

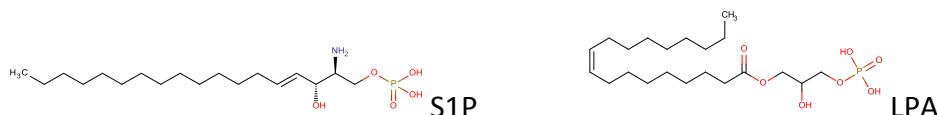
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Lipid GPCR (EDG) Receptor Screening Library

8,000 compounds targeting S1P1-5 and LPA1-3; GPR3/6/12 (orphans with some binding site similarity), GPR23/GPR92/P2Y5 (LPA4-6) (newly identified LPA receptors)

Background

There is significant interest in the EDG class of G-Protein Coupled Receptors as drug targets, particularly following the regulatory approval of the S1P1 functional antagonist Fingolimod (Gilenya, Novartis 2010 in US, 2011 in Europe). The compound is the first orally available disease-modifying treatment for relapsing-remitting Multiple Sclerosis (MS)¹. Compounds with enhanced selectivity are being sought for this indication²⁻⁸, with other members of the receptor family offering scope for a wide variety of additional indications, including LPA1 where antagonists are in development for fibrotic diseases (BMS-986020 and SAR100842).



The tractability of the receptor class has been demonstrated by an increasing number of chemotypes with known activity: currently there are 1,393 compounds across 73 papers in ChEMBL⁹. Broadly, these may be partitioned into 2 types: lipophilic acid compounds which somewhat mimic the endogenous ligands (above) and are presumably orthosteric; and non-acidic ligands which may be orthosteric or allosteric. There are also a modest number of compounds derived from the acidic ligands where the acidic head-group has been successfully replaced with a non-acid.

A screening library of ~8,000 compounds has been designed based on available and newly synthesized compounds from Enamine. These target the family of 8 EDG receptors (S1P1-S1P5 and LPA1-3). The compounds may also be appropriate for screening at GPR3, GPR6 and GPR12 orphan receptors given some TM bundle binding site similarity¹⁰ and/or GPR23, GPR92 and P2Y5 given their more recent classification as additional, albeit distinct, LPA receptors¹¹. The compounds have been selected using a combination of ligand-based methods including chemical fingerprints, 2D pharmacophores and 3D shape/feature matches. They represent a mixture of compounds for expanding SAR around known chemotypes and scaffold hops seeking novelty. The current set of compounds covers the non-acidic classes of ligand, with acidic compounds being designed via a different procedure and offered separately.

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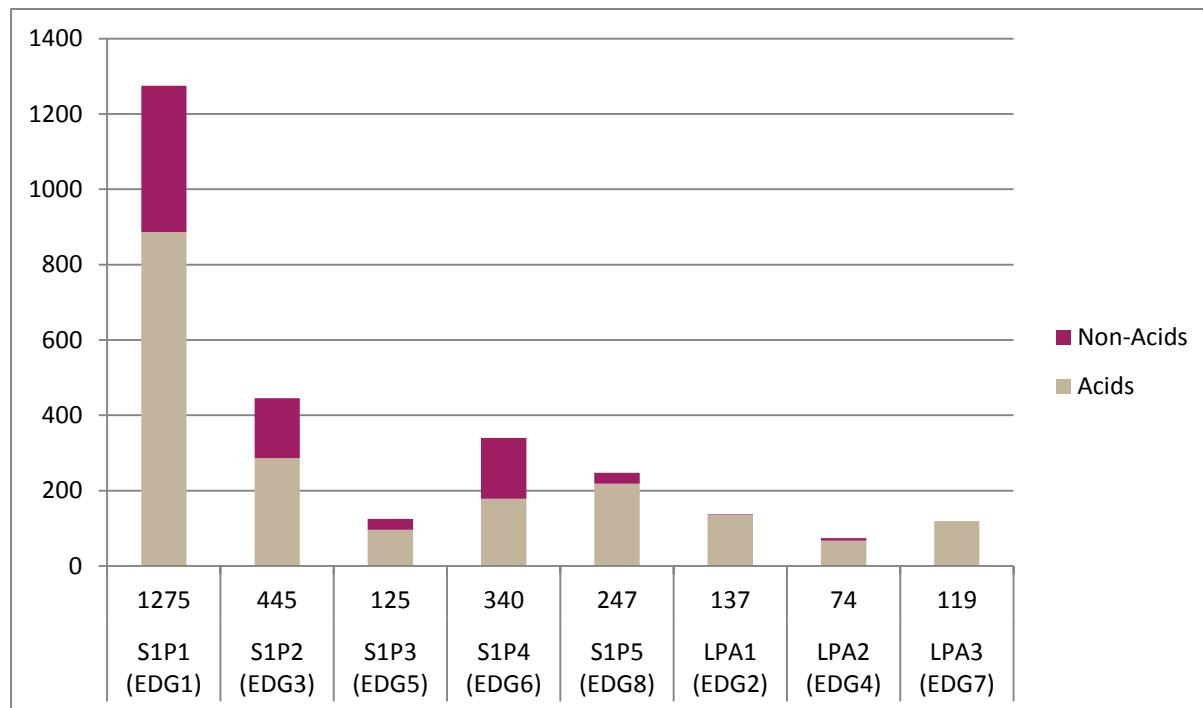
Biological Roles Associated with S1P1-5 and LPA1-3 (EDG1-8) Receptors

Receptor	Biological Roles/Potential Indications
S1P Family S1P1-5	Immune System ¹² , Cancer ¹³⁻¹⁵ , Kidney Disease ¹⁶ , Kidney Injury ¹⁷ , Acute Lung Injury ¹⁸ , Acute CNS Diseases ¹⁹ , Pain ²⁰ , Age-Related Macular Degeneration ²¹ and Bone Formation/Resorption ²² .
S1P1	Multiple Sclerosis (MS) ^{1-8,23-25} , Immunosuppression for Transplants ²⁶⁻²⁸ , Inflammatory Bowel Disease ²⁹ , Auto-Immune Diabetes ³⁰ , Diabetic Heart Disease ³¹ , Bradycardia ³² , Vasorelaxation ³³ , Cancer ^{34,35} , Chemotherapy-Induced Painful Peripheral Neuropathy ³⁶ , Hepatic Injury ^{37,38} , Psoriasis ³⁹ , Thrombopoiesis ^{40,41} and Bone Resorption ⁴² .
S1P2	Reviewed ⁴³ , Autoimmune Disease ⁴⁴ and Immune Response ⁴⁵ , Synaptic Plasticity ⁴⁶ , Seizures ⁴⁷ , Diabetes ^{48,49} , Kidney Disease ⁵⁰⁻⁵⁴ , Vascular Inflammation ⁵⁵ , Abdominal Aortic Aneurysms ⁵⁶ , Portal Hypertension ⁵⁷ , Cholangiocarcinoma ⁵⁸ , Chronic Myeloid Leukemia (CML) ⁵⁹ , Lymphoma ⁶⁰ , Bone Resorption ⁴² , Fibrosis ⁶¹ , Recovery from Anaphylaxis ^{62,63} and others ⁶⁴⁻⁶⁹ .
S1P3	Diabetic Heart Disease ³¹ , Hypertension ³² , Heart Rate and Blood Pressure ⁷⁰⁻⁷² , Aneurysms ⁵⁶ , Fibrosis ^{61,73,74} , Asthma ⁷⁵ , Sepsis-Associated Acute Respiratory Distress Syndrome ⁷⁶ , Ischemia Reperfusion Injury ^{67,77,78} , Inflammatory Diseases ⁷⁹⁻⁸³ , Post-Traumatic Pain ⁸⁴ , Breast Cancer ⁸⁵ and Lung Adenocarcinoma ⁸⁶ .
S1P4	Breast Cancer ^{87,88} , Thrombopoiesis ⁴⁰ , Vasoconstriction ⁸⁹ , Autoimmune Diseases ⁹⁰ , Viral Infections and Thrombocytopenia ^{91,92} .
S1P5	MS ^{8,93} , Monocyte Trafficking ⁹⁴ , Brain Endothelial Barrier Function, Inflammatory Bowel Disease ²⁹ , Kidney Disease ⁹⁵ , Glioblastomas ⁹⁶ and Prostate Cancer ⁹⁷ .

Receptor	Biological Roles/Potential Indications
LPA Family LPA1-3 or LPA1-6	Reviews ⁹⁸⁻¹⁰⁰ , Cancer ¹⁰¹⁻¹¹⁰ , CNS Diseases ^{19,111} , Pain ^{112,113} , Anxiety ^{114,115} , Formation of the Nervous System ¹¹⁶ and Neurodegenerative Diseases ¹¹⁷ , Brain Penetration ¹¹⁸ , Spinal Cord Injury ¹¹⁹ , Development of the Vasculature ¹²⁰ , Pregnancy Induced Hypertension ¹²¹ , Fertility ¹²² and Reproduction ¹²³ , Atherosclerosis ^{124,125} and Athrombosis ¹²⁶ , Bone Formation / Resorption ^{22,127} , Fibrosis ^{128,129} , Asthma ¹³⁰ and Acute Lung Injury ^{131,132} and others ¹³³⁻¹³⁶ .
LPA1	Lung Fibrosis ^{21,122,137-139} , Systemic Sclerosis and Related Fibrotic Diseases ^{122,140} , Silicosis ¹⁴¹ , Neurogenesis, Synaptic Plasticity and Anxiety-Related Behaviour ¹⁴² , Myelination in the CNS ¹⁴³ , Neuropsychiatric Disorders ¹⁴⁴ , Cocaine Addiction ¹⁴⁵ , Pain ¹⁴⁶⁻¹⁴⁹ , Inflammation ¹⁵⁰ , Bladder Cancer ¹⁵¹ , Breast Cancer ^{152,153} , Pancreatic Cancer ^{154,155} , Metastasis ^{156,157} , Arthritis ¹⁵⁸⁻¹⁶⁰ , Bone Loss ^{127,161} , Obesity-Associated Metabolic Diseases ¹⁶² , Atopic Dermatitis ¹⁶³ , Fetal Hydrocephalus ¹⁶⁴ .
LPA2	Arthritis ¹⁵⁹ , T-Cell Motility ¹⁶⁵ , Lung Fibrosis ¹⁶⁶ , Gastric Cancer ¹⁶⁷ , Cervical Cancer ¹⁶⁸ , Pancreatic Cancer ^{169,170} , Radiation Injury ^{171,172} , Amelioration of Stress- or Aspirin-Induced Stomach Injury ^{173,174} and Diarrhea ¹⁷⁵ .
LPA3	Cancer ^{154,155,168,176-181} , Inflammation and Reproductive Biology ¹⁸² , Pain ^{147,149} , Scleroderma ¹⁴⁰ , Pregnancy Induced Hypertension ¹⁸³ , Silicosis ¹⁴¹ , and Erythropoiesis ¹⁸⁴ .

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Library Profile

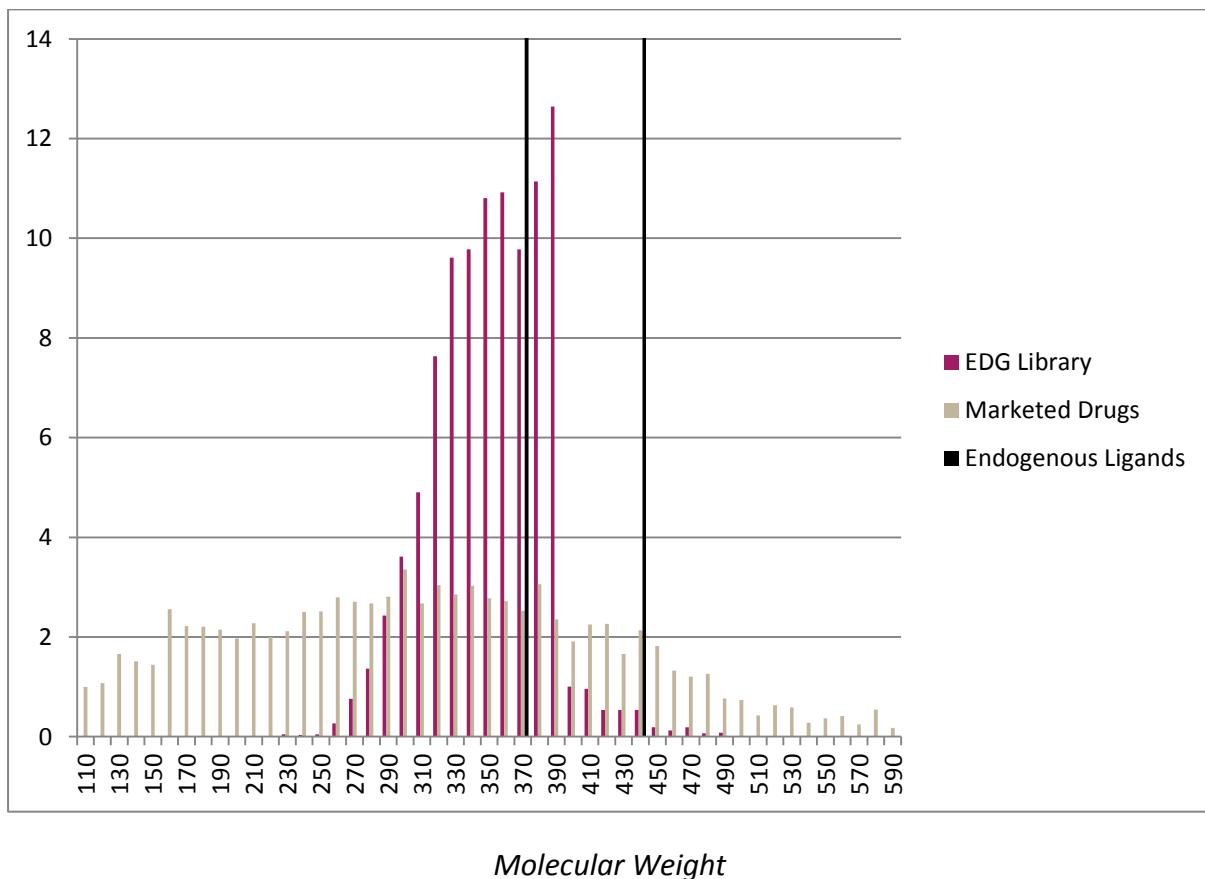


Activity Distribution of Training Set

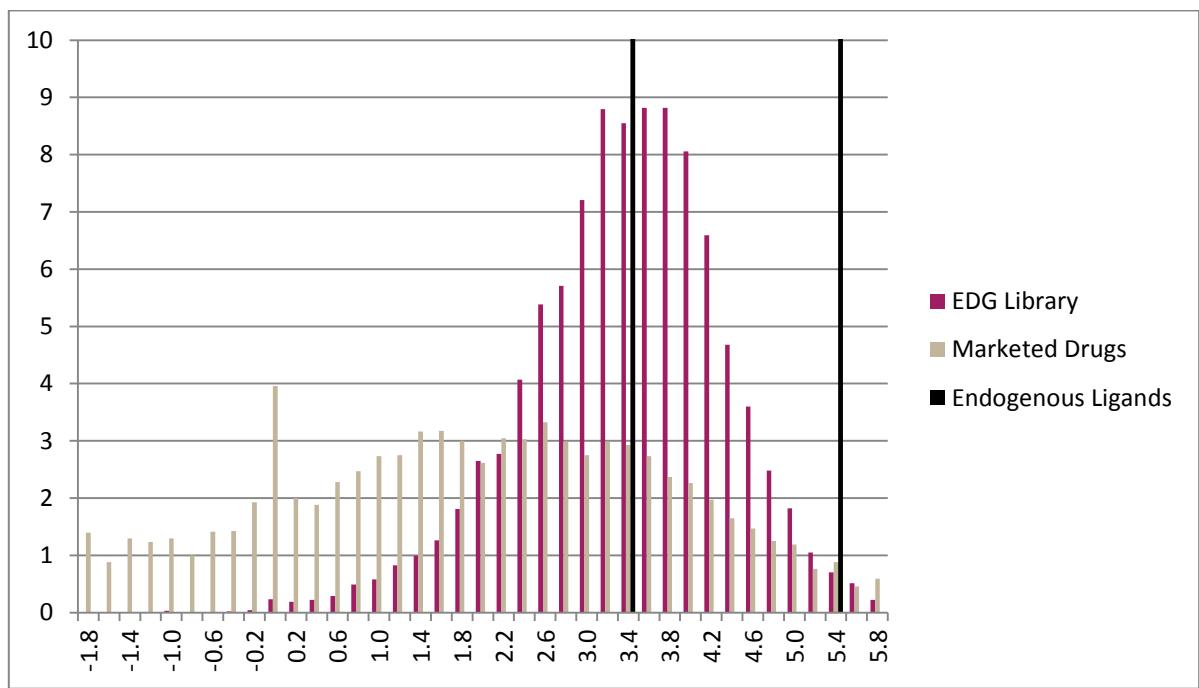
The total number of unique compounds with activity better than 1uM is 1,393 of which 870 are acidic and 523 are non-acidic. Publications detailing the non-acidic ligands are cited^{6,91,92,185–211} and formed the basis for the library design via a combination of ligand-based selection methods. Acidic compounds were also included in the analysis but only one yielded any matches; a structure-based selection has been performed for these instead and is available separately (see below).

The library profile is shown (red) versus marketed drugs (grey) and the two endogenous ligands (black) as benchmarks. These plots demonstrate a good balance of properties, with the distributions consistently within the envelope of marketed drugs and generally quite left-shifted. This suggests head-room for the optimization of the compounds whilst remaining within drug-like ranges. The main exception to this is the cLogP distribution which is towards the upper end of typical ranges due to the more lipophilic nature of the known ligands – something that is probably not a surprise given that they are ligands for a class of lipid receptors.

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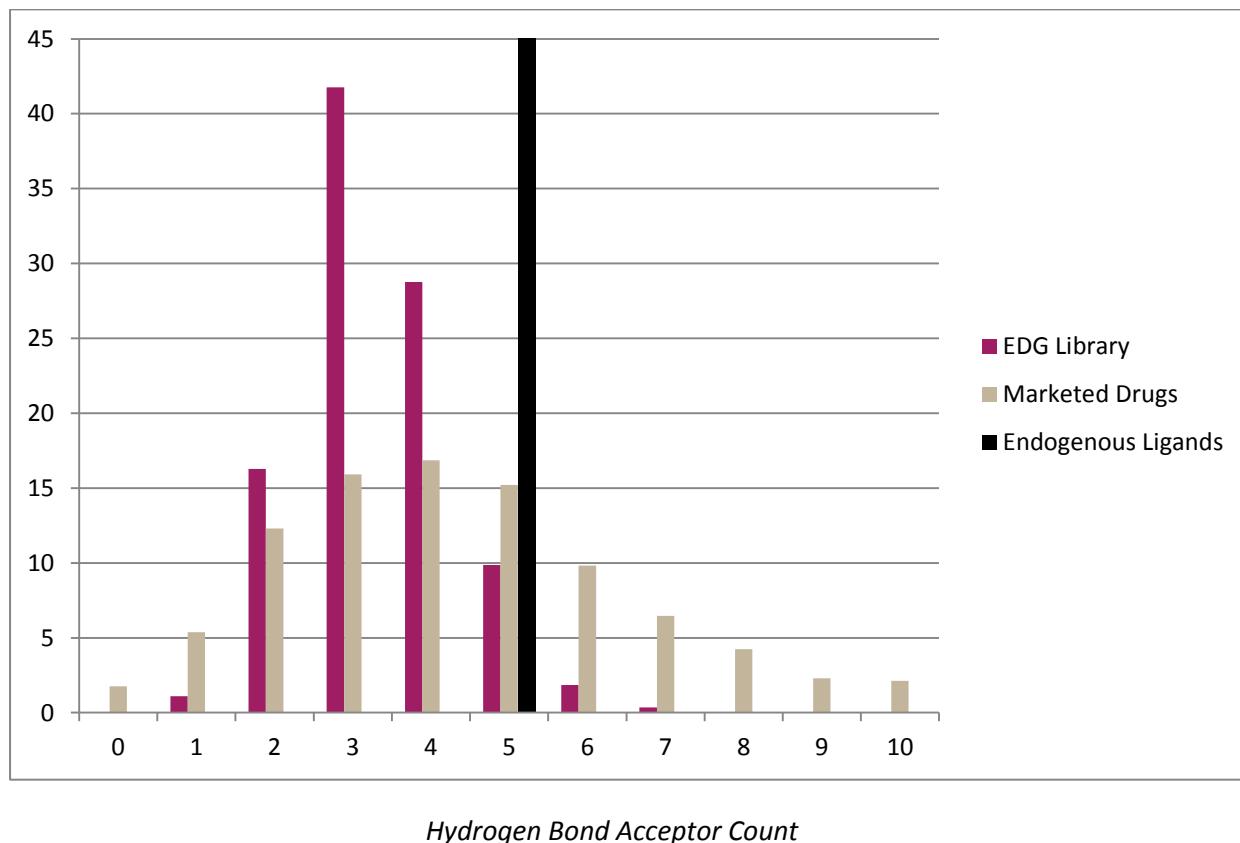


Molecular Weight

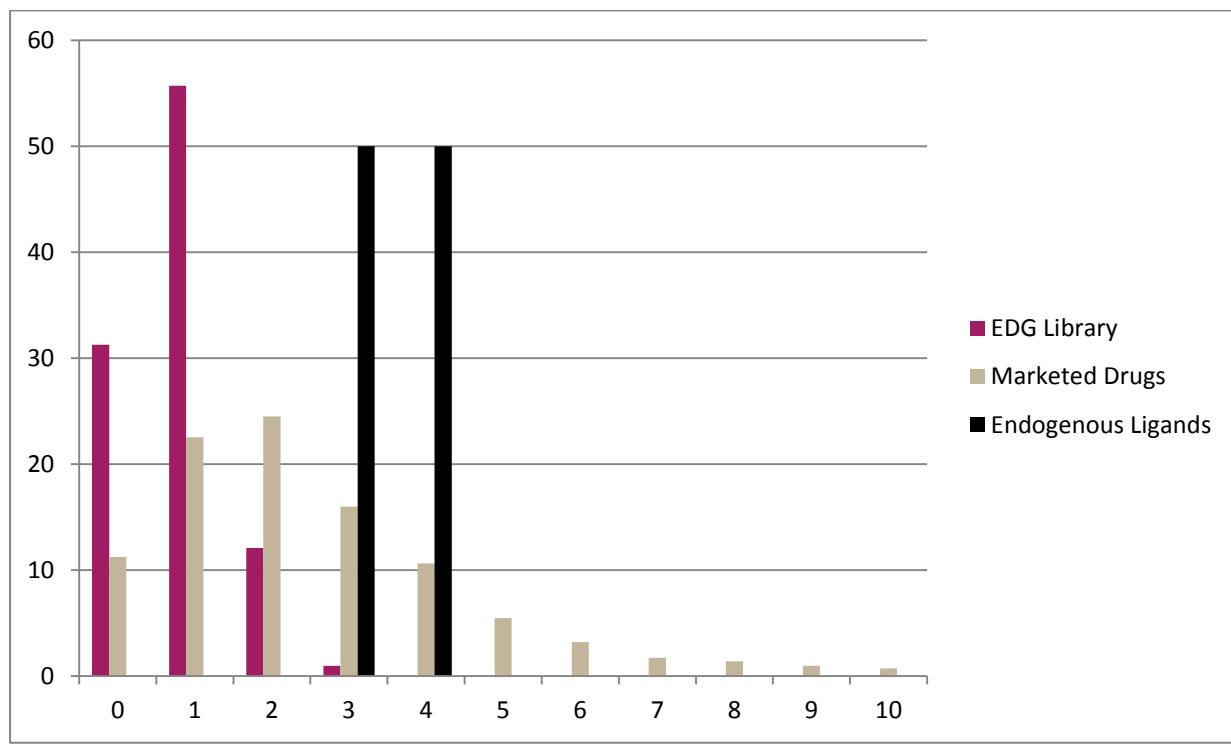


cLogP

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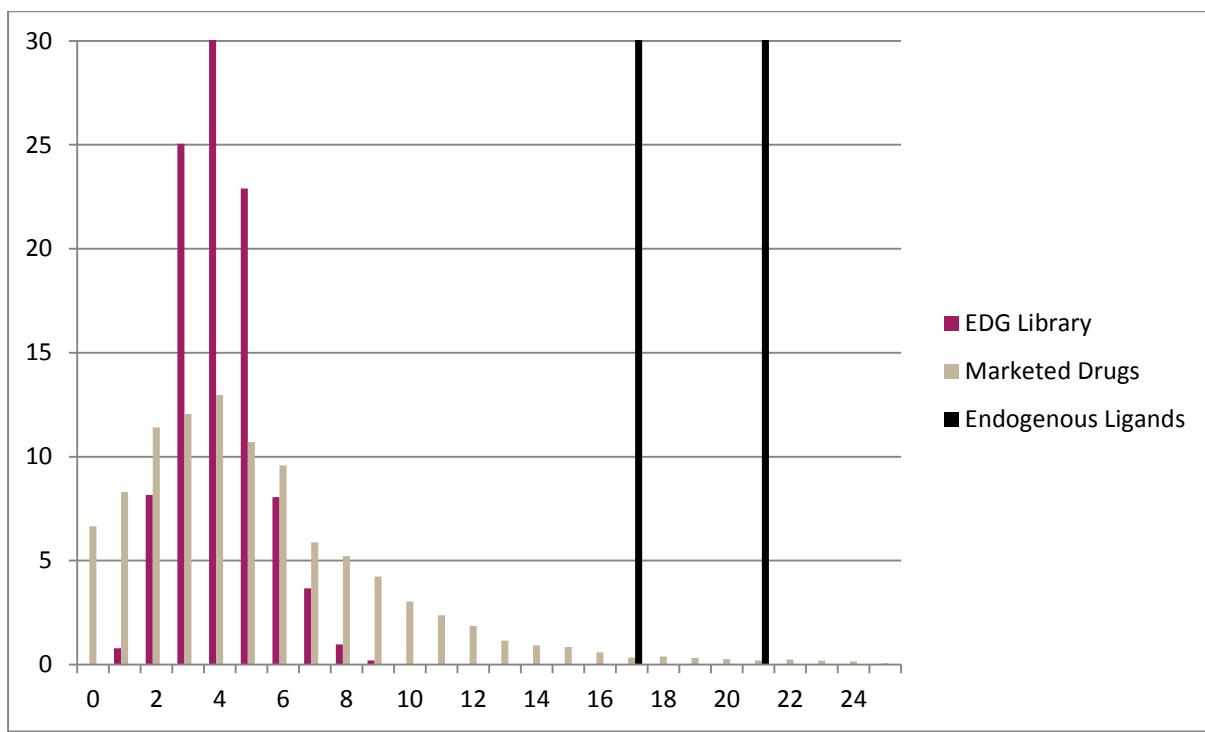
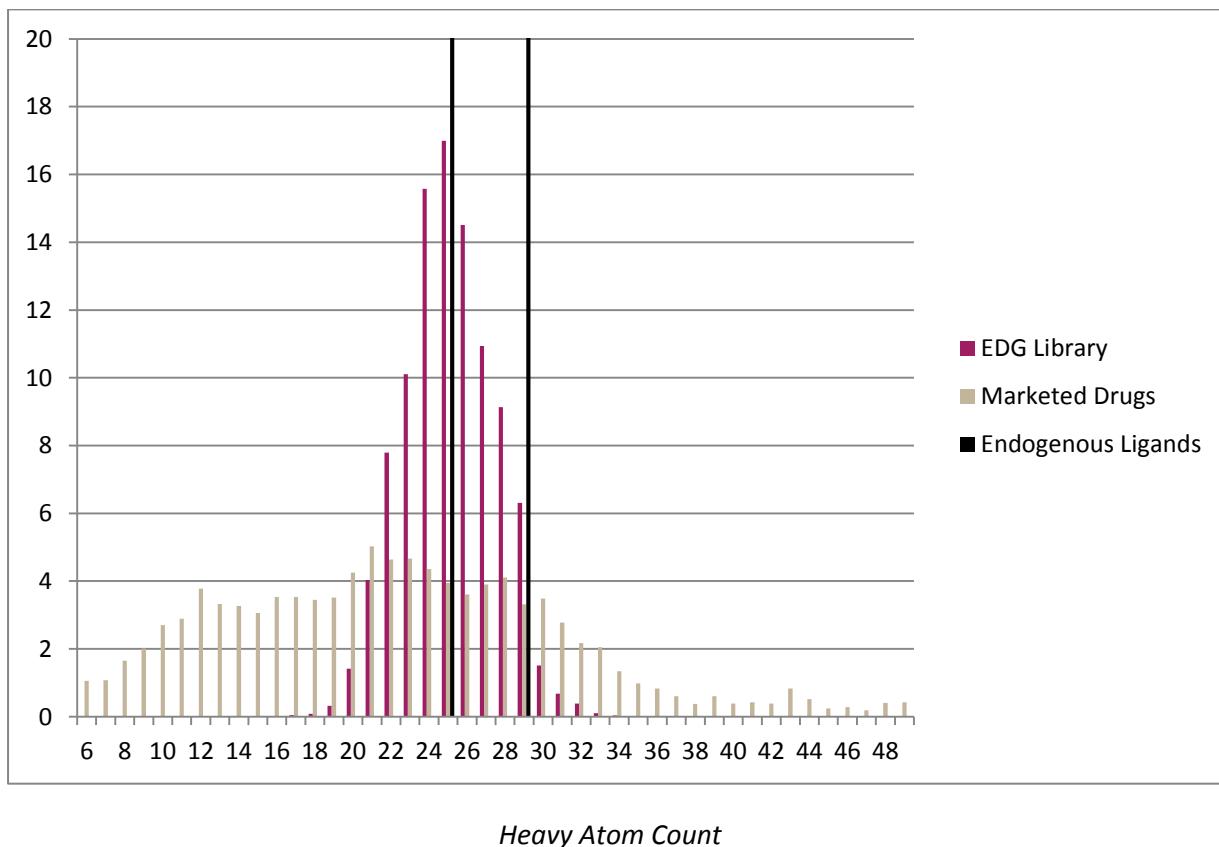


Hydrogen Bond Acceptor Count



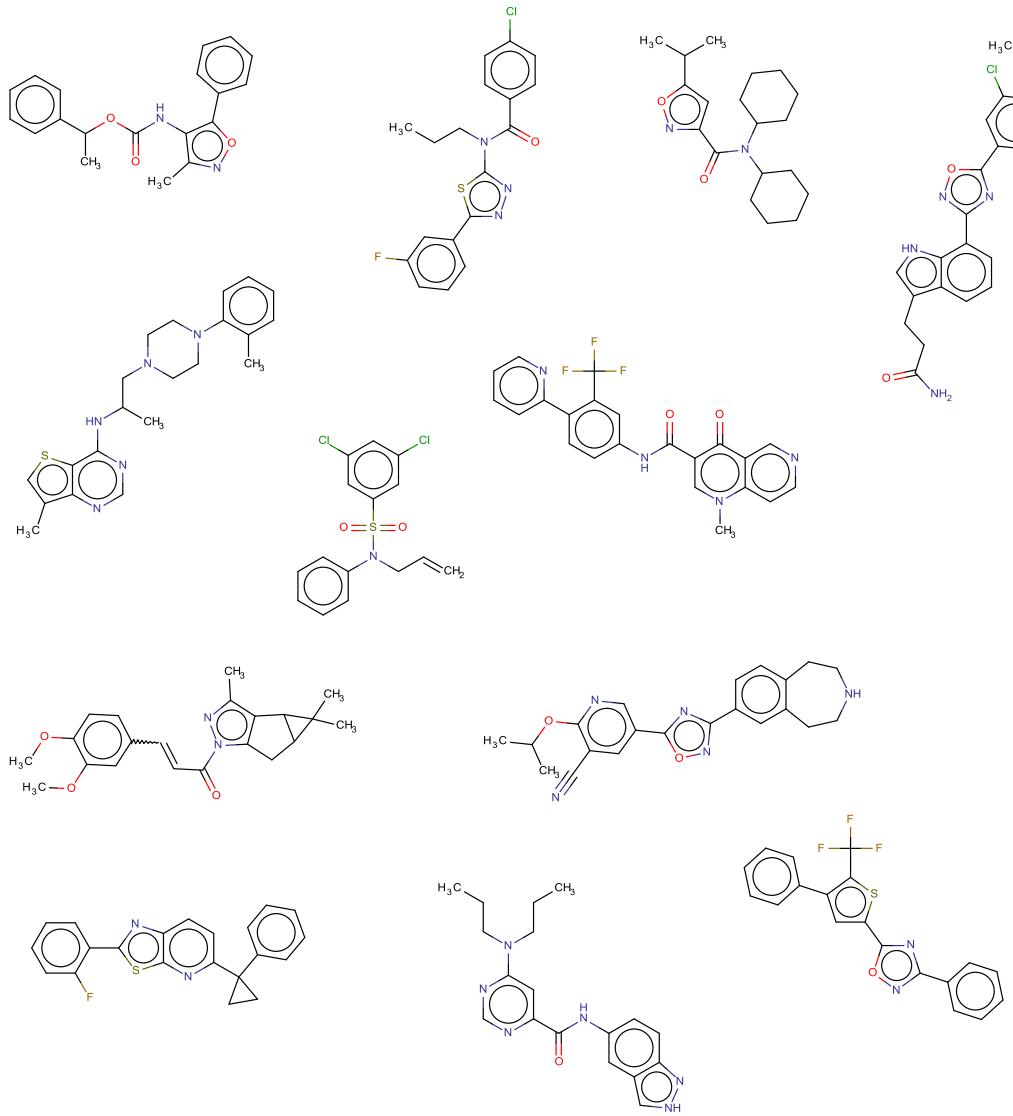
Hydrogen Bond Donor Count

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The selected compounds map to >140 actives across a range of different chemotypes and cover ~60% of the 242 known actives passing NQuX substructural and property filters.



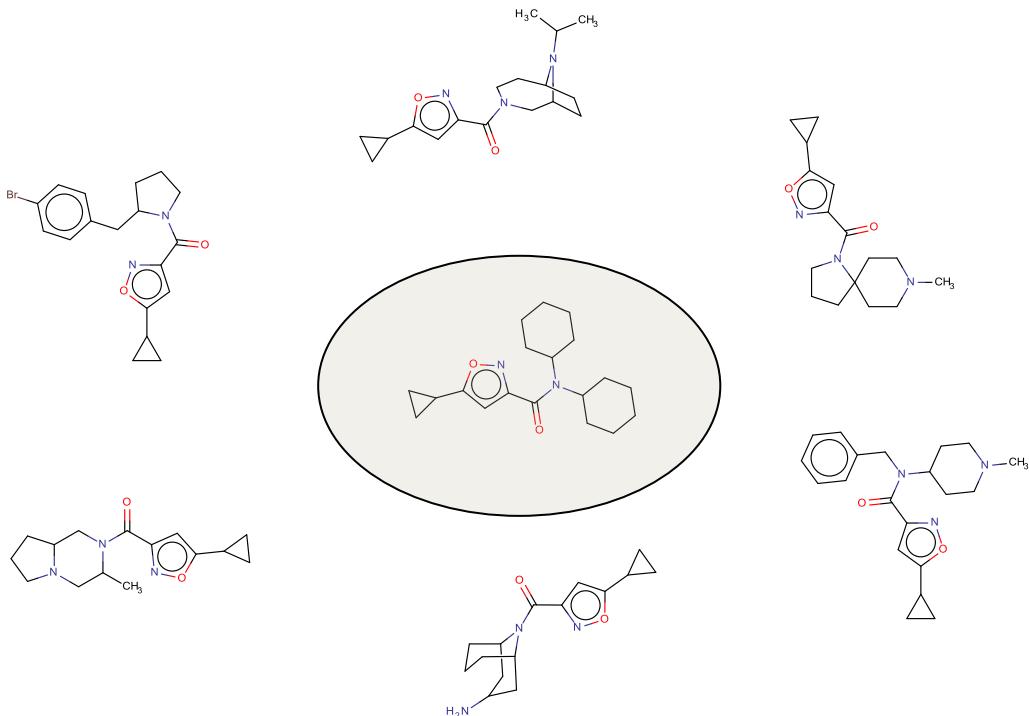
Example known active molecules yielding matches within the Enamine collections

Further Information

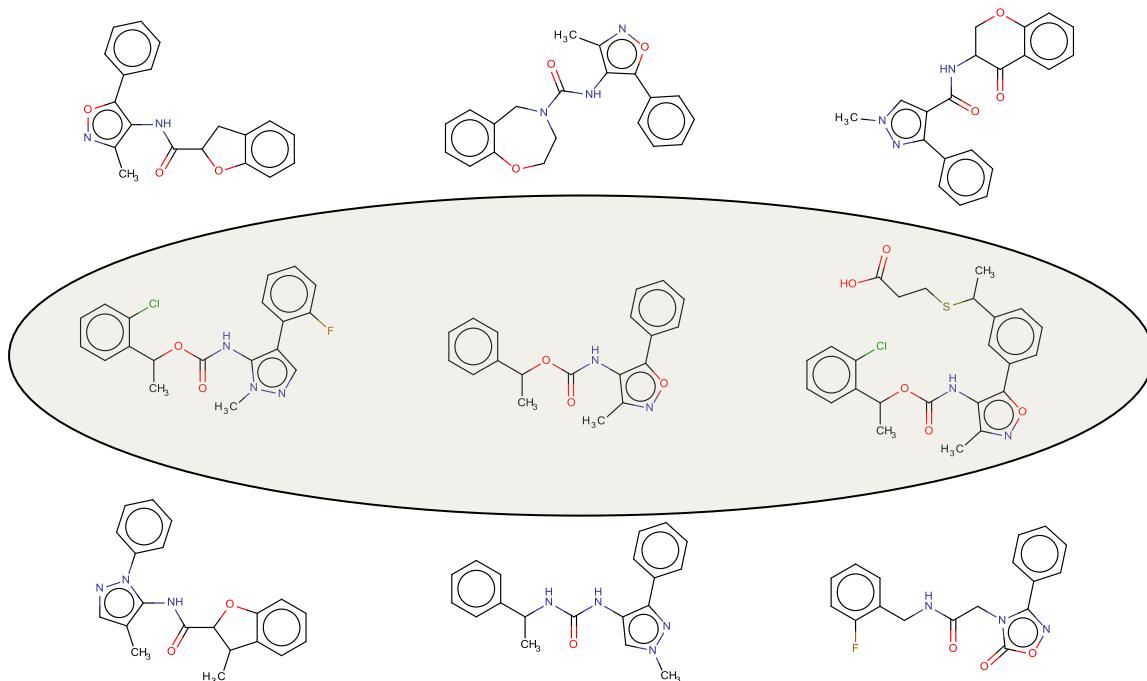
A second library of ~250 compounds has been designed targeting the orthosteric site of S1P1 based on high-throughput docking of acidic moieties to an optimized form of the available crystal structure (3V2Y)²¹². These compounds are available on an exclusive or semi-exclusive basis. Crystal structures for the LPA1 receptor have been solved very recently (4Z34, 4Z35, 4Z36)²¹³ and are being used for a second structure-based selection. Further custom libraries can be designed on request targeting orthosteric or allosteric sites as required. Please contact NQuX for details (info@nquix.com).

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Example Selections



The S1P3 allosteric agonist ML249/CYM 5541 ($EC_{50}=72\text{-}132\text{nM}$) surrounded by a selection of compounds from the library.



LPA1 antagonists^{192,196} surrounded by a selection of compounds from the library.



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References

1. Chiba, K.; Adachi, K. Discovery of fingolimod, the sphingosine 1-phosphate receptor modulator and its application for the therapy of multiple sclerosis. *Future Med. Chem.* **2012**, *4*, 771–81.
2. Bigaud, M.; Guerini, D.; Billich, A.; et al. Second generation S1P pathway modulators: research strategies and clinical developments. *Biochim. Biophys. Acta* **2014**, *1841*, 745–58.
3. Meng, Q.; Zhao, B.; Xu, Q.; et al. Indole-propionic acid derivatives as potent, S1P₃-sparing and EAE efficacious sphingosine-1-phosphate 1 (S1P₁) receptor agonists. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2794–7.
4. Nakamura, T.; Asano, M.; Sekiguchi, Y.; et al. Discovery of CS-2100, a potent, orally active and S1P₃-sparing S1P₁ agonist. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1788–92.
5. Xu, H.; Zhang, H.; Luan, L.; et al. Discovery of thiadiazole amides as potent, S1P₃-sparing agonists of sphingosine-1-phosphate 1 (S1P₁) receptor. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2456–9.
6. Demont, E. H.; Arpino, S.; Bit, R. A.; et al. Discovery of a brain-penetrant S1P₃-sparing direct agonist of the S1P₁ and S1P₅ receptors efficacious at low oral dose. *J. Med. Chem.* **2011**, *54*, 6724–33.
7. Asano, M.; Nakamura, T.; Sekiguchi, Y.; et al. Synthesis and SAR of 1,3-thiazolyl thiophene and pyridine derivatives as potent, orally active and S1P₃-sparing S1P₁ agonists. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3083–8.
8. Yamamoto, R.; Okada, Y.; Hirose, J.; et al. ASP4058, a novel agonist for sphingosine 1-phosphate receptors 1 and 5, ameliorates rodent experimental autoimmune encephalomyelitis with a favorable safety profile. *PLoS One* **2014**, *9*, e110819.
9. Bento, A. P.; Gaulton, A.; Hersey, A.; et al. The ChEMBL bioactivity database: an update. *Nucleic Acids Res.* **2014**, *42*, D1083–90.
10. Gloriam, D. E.; Foord, S. M.; Blaney, F. E.; et al. Definition of the G protein-coupled receptor transmembrane bundle binding pocket and calculation of receptor similarities for drug design. *J. Med. Chem.* **2009**, *52*, 4429–42.
11. Yanagida, K.; Ishii, S. Non-Edg family LPA receptors: the cutting edge of LPA research. *J. Biochem.* **2011**, *150*, 223–32.
12. Simmons, S.; Ishii, M. Sphingosine-1-phosphate: a master regulator of lymphocyte egress and immunity. *Arch. Immunol. Ther. Exp. (Warsz.)* **2014**, *62*, 103–15.
13. Tabasinezhad, M.; Samadi, N.; Ghanbari, P.; et al. Sphingosin 1-phosphate contributes in tumor progression. *J. Cancer Res. Ther.* **9**, 556–63.
14. Zhang, L.; Wang, H.-D.; Ji, X.-J.; et al. FTY720 for cancer therapy (Review). *Oncol. Rep.* **2013**, *30*, 2571–8.
15. Pyne, N. J.; Tonelli, F.; Lim, K. G.; et al. Sphingosine 1-phosphate signalling in cancer. *Biochem. Soc. Trans.* **2012**, *40*, 94–100.

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16. Koch, A.; Pfeilschifter, J.; Huwiler, A. Sphingosine 1-phosphate in renal diseases. *Cell. Physiol. Biochem.* **2013**, *31*, 745–60.
17. Kusch, A.; Hoff, U.; Bubalo, G.; et al. Novel signalling mechanisms and targets in renal ischaemia and reperfusion injury. *Acta Physiol. (Oxf)*. **2013**, *208*, 25–40.
18. Natarajan, V.; Dudek, S. M.; Jacobson, J. R.; et al. Sphingosine-1-phosphate, FTY720, and sphingosine-1-phosphate receptors in the pathobiology of acute lung injury. *Am. J. Respir. Cell Mol. Biol.* **2013**, *49*, 6–17.
19. Choi, J. W.; Chun, J. Lysophospholipids and their receptors in the central nervous system. *Biochim. Biophys. Acta* **2013**, *1831*, 20–32.
20. Welch, S. P.; Sim-Selley, L. J.; Selley, D. E. Sphingosine-1-phosphate receptors as emerging targets for treatment of pain. *Biochem. Pharmacol.* **2012**, *84*, 1551–62.
21. Pyne, N. J.; Dubois, G.; Pyne, S. Role of sphingosine 1-phosphate and lysophosphatidic acid in fibrosis. *Biochim. Biophys. Acta* **2013**, *1831*, 228–38.
22. Dziak, R. The role of sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA) in regulation of osteoclastic and osteoblastic cells. *Immunol. Invest.* **2013**, *42*, 510–8.
23. Deng, H.; Bernier, S. G.; Doyle, E.; et al. Discovery of Clinical Candidate GSK1842799 As a Selective S1P1 Receptor Agonist (Prodrug) for Multiple Sclerosis. *ACS Med. Chem. Lett.* **2013**, *4*, 942–7.
24. Groves, A.; Kihara, Y.; Chun, J. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. *J. Neurol. Sci.* **2013**, *328*, 9–18.
25. Komiya, T.; Sato, K.; Shioya, H.; et al. Efficacy and immunomodulatory actions of ONO-4641, a novel selective agonist for sphingosine 1-phosphate receptors 1 and 5, in preclinical models of multiple sclerosis. *Clin. Exp. Immunol.* **2013**, *171*, 54–62.
26. Jia, L.; Liu, Y.; Wang, L.; et al. Effects of topical sphingosine-1-phosphate 1 receptor agonist on corneal allograft in mice. *Cornea* **2014**, *33*, 398–404.
27. Zhu, J.; Liu, Y.; Pi, Y.; et al. Systemic application of sphingosine 1-phosphate receptor 1 immunomodulator inhibits corneal allograft rejection in mice. *Acta Ophthalmol.* **2014**, *92*, e12–21.
28. Song, J.; Hagiya, H.; Kurata, H.; et al. Prevention of GVHD and graft rejection by a new S1P receptor agonist, W-061, in rat small bowel transplantation. *Transpl. Immunol.* **2012**, *26*, 163–70.
29. P032. Pharmacokinetic Properties of RPC1063, a Selective S1P1 and S1P5 Receptor Agonist, Significantly Contribute to Efficacy in Animal Models of Inflammatory Bowel Disease. *J. Crohns. Colitis* **2015**, *9 Suppl 1*, S93.
30. You, S.; Piali, L.; Kuhn, C.; et al. Therapeutic use of a selective S1P1 receptor modulator ponesimod in autoimmune diabetes. *PLoS One* **2013**, *8*, e77296.
31. Yin, Z.; Fan, L.; Wei, L.; et al. FTY720 protects cardiac microvessels of diabetes: a critical role of S1P1/3 in diabetic heart disease. *PLoS One* **2012**, *7*, e42900.

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32. Fryer, R. M.; Muthukumarana, A.; Harrison, P. C.; et al. The clinically-tested S1P receptor agonists, FTY720 and BAF312, demonstrate subtype-specific bradycardia (S1P₁) and hypertension (S1P₃) in rat. *PLoS One* **2012**, *7*, e52985.
33. Roviezzo, F.; De Angelis, A.; De Gruttola, L.; et al. Involvement of proteinase activated receptor-2 in the vascular response to sphingosine 1-phosphate. *Clin. Sci. (Lond.)* **2014**, *126*, 545–56.
34. Fujii, Y.; Ueda, Y.; Ohtake, H.; et al. Blocking S1P interaction with S1P₁ receptor by a novel competitive S1P₁-selective antagonist inhibits angiogenesis. *Biochem. Biophys. Res. Commun.* **2012**, *419*, 754–60.
35. Kluk, M. J.; Ryan, K. P.; Wang, B.; et al. Sphingosine-1-phosphate receptor 1 in classical Hodgkin lymphoma: assessment of expression and role in cell migration. *Lab. Invest.* **2013**, *93*, 462–71.
36. Janes, K.; Little, J. W.; Li, C.; et al. The development and maintenance of paclitaxel-induced neuropathic pain require activation of the sphingosine 1-phosphate receptor subtype 1. *J. Biol. Chem.* **2014**, *289*, 21082–97.
37. Liu, G.; Bi, Y.; Wang, R.; et al. Targeting S1P1 receptor protects against murine immunological hepatic injury through myeloid-derived suppressor cells. *J. Immunol.* **2014**, *192*, 3068–79.
38. Ham, A.; Kim, M.; Kim, J. Y.; et al. Selective deletion of the endothelial sphingosine-1-phosphate 1 receptor exacerbates kidney ischemia-reperfusion injury. *Kidney Int.* **2014**, *85*, 807–23.
39. Gooderham, M. Small molecules: an overview of emerging therapeutic options in the treatment of psoriasis. *Skin Therapy Lett.* **18**, 1–4.
40. Hla, T.; Galvani, S.; Rafii, S.; et al. S1P and the birth of platelets. *J. Exp. Med.* **2012**, *209*, 2137–40.
41. Zhang, L.; Orban, M.; Lorenz, M.; et al. A novel role of sphingosine 1-phosphate receptor S1pr1 in mouse thrombopoiesis. *J. Exp. Med.* **2012**, *209*, 2165–81.
42. Quint, P.; Ruan, M.; Pederson, L.; et al. Sphingosine 1-Phosphate (S1P) Receptors 1 and 2 Coordinately Induce Mesenchymal Cell Migration through S1P Activation of Complementary Kinase Pathways. *J. Biol. Chem.* **2013**, *288*, 5398–5406.
43. Adada, M.; Canals, D.; Hannun, Y. A.; et al. Sphingosine-1-phosphate receptor 2. *FEBS J.* **2013**, *280*, 6354–66.
44. Cruz-Orengo, L.; Daniels, B. P.; Dorsey, D.; et al. Enhanced sphingosine-1-phosphate receptor 2 expression underlies female CNS autoimmunity susceptibility. *J. Clin. Invest.* **2014**, *124*, 2571–84.
45. Moriyama, S.; Takahashi, N.; Green, J. A.; et al. Sphingosine-1-phosphate receptor 2 is critical for follicular helper T cell retention in germinal centers. *J. Exp. Med.* **2014**, *211*, 1297–305.
46. Kempf, A.; Tews, B.; Arzt, M. E.; et al. The sphingolipid receptor S1PR2 is a receptor for Nogo-a repressing synaptic plasticity. *PLoS Biol.* **2014**, *12*, e1001763.
47. Akahoshi, N.; Ishizaki, Y.; Yasuda, H.; et al. Frequent spontaneous seizures followed by spatial working memory/anxiety deficits in mice lacking sphingosine 1-phosphate receptor 2. *Epilepsy Behav.* **2011**, *22*, 659–65.

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48. Japtok, L.; Schmitz, E. I.; Fayyaz, S.; et al. Sphingosine 1-phosphate counteracts insulin signaling in pancreatic β -cells via the sphingosine 1-phosphate receptor subtype 2. *FASEB J.* **2015**.
49. Fayyaz, S.; Henkel, J.; Japtok, L.; et al. Involvement of sphingosine 1-phosphate in palmitate-induced insulin resistance of hepatocytes via the S1P2 receptor subtype. *Diabetologia* **2014**, *57*, 373–82.
50. Ishizawa, S.; Takahashi-Fujigasaki, J.; Kanazawa, Y.; et al. Sphingosine-1-phosphate induces differentiation of cultured renal tubular epithelial cells under Rho kinase activation via the S1P2 receptor. *Clin. Exp. Nephrol.* **2014**, *18*, 844–52.
51. Völzke, A.; Koch, A.; Meyer Zu Heringdorf, D.; et al. Sphingosine 1-phosphate (S1P) induces COX-2 expression and PGE2 formation via S1P receptor 2 in renal mesangial cells. *Biochim. Biophys. Acta* **2014**, *1841*, 11–21.
52. Park, S. W.; Kim, M.; Brown, K. M.; et al. Inhibition of sphingosine 1-phosphate receptor 2 protects against renal ischemia-reperfusion injury. *J. Am. Soc. Nephrol.* **2012**, *23*, 266–80.
53. Huang, K.; Liu, W.; Lan, T.; et al. Berberine reduces fibronectin expression by suppressing the S1P-S1P2 receptor pathway in experimental diabetic nephropathy models. *PLoS One* **2012**, *7*, e43874.
54. Liu, W.; Lan, T.; Xie, X.; et al. S1P2 receptor mediates sphingosine-1-phosphate-induced fibronectin expression via MAPK signaling pathway in mesangial cells under high glucose condition. *Exp. Cell Res.* **2012**, *318*, 936–43.
55. Zhang, G.; Yang, L.; Kim, G.; et al. Critical role of sphingosine-1-phosphate receptor 2 (S1PR2) in acute vascular inflammation. *Blood* **2013**, *122*, 443–55.
56. Qu, Z.; Cheuk, B. L. Y.; Cheng, S. W. K. Differential expression of sphingosine-1-phosphate receptors in abdominal aortic aneurysms. *Mediators Inflamm.* **2012**, *2012*, 643609.
57. Kageyama, Y.; Ikeda, H.; Watanabe, N.; et al. Antagonism of sphingosine 1-phosphate receptor 2 causes a selective reduction of portal vein pressure in bile duct-ligated rodents. *Hepatology* **2012**, *56*, 1427–38.
58. Liu, R.; Zhao, R.; Zhou, X.; et al. Conjugated bile acids promote cholangiocarcinoma cell invasive growth through activation of sphingosine 1-phosphate receptor 2. *Hepatology* **2014**, *60*, 908–18.
59. Salas, A.; Ponnusamy, S.; Senkal, C. E.; et al. Sphingosine kinase-1 and sphingosine 1-phosphate receptor 2 mediate Bcr-Abl1 stability and drug resistance by modulation of protein phosphatase 2A. *Blood* **2011**, *117*, 5941–52.
60. Green, J. A.; Suzuki, K.; Cho, B.; et al. The sphingosine 1-phosphate receptor S1P₂ maintains the homeostasis of germinal center B cells and promotes niche confinement. *Nat. Immunol.* **2011**, *12*, 672–80.
61. Sobel, K.; Menyhart, K.; Killer, N.; et al. Sphingosine 1-phosphate (S1P) receptor agonists mediate pro-fibrotic responses in normal human lung fibroblasts via S1P2 and S1P3 receptors and Smad-independent signaling. *J. Biol. Chem.* **2013**, *288*, 14839–51.

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62. Olivera, A.; Dillahunt, S. E.; Rivera, J. Interrogation of sphingosine-1-phosphate receptor 2 function in vivo reveals a prominent role in the recovery from IgE and IgG-mediated anaphylaxis with minimal effect on its onset. *Immunol. Lett.* **2013**, *150*, 89–96.
63. Cui, H.; Okamoto, Y.; Yoshioka, K.; et al. Sphingosine-1-phosphate receptor 2 protects against anaphylactic shock through suppression of endothelial nitric oxide synthase in mice. *J. Allergy Clin. Immunol.* **2013**, *132*, 1205–1214.e9.
64. Wang, X. Q.; Mao, L. J.; Fang, Q. H.; et al. Sphingosylphosphorylcholine induces α -smooth muscle actin expression in human lung fibroblasts and fibroblast-mediated gel contraction via S1P2 receptor and Rho/Rho-kinase pathway. *Prostaglandins Other Lipid Mediat.* **2014**, *108*, 23–30.
65. Japtok, L.; Schaper, K.; Bäumer, W.; et al. Sphingosine 1-phosphate modulates antigen capture by murine Langerhans cells via the S1P2 receptor subtype. *PLoS One* **2012**, *7*, e49427.
66. Germinario, E.; Peron, S.; Toniolo, L.; et al. S1P2 receptor promotes mouse skeletal muscle regeneration. *J. Appl. Physiol.* **2012**, *113*, 707–13.
67. Means, C. K.; Xiao, C.-Y.; Li, Z.; et al. Sphingosine 1-phosphate S1P2 and S1P3 receptor-mediated Akt activation protects against in vivo myocardial ischemia-reperfusion injury. *Am. J. Physiol. Heart Circ. Physiol.* **2007**, *292*, H2944–51.
68. Nakayama, M.; Tabuchi, K.; Hoshino, T.; et al. The influence of sphingosine-1-phosphate receptor antagonists on gentamicin-induced hair cell loss of the rat cochlea. *Neurosci. Lett.* **2014**, *561*, 91–5.
69. Gandy, K. A. O.; Canals, D.; Adada, M.; et al. Sphingosine 1-phosphate induces filopodia formation through S1PR2 activation of ERM proteins. *Biochem. J.* **2013**, *449*, 661–72.
70. Forrest, M.; Sun, S.-Y.; Hajdu, R.; et al. Immune cell regulation and cardiovascular effects of sphingosine 1-phosphate receptor agonists in rodents are mediated via distinct receptor subtypes. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 758–68.
71. Sanna, M. G.; Liao, J.; Jo, E.; et al. Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P3, respectively, regulate lymphocyte recirculation and heart rate. *J. Biol. Chem.* **2004**, *279*, 13839–48.
72. Nofer, J.-R.; van der Giet, M.; Tölle, M.; et al. HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P3. *J. Clin. Invest.* **2004**, *113*, 569–81.
73. Takuwa, N.; Ohkura, S.-I.; Takashima, S.-I.; et al. S1P3-mediated cardiac fibrosis in sphingosine kinase 1 transgenic mice involves reactive oxygen species. *Cardiovasc. Res.* **2010**, *85*, 484–93.
74. Murakami, K.; Kohno, M.; Kadoya, M.; et al. Knock out of S1P3 receptor signaling attenuates inflammation and fibrosis in bleomycin-induced lung injury mice model. *PLoS One* **2014**, *9*, e106792.
75. Trifilieff, A.; Fozard, J. R. Sphingosine-1-phosphate-induced airway hyper-reactivity in rodents is mediated by the sphingosine-1-phosphate type 3 receptor. *J. Pharmacol. Exp. Ther.* **2012**, *342*, 399–406.
76. Sun, X.; Ma, S.-F.; Wade, M. S.; et al. Functional promoter variants in sphingosine 1-phosphate receptor 3 associate with susceptibility to sepsis-associated acute respiratory distress syndrome. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2013**, *305*, L467–77.

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77. Theilmeier, G.; Schmidt, C.; Herrmann, J.; et al. High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. *Circulation* **2006**, *114*, 1403–9.
78. Zhang, G.-Q.; Liang, Z.; Zhang, X.-J. Sphingosine-1-phosphate receptors respond differently to early myocardial ischemia and ischemia-reperfusion in vivo. *Sheng Li Xue Bao* **2014**, *66*, 169–74.
79. Niessen, F.; Schaffner, F.; Furlan-Freguia, C.; et al. Dendritic cell PAR1-S1P3 signalling couples coagulation and inflammation. *Nature* **2008**, *452*, 654–8.
80. Fischer, I.; Alliod, C.; Martinier, N.; et al. Sphingosine kinase 1 and sphingosine 1-phosphate receptor 3 are functionally upregulated on astrocytes under pro-inflammatory conditions. *PLoS One* **2011**, *6*, e23905.
81. Nussbaum, C.; Bannenberg, S.; Keul, P.; et al. Sphingosine-1-phosphate receptor 3 promotes leukocyte rolling by mobilizing endothelial P-selectin. *Nat. Commun.* **2015**, *6*, 6416.
82. Van Hooren, K. W. E. M.; Spijkers, L. J. A.; van Breevoort, D.; et al. Sphingosine-1-phosphate receptor 3 mediates sphingosine-1-phosphate induced release of weibel-palade bodies from endothelial cells. *PLoS One* **2014**, *9*, e91346.
83. Awojoodu, A. O.; Ogle, M. E.; Sefcik, L. S.; et al. Sphingosine 1-phosphate receptor 3 regulates recruitment of anti-inflammatory monocytes to microvessels during implant arteriogenesis. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 13785–90.
84. Camprubí-Robles, M.; Mair, N.; Andratsch, M.; et al. Sphingosine-1-Phosphate-Induced Nociceptor Excitation and Ongoing Pain Behavior in Mice and Humans Is Largely Mediated by S1P3 Receptor. *J. Neurosci.* **2013**, *33*, 2582–2592.
85. Sukacheva, O.; Wadham, C.; Xia, P. Estrogen defines the dynamics and destination of transactivated EGF receptor in breast cancer cells: role of S1P₃ receptor and Cdc42. *Exp. Cell Res.* **2013**, *319*, 455–65.
86. Hsu, A.; Zhang, W.; Lee, J.-F.; et al. Sphingosine-1-phosphate receptor-3 signaling up-regulates epidermal growth factor receptor and enhances epidermal growth factor receptor-mediated carcinogenic activities in cultured lung adenocarcinoma cells. *Int. J. Oncol.* **2012**, *40*, 1619–26.
87. Ohotski, J.; Rosen, H.; Bittman, R.; et al. Sphingosine kinase 2 prevents the nuclear translocation of sphingosine 1-phosphate receptor-2 and tyrosine 416 phosphorylated c-Src and increases estrogen receptor negative MDA-MB-231 breast cancer cell growth: The role of sphingosine 1-phosphate receptor. *Cell. Signal.* **2014**, *26*, 1040–7.
88. Ohotski, J.; Long, J. S.; Orange, C.; et al. Expression of sphingosine 1-phosphate receptor 4 and sphingosine kinase 1 is associated with outcome in oestrogen receptor-negative breast cancer. *Br. J. Cancer* **2012**, *106*, 1453–9.
89. Ota, H.; Beutz, M. A.; Ito, M.; et al. S1P(4) receptor mediates S1P-induced vasoconstriction in normotensive and hypertensive rat lungs. *Pulm. Circ.* **1**, 399–404.
90. Schulze, T.; Golfier, S.; Tabeling, C.; et al. Sphingosine-1-phosphate receptor 4 (S1P₄) deficiency profoundly affects dendritic cell function and TH17-cell differentiation in a murine model. *FASEB J.* **2011**, *25*, 4024–36.

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91. Guerrero, M.; Urbano, M.; Zhao, J.; et al. Discovery, design and synthesis of novel potent and selective sphingosine-1-phosphate 4 receptor (S1P₄-R) agonists. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 537–42.
92. Urbano, M.; Guerrero, M.; Velaparthi, S.; et al. Discovery, synthesis and SAR analysis of novel selective small molecule S1P₄-R agonists based on a (2Z,5Z)-5-((pyrrol-3-yl)methylene)-3-alkyl-2-(alkylimino)thiazolidin-4-one chemotype. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6739–45.
93. Kappos, L.; Bar-Or, A.; Cree, B.; et al. Siponimod (BAF312) for the treatment of secondary progressive multiple sclerosis: Design of the phase 3 EXPAND trial. *Mult. Scler. Relat. Disord.* **2014**, *3*, 752.
94. Debien, E.; Mayol, K.; Biajoux, V.; et al. S1PR5 is pivotal for the homeostasis of patrolling monocytes. *Eur. J. Immunol.* **2013**, *43*, 1667–75.
95. Wünsche, C.; Koch, A.; Goldschmeding, R.; et al. Transforming growth factor β 2 (TGF- β 2)-induced connective tissue growth factor (CTGF) expression requires sphingosine 1-phosphate receptor 5 (S1P5) in human mesangial cells. *Biochim. Biophys. Acta* **2015**, *1851*, 519–26.
96. Quint, K.; Stiel, N.; Neureiter, D.; et al. The role of sphingosine kinase isoforms and receptors S1P1, S1P2, S1P3, and S1P5 in primary, secondary, and recurrent glioblastomas. *Tumour Biol.* **2014**, *35*, 8979–89.
97. Huang, Y.-L.; Chang, C.-L.; Tang, C.-H.; et al. Extrinsic sphingosine 1-phosphate activates S1P5 and induces autophagy through generating endoplasmic reticulum stress in human prostate cancer PC-3 cells. *Cell. Signal.* **2014**, *26*, 611–8.
98. Yung, Y. C.; Stoddard, N. C.; Chun, J. LPA receptor signaling: pharmacology, physiology, and pathophysiology. *J. Lipid Res.* **2014**, *55*, 1192–1214.
99. Fukushima, N.; Ishii, S.; Tsujiuchi, T.; et al. Comparative analyses of lysophosphatidic acid receptor-mediated signaling. *Cell. Mol. Life Sci.* **2015**.
100. Stoddard, N. C.; Chun, J. Promising pharmacological directions in the world of lysophosphatidic Acid signaling. *Biomol. Ther. (Seoul)*. **2015**, *23*, 1–11.
101. Leblanc, R.; Peyruchaud, O. New insights into the autotaxin/LPA axis in cancer development and metastasis. *Exp. Cell Res.* **2014**, *333*, 183–189.
102. Parrill, A. L. Design of anticancer lysophosphatidic acid agonists and antagonists. *Future Med. Chem.* **2014**, *6*, 871–83.
103. Tsujiuchi, T.; Araki, M.; Hirane, M.; et al. Lysophosphatidic acid receptors in cancer pathobiology. *Histol. Histopathol.* **2014**, *29*, 313–21.
104. Willier, S.; Butt, E.; Grunewald, T. G. P. Lysophosphatidic acid (LPA) signalling in cell migration and cancer invasion: a focussed review and analysis of LPA receptor gene expression on the basis of more than 1700 cancer microarrays. *Biol. Cell* **2013**, *105*, 317–33.
105. Gotoh, M.; Fujiwara, Y.; Yue, J.; et al. Controlling cancer through the autotaxin-lysophosphatidic acid receptor axis. *Biochem. Soc. Trans.* **2012**, *40*, 31–6.

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106. Houben, A. J. S.; Moolenaar, W. H. Autotaxin and LPA receptor signaling in cancer. *Cancer Metastasis Rev.* **2011**, *30*, 557–65.
107. Chen, Y.; Ramakrishnan, D. P.; Ren, B. Regulation of angiogenesis by phospholipid lysophosphatidic acid. *Front. Biosci. (Landmark Ed.)* **2013**, *18*, 852–61.
108. Liao, Y.; Mu, G.; Zhang, L.; et al. Lysophosphatidic acid stimulates activation of focal adhesion kinase and paxillin and promotes cell motility, via LPA1-3, in human pancreatic cancer. *Dig. Dis. Sci.* **2013**, *58*, 3524–33.
109. Lou, L.; Chen, Y. X.; Jin, L.; et al. Enhancement of invasion of hepatocellular carcinoma cells through lysophosphatidic acid receptor. *J. Int. Med. Res.* **2013**, *41*, 55–63.
110. Sokolov, E.; Eheim, A. L.; Ahrens, W. A.; et al. Lysophosphatidic acid receptor expression and function in human hepatocellular carcinoma. *J. Surg. Res.* **2013**, *180*, 104–13.
111. Yung, Y. C.; Stoddard, N. C.; Mirendil, H.; et al. Lysophosphatidic Acid Signaling in the Nervous System. *Neuron* **2015**, *85*, 669–682.
112. Oude Elferink, R. P. J.; Bolier, R.; Beuers, U. H. Lysophosphatidic acid and signaling in sensory neurons. *Biochim. Biophys. Acta* **2015**, *1851*, 61–5.
113. Ohsawa, M.; Miyabe, Y.; Katsu, H.; et al. Identification of the sensory nerve fiber responsible for lysophosphatidic acid-induced allodynia in mice. *Neuroscience* **2013**, *247*, 65–74.
114. Yamada, M.; Tsukagoshi, M.; Hashimoto, T.; et al. Lysophosphatidic acid induces anxiety-like behavior via its receptors in mice. *J. Neural Transm.* **2015**, *122*, 487–94.
115. Castilla-Ortega, E.; Escuredo, L.; Bilbao, A.; et al. 1-Oleoyl lysophosphatidic acid: a new mediator of emotional behavior in rats. *PLoS One* **2014**, *9*, e85348.
116. Frisca, F.; Sabbadini, R. A.; Goldshmit, Y.; et al. Biological effects of lysophosphatidic acid in the nervous system. *Int. Rev. Cell Mol. Biol.* **2012**, *296*, 273–322.
117. Park, H.; Kim, S.; Rhee, J.; et al. Synaptic enhancement induced by gintonin via lysophosphatidic acid receptor activation in central synapses. *J. Neurophysiol.* **2015**, *113*, 1493–500.
118. On, N. H.; Savant, S.; Toews, M.; et al. Rapid and reversible enhancement of blood-brain barrier permeability using lysophosphatidic acid. *J. Cereb. Blood Flow Metab.* **2013**, *33*, 1944–54.
119. Goldshmit, Y.; Matteo, R.; Sztal, T.; et al. Blockage of lysophosphatidic acid signaling improves spinal cord injury outcomes. *Am. J. Pathol.* **2012**, *181*, 978–92.
120. Sheng, X.; Yung, Y. C.; Chen, A.; et al. Lysophosphatidic acid signalling in development. *Development* **2015**, *142*, 1390–1395.
121. Fujii, T. [313-POS]: Enhanced expression of LPA receptors in preeclamptic placenta. *Pregnancy Hypertens.* **2015**, *5*, 154.
122. Kihara, Y.; Mizuno, H.; Chun, J. Lysophospholipid receptors in drug discovery. *Exp. Cell Res.* **2015**, *333*, 171–177.

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123. Woćawek-Potocka, I.; Rawińska, P.; Kowalczyk-Zieba, I.; et al. Lysophosphatidic acid (LPA) signaling in human and ruminant reproductive tract. *Mediators Inflamm.* **2014**, *2014*, 649702.
124. Schober, A.; Siess, W. Lysophosphatidic acid in atherosclerotic diseases. *Br. J. Pharmacol.* **2012**, *167*, 465–482.
125. Binder, B. Y. K.; Sondergaard, C. S.; Nolta, J. A.; et al. Lysophosphatidic acid enhances stromal cell-directed angiogenesis. *PLoS One* **2013**, *8*, e82134.
126. Cui, M.-Z. Lysophosphatidic acid effects on atherosclerosis and thrombosis. *Clin. Lipidol.* **2011**, *6*, 413–426.
127. Blackburn, J.; Mansell, J. P. The emerging role of lysophosphatidic acid (LPA) in skeletal biology. *Bone* **2012**, *50*, 756–62.
128. Llona-Minguez, S.; Ghassemian, A.; Helleday, T. Lysophosphatidic acid receptor (LPAR) modulators: The current pharmacological toolbox. *Prog. Lipid Res.* **2015**, *58*, 51–75.
129. Budd, D. C.; Qian, Y. Development of lysophosphatidic acid pathway modulators as therapies for fibrosis. *Future Med. Chem.* **2013**, *5*, 1935–52.
130. Park, G. Y.; Lee, Y. G.; Berdyshev, E.; et al. Autotaxin production of lysophosphatidic acid mediates allergic asthmatic inflammation. *Am. J. Respir. Crit. Care Med.* **2013**, *188*, 928–40.
131. Zhao, Y.; Natarajan, V. Lysophosphatidic acid (LPA) and its receptors: role in airway inflammation and remodeling. *Biochim. Biophys. Acta* **2013**, *1831*, 86–92.
132. Shea, B. S.; Tager, A. M. Role of the lysophospholipid mediators lysophosphatidic acid and sphingosine 1-phosphate in lung fibrosis. *Proc. Am. Thorac. Soc.* **2012**, *9*, 102–10.
133. Aikawa, S.; Hashimoto, T.; Kano, K.; et al. Lysophosphatidic acid as a lipid mediator with multiple biological actions. *J. Biochem.* **2015**, *157*, 81–9.
134. Park, S. J.; Jun, Y. J.; Lee, K. J.; et al. Chronic rhinosinusitis with nasal polyps and without nasal polyps is associated with increased expression of lysophosphatidic acid-related molecules. *Am. J. Rhinol. Allergy* **28**, 199–207.
135. Torres, A. C.; Boruszewska, D.; Batista, M.; et al. Lysophosphatidic acid signaling in late cleavage and blastocyst stage bovine embryos. *Mediators Inflamm.* **2014**, *2014*, 678968.
136. Li, H.; Yue, R.; Wei, B.; et al. Lysophosphatidic acid acts as a nutrient-derived developmental cue to regulate early hematopoiesis. *EMBO J.* **2014**, *33*, 1383–96.
137. Im, D.-S. First-in-class antifibrotic therapy targeting type 1 lysophosphatidic acid receptor. *Arch. Pharm. Res.* **2012**, *35*, 945–8.
138. Tang, N.; Zhao, Y.; Feng, R.; et al. Lysophosphatidic acid accelerates lung fibrosis by inducing differentiation of mesenchymal stem cells into myofibroblasts. *J. Cell. Mol. Med.* **2014**, *18*, 156–69.
139. Rancoule, C.; Viaud, M.; Gres, S.; et al. Pro-fibrotic activity of lysophosphatidic acid in adipose tissue: in vivo and in vitro evidence. *Biochim. Biophys. Acta* **2014**, *1841*, 88–96.

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140. Ohashi, T.; Yamamoto, T. Anti-fibrotic effect of lysophosphatidic acid receptors LPA1 and LPA3 antagonist on experimental murine scleroderma induced by bleomycin. *Exp. Dermatol.* **2015**.
141. Cong, C.; Mao, L.; Zhang, Y.; et al. Regulation of silicosis formation by lysophosphatidic acid and its receptors. *Exp. Lung Res.* **2014**, *40*, 317–26.
142. Olianas, M. C.; Dedoni, S.; Onali, P. Antidepressants activate the lysophosphatidic acid receptor LPA1 to induce insulin-like growth factor-I receptor transactivation, stimulation of ERK1/2 signaling and cell proliferation in CHO-K1 fibroblasts. *Biochem. Pharmacol.* **2015**.
143. García-Díaz, B.; Riquelme, R.; Varela-Nieto, I.; et al. Loss of lysophosphatidic acid receptor LPA1 alters oligodendrocyte differentiation and myelination in the mouse cerebral cortex. *Brain Struct. Funct.* **2014**.
144. Mirendil, H.; Thomas, E. A.; De Loera, C.; et al. LPA signaling initiates schizophrenia-like brain and behavioral changes in a mouse model of prenatal brain hemorrhage. *Transl. Psychiatry* **2015**, *5*, e541.
145. Orio, L.; Pavón, F. J.; Blanco, E.; et al. Lipid transmitter signaling as a new target for treatment of cocaine addiction: new roles for acylethanolamides and lysophosphatidic acid. *Curr. Pharm. Des.* **2013**, *19*, 7036–49.
146. Suardíaz, M.; Galan-Arriero, I.; Avila-Martin, G.; et al. Spinal cord compression injury in lysophosphatidic acid 1 receptor-null mice promotes maladaptive pronociceptive descending control. *Eur. J. Pain* **2015**.
147. Uchida, H.; Nagai, J.; Ueda, H. Lysophosphatidic acid and its receptors LPA1 and LPA3 mediate paclitaxel-induced neuropathic pain in mice. *Mol. Pain* **2014**, *10*, 71.
148. Halder, S. K.; Yano, R.; Chun, J.; et al. Involvement of LPA1 receptor signaling in cerebral ischemia-induced neuropathic pain. *Neuroscience* **2013**, *235*, 10–5.
149. Ueda, H. Lysophosphatidic acid as the initiator of neuropathic pain. *Biol. Pharm. Bull.* **2011**, *34*, 1154–8.
150. Zhao, J.; Wei, J.; Weathington, N.; et al. Lysophosphatidic acid receptor 1 antagonist ki16425 blunts abdominal and systemic inflammation in a mouse model of peritoneal sepsis. *Transl. Res.* **2015**.
151. Kataoka, M.; Ishibashi, K.; Kumagai, S.; et al. Expression and Function of LPAR1 in Bladder Cancer. *J. Urol.* **2014**.
152. Marshall, J.-C. A.; Collins, J. W.; Nakayama, J.; et al. Effect of inhibition of the lysophosphatidic acid receptor 1 on metastasis and metastatic dormancy in breast cancer. *J. Natl. Cancer Inst.* **2012**, *104*, 1306–19.
153. David, M.; Ribeiro, J.; Descotes, F.; et al. Targeting lysophosphatidic acid receptor type 1 with Debio 0719 inhibits spontaneous metastasis dissemination of breast cancer cells independently of cell proliferation and angiogenesis. *Int. J. Oncol.* **2012**, *40*, 1133–41.
154. Kato, K.; Yoshikawa, K.; Tanabe, E.; et al. Opposite roles of LPA1 and LPA3 on cell motile and invasive activities of pancreatic cancer cells. *Tumour Biol.* **2012**, *33*, 1739–44.

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155. Komachi, M.; Sato, K.; Tobe, M.; et al. Orally active lysophosphatidic acid receptor antagonist attenuates pancreatic cancer invasion and metastasis in vivo. *Cancer Sci.* **2012**, *103*, 1099–104.
156. Lee, S.-C.; Fujiwara, Y.; Liu, J.; et al. Autotaxin and LPA1 and LPA5 receptors exert disparate functions in tumor cells versus the host tissue microenvironment in melanoma invasion and metastasis. *Mol. Cancer Res.* **2015**, *13*, 174–85.
157. Wei, J. S.; Johansson, P.; Chen, L.; et al. Massively parallel sequencing reveals an accumulation of de novo mutations and an activating mutation of LPAR1 in a patient with metastatic neuroblastoma. *PLoS One* **2013**, *8*, e77731.
158. Miyabe, Y.; Miyabe, C.; Iwai, Y.; et al. Necessity of lysophosphatidic acid receptor 1 for development of arthritis. *Arthritis Rheum.* **2013**, *65*, 2037–47.
159. Wu, L.; Petriglano, F. A.; Ba, K.; et al. Lysophosphatidic acid mediates fibrosis in injured joints by regulating collagen type I biosynthesis. *Osteoarthritis Cartilage* **2015**, *23*, 308–18.
160. Orosa, B.; García, S.; Martínez, P.; et al. Lysophosphatidic acid receptor inhibition as a new multipronged treatment for rheumatoid arthritis. *Ann. Rheum. Dis.* **2014**, *73*, 298–305.
161. David, M.; Machuca-Gayet, I.; Kikuta, J.; et al. Lysophosphatidic acid receptor type 1 (LPA1) plays a functional role in osteoclast differentiation and bone resorption activity. *J. Biol. Chem.* **2014**, *289*, 6551–64.
162. Rancoule, C.; Dusaulcy, R.; Tréguer, K.; et al. Involvement of autotaxin/lysophosphatidic acid signaling in obesity and impaired glucose homeostasis. *Biochimie* **2014**, *96*, 140–143.
163. Shimizu, Y.; Morikawa, Y.; Okudaira, S.; et al. Potentials of the circulating pruritogenic mediator lysophosphatidic acid in development of allergic skin inflammation in mice: role of blood cell-associated lysophospholipase D activity of autotaxin. *Am. J. Pathol.* **2014**, *184*, 1593–603.
164. Yung, Y. C.; Mutoh, T.; Lin, M.-E.; et al. Lysophosphatidic acid signaling may initiate fetal hydrocephalus. *Sci. Transl. Med.* **2011**, *3*, 99ra87.
165. Knowlden, S. A.; Capece, T.; Popovic, M.; et al. Regulation of T cell motility in vitro and in vivo by LPA and LPA2. *PLoS One* **2014**, *9*, e101655.
166. Huang, L. S.; Fu, P.; Patel, P.; et al. Lysophosphatidic acid receptor-2 deficiency confers protection against bleomycin-induced lung injury and fibrosis in mice. *Am. J. Respir. Cell Mol. Biol.* **2013**, *49*, 912–22.
167. Yang, D.; Yang, W.; Zhang, Q.; et al. Migration of gastric cancer cells in response to lysophosphatidic acid is mediated by LPA receptor 2. *Oncol. Lett.* **2013**, *5*, 1048–1052.
168. Chen, R.-J.; Chen, S.-U.; Chou, C.-H.; et al. Lysophosphatidic acid receptor 2/3-mediated IL-8-dependent angiogenesis in cervical cancer cells. *Int. J. Cancer* **2012**, *131*, 789–802.
169. Yoshikawa, K.; Tanabe, E.; Shibata, A.; et al. Involvement of oncogenic K-ras on cell migration stimulated by lysophosphatidic acid receptor-2 in pancreatic cancer cells. *Exp. Cell Res.* **2013**, *319*, 105–12.

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170. Gong, Y. L.; Tao, C. J.; Hu, M.; et al. Expression of lysophosphatidic acid receptors and local invasiveness and metastasis in Chinese pancreatic cancers. *Curr. Oncol.* **2012**, *19*, eS15–21.
171. Kiss, G. N.; Lee, S.-C.; Fells, J. I.; et al. Mitigation of radiation injury by selective stimulation of the LPA(2) receptor. *Biochim. Biophys. Acta* **2013**, *1831*, 117–25.
172. Patil, R.; Szabó, E.; Fells, J. I.; et al. Combined mitigation of the gastrointestinal and hematopoietic acute radiation syndromes by an LPA2 receptor-specific nonlipid agonist. *Chem. Biol.* **2015**, *22*, 206–16.
173. Tanaka, T.; Ohmoto, M.; Morito, K.; et al. Type 2 lysophosphatidic acid receptor in gastric surface mucous cells: Possible implication of prostaglandin E2 production. *Biofactors* **40**, 355–61.
174. Tanaka, T.; Morito, K.; Kinoshita, M.; et al. Orally administered phosphatidic acids and lysophosphatidic acids ameliorate aspirin-induced stomach mucosal injury in mice. *Dig. Dis. Sci.* **2013**, *58*, 950–8.
175. Singla, A.; Kumar, A.; Priyamvada, S.; et al. LPA stimulates intestinal DRA gene transcription via LPA2 receptor, PI3K/AKT, and c-Fos-dependent pathway. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2012**, *302*, G618–27.
176. Sun, K.; Cai, H.; Duan, X.; et al. Aberrant expression and potential therapeutic target of lysophosphatidic acid receptor 3 in triple-negative breast cancers. *Clin. Exp. Med.* **2014**.
177. Popnikolov, N. K.; Dalwadi, B. H.; Thomas, J. D.; et al. Association of autotaxin and lysophosphatidic acid receptor 3 with aggressiveness of human breast carcinoma. *Tumour Biol.* **2012**, *33*, 2237–43.
178. Okabe, K.; Hayashi, M.; Kato, K.; et al. Lysophosphatidic acid receptor-3 increases tumorigenicity and aggressiveness of rat hepatoma RH7777 cells. *Mol. Carcinog.* **2013**, *52*, 247–54.
179. Fukui, R.; Kato, K.; Okabe, K.; et al. Enhancement of Drug Resistance by Lysophosphatidic Acid Receptor-3 in Mouse Mammary Tumor FM3A Cells. *J. Toxicol. Pathol.* **2012**, *25*, 225–8.
180. Brusevold, I. J.; Tveteraas, I. H.; Aasrum, M.; et al. Role of LPAR3, PKC and EGFR in LPA-induced cell migration in oral squamous carcinoma cells. *BMC Cancer* **2014**, *14*, 432.
181. Tanabe, E.; Kitayoshi, M.; Yoshikawa, K.; et al. Loss of lysophosphatidic acid receptor-3 suppresses cell migration activity of human sarcoma cells. *J. Recept. Signal Transduct. Res.* **2012**, *32*, 328–34.
182. Zhao, C.; Sardella, A.; Davis, L.; et al. A transgenic mouse model for the in vivo bioluminescence imaging of the expression of the lysophosphatidic acid receptor 3: relevance for inflammation and uterine physiology research. *Transgenic Res.* **2015**.
183. Ichikawa, M.; Nagamatsu, T.; Fujii, T.; et al. [61-OR]: Functional regulation of trophoblast cells by lysophosphatidic acid signaling and its pathologic relevance to PIH. *Pregnancy Hypertens.* **2015**, *5*, 32.
184. Chiang, C.-L.; Chen, S.-S. A.; Lee, S. J.; et al. Lysophosphatidic acid induces erythropoiesis through activating lysophosphatidic acid receptor 3. *Stem Cells* **2011**, *29*, 1763–73.
185. Ren, F.; Deng, G.; Wang, H.; et al. Discovery of novel 1,2,4-thiadiazole derivatives as potent, orally active agonists of sphingosine 1-phosphate receptor subtype 1 (S1P(1)). *J. Med. Chem.* **2012**, *55*, 4286–96.

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186. Buzard, D.; Han, S.; Thoresen, L.; et al. Discovery and characterization of potent and selective 4-oxo-4-(5-(5-phenyl-1,2,4-oxadiazol-3-yl)indolin-1-yl)butanoic acids as S1P₁ agonists. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6013–8.
187. Bolli, M. H.; Müller, C.; Mathys, B.; et al. Novel S1P1 receptor agonists--part 1: From pyrazoles to thiophenes. *J. Med. Chem.* **2013**, *56*, 9737–55.
188. Bolli, M. H.; Velker, J.; Müller, C.; et al. Novel S1P 1 Receptor Agonists - Part 2: From Bicyclo[3.1.0]hexane-Fused Thiophenes to Isobutyl Substituted Thiophenes. *J. Med. Chem.* **2014**, *57*, 78–97.
189. Bolli, M. H.; Abele, S.; Birker, M.; et al. Novel S1P(1) receptor agonists--part 3: from thiophenes to pyridines. *J. Med. Chem.* **2014**, *57*, 110–30.
190. Bolli, M. H.; Abele, S.; Binkert, C.; et al. 2-imino-thiazolidin-4-one derivatives as potent, orally active S1P1 receptor agonists. *J. Med. Chem.* **2010**, *53*, 4198–211.
191. Guerrero, M.; Urbano, M.; Velaparthi, S.; et al. Discovery, design and synthesis of the first reported potent and selective sphingosine-1-phosphate 4 (S1P4) receptor antagonists. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3632–6.
192. Qian, Y.; Hamilton, M.; Sidduri, A.; et al. Discovery of highly selective and orally active lysophosphatidic acid receptor-1 antagonists with potent activity on human lung fibroblasts. *J. Med. Chem.* **2012**, *55*, 7920–39.
193. Meng, Q.; Zhao, B.; Xu, Q.; et al. Indole-propionic acid derivatives as potent, S1P3-sparing and EAE efficacious sphingosine-1-phosphate 1 (S1P1) receptor agonists. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2794–7.
194. Urbano, M.; Guerrero, M.; Zhao, J.; et al. SAR analysis of innovative selective small molecule antagonists of sphingosine-1-phosphate 4 (S1P₄) receptor. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5470–4.
195. Zécri, F. J.; Albert, R.; Landrum, G.; et al. Pyrazole derived from (+)-3-carene; a novel potent, selective scaffold for sphingosine-1-phosphate (S1P(1)) receptor agonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 35–7.
196. Beck, H. P.; Kohn, T.; Rubenstein, S.; et al. Discovery of potent LPA2 (EDG4) antagonists as potential anticancer agents. *Bioorganic Med. Chem. Lett.* **2008**, *18*, 1037–1041.
197. Yan, L.; Huo, P.; Doherty, G.; et al. Discovery of 3-arylpropionic acids as potent agonists of sphingosine-1-phosphate receptor-1 (S1P1) with high selectivity against all other known S1P receptor subtypes. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3679–83.
198. Pennington, L. D.; Croghan, M. D.; Sham, K. K. C.; et al. Quinolinone-based agonists of S1P₁: use of a N-scan SAR strategy to optimize in vitro and in vivo activity. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 527–31.
199. Ibrahim, M. A.; Johnson, H. W. B.; Jeong, J. W.; et al. Discovery of a novel class of potent and orally bioavailable sphingosine 1-phosphate receptor 1 antagonists. *J. Med. Chem.* **2012**, *55*, 1368–81.
200. Reed, A. B.; Lanman, B. A.; Neira, S.; et al. Isoform-selective thiazolo[5,4-b]pyridine S1P1 agonists possessing acyclic amino carboxylate head-groups. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1779–83.



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201. Xu, H.; Zhang, H.; Luan, L.; et al. Discovery of thiadiazole amides as potent, S1P₃-sparing agonists of sphingosine-1-phosphate 1 (S1P₁) receptor. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2456–9.
202. Li, Z.; Chen, W.; Hale, J. J.; et al. Discovery of potent 3,5-diphenyl-1,2,4-oxadiazole sphingosine-1-phosphate-1 (S1P1) receptor agonists with exceptional selectivity against S1P2 and S1P3. *J. Med. Chem.* **2005**, *48*, 6169–73.
203. Yan, L.; Hale, J. J.; Lynch, C. L.; et al. Design and synthesis of conformationally constrained 3-(N-alkylamino)propylphosphonic acids as potent agonists of sphingosine-1-phosphate (S1P) receptors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4861–6.
204. Clemens, J. J.; Davis, M. D.; Lynch, K. R.; et al. Synthesis of benzimidazole based analogues of sphingosine-1-phosphate: discovery of potent, subtype-selective S1P4 receptor agonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4903–6.
205. Clemens, J. J.; Davis, M. D.; Lynch, K. R.; et al. Synthesis of 4(5)-phenylimidazole-based analogues of sphingosine-1-phosphate and FTY720: discovery of potent S1P1 receptor agonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3568–72.
206. Hale, J. J.; Doherty, G.; Toth, L.; et al. The discovery of 3-(N-alkyl)aminopropylphosphonic acids as potent S1P receptor agonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3495–9.
207. Hale, J. J.; Lynch, C. L.; Neway, W.; et al. A rational utilization of high-throughput screening affords selective, orally bioavailable 1-benzyl-3-carboxyazetidine sphingosine-1-phosphate-1 receptor agonists. *J. Med. Chem.* **2004**, *47*, 6662–5.
208. Urbano, M.; Guerrero, M.; Rosen, H.; et al. Modulators of the Sphingosine 1-phosphate receptor 1. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6377–89.
209. Hale, J. J.; Neway, W.; Mills, S. G.; et al. Potent S1P receptor agonists replicate the pharmacologic actions of the novel immune modulator FTY720. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3351–5.
210. Guerrero, M.; Poddutoori, R.; Urbano, M.; et al. Discovery, design and synthesis of a selective S1P(3) receptor allosteric agonist. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6346–9.
211. Crosignani, S.; Bombrun, A.; Covini, D.; et al. Discovery of a novel series of potent S1P1 agonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1516–9.
212. Hanson, M. A.; Roth, C. B.; Jo, E.; et al. Crystal structure of a lipid G protein-coupled receptor. *Science* **2012**, *335*, 851–5.
213. Chrencik, J. E.; Roth, C. B.; Terakado, M.; et al. Crystal Structure of Antagonist Bound Human Lysophosphatidic Acid Receptor 1. *Cell* **2015**, *161*, 1633–43.