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Design and synthesis of conformationally constrained 3-(*N*-alkylamino)propylphosphonic acids as potent agonists of sphingosine-1-phosphate (S1P) receptors

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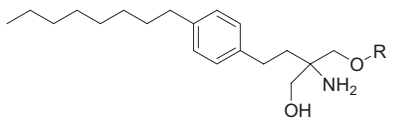
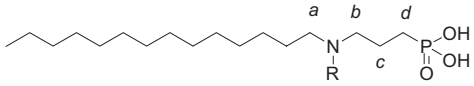
Abstract—A series of conformationally constrained 3-(*N*-alkylamino)propylphosphonic acids were systematically synthesized and their activities as S1P receptor agonists were evaluated. Several pyrrolidine and cyclohexane analogs had S1P receptor profiles comparable to the acyclic lead compound, 3-(*N*-tetradecylamino)propylphosphonic acid (**3**), lowered circulating lymphocytes in mice after iv administration and were thus identified as being suitable for further investigations.

FTY720 (**1**, Fig. 1) is a novel immunosuppressant that prolongs the survival of organ allografts in animals; it has progressed through the clinic and is currently in Phase III trials for the prevention of kidney transplant rejection.[1] The mechanism of FTY720-mediated immunosuppression, while not being fully understood, appears to be different from those of existing immunosuppressants. Recent studies have shown that FTY720 is phosphorylated in vivo by sphingosine kinase and that FTY720-phosphate (**2**) is a potent agonist of a family of sphingosine-1-phosphate (S1P) G protein-coupled receptors.[2,3] The activation of $S1P_1$ receptor by **2** is presumably responsible for the observed immunosuppressive efficacy due to the subsequent sequestration of lymphocytes into secondary lymphoid organs, which reduces and/or inhibits infiltration of lymphocytes into graft sites and inflamed tissues.[4]

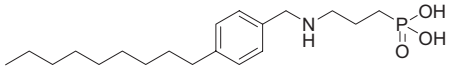
Previous studies from these laboratories[5] have shown that 3-(*N*-tetradecylamino)propylphosphonic acid (**3**) is



1, R = -H, FTY720
2, R = $-PO_3H_2$, FTY720 phosphate



3, R = -H, $S1P_1$ IC_{50} = 3.0 nM
4, R = $-CH_3$, $S1P_1$ IC_{50} = 16 nM



5, $S1P_1$ IC_{50} = 0.2 nM

Figure 1. FTY720 (**1**), FTY720-phosphate (**2**), and analogs **3**–**5** are all potent agonists of S1P receptors. The letters shown by structure **3** mark the positions that were identified for tethering using short alkyl chains.

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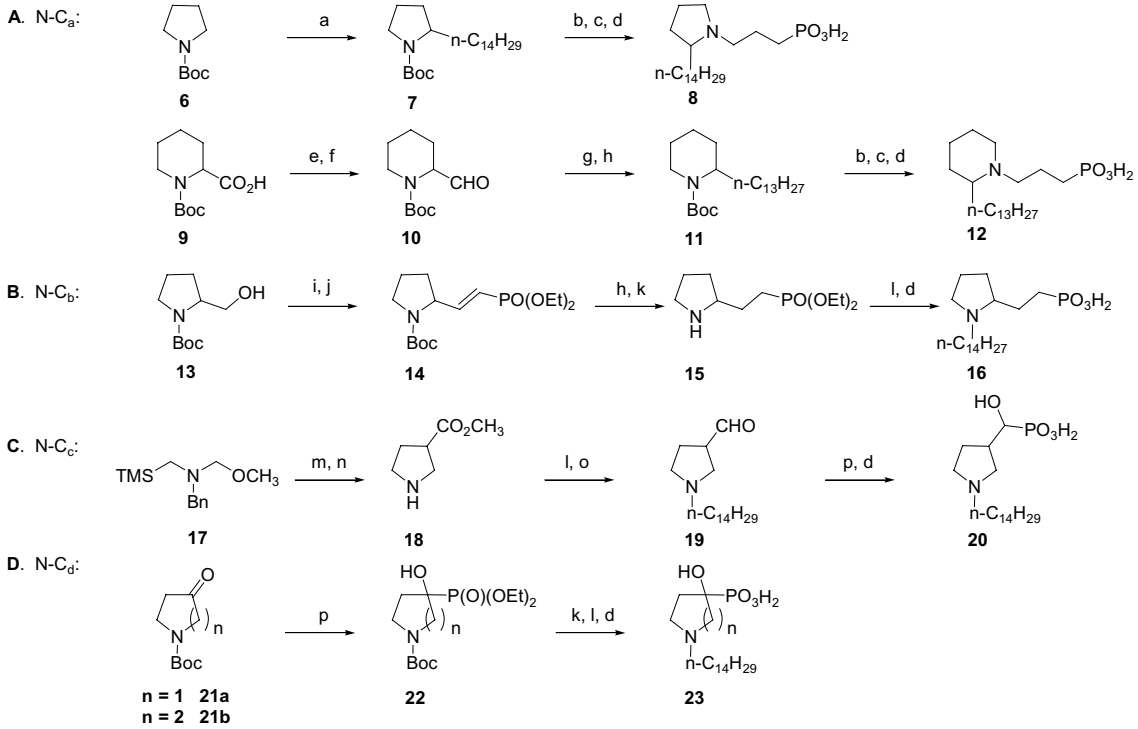
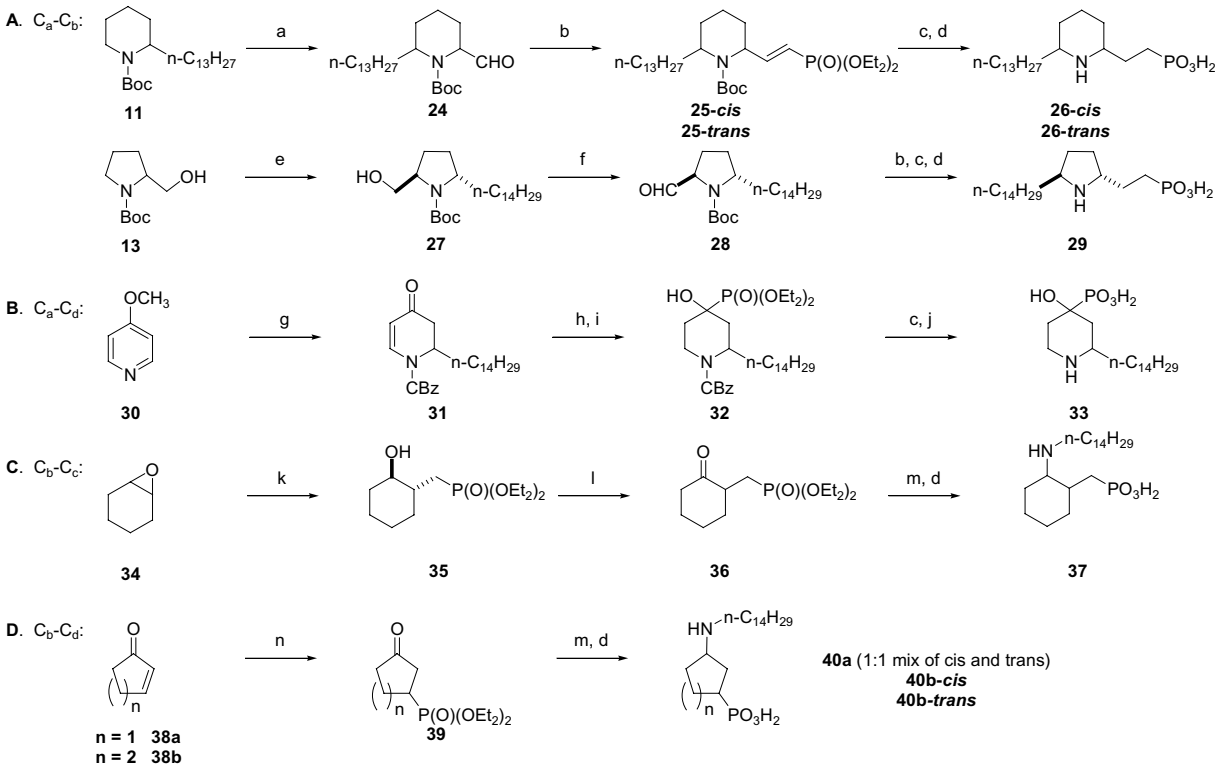
a potent agonist of S1P receptors and that the proper incorporation of a phenyl ring into the long alkyl chain of this compound gives **5**, which has 15-fold greater affinity for $S1P_1$ than does **3**. *N*-Methylation of **3**, giving **4**, results in a 5-fold loss of affinity for $S1P_1$. To extend the scope of this work, efforts were undertaken to systematically synthesize analogs of **3** in which the nitrogen and a neighboring carbon atom or a pair of adjacent carbons of this compound were tethered with short alkyl chains, with the goal of identifying novel scaffolds for S1P receptor agonists. This paper describes the synthesis and evaluation of these conformationally constrained amino phosphonic acids and amino α-hydroxyl phosphonic acids.[6] Scaffolds identified here as being suitable for S1P receptor agonists were elaborated into analogs of **5** to determine whether $S1P_1$ receptor affinity was enhanced similarly to that observed on going from **3** to **5**.

The syntheses of analogs of **3** in which the nitrogen and an adjacent carbon are linked are described in Scheme 1. To tether the nitrogen to C_a with a propyl chain, treatment of **6** with *s*-BuLi in the presence of TMEDA[7] followed by tetradecyl bromide gave pyrrolidine **7**. Removal of Boc followed by *N*-alkylation of the resulting pyrrolidine with diethyl 3-bromopropylphosphonate and ester cleavage led to pyrrolidine **8**. For the corresponding piperidine analog **12**, reduction of *N*-Boc-piperidine-2-carboxylic acid (**9**) followed by TPAP oxidation[8] provided aldehyde **10**. This was condensed with *n*-dodecylphosphorane and then hydrogenated to supply **11**. Piperidine **12** was then obtained using procedures analogous to those used to convert **7** to **8**. To link the nitrogen and C_b, Swern oxidation of *N*-Boc-pyrrolidinemethanol (**13**) followed by Horner–Emmons olefination gave **14**. This was hydrogenated and then treated with anhydrous HCl in EtOH to furnish **15**. Reductive amination of **15** with *n*-tetradecylaldehyde followed by ester cleavage delivered pyrrolidine **16**. Connecting the nitrogen atom and C_c with an ethylene chain, featured the use of 1,3-dipole cyclization chemistry.[9] Reacting **17** and methyl acrylate in the presence of catalytic TFA followed by hydrogenation gave **18**. Reductive amination and DIBAL-H reduction of the ester provided aldehyde **19**, which was coupled with diethyl phosphite under Pudovik conditions[10] followed by ester cleavage to give **20**.[11] Tethering the nitrogen and C_d with ethyl and propyl chains was accomplished starting from **21a** and **21b**, respectively, and also featured the Pudovik reaction.

The syntheses of analogs in which a pair of adjacent carbons are tethered are shown in Scheme 2. To connect C_a and C_b with a propyl chain, formylation of **11** using *s*-BuLi in the presence of TMEDA[12] gave **24** as a 2:3 mixture of *cis* and *trans* isomers. The mixture could be enriched in the *cis* isomer (6:1 *cis*/*trans*) by treating it with silica gel. Condensation of **24** with tetraethyl methylenediphosphonate provided a mixture of phosphonate esters, which were readily separated by silica



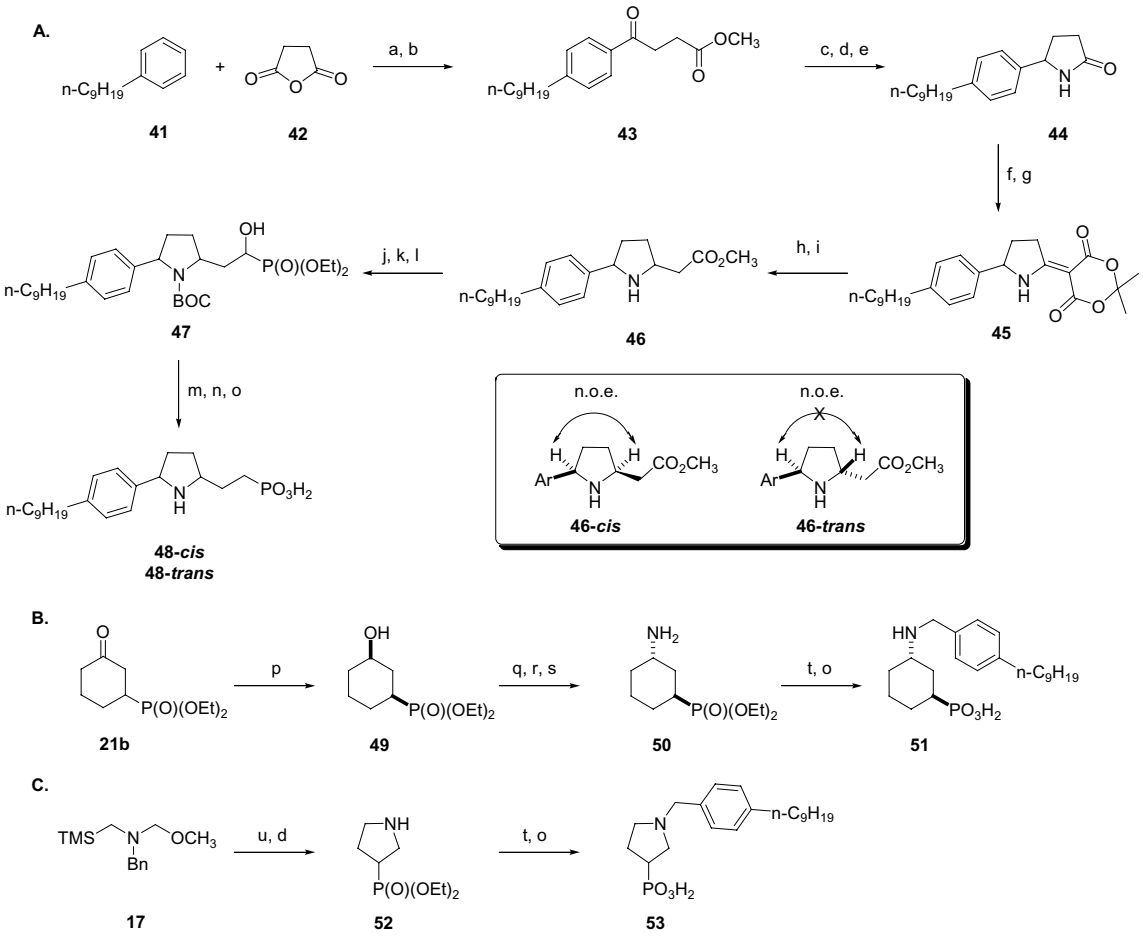
Scheme 1. Reagents and conditions: (a) *s*-BuLi, TMEDA, THF, −78 °C, then *n*-$C_{14}H_{29}Br$, −78 °C to rt (11%); (b) 9:1 CH_2Cl_2/TFA, rt; (c) diethyl 3-bromopropylphosphonate, K_2CO_3, DMF, 100 °C (32–100%, two steps); (d) TMSI, CH_2Cl_2, rt (55–83%); (e) BH_3·THF, THF, rt (100%); (f) NMO, cat. TPAP, 4 Å molecular sieves, CH_2Cl_2, rt (68%); (g) *n*-$C_{12}H_{25}P(Ph)_3Br$, *n*-BuLi, THF, −78 °C to rt (100%); (h) H_2, 10% Pd/C, EtOH, rt (97%); (i) $(COCl)_2$, DMSO, DIEA, CH_2Cl_2, −78 to 0 °C; (j) tetraethyl methylenediphosphonate, NaHMDS, THF, (95%, two steps); (k) HCl, EtOH (100%); (l) *n*-$C_{13}H_{27}CHO$, DIEA, $NaB(OAc)_3H$, CH_2Cl_2 (92%); (m) methyl acrylate, cat. TFA, CH_2Cl_2, 0 °C to rt (100%); (n) Pd/C, $NH_4^+CHO_2^-$, CH_3OH, 40 °C (64%); (o) DIBAL, CH_2Cl_2, −78 to −65 °C (50%); (p) diethyl phosphite, Et_3N, 100 °C (24–71%). All final analogs are racemic or equal mixtures of isomers.



Scheme 2. Reagents and conditions: (a) (1) *s*-BuLi, TMEDA, THF, −78 to −30 °C, (2) DMF, −78 °C (83%); (b) tetraethyl methylenediphosphonate, $NaN(TMS)_2$, THF, 0 °C to rt (67–85%); (c) H_2, Pd/C, EtOH, rt (66–100%); (d) TMSBr, CH_3CN, 70 °C (44–100%); (e) (1) *s*-BuLi, TMEDA, THF, −78 °C, then *n*-$C_{14}H_{29}Br$, −78 °C to rt (4–9%); (f) NMO, cat. TPAP, 4 Å molecular sieves, CH_2Cl_2, rt (60–77%); (g) (1) CBZ-Cl, THF, −23 °C, (2) *n*-$C_{14}H_{29}MgCl$, THF, −23 to −16 °C, (3) 10% HCl, rt (100%); (h) L-Selectride, THF, −20 °C to rt (56%); (i) diethyl phosphite, Et_3N, 100 °C (15%); (j) TMSI, CH_2Cl_2, rt; (k) *n*-BuLi, diethyl methylphosphonate, $BF_3{\cdot}Et_2O$, THF, −78 °C (100%); (l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C (87%); (m) *n*-$C_{14}H_{29}NH_2$, $NaB(OAc)_3H$, CH_2Cl_2, rt (38%); (n) (1) diethyl phosphite, *N*,*N*-bis(trimethylsilyl)acetamide, TMSOTf, CH_2Cl_2, 0 °C to rt, (2) 1.0 N HCl, rt (70–91%). All final analogs are racemic or equal mixtures of isomers.

gel chromatography. The individual diastereomers, **25-*cis*** and **25-*trans***, were hydrogenated then treated with iodotrimethylsilane to deliver the final piperidines, **26-*cis*** and **26-*trans***. For the corresponding 2,5-*trans* pyrrolidine analog **29**, treatment of **13** with *s*-BuLi in the presence of TMEDA followed by *n*-tetradecyl bromide led to **27**.[13] Alcohol **27** was oxidized to aldehyde **28**, which was readily converted to pyrrolidine **29**.[14] To tether C_a and C_d, acylation of 4-methoxypyridine (**30**) with benzyl chloroformate followed by alkylation with *n*-tetradecylmagnesium chloride[15] gave 1,2,3,4-tetrahydropyridine **31**. Conjugate reduction of **31** with L-Selectride followed by a Pudovik reaction afforded α-hydroxyl phosphonate **32**, which was readily converted to piperidine **33**. Epoxy ring opening of cyclohexene oxide (**34**) by diethyl methylphosphonate[16] was the first step in a route used to link C_b and C_c. Swern oxidation of alcohol **35** followed by reductive amination and ester cleavage resulted in cyclohexane **37**. To tether C_b and C_d, Michael addition of diethyl phosphate to either cyclopentenone or cyclohexenone[17] was featured in the syntheses of cyclopentane **40a** (obtained as a mixture of *cis* and *trans* isomers) and cyclohexanes **40b-*cis*** and **40b-*trans***.

Three different scaffolds, exemplified by pyrrolidine **23**, pyrrolidine **29** and cyclohexane **40b-*trans***, were among those found to be tolerated as scaffolds for S1P receptor agonists, so analogs of these with a phenyl ring incorporated into their long alkyl chains[5] were prepared (Scheme 3). For the *cis* and *trans* analogs of **29**, Friedel–Crafts acylation of 1-phenylnonane (**38**) with succinic anhydride followed by esterification of the resulting carboxylic acid gave a γ-keto ester **43**. The ketone carbonyl group was converted into an oxime, which was subsequently reduced and cyclized to furnish lactam **44**. Treatment of **44** with Meerwein's salt led to an imino ether, which was condensed with Meldrum's acid to afford isopropylidene malonate adduct **45**.[18] Methanolysis of **45** provided an enamine ester, which was subsequently reduced by sodium cyanoborohydride to give a separable 2:1 *cis*/*trans* mixture of β-amino esters **46**. The relative stereochemistry of substituents on the pyrrolidine rings were determined with NOE NMR experiments. Reduction of **46-*cis*** with LAH followed by *N*-Boc protection and TPAP oxidation delivered an aldehyde, which was condensed with diethyl phosphite to provide α-hydroxyl phosphonate **47**. The hydroxyl group was reduced using the Barton–McCombie protocol;[19] this was followed by global deprotection to furnish **48-*cis***. **48-*Trans*** was obtained analogously from **46-*trans***. To stereospecifically prepare the analog of cyclohexane **37**, ketone **21b** was reduced to 1,2-*cis* alcohol with L-Selectride. The hydroxyl group was converted to inverted amine **50** with in three steps; this was



Scheme 3. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, 0 °C to rt; (b) CH_3OH, toluene, *c*.H_2SO_4, 80 °C (77%, two steps); (c) $H_2NOH{\cdot}HCl$, NaOAc, EtOH, reflux; (d) H_2 (50 psi), Pd/C, AcOH; (e) pyridine, 80 °C (79–83%, three steps); (f) $(CH_3)_3O{\cdot}BF_4$, CH_2Cl_2, rt; (g) Meldrum's acid, Et_3N, benzene, reflux (35%, two steps); (h) $NaOCH_3$, CH_3OH, reflux (58–61%); (i) $Na(CN)BH_3$, pH 3–4, CH_3OH, rt (96–99%); (j) (1) LAH, THF, rt, then $(BOC)_2O$, rt (65–86%); (k) cat. TPAP, NMO, CH_2Cl_2, 0 °C to rt (60–74%); (l) diethyl phosphite, NaHMDS, 0 °C to rt (63–100%); (m) NaH, CS_2, imidazole, CH_3I, THF, 0 °C (39–41%); (n) Bu_3SnH, cat. AIBN, toluene, reflux (80–100%); (o) TMSBr, CH_3CN, 65 °C (66%); (p) L-Selectride, THF, −78 °C (54%); (q) MsCl, DIEA, CH_2Cl_2, 0 °C (65%); (r) NaN_3, DMF, 60 °C (55%); (s) H_2 (40 psi), 10% Pd/C, EtOH (100%); (t) 4-nonylbenzaldehyde, $NaB(OAc)_3H$, CH_2Cl_2, rt (32%); (u) diethyl vinylphosphonate, cat. TFA, CH_2Cl_2, rt (100%). All final analogs are racemic or equal mixtures of isomers.

followed by reductive amination and ester cleavage to provide **51**. For the des-hydroxy analog of pyrrolidine **23**, 1,3-dipole cyclization of diethyl vinylphosphonate and **17** was featured in the sequence that gave pyrrolidine **53**.

The S1P receptor binding affinities (IC_{50}s) of test compounds were determined in competitive binding assays with human S1P receptors transfected in Chinese hamster ovary (CHO) cell membranes using [^{33}P]-labeled S1P as the ligand.[2] Agonism of S1P receptors was determined by measuring the uptake of [^{35}S]-GTPγS by transfected CHO cell membranes expressing S1P receptors. All compounds were found to be agonists of S1P receptors while calculated IC_{50} and EC_{50} values were generally found to agree within a factor of 10 (only **40b** has a factor of 26). The binding affinities of lead compounds **3** and **4** and those of the conformationally constrained analogs can be compared in Table 1. The binding affinities of all of the new analogs for $S1P_1$, $S1P_3$, and $S1P_5$ receptors were significantly affected by the tethering position, while most compounds had lower affinities for $S1P_2$ and $S1P_4$. Three *n*-alkyl analogs that maintained the secondary amine group of **3**, piperidine **26-*trans***, pyrrolidine **29** and cyclohexane **40b-*trans***, were found to have single digit nanomolar $S1P_1$ affinities comparable to that of **3**. Comparing the receptor data for the diastereomers of piperidine **26** and cyclohexane **40** indicates that the *trans* stereochemistry is preferred for both of these scaffolds. Of the other scaffolds, pyrrolidines **20** and **23a** also appeared promising since their $S1P_1$ affinities were both found to be within a factor of three to that of tertiary amine **4**. Unfortunately, none of the new scaffolds appeared to offer advantages over **3** or **4** regarding S1P receptor subtype selectivity.

From the new scaffolds, three were chosen for further investigation and analogs with a phenyl ring in their long alkyl chains were prepared. Pyrrolidine analogs **48-*cis*** and **48-*trans*** and cyclohexane analog **51** were all found to have greatly enhanced affinity for $S1P_1$ as compared to their *n*-alkyl counterparts (Table 2). A similar

Table 1. Inhibition (IC_{50}, nM) of [^{33}P]-S1P binding to S1P receptors[a] by conformationally constrained analogs of **3**

Compound	$S1P_1$	$S1P_2$	$S1P_3$	$S1P_4$	$S1P_5$
2	0.28	1100	6.3	15	0.77
3	3.7	580	3.6	140	13
4	16	2200	9.8	—	24
8	1100	>1000	1200	>10000	680
12	200	>1000	410	>10000	230
16	89	>1000	190	870	660
20	50	>1000	17	150	40
23a	49	>1000	19	920	34
23b	220	>1000	51	>10000	270
26-*cis*	16	250	8.2	310	15
26-*trans*	4.9	760	7.0	180	61
29	6.9	330	5.2	120	17
33	260	>1000	220	>10000	>1000
37	360	>1000	370	6300	>1000
40a	82	>1000	30	760	130
40b-*cis*	23	>1000	27	2000	110
40b-*trans*	3.1	320	3.1	260	8.2

[a] Displacement of [^{33}P]-labeled sphingosine-1-phosphate (S1P) by test compounds from human S1P receptors expressed on CHO cell membranes. Data are reported as mean for $n = 3$ determinations. SD were generally ±20% of the average. See Ref. 2 for assay protocol.

Table 2. Inhibition (IC_{50}, nM) of [^{33}P]-S1P binding to S1P receptors[a] and mouse peripheral lymphocyte lowering[b] (PLL) for selected analogs

Compound	$S1P_1$	$S1P_2$	$S1P_3$	$S1P_4$	$S1P_5$	PPL ED_{50} (mg/kg iv)
5	0.16	750	2.7	8.4	0.73	87% @ 0.25[c]
48-*cis*	0.10	422	2.8	31	0.58	89% @ 0.25[c]
48-*trans*	0.16	>1000	4.7	32	1.2	82% @ 0.25[c]
51	0.33	>1000	18	86	2.2	45% @ 0.1[c]
53	6.9	>1000	220	45	6.3	2.2

[a] Displacement of [^{33}P]-labeled sphingosine-1-phosphate (S1P) by test compounds from human S1P receptors expressed on CHO cell membranes. Data are reported as mean for $n = 3$ determinations. SD were generally ±20% of the average. See Ref. 2 for assay protocol.
[b] See Ref. 6 for assay protocol.
[c] Percentage decrease of peripheral blood lymphocyte counts in test animals at the dose indicated ($n = 3$) versus control.

effect had previously been seen on going from **3** to **5**.[5] Selecting against $S1P_3$ has been reported to be desirable due to the cardiovascular pharmacology associated with this receptor.[20] Cyclohexane **51** was found to be the best of these analogs in this regard being 50-fold selective for $S1P_1$ over $S1P_3$. Pyrrolidine **53** showed almost 10-fold higher affinity for $S1P_1$ than **23a** with 30-fold selectivity of $S1P_1$ over $S1P_3$.

The lowering of circulating lymphocytes appears to correlate with the immunosuppressive activity of S1P receptor agonists and appears to be a reasonable surrogate marker of efficacy.[6] Pyrrolidines **48-*cis*** and **48-*trans*** were found to induce a maximal peripheral lowering of lymphocytes in the mouse 3 h after the administration of a 0.25 mg/kg iv dose while cyclohexane **51** induced a 45% lowering of circulating lymphocytes after a 0.1 mpk iv dose. These compounds were all found to be acutely toxic at higher doses, which is consistent with what has been previously reported for potent $S1P_3$ agonists.[20a] This precluded the determination of ED_{50} values for these compounds. Pyrrolidine **53** was determined to have an ED_{50} value of 2.2 mg/kg iv in this assay. No attempts were made to administer any of these compounds orally after it was determined that the maximum plasma concentrations in the rat after a 2 mg/kg po dose of **48-*cis*** were found to be less than 10 ng/mL at all time points.

In conclusion, conformationally constrained 3-(*N*-alkylamino)propylphosphonic acids were systematically synthesized and evaluated as S1P receptor agonists, which led to the identification of several suitable scaffolds for further investigations. The proper incorporation of a phenyl ring into the long alkyl chains of these compounds significantly enhanced their binding affinities and some of these new compounds were shown to induce a lowering of peripheral lymphocytes in the mouse. While none of the constrained compounds prepared here had improved selectivity for $S1P_1$ over $S1P_3$ (or other S1P receptor subtypes) as compared to acyclic compounds such as **3** or **4**, they do provide a set of novel structure classes of $S1P_1$ receptor agonists. Further elaboration of these leads with the objective of identifying potent, selective, and orally bioavailable S1P receptor agonists is currently underway and will be reported in the future.

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