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Identification and Structure–Activity Relationship (SAR) of potent and selective oxadiazole-based agonists of sphingosine-1-phosphate receptor ($S1P_1$)

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ABSTRACT

Agonism of $S1P_1$ receptor has been proven to be responsible for peripheral blood lymphopenia and elicts the identification of various $S1P_1$ modulators. In this paper we described a series of oxadiazole-based $S1P_1$ direct-acting agonists disubstituted on terminal benzene ring, with high potency for $S1P_1$ receptor and favorable selectivity against $S1P_3$ receptor. In addition, two representative agents named **16-3b** and **16-3g** demonstrated impressive efficacy in lymphocyte reduction along with reduced effect on heart rate when orally administered. Furthermore, these compounds have been shown to possess desired pharmacokinetic (PK) and physicochemical profiles. The binding mode between **16-3b** and the activated $S1P_1$ model was also studied.

1. Introduction

Sphingolipids are important plasma-membrane lipids, where sphingosine-1 phosphate (S1P, Fig. 1) is the endogenous ligand for a family of five G-protein coupled receptors known as $S1PR_{1\text{-}5}$, regulating a variety of physiological processes including cell differentiation, vascular stabilization, inflammation, endothelium integrity and angiogenesis [1–5]. In recent studies, $S1P_1$ receptor has become an attractive drug target, involved in occurrence and development of many diseases, especially for immune-mediated diseases [6,7]. Notably, sustained activation of $S1P_1$ receptor by the synthetic modulators instead of S1P results in the internalization and degradation of $S1P_1$ receptors, thereby lymphocytes are sequestrated in the lymph nodes and secondary lymphoid organs, restricting the auto immune reactivity, which is mechanistically identified as “functional antagonism” [8–12].

Along with the research for the mechanism of $S1P_1$ receptor toward lymphocyte migration, a great deal of effort has been devoted to the discovery of potent $S1P_1$ agonists, including FTY720 (**2**), BAF312, ACT-12800, ONO-4641 (**3**), RPC1063 (**4**), etc. [13–16]. In 2010, Fingolimod (FTY720, Fig. 1) is the first oral drug approved for the treatment of relapsing remitting multiple sclerosis (RRMS) [17]. As a pro-drug, FTY720 can be phosphorylated to (S)-FTY720-P, which exhibits affinity for 4 of the 5 S1P receptors ($S1P_{1,3,4,5}$) [18–21]. During the clinical trial of FTY720, several researches reveal that there exist some potential side effects which are related to the activation of $S1P_3$ receptor in rodent, such as the risk of cardiovascular effects [22,23]. On the other hand, the overlong half-life of FTY720 raises some concerns about the prognosis after the drug administration is ceased. As a result, more potent $S1P_3$-sparing $S1P_1$ direct-acting agonists with improved pharmacokinetic profile remain to be the focus in drug discovery.

Despite structural diversity of $S1P_1$ agonists, the key features can be generally divided into three parts: polar head, aromatic region, and lipophilic tail. In our previous study, highly predictive 3D QSAR pharmacophore model of $S1P_1$ agonists has been constructed, which indicated that properly rigid hydrophobic region was favorable for $S1P_1/S1P_3$ receptor selectivity [24]. Moreover, in 2012 Stevens’s group disclosed the crystal structure of the $S1P_1$ receptor fused to T4-lysozyme ($S1P_1$-T4L) in complex with an antagonist ML056, which suggested that binding pocket appeared to be amphiphilic and significant π-π stacking was observed between Phe125 and aromatic heterocyclic region [25].

Inspired by the valuable results above, we intended to employ diphenyl ether scaffold to maintain the rigidity of hydrophobic tail, which

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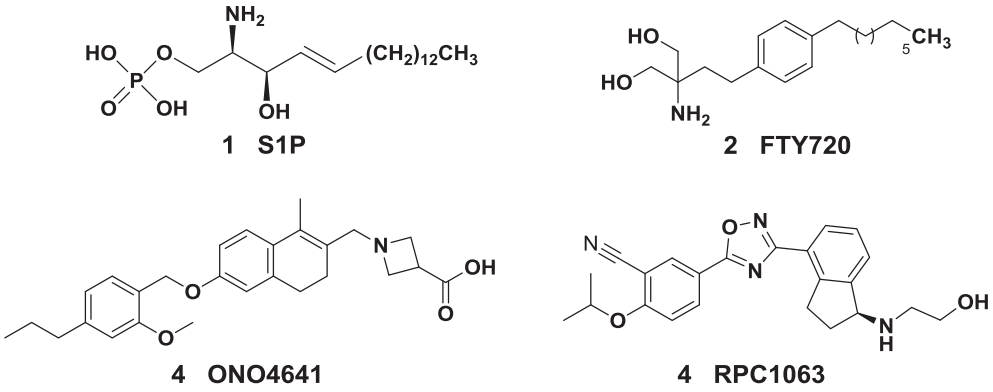

Fig. 1. Structures of sphingosine, Fingolimod (FTY720), and their phosphates.

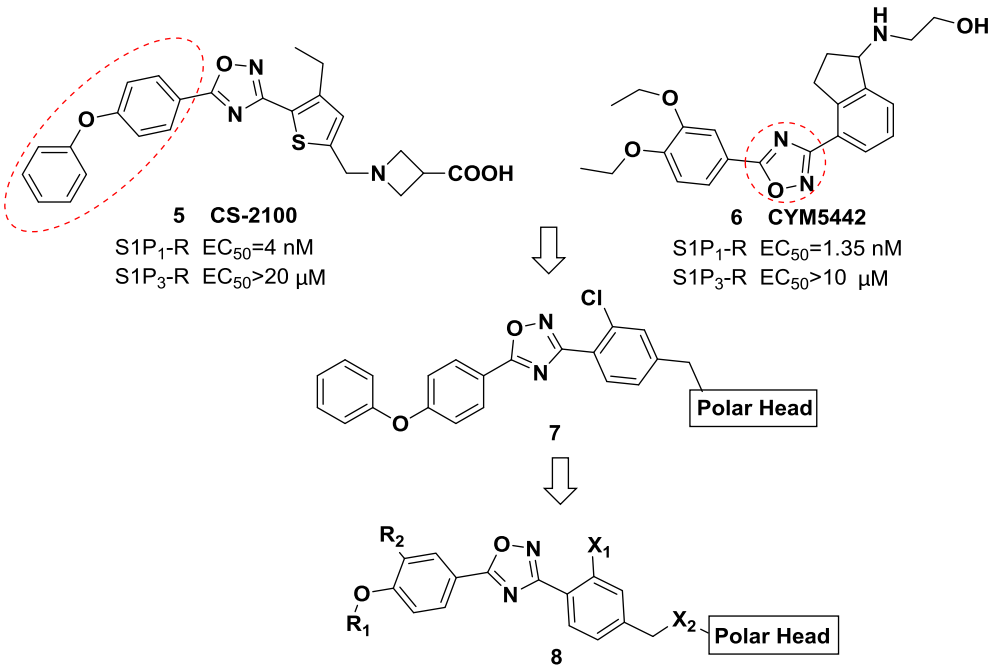

Fig. 2. Design of oxadiazole-based $S1P_1$ modulators.

is derived from CS2100 (**5,** Fig. 2), a potent $S1P_1$ agonist with 5000-fold selectivity against $S1P_3$ receptor reported by Nakamura et al. [26] Meanwhile, in order to further decrease the electricity of aromatic region, the oxadiazole group derived from CYM5442 and CS-2100 was also adopted as part of the linker to enhance its interaction with $S1P_1$ receptor [27]. As illustrated in Fig. 2, selective $S1P_1$ modulators were synthesized on the basis of rational design. After several rounds of cascade modification, highly potent oxadiazole-based $S1P_1$ agonists (structures 8) were identified, where terminal phenyl ring was disubstituted, represented by compound **16-3b** and **16-3g**. In addition to the exploration of structure–activity relationship (SAR) *in vitro*, effects on lymphocyte reduction and heart rate, pharmacokinetic and physicochemical profiles, in silico docking results were fully evaluated and analyzed in detail.

2. Results and discussion

2.1. Chemistry

The synthetic pathway utilized in the preparation of oxadiazole-based derivatives is outlined in Scheme 1. Polysubstituted aromatic aldehydes (**10**) were either commercially available or easily prepared from aryl halides (**9**) by using isopropylmagnesium chloride and 1-formylpiperidine [28]. Initially, aromatic aldehydes (**10**) were converted to acetals (**11**) under the catalysis of PTSA to protect the formyl group in advance [29]. Subsequent addition reaction was performed between **11** and hydroxylamine hydrochloride to provide N'-hydroxybenzimidamides (**12**) [30]. Intermediates **12** were then coupled with different substituted benzoic acids, which were commercially available or prepared according to literature in two steps, employing HOBt and EDCI·HCl as activating reagents to afford 1,2,4-oxadiazoles **13** [31]. After deprotection of **13** with hydrochloric acid, the corresponding aldehydes **14** were then reacted with amino carboxylic ester or alkamine through reductive amination, using either sodium cyanoborohydride or sodium triacetoxyborohydride as the reducing agent to give corresponding intermediates **15** or alkamine end-products [32,33]. Finally, hydrolysis of amino carboxylic esters **15** with lithium hydroxide followed by hydrochloric acid treatment afforded the desired hydrochloride of oxadiazole-based derivatives **16**. Besides, wittig reaction of **14a** with Methyl (triphenylphosphoranylidene) acetate was carried out to prepare substituted α, β-unsaturated ester **17** [34]. Reduction of **17** was performed with Pd/C and H_2, subsequent hydrolysis of the reduction product furnished phenylpropionic acid derivative **16-11**.