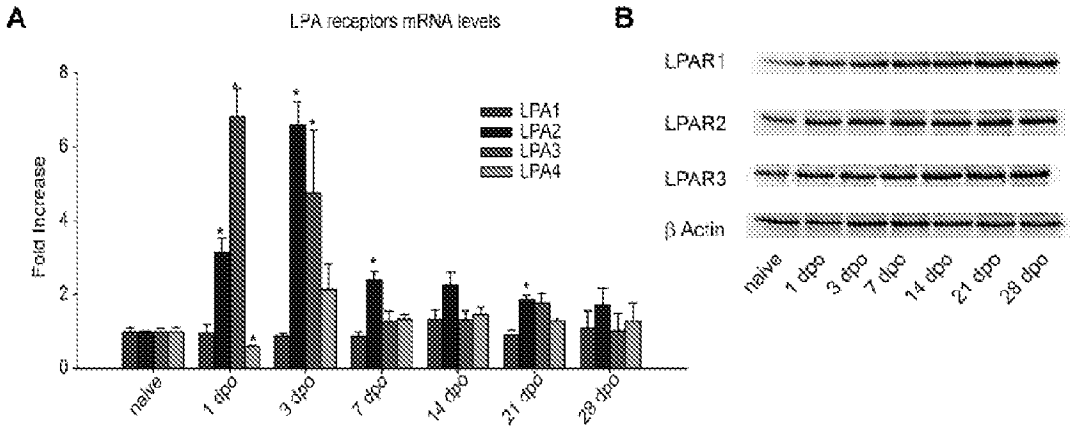
Changes in the Expression of LPA Receptors in SCI

[0052] It has so far been demonstrated that LPA activates an inflammatory response that leads to transient demyelination and functional impairments, suggesting it could exert an important role on the neuroinflammatory response that occurs after SCI. Since LPA plays many important physiological roles in mammals, it is important to block or activate only those receptors that might be involved in the detrimental or protective actions of LPA in the SCI. There is therefore a need to know which of the LPARs are up-regulated after SCI, and thus, exert the potential detrimental/protective effects. We therefore assessed which LPARs are up-regulated after SCI using Real-Time PCR. Our data revealed that mRNA levels for LPAR2 and LPAR3 are up-regulated after SCI (Fig. 8A), whereas LPAR1 and LPAR4 levels either remain unchanged or are down-regulated (Fig. 8A). mRNA levels for LPAR5 are almost undetectable (data not shown).

[0053] To further confirm that LPAR2 and LPAR3 are up-regulated after SCI, we performed a preliminary study to assess the protein levels of these two LPARs by using western blot (Fig. 8B). These experiments suggested that LPAR2 and LPAR3 protein levels are up-regulated after SCI (Fig. 8B). Interestingly, and in contrast to mRNA levels, protein levels for LPAR1 are also up-regulated in SCI. (Fig. 8B). Nevertheless, we need to increase the number of mice to be sure about the reliability of these results.

Figure 8

(A) Quantification of mRNA levels changes of the LPARs after SCI. (B) Representative western blots showing changes in LPAR1, LPAR2 and LPAR3 protein levels after SCI.



*p<0.05

Localization of LPA Receptors in SCI

[0054] In order to determine which cells express the three LPARs that are up-regulated in SCI, TSA amplification was performed due to the absence of signal using regular immunofluorescence. Histological analyses revealed a constitutive expression of LPAR1 in neurons, axons and blood vessels. A 10 μm z-stack reconstruction (x-z and y-z) revealed that endothelial cells but not astrocytes are responsible for the expression of LPAR1 in blood vessels. Interestingly, at 7 days after SCI, LPAR1 was also found in activated microglia/macrophages). LPAR2 was expressed constitutively in motoneurons and their projecting axons/dendrites, as revealed by the double immunofluorescene with ChAT. Astrocytes surrounding motoneurons, however, did not colocalize with LPAR2, suggesting that the processes surrounding the motoneurons were in fact axons/dendrites of the motoneurons. After SCI, LPAR2 was also found in motoneurons. LPAR3 was not detected in naive spinal cord. There was, however, a great increase in LPAR3 immunoreactivity in spinal cord parenchyma at 7 days post-injury in areas associated with the glial scar. Double immunofluorescence revealed that LPAR3 was expressed in the reactive astrocytes forming the glial scar, but not in axons.

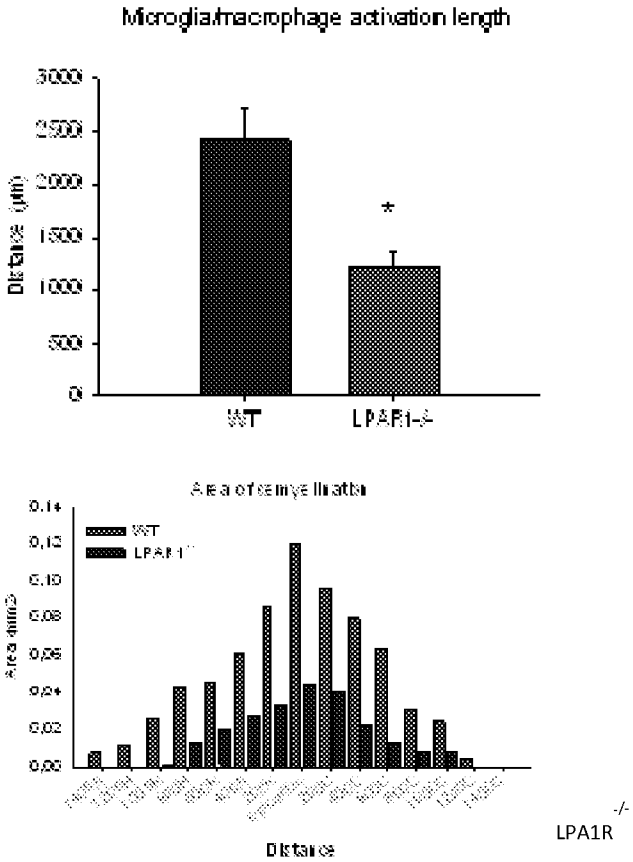
Potential Involvement of LPAR1 in Spinal Cord Injury

[0055] Based on the foregoing, LPA levels may increase in the spinal cord parenchyma after injury and act via LPAR1-3. LPAR1 is the most expressed receptor for LPA in the uninjured spinal cord. Therefore, the potential contribution of LPAR1 in triggering inflammation in the CNS was assessed. Intraspinal injections of LPA in mice

lacking LPAR1 were made. Four days following LPA injection, spinal cords from LPAR1 null mice showed a marked reduction in inflammation as compared to wildtype littermate mice. Similarly, the lack of LPAR1 also protected against demyelination. These results suggest that an increase in LPA levels in the spinal cord parenchyma after lesion may act via LPAR1 and lead to inflammation and demyelination, and thus, pharmacological blockade of LPAR1 is a viable new therapeutic approach to promote functional recovery and tissue protection after SCI.

Figure 9

(A) Quantification of microglia/macrophage activation length and area of demyelination injury at 4 days after intraspinal injection LPA in LPAR1 null mice and wild type littermates. (B) Representative images of spinal cords stained with LUXOL® fast blue at the injection site in WT mice and mice lacking LPAR1.



* $p<0.05$

Example 1

Pharmacological Blockade of LPAR1 Reduces Functional and Histological Outcomes

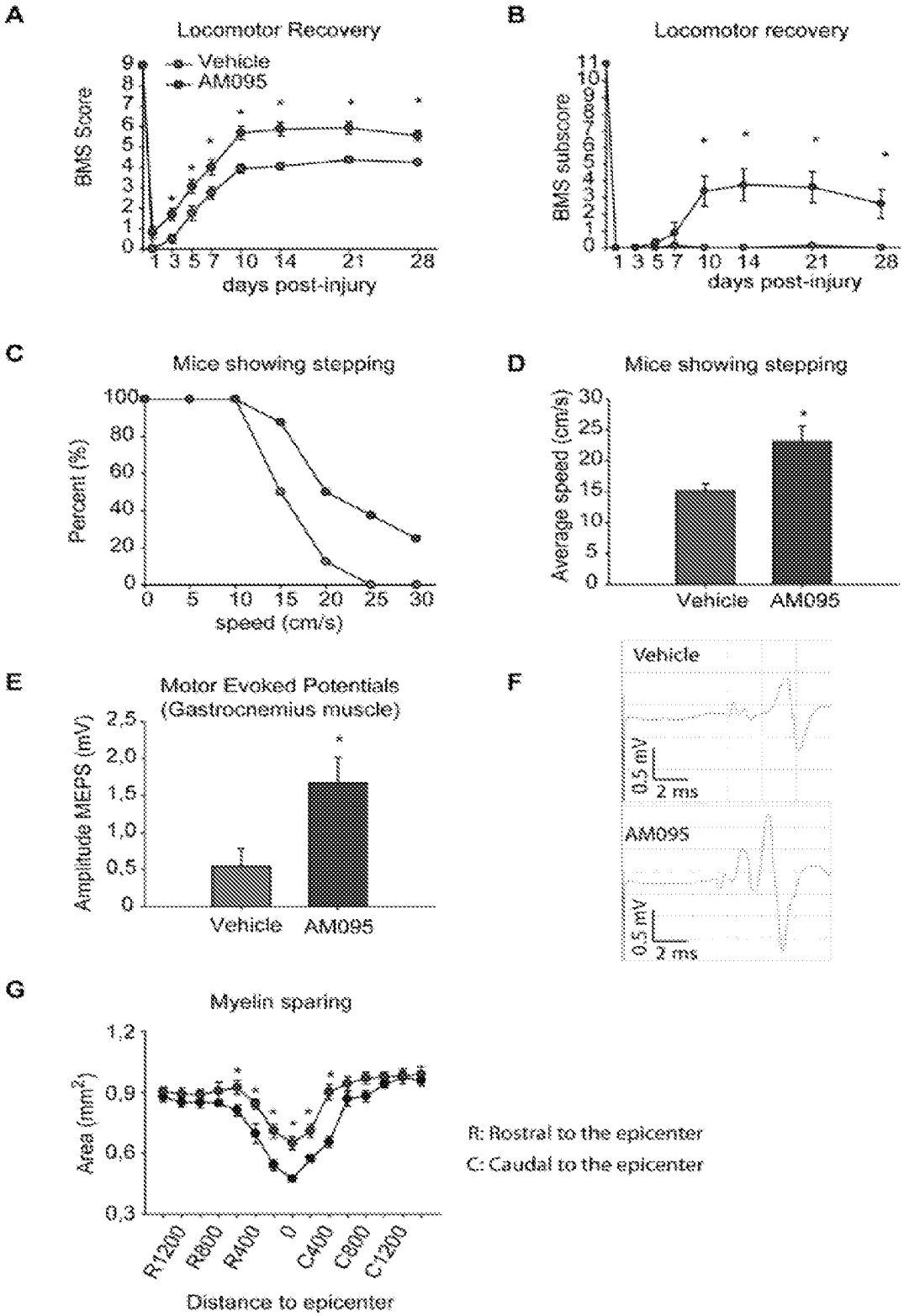
[0056] AM095, a highly selective antagonist for LPAR1 was used to assess the role of LPAR1 after SCI. Oral administration of AM095, starting 1 hour after injury and then every 12 hours for seven days, significantly improved locomotor function as evaluated by the BMS score, beginning at 3 dpi until day 28, the longest time point examined (Fig. 10A). At 28 days post-injury, vehicle treated mice showed plantar placement of the paw with weight support and occasional plantar stepping (score 4), but none of them displayed frequent plantar stepping or showed any sign of coordination. In contrast, all the mice treated with AM095 displayed frequent plantar stepping and ~70% of them showed coordinated locomotion. In addition, BMS subscores, which assess finer aspects of locomotion, were also improved with the AM095 treatment (Fig. 10B). Moreover, mice treated with AM095 displayed plantar stepping on a treadmill at higher speed (Fig. 10C, D).An electrophysical test (motor evoked potentials; MEPs) was then performed to assess whether the greater motor skills observed after AM095 were due to enhanced preservation of motor spinal cord axonal pathways. At day 28 following injury, mice treated with AM095 showed 3 fold greater amplitude of MEPS than vehicle treated mice, indicating the AM095 lead to greater preservation of motor spinal cord axonal pathways after injury (Fig. 10 E, F).

[0057] Additionally, histological sections of the spinal cord stained with LUXOL® fast blue, which stains myelin, revealed that AM095 treatment reduced myelin loss at the epicenter of the injury and in adjacent regions (Fig. 10G). This suggests locomotor and electrophysiological improvement observed after AM095 administration is associated with amelioration of secondary tissue damage.

Figure 10

(A, B) Time course of locomotor recovery in mice treated with AM095 or vehicle after SCI. Graphs showing locomotor skills evaluated in the BMS score (A) and the BMS subscore (B). Note that animals treated with AM095 showed significant improvement in locomotor recovery. (C, D) Graph showing the percent of mice that displayed weighted plantar stepping at different speeds on a treadmill at day 28 post-injury (C), and the maximal average speed (D). Note that mice treated with AM095 were able to steep at higher speeds. (E, F) Motor evoked potentials (MEPs) recorded at the gastrocnemius

muscle at day 28 post-injury (E). Mice treated with AM095 showed greater amplitude of MEPs, indicating greater preservation of motor spinal cord axonal pathways. (F) Representative MEPs recordings from a mouse treated with AM095 or Vehicle. (G) Quantification of myelin preservation at various distances rostral and caudal to the injury epicenter revealed significant reduction in myelin loss in mice treated with AM095 at the epicenter of the injury and at rostral and caudal regions.



(* p<0,05). Error bars indicate SEM

[0058] Overall, these data provide clear evidences that LPA by acting via LPAR1 leads to inflammation, locomotor deficits and myelin loss in SCI. Thus, LPAR1 receptor antagonists, such as AM095, could be good therapeutic candidates for acute SCI in humans, or other injuries affecting the CNS, such as brain trauma. In addition, since activation of LPAR1 leads to inflammation and demyelination in the CNS, LPAR1 antagonists could also promote beneficial effects in CNS conditions where inflammation and/or demyelination is involved in the course of the pathology such as in multiple sclerosis, stroke, Alzheimer's disease, Parkinson's Disease, amyotrophic lateral sclerosis, among others.

[0059] These data suggest that LPA receptors other than LPA1 may also play a role in inflammation, locomotor deficits and myelin loss associated with SCI. Autotaxin is the major LPA-producing enzyme for circulating LPA. Based on the potential role for multiple LPA receptors in regulating inflammation, locomotor deficits and myelin loss associated with SCI and because there is broad functional redundancy between the different LPA receptors, it may be more efficacious to treat SCI by limiting production of the ligand, LPA, using inhibitors of the autotaxin enzyme.

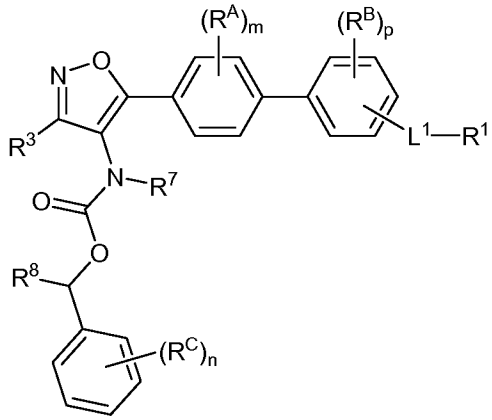
CLAIMS

What is Claimed is:

1. A method for treating a central nervous system injury in a patient in need of such treatment comprising administering to a patient a therapeutically effective amount of an LPA1 receptor antagonist.

2. The method according to claim 1, wherein said LPA1 receptor antagonist is selected from the group consisting of antisense nucleic acids, siRNAs and antagonist antibodies against LPA1, soluble LPA1 and small molecule inhibitors that bind to LPA1 to inhibit signaling.

3. The method according to claim 2 wherein said LPA1 receptor antagonist is a small molecule having the following structure:



Formula (I)

wherein

R^1 is $-CO_2H$, $-CO_2R^D$, -CN, tetrazolyl, $-C(=O)NH_2$, $-C(=O)NHR^{10}$, $-C(=O)NHSO_2R^{10}$ or $-C(=O)NHCH_2CH_2SO_3H$; R^D is H or C_1-C_4alkyl;

L^1 is absent or C_1-C_6alkylene;

R^3 is H, C_1-C_4alkyl, C_3-C_6cycloalkyl, or C_1-C_4fluoroalkyl;

R^7 is H or C_1-C_4alkyl;

R^8 is H, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

R^{10} is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, or a substituted or unsubstituted phenyl;

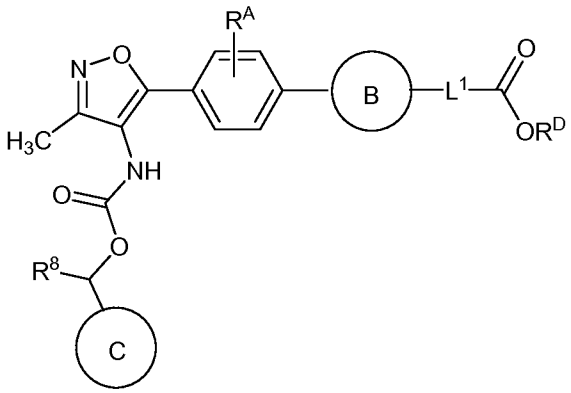
each of R^A, R^B, and R^C are independently selected from H, F, Cl, Br, I, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0, 1, or 2.

4. The method according to claim 3 wherein said compound has the following Formula Ia, or is a pharmaceutically acceptable salt thereof:



Formula 1a

wherein

C is optionally substituted phenyl;

R^8 is alkyl;

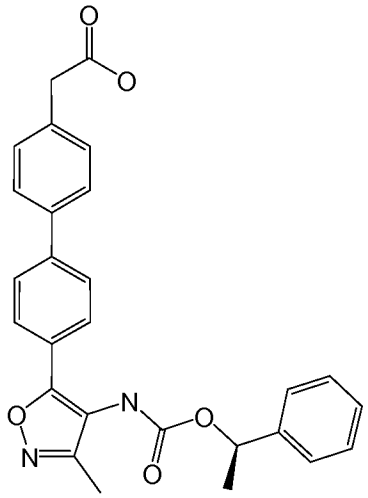
R^A is H, alkyl;

B is optionally substituted phenylene;

L^1 is optionally substituted alkylenyl; and

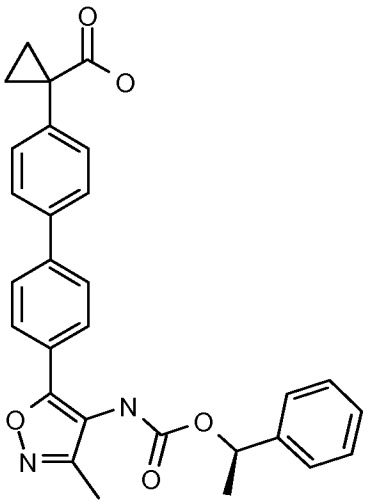
R^D is H, halo, or alkyl.

5. The method according to claim 4 wherein said compound is



or a pharmaceutically acceptable salt thereof.

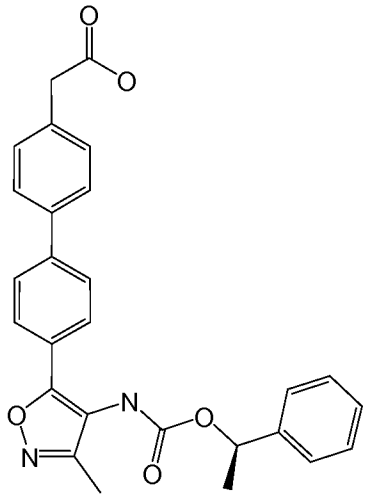
6. The method according to claim 2 wherein said compound is



or a pharmaceutically acceptable salt thereof.

7. The method according claim 2 wherein said central nervous system injury is a spinal cord injury, brain trauma or stroke.

8. The method according to claim 7 wherein said central nervous system injury is treated by administering to said patient a compound having the following structure:



or a pharmaceutically acceptable salt thereof.

8. A method for ameliorating inflammation or demyelination in a patient that is suffering from a neural condition comprising administering to said patient a therapeutically effective amount of an LPA1 receptor antagonist.

9. The method according to claim 8 wherein said neural condition is selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or neuropathic pain.

10. A method for treating a central nervous system injury in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of an autotaxin inhibiting substance.

11. The method according to claim 10, wherein said autotaxin inhibiting substance is selected from the group consisting of antisense nucleic acids, siRNAs, and inhibitory antibodies against autotaxin and small molecule compounds that inhibit the enzyme activity of autotaxin.

12. The method according to claim 10 wherein said central nervous system injury is a spinal cord injury, brain trauma or stroke.

13. A method for ameliorating inflammation or demyelination in a patient suffering from a neural condition comprising administering to said patient a therapeutically effective amount of an autotaxin inhibiting substance.

14. A pharmaceutical composition for the treatment of spinal cord injury comprising a therapeutically effective amount of an LPA1 receptor antagonist in a pharmaceutically acceptable carrier.

15. A pharmaceutical composition for the treatment of a CNS injury comprising a therapeutically effective amount of an autotaxin inhibitor and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/064098

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/42 A61K39/00 A61P25/00
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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 474 120 A (AMIRA PHARMACEUTICALS INC [US]) 6 April 2011 (2011-04-06) abstract page 1 - page 4 page 15, paragraph 82 -----	1,2,6, 8-15
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2013	04/03/2013

Name and mailing address of the ISA/	Authorized officer
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International application No
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Y	WO 2011/005581 A2 (LPATH INC [US]; PEBAY ALICE MARIE [AU]; TURNLEY ANN MAREE [AU]) 13 January 2011 (2011-01-13) claims	1-15
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Y	EP 2 324 852 A1 (UNIV NAGASAKI [JP]; M S S KK [JP]) 25 May 2011 (2011-05-25) page 1, paragraph 4 - paragraph 5 page 2, paragraph 9	1-15

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