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Spiro-1-benzofuranpiperidinylalkanoic acids as a novel and selective sphingosine $S1P_5$ receptor agonist chemotype

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ABSTRACT

The synthesis and SAR of a novel class of spirobenzofuranpiperidinyl-derived alkanoic acids **6**–**34** as sphingosine $S1P_5$ receptor agonists are described. The target compounds generally elicit high $S1P_5$ receptor agonistic potencies and in general are selective against both $S1P_1$ and $S1P_3$ receptor subtypes. The key compound **32** shows a high bioavailability of 73% and a CNS/plasma ratio of 0.8 after oral administration in rats.

Sphingosine-1-phosphate (S1P, **1**) is a bioactive lipid with important functions in multiple cellular signaling systems.[1] S1P affects the central nervous system,[2] cardiovascular system and immune system and has been implicated in a broad range of diseases[3] (Fig. 1). S1P also activates the G protein-coupled sphingosine receptors $S1P_1$–$S1P_5$. The approval of the S1P receptor agonist fingolimod (**2**, FTY720, Gilenya®) in 2010 for the treatment of relapsing multiple sclerosis has intensified sphingosine research efforts.[4] Compound **2** acts as a pro-drug by phosphorylation into the active (*S*)-Fingolimod-phosphate (**3**) which is an analogue of **1**. Compound **2** was reported[5] to act (*via* **3**) on four of the five S1P receptor subtypes (excluding $S1P_2$) and to lead to lymphopenia. More S1P receptor subtype selective ligands with better pharmacokinetic profiles and fewer side effects will be required[4,6] to further elucidate the physiological background and therapeutic roles of $S1P_{1\text{-}5}$. Several selective $S1P_{1/5}$ receptor dual agonists have been discovered such as siponimod, ozanimod, ceralifimod, AMG369[7] and GSK2018682 for the treatment of multiple sclerosis and other autoimmune and inflammatory disorders.[4,8]

The $S1P_5$ receptor is most highly expressed in the central nervous system, particularly on oligodendrocytes and brain endothelium. The $S1P_5$ receptor was shown to mediate the immune quiescence of the human endothelium barrier.[9] The number of orally available, selective $S1P_5$ receptor agonists is very limited. The 2*H*-phthalazin-1-one analogue **4** was reported[10] by Novartis as a selective and orally active $S1P_5$ receptor agonist. Recently, A-971432 was disclosed[11] as a highly selective $S1P_5$ receptor agonist. A-971432 exhibited excellent plasma and CNS exposure after oral dosing in several preclinical species and reversed lipid accumulation as well as age-related cognitive decline in rodents. Hanessian reported[12] the chiral pyrrolidine derivative **5** which acted as an agonist on both $S1P_4$ and $S1P_5$, being devoid of activity at $S1P_1$ and $S1P_3$. Compound **5** can be regarded as a constrained azacyclic analogue of **3** and has a relatively poor pharmacokinetic profile. It serves in the present study as a molecular modeling tool.

Herein, a set of novel spirocyclic benzofuranpiperidinylalkanoic acids **6**–**34** and the phosphate analogue **35** are disclosed as a new selective $S1P_5$ receptor agonist chemotype.

The synthesis of the target 2*H*-spiro(1-benzofuran-3,4′-piperidine) compounds **6**–**21** is depicted in Scheme 1. 2-Bromo-5-methoxyphenol **36** was coupled to the protected tetrahydropyridinemethanol derivative[13] **37** in a Mitsunobu reaction to give **38** in 63% yield. Radical spirocyclization of **38** in the presence of tributyltin hydride and a catalytic amount of the radical initiator

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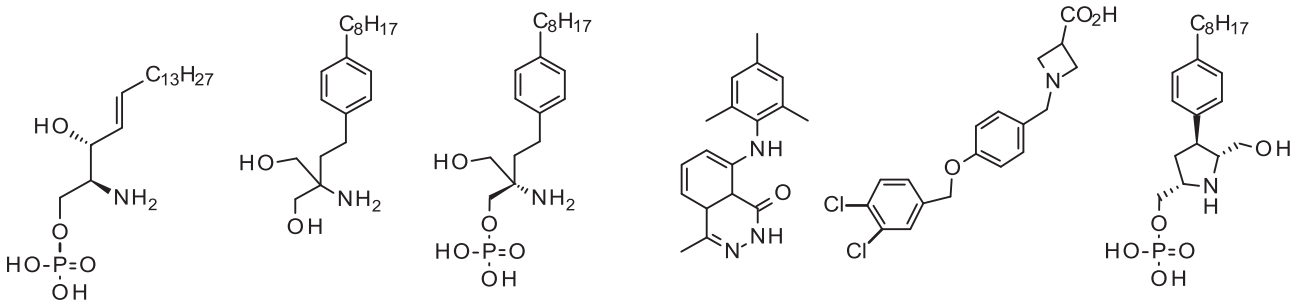
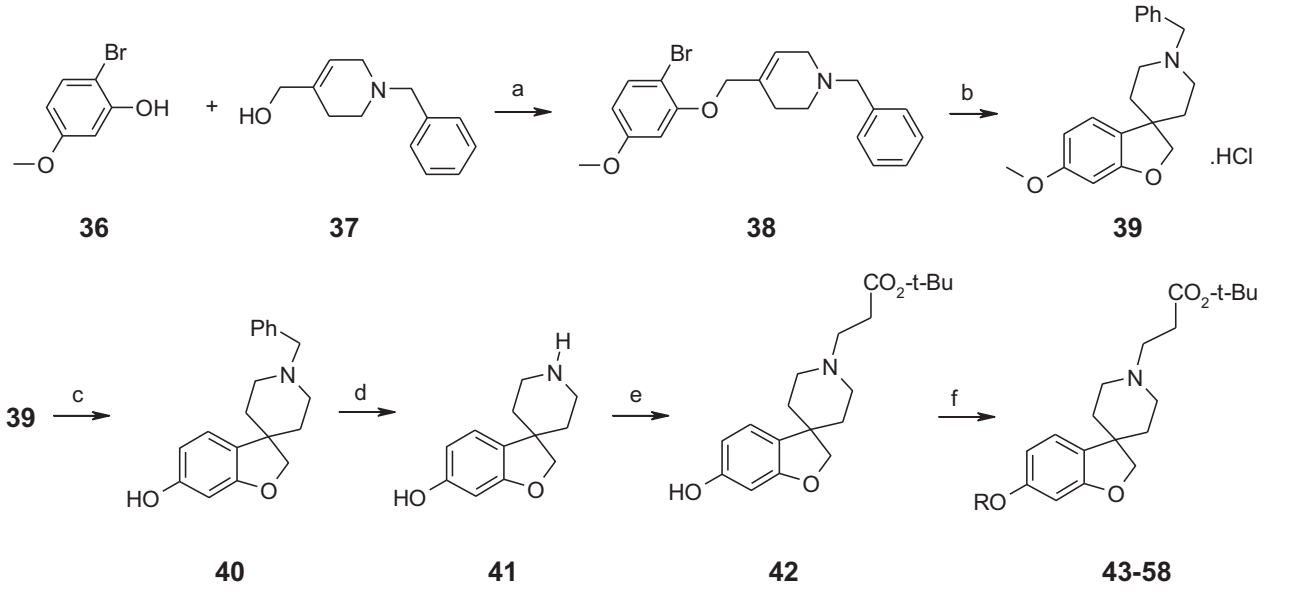


Fig. 1. Chemical structures of selected S1P receptor agonists.



Compound	R	Compound	R
6 .HCl	phenylpropyl	**14** .HCl	2-Cl-6-CF_3-benzyl
7 .HCl	benzyl	**15** .HCl	2-Cl-6-Et-benzyl
8 .TFA	2-Cl-benzyl	**16** .HCl	2-Cl-6-*i*-Pr-benzyl
9 .HCl	3-Cl-benzyl	**17** .HCl	2-Cl-6-*c*-Pr-benzyl
10 .HCl	2,6-Cl_2-benzyl	**18** .HCl	2-Cl-6-OCF_3-benzyl
11 .HCl	2,5-Cl_2-benzyl	**19** .HCl	3,5-Cl_2-pyridin-4-ylmethyl
12 .HCl	2,3-Cl_2-benzyl	**20** .HCl	2,6-Cl_2-4-Me-benzyl
13 .HCl	2-Cl-6-F-benzyl	**21**	2,6-$(C_2H_5)_2$-benzyl

Scheme 1. Reagents and conditions: (a) PPh_3, DIAD, THF, <10 °C, 2 h followed by rt, 16 h (63%). (b) *n*-Bu_3SnH, AIBN (cat.), benzene, N_2, reflux, 16 h (68%). (c) 48% HBr, AcOH, reflux, 24 h (quantitative yield). (d) H_2, $Pd(OH)_2$, 4N HCl, MeOH, rt, 48 h (68%). (e) *tert*-butylacrylate, $(i\text{-}Pr)_2NH$, MeOH, reflux, 16 h (91%). (f) R-OH, PPh_3, DIAD, CH_2Cl_2, rt, 16 h (50–90%). (g) 4M HCl, 1,4-dioxane, 50 °C, 16 h (80–95%).

AIBN provided **39** in a chemical yield of 68%. The methoxy group in **39** was removed under strongly acidic conditions to furnish **40** in quantitative yield. Reductive debenzylation of **40** efficiently led to **41** which was converted into **42** by reaction with *tert*-butylacrylate in the presence of diisopropylamine as organic base. Mitsunobu coupling of **42** with a set of appropriate alcohols gave the *tert*-butyl esters **43**–**58**, respectively. The target compounds **6**–**21** were obtained from **43** to **58** by acidic removal of their *tert*-butyl protective group, thereby liberating the carboxylic acid moiety.

The synthesis of the fluoro analogue **22** is depicted in Scheme 2. The aromatic difluoride[14] **59** was coupled to 4-pyridinemethanol **60** to furnish **61**. Benzylation of **61**, followed by partial reduction of the *in situ* formed positively charged quaternary pyridine ring by sodium borohydride in methanol at low temperature gave **62**.