

Sphingosine-1-phosphate (S1P) Receptor Modulators Provide Potential for Diverse Treatments

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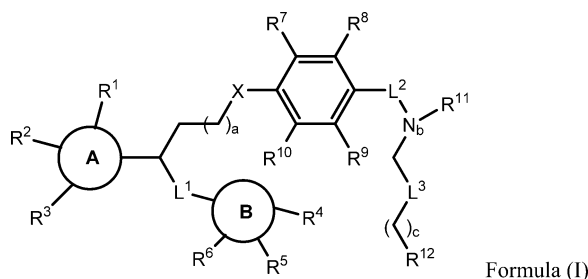
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Title:	Sulfinylbenzyl and Thiobenzyl Derivatives as Sphingosine-1-phosphate (S1P) Receptor Modulators		
Patent Application Number:	WO 2013/126438 A1	Publication date:	29 August 2013
Priority Application:	US 61/601,152	Priority date:	21 February 2012
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Assignee Company:	Allergan, Inc. 2525 DuPont Drive, Irvine, California 92612, USA		
Disease Area:	Conditions and diseases that are alleviated by S1P modulation such as cancer, ocular diseases, cardiovascular disorders, and others	Biological Target:	sphingosine-1-phosphate (S1P) receptor

Summary: The invention in this patent application describes several thiobenzyl and sulfinylbenzyl derivatives, represented generally by formula (I), which are selective sphingosine-1-phosphate modulators. These compounds may potentially be used for the treatment of diseases and conditions that are alleviated by S1P modulation.

Sphingosine-1-phosphate (S1P) (structure below) belongs to a large group of bioactive lipids, which act as signaling mediators. A family of five specific G protein-coupled receptors mediates most of the known actions of S1P. It is a critical regulator of many physiological and pathophysiological processes, including cancer, cardiovascular diseases, atherosclerosis, diabetes, and osteoporosis. Studies have shown that S1P has important intracellular targets involved in inflammation, cancer, and Alzheimer's disease. There is evidence that implicates S1P in the pathogenesis of wet age-related macular degeneration (wet AMD), and its inhibition may provide effective therapeutic treatment for this disease. Other studies suggest a role for S1P in the beneficial clinical effects of high-density lipoprotein (HDL) through stimulating the production of nitric oxide as well as a role in cell division or proliferation, which may have an influence on the development of cancers. These and other findings suggest that S1P activities are very diverse and very complex. Modulation of these activities may provide attractive targets for development of treatments for multiple disorders. The active molecules reported in this patent application may potentially provide useful treatments for many diseases and disorders through modulation of S1P. The inventors defined the term modulator as "receptor agonist, antagonist, inverse agonist, inverse antagonist, partial agonist, and partial antagonist."

Important Compound Classes:



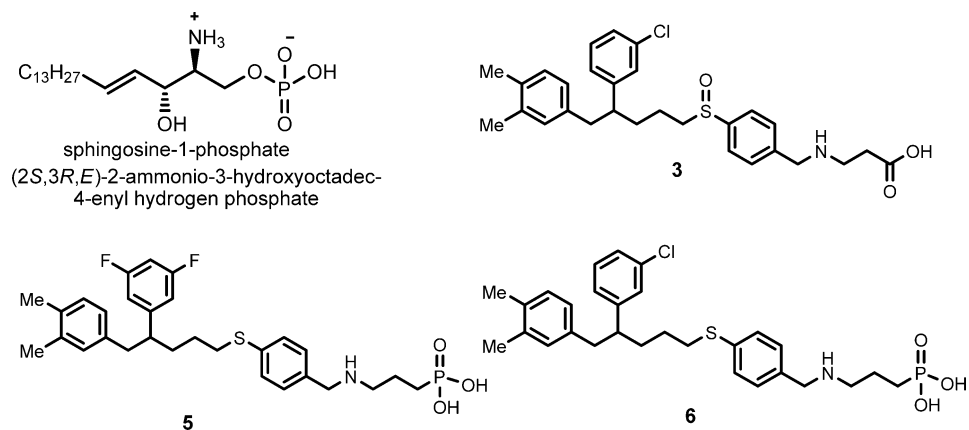
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Key Structures:

The structure and systematic name of sphingosine-1-phosphate are shown below.

The inventors described the synthesis and structures of six examples of the compounds of formula (1) including compounds 3, 5, and 6 illustrated below:

**Biological Assay:**

S1P1 activity using the GTP $\gamma^{35}\text{S}$ binding assay

Biological Data:

The EC_{50} values in nM was reported for 5 examples including compounds 3, 5, and 6 listed in the following table:

Compound	S1P1 EC ₅₀ (nM)
3	81.74
5	2.65
6	0.76

Claims:

Claims 1–10: Composition of matter; variations of formula (1)

Claim 11: Six specific compounds of formula (1) listed by chemical name

Claim 12–13: Pharmaceutical compositions

Claims 14–15: Method of treating a disorder associated with sphingosine-1-phosphate receptor modulation with a listing of possible disorders and diseases

Recent Review Articles:

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Notes

The authors declare no competing financial interest.