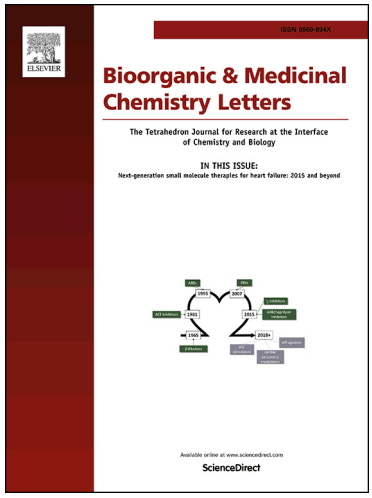
# Accepted Manuscript




Discovery of super soft-drug modulators of sphingosine-1-phosphate receptor 1

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# Discovery of super soft-drug modulators of sphingosine-1-phosphate receptor 1.

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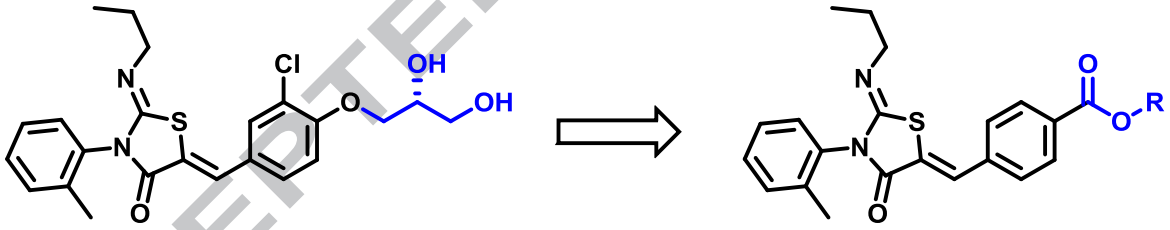
**Abstract**

The oral S1PR1 agonist ponesimod demonstrated substantial efficacy in a phase II clinical trial of psoriasis. Unfortunately, systemic side effects were observed, which included lymphopenia and transient bradycardia. We sought to develop a topical soft-drug S1PR1 agonist with an improved therapeutic index. By modifying ponesimod, we discovered an ester series of S1PR agonists. To increase metabolic instability in plasma we synthesised esters described as specific substrates for paraoxonase and butyrylcholinesterases, esterases present in human plasma.

**Graphical abstract**




**Keywords**

S1PR1, soft-drug, plasma stability, psoriasis, topical

Psoriasis is a common chronic inflammatory skin disease that affects 2% of the population.[1] 52.3% of patients were dissatisfied with current treatments in a recent survey from the National Psoriasis Foundation in the US.[1] Recently approved biological drugs targeting disease relevant receptors, such as secukinumab[2] or ixekizumab[3] for interleukin (IL)-17 and ustekinumab for IL-12/23[4] have brought great benefit to patients with severe symptoms of the disease. However, a need remains for safe, convenient, efficacious therapies for mild and moderate psoriasis.

Sphingosine-1-phosphate receptor (S1PR) agonists are of interest to the pharmaceutical industry, due to their potential to treat diseases of the immune system such as psoriasis and multiple sclerosis as well as cancer.[5,6] S1PR agonists, such as fingolimod and ponesimod (Figure 1), initially activate sphingosine-1-phosphate receptors, but subsequently trigger receptor internalisation. This shuts down the sphingosine 1-phosphate signalling pathway, which then prevents the maturation and migration of lymphocytes.[7] In 2010 fingolimod was approved for the treatment of relapsing/remitting multiple sclerosis and is the only S1PR1 agonist approved to date.[8]