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Discovery of 3-arylpropionic acids as potent agonists of sphingosine-1-phosphate receptor-1 ($S1P_1$) with high selectivity against all other known S1P receptor subtypes

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Abstract—A series of 3-arylpropionic acids were synthesized as $S1P_1$ receptor agonists. Structure–activity relationship studies on the pendant phenyl ring revealed several structural features offering selectivity of $S1P_1$ binding against $S1P_{2-5}$. These highly selective $S1P_1$ agonists induced peripheral blood lymphocyte lowering in mice and one of them was found to be efficacious in a rat skin transplantation model, supporting that $S1P_1$ agonism is primarily responsible for the immunosuppressive efficacy observed in preclinical animal models.

Modulation of biological actions of sphingosine-1-phosphate receptors (S1Ps)—members of the G protein-coupled receptor superfamily—has emerged as a new paradigm for the discovery of therapeutic agents.[1] FTY720 (**1**, Fig. 1) is a synthetic analog of myriocin, an antifungal antibiotic isolated from entomopathogenic fungus *Isaria sinclairii*.[2] As a novel immunosuppressant, FTY720 has progressed to phase III clinical trials in the prevention of allograft rejection after renal transplantation and phase II for the treatment of multiple sclerosis.[3] The mechanism of its action has been proposed to be that **1** is phosphorylated in vivo to monophosphate **2**[4] which is an agonist of $S1P_{1,3,4,5}$ receptors but not $S1P_2$,[5] and that $S1P_1$ agonism redirects the trafficking of peripheral naïve and activated CD4 and

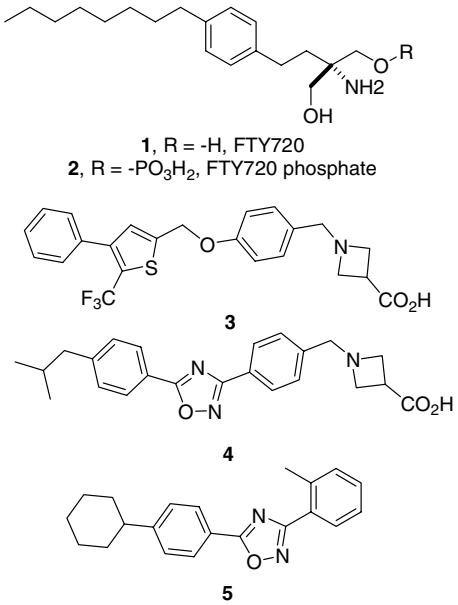

Figure 1. Structures of FTY720 (**1**), its metabolite FTY720-phosphate (**2**), two azetidine-3-carboxylic acids (**3** and **4**), and lead $S1P_1$ receptor agonist **5**.

Keywords: Sphingosine-1-phosphate (S1P) receptors; Agonists; Lymphocyte lowering; Immunosuppression; Transplantation; 3-Arylpropionic acids.
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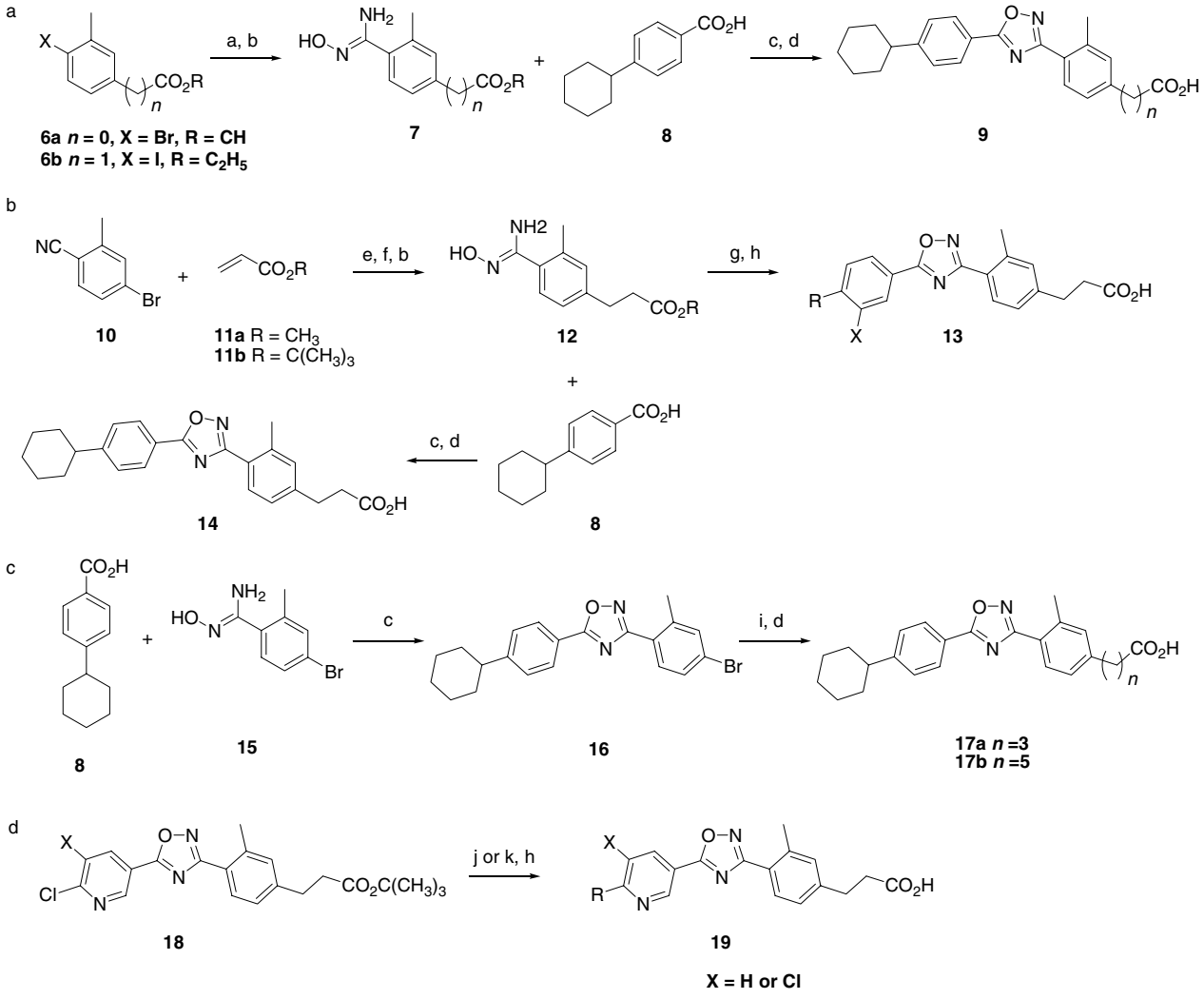
CD8 T cells and B cells from systemic circulation into secondary lymphoid organs, resulting in the observed immunosuppressive efficacy in preclinical animal models.[6] The primary adverse effect observed in clinical trials of FTY720 is transient and asymptomatic bradycardia; $S1P_3$ agonism has been shown to be responsible for the acute cardiovascular toxicity observed in rodents.[7]

We have recently disclosed several series of amino acids as potent and orally bioavailable $S1P_1$ agonists selective against $S1P_3$ (exemplified by **3** and **4**, Fig. 1).[8–11] Compound **3** is a potent $S1P_1$ agonist (IC_{50} = 1.2 nM) with good to moderate selectivity over other S1P subtypes (440-fold over $S1P_3$, 1350-fold against $S1P_4$, and 20-fold over $S1P_5$). In comparison, compound **4** is a more potent $S1P_1$ agonist (IC_{50} = 0.6 nM) with excellent selectivity against $S1P_3$ (20,000-fold), but its selectivity over other subtypes is low (120-fold over $S1P_4$ as a weak antagonist and non-selective against $S1P_5$). While physiological actions of other S1P subtypes remain to be further elucidated,[12–14] investigation that establishes the connection of $S1P_1$ and alterations in lymphocyte trafficking makes it desirable to have an $S1P_1$-specific agonist as an immunosuppressant. Here we describe the discovery of a series of 3-arylpropionic acids as potent $S1P_1$ agonists derived from lead compound **5**.[15] Structure–activity relationship studies of the left-hand side pendant phenyl ring identify several structural motifs offering $S1P_1$ agonists selective against all other known S1P subtypes.

Based on the structural similarity between azetidine-3-carboxylic acid **4** and lead compound **5**, we decided to introduce a carboxylic acid group to the right-hand side phenyl ring of **5** at the position *para* to the oxadiazole ring, where it may interact potentially with negatively charged residues of $S1P_1$ receptor (e.g., Arg120 and Arg292).[16] The distance—defined by the number (*n*) of methylene groups—between the carboxylic acid group and the phenyl ring was varied incrementally to optimize



Scheme 1. (a) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, H_2O, DMF, 120 °C; (b) $NH_2OH{\cdot}HCl$, $NaHCO_3$, CH_3OH, 60 °C (10–90%); (c) EDC, $ClCH_2CH_2Cl$, rt (4 h)—100 °C (14 h) (14–60%); (d) NaOH, CH_3OH, rt (63–100%); (e) methyl acrylate or *tert*-butyl acrylate, $Pd[P(tBu)_3]_2$, Cy_2NCH_3, 1,4-dioxane, 70 °C; (f) 10% Pd/C, H_2 (15 Psi), CH_3OH, rt, (49% over two steps); (g) derivatized benzoic acids, EDC, $ClCH_2CH_2Cl$, rt (4 h)—100 °C (14 h); (h) 20% TFA, CH_2Cl_2, rt (81%); (i) $BrZn(CH_2)_nCO_2Et$, *n* = 3 and 5, $Pd[P(tBu)_3]_2$, 1,4-dioxane, 75 °C; (j) ROH, NaH, DMF, 120 °C; (k) RZnBr, $Pd[P(tBu)_3]_2$, NMP, THF, 80 °C.

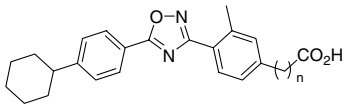
$S1P_1$ binding potency. These analogs can be readily prepared from commercial materials using known synthetic methods. Synthesis of analogs having $n = 0$ and 1 featured palladium catalyzed cyanation (Scheme 1a). Synthesis of analogs having $n = 2$ utilized Heck coupling reaction (Scheme 1b). The low yielding (~10%) for the formation of amidoxine **12** from methyl 3-phenylpropionate was circumvented by using corresponding *tert*-butyl ester instead. Synthesis of analogs having $n = 3$ and 5 exploited Neigishi coupling (Scheme 1c).[17] Finally, preparation of pyridine analogs was achieved using either properly derivatized pyridine carboxylic acids or chemical modification of intermediate **19** (Scheme 1d).

S1P binding affinities (IC_{50}) of the new compounds were determined in competitive binding assays of [^{33}P]-labeled S1P ligand on Chinese hamster ovary (CHO) cell membranes stably expressing S1P receptors.[5a] Their respective functional binding affinities (EC_{50}) were determined by measuring the ligand-induced uptake of [^{35}S]GTPγS by CHO cell membranes stably expressing S1P receptors.[5a] All tested compounds were found to be full agonists of $S1P_{1,3,5}$ and inactive ($IC_{50} > 10$ μM) against both $S1P_2$ and $S1P_4$. This class of carboxylic acids appeared significantly more potent when evaluated for functional activity as compared to receptor binding. While reasons for such shift are not fully understood at present, they are not unprecedented and with these compounds we found EC_{50} values a better guide for interpreting in vivo activity. Compound-induced peripheral blood lymphocyte (PBL) lowering in mice was measured by the reduction percentage of the absolute PBL counts determined at a three-hour time point after the oral administration of the test compound in comparison to those from vehicle controls.[5a] The murine PBL lowering has been previously shown to correlate with immunosuppressive efficacy in rodents.[18]

Among all carboxylic acids with varying distance between the phenyl ring and the carboxylic acid group, 3-phenylpropionic acid **14** was the most potent $S1P_1$ agonist (Table 1). Its $S1P_1$ binding affinity was improved about sixfold in comparison to **5**; whereas, its selectivity against $S1P_3$ was significantly decreased and selectivity against $S1P_5$ was enhanced just about twofold. Compound **14** was also found to lower murine PBL modestly versus vehicle after a 1 mpk po dose. In contrast, compounds having distance other than $n = 2$ showed greater than fivefold $S1P_1$ binding potency loss. Based on these data, 3-arylpropionic acids were selected for further investigation.

3-Arylpropionic acids having a pendant 3,4-disubstituted phenyl group demonstrated significant potency enhancement (Table 2). Analog **13a** is a 90 pM $S1P_1$

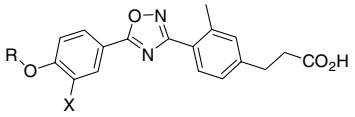
Table 1. S1P functional binding affinities (EC_{50}, nM) for compounds with varying distance between the carboxylic acid and the right-hand side phenyl group[a,b]



Compound	*n*	$S1P_1$	$S1P_3$	$S1P_5$
5	—	2.4	>10,000	266
9a	0	467	>10,000	>10,000
9b	1	830	>10,000	4000
14	2	0.4	160	591
17a	3	14	1100	840
17b	5	12	1220	1080

[a] Ligand-induced uptake of [^{35}S]GTPγS on CHO cell membranes expressing S1P receptors. Data are reported as means for $n = 3$ measurements. SD were generally within ±20% of the average.
[b] The EC_{50} values of $S1P_2$ and $S1P_4$ are generally greater than 10 μM.

Table 2. S1P functional binding affinities (EC_{50}, nM) for compounds having 3,4-disubstituted pendant phenyl ring[a]



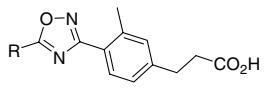
Compound	R	X	$S1P_1$	$S1P_3$	$S1P_5$
13a		CF_3	0.09	110	40
13b		CF_3	0.4	460	260
13c		CF_3	3.2	>10,000	2600
13d		F	1.9	4070	530
13e		Cl	0.2	1500	140
13f		CH_3	0.2	460	210
13g		Br	<0.08	230	43
13h		OCH_3	1.1	620	270
13i		CN	<0.08	1100	6.5
13j		CN	0.07	470	15
13k		CN	0.03	500	3.1
13l		CN	0.1	340	0.7
13m		CN	0.11	1600	44

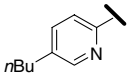
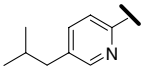
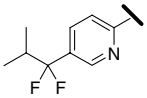
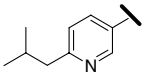
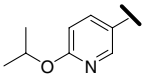
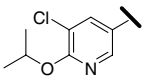
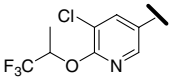
[a] Ligand-induced uptake of [^{35}S]GTPγS on CHO cell membranes expressing S1P receptors. Data are reported as means for $n = 3$ measurements. SD were generally within ±20% of the average.

agonist, and its selectivity against $S1P_3$ and $S1P_5$ was about 1200- and 450-fold, respectively. It was also able to lower murine PBL maximally versus vehicle after a 0.1 mpk po dose. Changing isopropyl group into ethyl and methyl groups led to the incremental loss of $S1P_1$ binding affinity. Replacement of 3-trifluoromethyl group of **13a** yielded a series of potent $S1P_1$ agonists. Among them, bromide **13g** and nitrile **13i** were found to be full agonists even at the lowest testing concentration (80 pM) in $S1P_1$ functional binding assay. Compound **13i** showed greater than 14,000-fold of selectivity against $S1P_3$ and 80-fold over $S1P_5$ and lowered PBL maximally versus vehicle after a 0.1 mpk po dose. Chloride **13e** is a potent $S1P_1$ agonist with good selectivity against both $S1P_3$ (7500-fold) and $S1P_5$ (700-fold). One methyl group extension of isopropyl group in **13i** led to **13j** having almost threefold decrease in selectivity against $S1P_3$. Fluorination on the isopropyl group of **13i** resulted in equipotent $S1P_1$ agonists but loss of selectivity against $S1P_3$. The latter, but not the former, was observed previously with 2-aryl(pyrrolidin-4-yl)acetic acids.[11] Analog **13m** is a potent $S1P_1$ agonist and has good selectivity against $S1P_3$ (16,000-fold) and $S1P_5$ (400-fold). Both **13e** and **13m** were able to lower murine PBL modestly and maximally versus vehicle after a 0.3 mpk po dose, respectively (Table 3).

Another lead structure we have pursued in the hope of identifying $S1P_1$ specific agonists was pyridine analog **19a**—a modest potent $S1P_1$ agonist with excellent selectivity against both $S1P_3$ and $S1P_5$. Replacement of *n*-butyl group with isobutyl resulted in about fivefold potency enhancement. Fluorination of isobutyl group led to further enhancement (fourfold); however, selectivity of $S1P_1$ against $S1P_3$ and $S1P_5$ was again attenuated; an instance was observed previously with 2-aryl(pyrrolidin-4-yl)acetic acids.[11] Translocation of the nitrogen on the pyridine ring of **19b** away from the oxadiazole ring gave **19d**, which was found to be 25-fold less potent. Conversion of isobutyl group of **19d** to isopropyloxy furnished **19e** with significant potency loss. Remarkably, introduction of chlorine *ortho* to isopropyloxy of **19e** exhibited almost 300-fold potency gain, with 1400-fold of selectivity against both $S1P_3$ and $S1P_5$ receptors. Again, fluorination of isobutyl group of **19f** led to further sevenfold potency increase, but its selectivity against both $S1P_3$ and $S1P_5$ was substantially decreased. Compounds **19f** and **19g** showed modest ability to lower murine PBL modestly versus vehicle after a 3 mpk po dose and modestly after a 0.3 mpk po dose, respectively.

Table 3. S1P functional binding affinities (EC_{50}, nM) for test compounds having substituted pyridyl ring[a]



Compound	R	$S1P_1$	$S1P_3$	$S1P_5$
19a		16.0	>10,000	>10,000
19b		3.4	1200	>1000
19c		0.9	470	820
19d		88	>1000	>1000
19e		208	>10,000	>10,000
19f		0.7	950	950
19g		0.1	160	24

[a] Ligand-induced uptake of [^{35}S]GTPγS on CHO cell membranes expressing S1P receptors. Data are reported as means for $n = 3$ measurements. SD were generally within ±20% of the average.

Rat pharmacokinetics for selected 3-arylpropionic acids generally showed low clearance (except for pyridine analog **19f**), low volume distribution, and good oral bioavailability (Table 4). But regardless of structural variations on the pendant phenyl ring, 3-arylpropionic acids all exhibited relatively short halflives in rat.

To demonstrate that an $S1P_1$ agonist selective against all other S1P subtypes could maintain the immunosuppressive efficacy of **1**, compound **13m**, which has the shortest half life in rat and good selectivity against $S1P_{3,5}$, was selected to test in a skin allograft model, using the MHC–disparate combination of DA (donor) and Lewis (recipient) rats.[19] Compound **13m** (1.5 mpk/day or 4.5 mpk/day, $n = 6$ rats, delivered via Alzet mini-osmotic pumps placed in the peritoneal cavity) and **1** (1 mpk/day, po, $n = 6$ rats) were administered one day prior to graft transplantation, until graft death. The median graft survival times were 11 days (vehicle, $n = 8$ rats), 13 days (**13m** at 1.5 mpk/day), 14 days (**13m** at 4.5 mpk/day), and 12 days (**1**). Graft survival was statistically significantly enhanced by treatment with either **1** or **13m** (at either dose), but there was no statistically significant difference between treatment with either **1** or **13m**. Treatment of **13m** at higher dose, however, prolonged graft survival significantly better than with lower one. The degree of PBL lowering achieved at day 7 in rat, post-transplantation, was found to be maximal for **1** and **13m** at both doses, respectively.

In conclusion, a series of 3-arylpropionic acids—structurally complementary to the other series of $S1P_1$ agonists discovered in these laboratories—have been identified as potent and selective $S1P_1$ receptor agonists. Structure–activity relationship studies on the pendant phenyl ring allowed for the identification of several $S1P_1$ potent agonists with high selectivity against other S1P subtypes. These highly selective $S1P_1$ agonists can effectively lower peripheral blood lymphocytes in mice. Compound **13m** was tested in a rat skin transplantation experiment and found to be immunosuppressive comparable to **1**. 3-Arylpropionic acids exhibit overall good pharmacokinetic properties except that they have

Table 4. Rat pharmacokinetic parameters of selected 3-arylpropionic acids[a]

Compound	Rat PK
13a	Cl_p = 8.7 mL/min/kg, V_{dss} = 1.1 L/kg, $t_{1/2}$ = 1.1 h, %F = 88.0
13e	Cl_p = 5.7 mL/min/kg, V_{dss} = 0.4 L/kg, $t_{1/2}$ = 0.8 h, %F = 80.0
13i	Cl_p = 2.3 mL/min/kg, V_{dss} = 0.2 L/kg, $t_{1/2}$ = 0.7 h, %F = 53.0
13m	Cl_p = 1.2 mL/min/kg, V_{dss} = 0.1 L/kg, $t_{1/2}$ = 0.6 h, %F = 59.0
19f	Cl_p = 13.5 mL/min/kg, V_{dss} = 0.9 L/kg, $t_{1/2}$ = 1.0 h, %F = 78.3

[a] Plasma compound concentrations used to calculate pharmacokinetic parameters were obtained after iv administration (1.0 mpk) and po administration (2.0 mpk) of test compounds to male Sprague–Dawley rats (n = 2), respectively.

relatively short half life in rat. Together, these results suggest that 3-arylpropionic acids are suitable for further investigation with the aim of identifying highly selective $S1P_1$ agonists with good overall physical properties and biological activities.

Acknowledgments

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