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Synthesis and SAR of 1,3-thiazolyl thiophene and pyridine derivatives as potent, orally active and $S1P_3$-sparing $S1P_1$ agonists

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ABSTRACT

We have previously disclosed 1,2,4-oxadiazole derivative **3** as a potent $S1P_3$-sparing $S1P_1$ agonist. Although compound **3** exhibits potent and manageable immunosuppressive efficacy in various in vivo models, recent studies have revealed that its 1,2,4-oxadiazole ring is subjected to enterobacterial decomposition. As provisions for unpredictable issues, a series of alternative compounds were synthesized on the basis of compound **3**. Extensive SAR studies led to the finding of 1,3-thiazole **24c** with the EC_{50} value of 3.4 nM for human $S1P_1$, and over 5800-fold selectivity against $S1P_3$. In rat on host versus graft reaction (HvGR), the ID_{50} value of **24c** was determined at 0.07 mg/kg. The pharmacokinetics in rat and monkey is also reported. Compared to compound **3**, **24c** showed excellent stability against enterobacteria.

Sphingosine-1-phosphate (S1P) (**1**, Fig. 1) is a bioactive sphingolipid that plays a role in a wide range of physiological processes such as cell differentiation, morphogenesis and motility, through its interaction with the five-membered S1P family ($S1P_1$–$S1P_5$) of G-protein coupled receptors (GPCRs).[1] Among these five receptors, in particular, $S1P_1$ modulators have recently been focused upon as a suppressant of autoimmunity by affecting lymphocyte trafficking, through a rapid progress of studies on FTY720 (fingolimod) (**2**).[2]

The systemic administration of FTY720 induces a dose–responsive lowering of circulating lymphocytes and its immunosuppressive actions have been reported to result from the active phosphate ester metabolite, FTY720-P,[3] which is an agonist of $S1P_{1,3,4,5}$ but not of $S1P_2$. Studies on both FTY720 and S1P receptors has also revealed that the agonism of $S1P_1$ alone is sufficient to control lymphocyte recirculation.[4] On the other hand, $S1P_3$ is implicated in bradycardia as reported in rodents.[5] Recent studies suggested that the removal of the $S1P_3$ agonism is insufficient to exclude the cardiovascular side effect.[6a] However, a great deal of research efforts has been focused on the exploration of $S1P_3$-sparing $S1P_1$ agonists,[6] with the aim of reducing potential side effects,

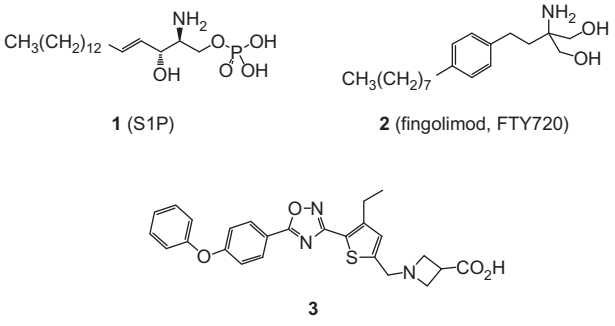

Figure 1. Structures of S1P, fingolimod (FTY720) and compound **3**.

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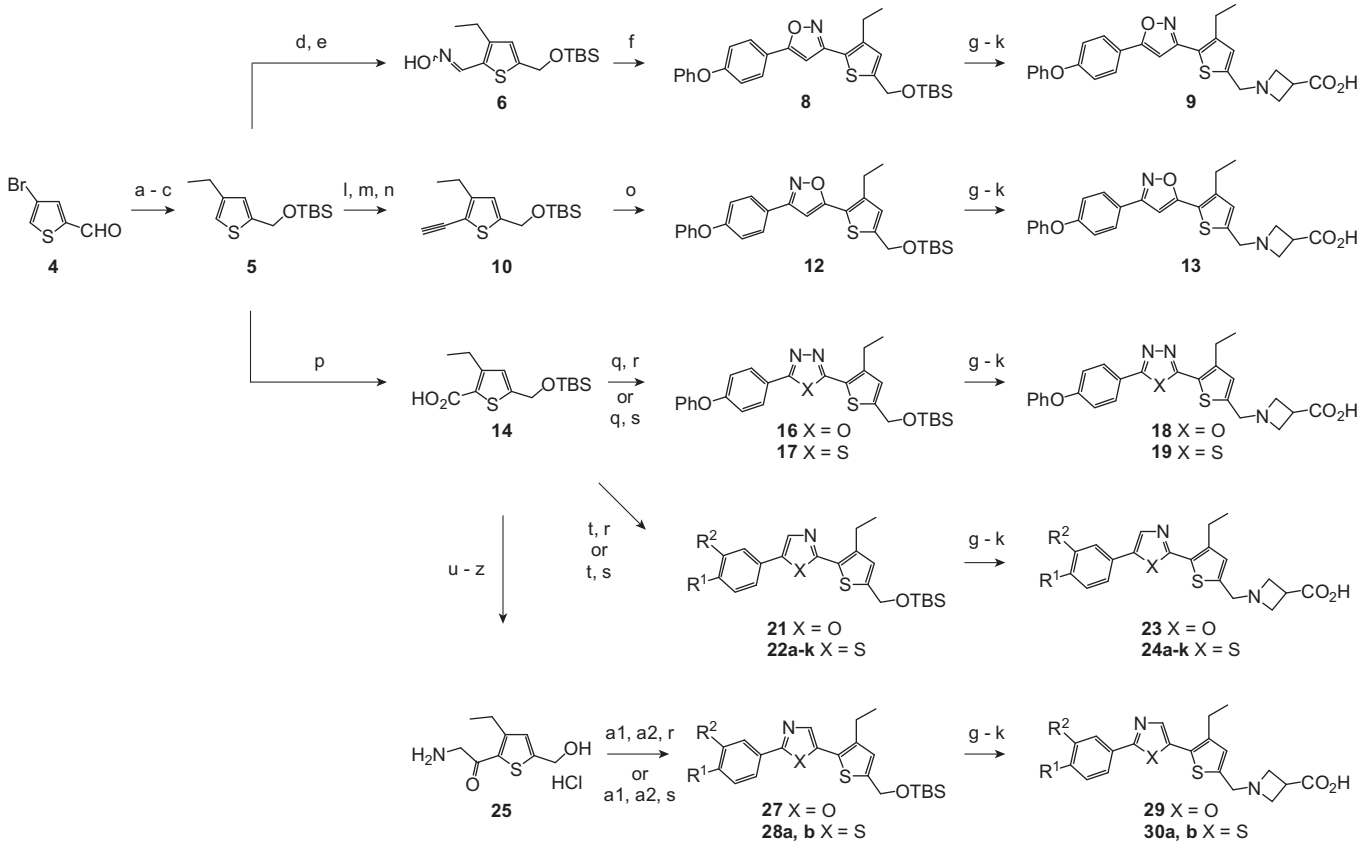
while preserving the impressive efficacy as demonstrated in the clinical trials of FTY720 for the treatment of transplant rejection[7] and remitting relapsing multiple sclerosis.[8]

In a previous paper, we disclosed 1,2,4-oxadiazole derivative **3** as a potent $S1P_1$ agonist.[9] This compound exhibits high agonistic activity to human $S1P_1$ (EC_{50} = 4.0 nM) with good selectivity against $S1P_3$ (>5000-fold), measured by an [^{35}S]GTPγ-S binding assay. In Lewis rats administered a single oral dose of 0.1 or 1 mg/kg of **3**, peripheral blood lymphocyte counts decreased to 27% and 11% of the vehicle-treated control values for the 0.1 and 1 mg/kg dose levels, respectively, 8 h after compound **3** administration. The decreased peripheral blood lymphocyte counts were returned to the vehicle control levels by 24–48 h post-dose. In regards to the immunosuppressive effect on transplant rejection, compound **3** showed fair efficacy in rat on host versus graft reaction[10] (HvGR), (ID_{50} = 0.41 mg/kg, orally administered once daily for 4 successive days from the day of immunization).

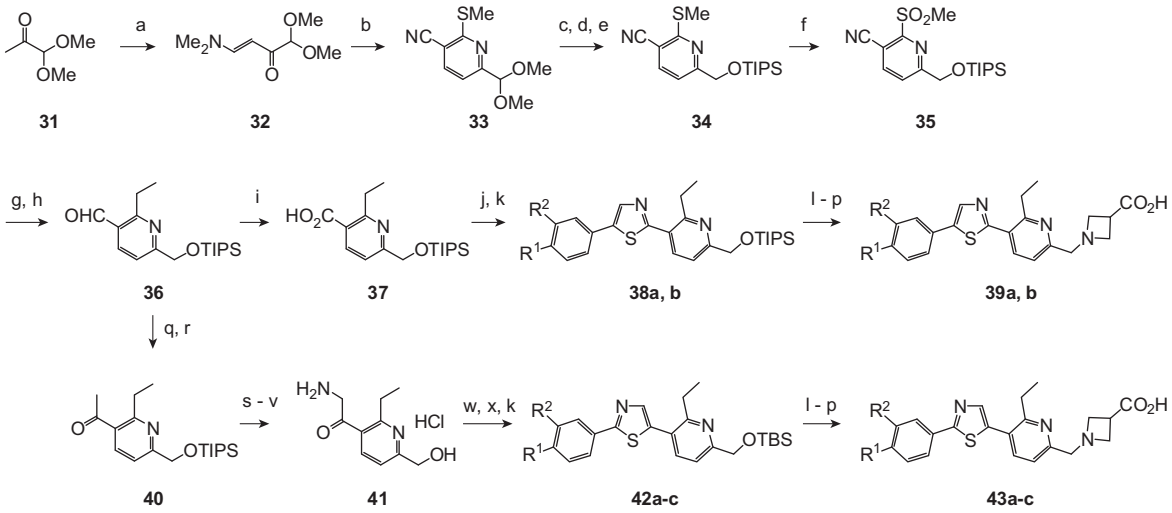
However, further studies on **3** revealed that the central 1,2,4-oxadiazole ring has a tendency to be unfavorably cleaved by enterobacteria in rat and monkey.[9b,11] This observation would arouse concern about broad differences in pharmacokinetics and pharmacodynamics between species or individuals.[12,13] Therefore, we started to explore new structural classes on the basis of compound **3**. Herein, we report the discovery of several potent $S1P_1$ agonists based on 1,3-thiazolyl thiophene and 1,3-thiazolyl pyridine scaffolds.

With the aim of avoiding cleavage of the central ring, we have initiated the replacement of the central 1,2,4-oxadiazole ring to other heteroaromatic rings.

The synthetic routes are shown in Scheme 1. In order to acquire diverse SAR information, 4-ethylthiophene **5** was set as a common intermediate, which was prepared from commercially available 4-bromo-2-thiophencarbaldehyde **4** in three steps; reduction, TBS-protection, and Ni-catalyzed cross coupling reaction with EtMgBr. Compound **5** was able to be functionalized variously at the C-5 position and provided multiple thiophene units (**6**, **10**, **14** and **25**) for heteroaromatic cyclization. For the preparation of 1,2-oxazole **9**, we obtained the precursor **8** by performing 1,3-dipolar cycloaddition with 1-ethynyl-4-phenoxybenzene **7** and nitrile *N*-oxide generated from oxime **6**. Subsequent deprotection of the TBS group, chlorination of the resultant primary hydroxyl group, substitution by methyl azetizine-3-carboxylate, and hydrolysis gave 1,2-oxazole derivative **9**. Likewise, the isomeric **13** was synthesized from corresponding ethynyl thiophene **10** and 4-phenoxybenzonitrile *N*-oxide **11** generated from available 4-phenoxybenzaldehyde. With regard to the preparation of the other heteroaromatics, namely 1,3,4-oxadiazole **18**, 1,3,4-thiadiazole **19**, 1,3-oxazole **23**, **29** and 1,3-thiazole **24a**–**k**, **30a**, **b**, thiophenyl carboxylic acid **14** was utilized as a second intermediate. In **18** and **19**, condensation of **14** with 4-phenoxyhydrazide **15**, followed by treatment of Burgess reagent or Lawesson's reagent provided 1,3,4-oxadiazole **16** or 1,3,4-thiadiazole **17**, respectively. After the juncture process with the azetizine unit, both **18** and **19** were obtained. 1,3-Oxazole **23** and 1,3-thiazoles **24a**–**k** were synthesized by the condensation of **14** with a variety of separately-prepared 2-aminoacetophenones **20a**–**k**,[14] following treatment of Burgess reagent or Lawesson's reagent. For the synthesis of 1,3-oxazole **29** or 1,3-thiazoles **30a**, **b**,

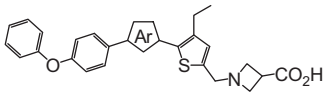


Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH. (b) TBSCl, imidazole (quant., 2 steps). (c) $NiCl_2$(dppp), EtMgBr (89%). (d) *n*-BuLi, DMF (79%). (e) NH_2OH–HCl, Et_3N, CH_2Cl_2, MeOH (96%). (f) NCS, pyridine, $CHCl_3$, then 1-ethynyl-4-phenoxybenzene (**7**), Et_3N, $CHCl_3$ (73%). (g) TBAF, THF. (h) $SOCl_2$, toluene. (i) Methyl azetidine-3-carboxylate HCl, *i*-Pr_2NEt, MeCN (66–97%, 3 steps). (j) aq. NaOH, EtOH (60–92%). (k) Oxalic acid (**9** and **13** were solidified as oxalates). (l) *n*-BuLi, THF, then I_2 (72%). (m) Trimethylsilylacetylene, CuI, $Pd(PPh_3)_4$, Et_3N (75%). (n) K_2CO_3, MeOH (75%). (o) 4-Phenoxybenzonitrile *N*-oxide (11), Et_3N, $CHCl_3$ (59%). (p) *n*-BuLi, THF then CO_2 (73%). (q) 4-Phenoxybenzhydrazide (**15**), DCC (46%). (r) Burgess reagent, Et_3N, MeCN, 80 °C (61–93%). (s) Lawesson's reagent, pyridine, toluene, 100 °C (70–97%). (t) EDCI, HOBt, various aminoacetophenones (**20a**–**k**), Et_3N, $CHCl_3$ (57–81%). (u) MeNHOMe, EDCI, HOBt, Et_3N, CH_2Cl_2 (52%). (v) MeLi, Et_2O (89%). (w) NaHMDS, TMSCl, Et_3N, THF. (x) NBS, THF. (y) $NaN(CHO)_2$, MeCN (3 steps, 59%). (z) HCl, EtOH (99%). (a1) EDCI, HOBt, benzoic acids (**26a**, **b**), Et_3N, CH_2Cl_2. (a2) TBSCl, imidazole, DMF (75–92%, 2 steps).



Scheme 2. Reagents and conditions: (a) *N*,*N*-Dimethylformamide dimethylacetal, MeCN, reflux. (b) 2-Cyanothioacetamide, MeONa then MeI (2 steps, 61%). (c) cat. DDQ, H_2O–MeCN (80%). (d) $NaBH_4$. (e) TIPSCl, imidazole (2 steps, 100%). (f) *m*-CPBA, EtOH (91%). (g) EtMgBr, Et_2O (98%). (h) DIBAL, toluene (98%). (i) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene (100%). (j) EDCI, HOBt, aminoacetophenones (**20c**, **d**), Et_3N, $CHCl_3$ (60–79%). (k) Lawesson's reagent, pyridine, toluene, 100 °C (79–95%). (l) TBAF, THF. (m) $SOCl_2$, toluene. (n) Methyl azetidine-3-carboxylate HCl, *i*-Pr_2NEt, MeCN (66–82%). (o) aq NaOH, EtOH. (p) Oxalic acid (54–83%, 2 steps). (q) MeLi. (r) PDC (2 steps, 85%). (s) NaHMDS, TMSCl, Et_3N, THF. (t) NBS, THF. (u) $NaN(CHO)_2$, MeCN (3 steps, 42%). (v) HCl, EtOH (96%) (w) EDCI, HOBt, various benzoic acids (**26b**, **c**, **d**), Et_3N, $CHCl_3$. (x) TBSCl, imidazole, DMF (71–80%, 2 steps).

Table 1
SAR of central rings



Compound	Ar	γ-GTP[a] EC_{50} (nM)		Rat HvGR[b] ID_{50} (mg/kg) or % inhibition @ 1 mg/kg
		$hS1P_1$	$hS1P_3$	
3		4.0	>20,000	0.41
9		22	>20,000	2% (±11)
13		15	>20,000	No inhibition
18		54	>20,000	NT
19		25	>20,000	No inhibition
23		90	>20,000	NT
29		300	>20,000	NT
24a		4.5	>20,000	42% (±5)
30a		35	>20,000	25% (±9)

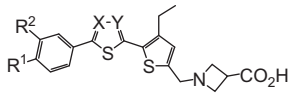
[a] EC_{50} is the mean of two experimental determinations.
[b] Each value of inhibition percentage is the mean of five rats, standard error is given in parentheses (NT = not tested). ID_{50} is determined by results of at least three different doses.

benzoic acids **26a**, **b**[15] were condensed with aminoketone **25** prepared from **14**, and the same subsequent processes were conducted.

In exploratory work, we established that the 6-ethylpyridine structure can be substituted for 4-ethylthiophene (data not shown). Therefore, further synthetic efforts were expanded to the 6-ethylpyridine derivatives. The synthetic routes are summarized in Scheme 2. Starting from **31**, the construction of the pyridine structure via reaction of **32** with 2-cyanothioacetoamide, followed by some conversions of each functional group, provided pyridylaldehyde **36** as an intermediate for 1,3-thiazoles **39a**,**b** and **43a**–**c**. After administration by sequences similar to those conducted in Scheme 1, 1,3-thiazole derivatives **39a**, **b** and **43a**–**c**[15] were obtained.

Initially, we measured the agonist activities against human $S1P_1$ and $S1P_3$ and then evaluated the in vivo immunosuppressive efficacy in rats on HvGR.

Table 2
SAR of thiophene derivatives



Compound	X	Y	R^1	R^2	γ-GTP[a] EC_{50} (nM)		Rat HvGR[b] ID_{50} (mg/kg) or % inhibition @ 1 mg/kg
					$hS1P_1$	$hS1P_3$	
3					4.0	>20,000	0.41
24a	C	N	PhO	H	4.5	>20,000	42% (±5)
24b	C	N	*i*-PrO	H	10	>20,000	52% (±2)
24c	C	N	*i*-PrO	Me	3.4	>20,000	0.07
24d	C	N	*i*-PrO	Et	3.4	>20,000	0.16
24e	C	N	*i*-PrO	*n*-Pr	1.1	400	73% (±4)
24f	C	N	*i*-PrO	*i*-Pr	1.3	>20,000	0.53
24g	C	N	*i*-PrO	F	5.8	>20,000	0.48
24h	C	N	*i*-PrO	Cl	3.2	>20,000	54% (±7)
24i	C	N	*i*-Pr	Me	3.5	>20,000	1.07
24j	C	N	(*S*)-*sec*-BuO	Me	6.0	>20,000	0.32
24k	C	N	(*R*)-*sec*-BuO	Me	8.0	>20,000	27% (±7)
30b	N	C	*i*-PrO	Me	11	>20,000	0.19

[a,b] See Table 1.

The SAR information about the central heteroaromatic ring is summarized in Table 1. The superior $S1P_1$ agonist activity was observed for 1,3-thiazole **24a** (EC_{50} = 4.5 nM) with sufficient $S1P_1$/$S1P_3$ selectivity (>4400-fold), which is almost equal to compound **3**. In contrast, the isomeric **30a** displayed lower but tolerable agonist activity (EC_{50} = 35 nM) relative to **24a**. In a previous report, Merck's group also reported a similar tendency between the isomers of 1,3-thiazoles in their scaffold.[16] 1,2-Oxazoles **9**, **13** and 1,3,4-thiadiazole **19** also showed moderate agonist activities.

In rat on HvGR, 1,3-thiazole **24a** showed reduced inhibitory activity (42% inhibition at 1 mg/kg), whose insufficient efficacy could presumably result from pharmacokinetic issues. Unexpectedly, the isomer **30a** showed fair efficacy on this model, despite comparatively lower $S1P_1$ agonist activity than 1,2-oxazoles **9**, **13** and 1,3,4-thiadiazole **19**.

Hence, based on identified alternative 1,3-thiazole **24** and the isomeric **30**, we conducted further investigation to explore optimal substituents of the benzene ring adjacent to the 1,3-thiazole.

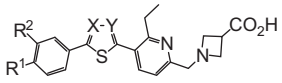
The SAR dataset is shown in Table 2. In the R^1 substituent, the isopropoxy group was identified as a good alternative to the phenoxy group, which led to the improvement of the in vivo efficacy (comparing **24a** with **24b**). On the other hand, the R^2 substituent was proved to considerably affect both the in vitro and in vivo aspects. Namely, the introduction of alkyl groups, such as methyl (**24c**), ethyl (**24d**), *n*-propyl (**24e**), or isopropyl group (**24f**) into the R^2 position of compound **24b** exhibited drastic improvement for the in vivo efficacy. In particular, **24c** and **24d** showed more potent inhibitory activity (ID_{50} = 0.069 mg/kg and 0.16 mg/kg, respectively) than **3**. Interestingly, installation of the *n*-propyl group (**24e**) largely worsened $S1P_1$/$S1P_3$ selectivity, suggesting a limitation on the bulkiness of the R^2 substituent. We also investigated the effect of halogen atoms exemplified by **24g** and **24h**, and the fluoro derivative (**24g**) showed favorable efficacy on HvGR (ID_{50} = 0.48 mg/kg). Subsequently, based on the structure of the most efficacious compound, **24c**, we tried to conduct further minute adjustments on the R^1 substituent as illustrated by the isopropyl (**24i**) and the (*S*) or (*R*)-*sec*-butoxy groups (**24j**, **k**). This scrutinization revealed that the (*S*)-*sec*-butoxy group (**24j**) was also maintained fair efficacy on HvGR (**24j**; ID_{50} = 0.32 mg/kg).

In accordance with the SAR information obtained regarding 1,3-thiazole derivatives **24a**–**k**, we applied effective substituents to the isomeric structure as illustrated by **30b**. As expected, **30b** showed high efficacy on HvGR, which corresponds to the isomer of **24c**.

The results of optimization for the pyridine derivatives are summarized in Table 3. Based on the results of the thiophene derivatives, we installed a combination of favorable substituents to the benzene ring, as illustrated in **39a** and **43a**. These compounds showed an insufficient in vivo immunosuppressive activity but maintained a good in vitro profile. Slight modification in both the R^1 and R^2 substituents revived the in vivo activity to afford the potent pyridine derivatives **39b**, **43b**, and **43c**.

The pharmacokinetics of **24c** and **39b** were evaluated in Lewis rats and Cynomolgus monkeys. The PK parameters of these animals after a single oral administration are shown in Table 4. The thiophene derivative **24c** showed remarkable bioavailability (F = 70.6% in rats, >90% in monkeys) and fair half-life ($T_{1/}$

Table 3
SAR of pyridine derivatives



Compound	X	Y	R^1	R^2	γ-GTP[a] EC_{50} (nM)		Rat HvGR[b] ID_{50} (mg/kg) or % inhibition @ 1 mg/kg
					$hS1P_1$	$hS1P_3$	
39a	C	N	*i*-PrO	Me	5.5	>20,000	39% (±9)
39b	C	N	*i*-PrO	Et	4.0	>20,000	0.49
43a	N	C	*i*-PrO	Me	2.8	>20,000	17% (±9)
43b	N	C	*i*-Bu	Me	4.1	>20,000	0.64
43c	N	C	*i*-Bu	Et	5.4	>20,000	0.74

[a,b] See Table 1.

Table 4
Pharmacokinetic parameters and bioavailabilities of **24c** and **39b** to rat and monkey

Compound	Animals	Dose[a] (mg/kg)	C_{max} (μg/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-inf} (μg h/mL)	F (%)	CL[b] (mL/min/kg)	Vd[b] (L/kg)
24c	Rat	3.0	0.34	5	11.5	5.14	70.6	6.72	5.37
24c	Monkey	1.0	0.63	4	7.2	8.69	>90	2.00	0.89
39b	Monkey	0.5	0.15	5	16.7	3.73	75.4	1.75	1.46

[a] po administration, rat (n = 4), monkey (n = 2).
[b] iv administration, rat (1.0 mg/kg, n = 2), monkey (0.5 mg/kg, n = 2).

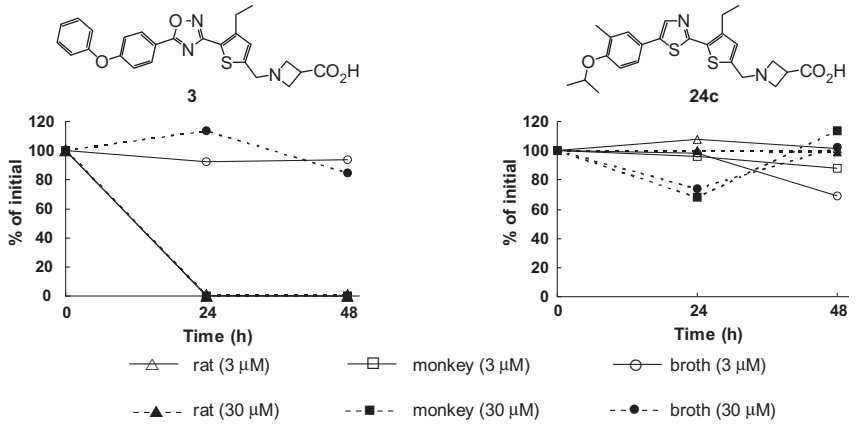


Figure 2. Compound stability against enterobacteria from rat cecal contents or monkey feces under anaerobic condition.

$_2$ = 11.5 h in rats, 7.2 h in monkeys). Meanwhile, the pyridine derivative **39b** exhibited favorable bioavailability (F = 75.4%) and over twice as long a half-life as **24c** in monkeys ($T_{1/2}$ = 16.7 h).

Finally, we evaluated compound stabilities against enterobacterial decomposition in rats and monkeys.[17,18] In order to compare **24c** with **3**, each compound solution (3.0 and 30 μM) was exposed to broth (control) and the culture fluid of enterobacteria, which was derived from rat cecal contents or monkey feces and incubated under anaerobic conditions. The stabilities were estimated by means of tracing the percentage of each remaining compound (24 and 48 h after). The results are shown in Figure 2. In contrast to **3**, 1,3-thiazole derivative **24c** was found to be stable and remained even 48 h later.

In short, we designed and synthesized a series of 1,3-thiazole compounds as $S1P_3$-sparing $S1P_1$ agonists. Compound **24c** exhibited high $S1P_1$ agonistic activity, $S1P_1/S1P_3$ selectivity, inhibitory activity in rat on HvGR, and good PK profile. This compound also demonstrated clear endurance to enterobacterial decomposition. As well, the pyridine derivative **39b** showed favorable efficacy. Further studies on the optimization of these analogues are being conducted at this time.

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10. The in vivo immunosuppressive effects of compounds on host versus graft reaction (HvGR) were evaluated by using a popliteal lymph node gain assay in rats. Spleen cells of WKAH rats were injected into the footpads of LEW rats to induce an enlargement of the draining popliteal lymph node. Compounds were

orally administrated once a day for four days from the day of spleen cell injection (day 0), and the weight of the popliteal lymph node was measured at day 4.

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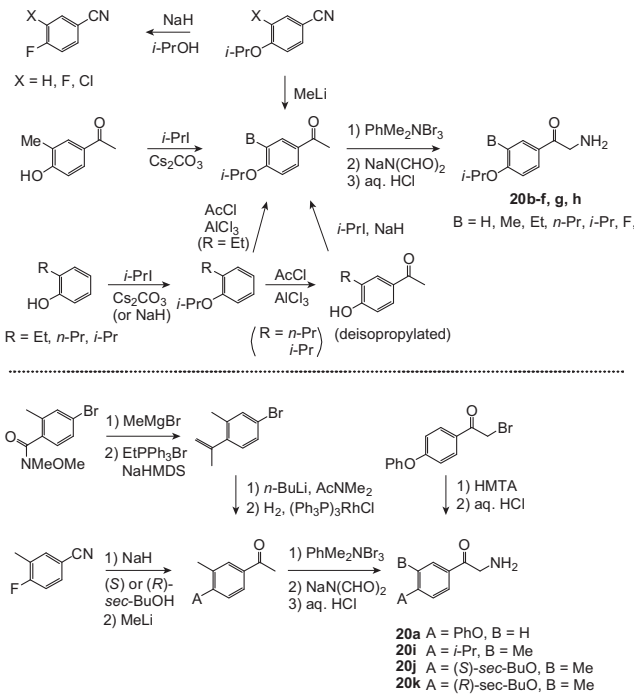
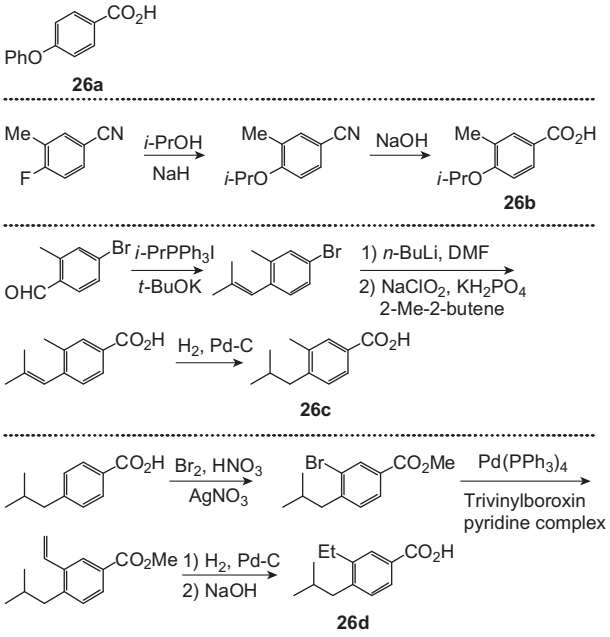
13. 4-Phenoxy benzoic acid (4-PBA) was identified as one of the major metabolites in rat and monkey plasma after oral administration of **3** (data not shown). 4-PBA showed weak PPARα agonism and a considerably long half-life in those animal species (data not shown).
14. Preparations for **20a–k** are outlined below.



15. Preparations for **26a–d** are outlined below.



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18. The stabilities were evaluated by the method of the Ref. 17, with some modifications. PYF broth was used instead of PYG. The cecal contents and feces were placed into the prereduced PYF broth instead of prereduced VPI buffer in the reference.