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New fluorinated agonists for targeting the sphingosin-1-phosphate receptor 1 ($S1P_1$)

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ABSTRACT

The sphingosine-1-phosphate receptor type 1 ($S1P_1$) is involved in fundamental biological processes such as regulation of immune cell trafficking, vascular barrier function and angiogenesis. This Letter presents multistep syntheses of various fluorine substituted 12-aryl analogues of the drug fingolimod (FTY720) and a seven-steps route to 2-amino-17,17-difluoro-2-(hydroxymethyl)heptadecan-1-ol. In vitro and in vivo tests proved all these compounds as potent $S1P_1$ receptor agonists.

Sphingosine-1-phosphate (**1**) is a signalling lysophospholipid that regulates pleiotropic biological functions including proliferation, inflammation and survival.[1] Phosphate **1** has a high affinity for five cognate G-protein coupled receptors ($S1P_{1-5}$), that function as key regulators in several biological processes such as cell growth, angiogenesis, immune regulation, morphogenesis, and cardiovascular functions.[2] Among the S1P receptors $S1P_1$ exhibits wide tissue distribution[3] and plays a key role in vascular maturation,[4] angiogenesis,[4] immune cell trafficking,[5] cell motility and neurogenesis.[3] $S1P_1$ agonists such as the phosphate of FTY720 (**2**, Fingolimod) FTY720-P (**3**) (Fig. 1) possess an immunosuppressive effect that results from lymphocyte trapping in secondary lymphoid tissues due to $S1P_1$ downregulation.[4] The role of S1P receptor modulation by its natural ligand S1P has been in the focus of intense activities form research organizations and pharmaceutical industries.[2]

FTY720 (**2**) was originally discovered by Fujita et al. based on structure activity relationship (SAR) studies on Myriocin (ISP-1).[6] Its biological efficacy indicated S1P receptors as potential targets for the treatment of autoimmune diseases and allograft rejection. In cells **2** undergoes sphingosine kinase 1 (SphK1) catalysed phosphorylation to produce the active compound FTY720-P (**3**). Binding of **3** to the $S1P_1$ receptor results in internalization and degradation of the receptor.[7] This process causes the inhibition of T- and B-lymphocyte exit from secondary lymphoid organs into peripheral blood resulting in so-called 'lymphopenia'. Effector and memory T cells remain in lymph nodes and thymus.[8] Phosphate **3** is also an agonist to other S1P receptors such as $S1P_3$, $S1P_4$, and $S1P_5$. $S1P_3$ agonism of **3** results in side effects such as bradycardia in rodents.[9] $S1P_4$ is mainly expressed hematopoietic, in dendritic cells and lymphocytes, which play a significant role in differentiation of T_H cells.[10] $S1P_5$ bears limited expression pattern in brain on oligodendrocytes. Upon activation it decreases transendothelial monocyte migration and enhances barrier integrity, respectively.[11]

Studying S1P receptor signalling and biology is an important area of research[12] and various structural analogues of S1P, FTY720 and compounds with completely different scaffold have been reported as $S1P_1$ receptor agonists.[13] Presence of five subtypes ($S1P_{1-5}$) makes it more complicated to design and synthesize subtype-selective agonists. Wide structural features of S1P receptors and the non-specific binding of currently known S1P receptor agonists leaves space for the development of S1P receptor-selective ligands, which can lead to better understanding in S1P receptor signalling and physiological processes.

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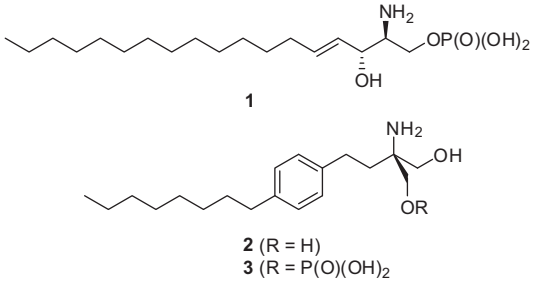


Figure 1. Structure of sphingosine-1-phosphate (**1**), FTY720 (**2**) and FTY720-P (**3**).

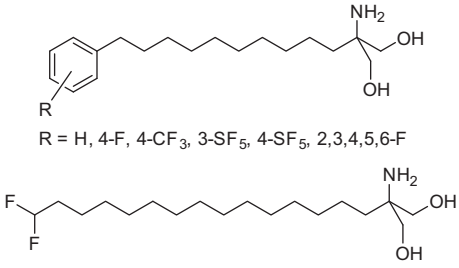


Figure 2. Structures of synthesized FTY720 analogues.

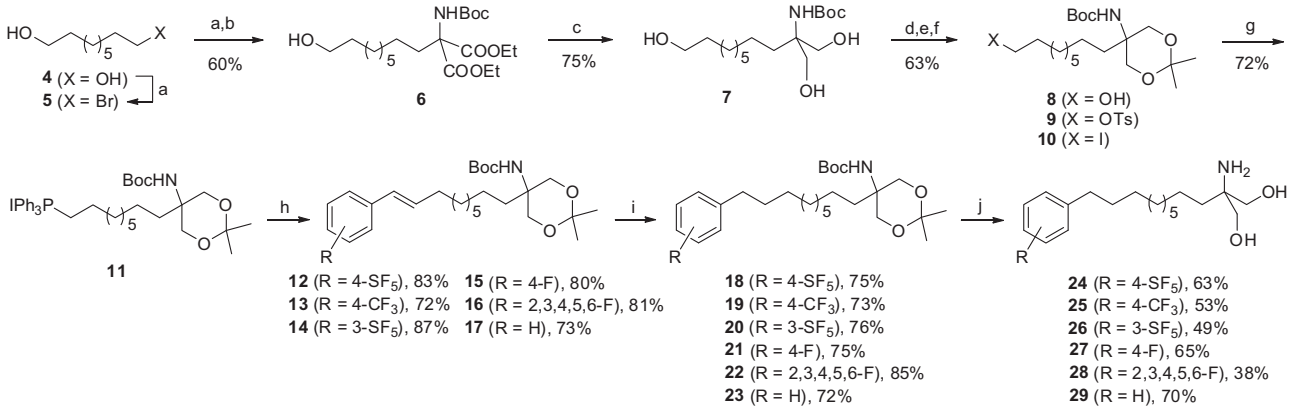
In 2012, Hanson et al. dissolved the crystal structure of $S1P_1$ with a bound antagonist, (*R*)-{3-amino-4-[(3-hexylphenyl) amino]-4-oxobutyl}phosphonic acid (W146), which bears an aminophosphonate head group. This study revealed the key interactions affiliated with the binding of phospho-sphingolipids and other class I ligands bearing the amino diol head group, which undergoes in vivo phosphorylation to give the zwitterionic aminophosphate prodrug. The binding site of the $S1P_1$ receptor is highly amphipathic, which reflects its nature towards hydrophobic and hydrophilic agonists and antagonists.[14] The crystal structure also explains the interaction of the *m*-alkylphenyl part of W146 with the short aliphatic residues surrounded by the large aromatic hydrophobic pocket. This gives brief information about the interaction of phenyl alkyl chain of both agonist and antagonist $S1P_1$ ligands with the hydrophobic pocket and the zwitterionic head group with amino acid residues in the binding pocket.[14,15]

Medicinal chemistry research of the last two decades has proved that the use of fluorine or fluorinated groups containing compounds has advantageous effects.[16,17] Fluorine can mimic hydrogen because of similar van-der-Waals radii (H is 1.2 Å and F 1.47 Å)[18] and thus fulfils the steric requirements in enzyme pocket. It can serve as well as bio-isosteric oxygen replacement.[19] Generally, fluorine increases the lipophilicity, enhances the rate of absorption, increases the metabolic stability and its high electronegativity alters the chemical reactivity of neighbouring functional groups as well as electronic and physical properties.[16,17,20] As compared to a single fluorine substituent, the trifluoromethyl (CF_3) and pentafluorosulfanyl (SF_5) groups are more electron withdrawing, more lipophilic and generally more inert to metabolic transformation. These properties all together are expected to improve nonpolar interactions of regioisomeric and substituted analogues of FTY720 with the membrane.

Recently, we have shown that monofluoro substitution of an OH group or of a hydrogen in the vicinity of the head group of saturated analogues of FTY720 caused a drop of potency, while a fluorine in terminal position did not significantly affect the in vivo activity.[21] Therefore, we also scheduled synthesis of an ω, ω-difluoroalkyl analogue of the mentioned agonist. Moreover, we designed structural analogues of FTY720 possessing 2-amino-1,3-diol head group for the polar interaction but shifted the phenyl ring at the end of a 10 carbon chain and introduced *p*-fluoro-, *p*-trifluoromethyl-, *m*- and *p*-pentafluorosulfanyl-, and perfluorinated phenyl rings in order to get more information about the role of fluorinated groups in terminal position of this type of S1P agonists (Fig. 2).

All the synthesized molecules were evaluated for biological activity in vivo by measuring their ability to induce lymphopenia as readout for their effectiveness as $S1P_1$ receptor agonists.

The linear synthetic route started from nonane-1,9-diol (**4**) to access the Wittig salt **11** as shown in Scheme 1. The commercially available **4** was refluxed with 48% HBr in toluene[22] to give 9-bromononan-1-ol (**5**).[23] Nucleophilic substitution of bromide **5** with diethyl *N*-Boc-2-aminomalonate under basic conditions gave the 2-alkylmalonate **6**. The ester groups of **6** were reduced to the corresponding 2-amino-1,3-diol **7** using lithium borohydride in THF.[24] The 1,3-diol was protected with dimethoxy propane in the presence of a catalytic amount of *p*-toluenesulfonic acid in DCM[25] to afford the acetonide **8**. Under standard Schotten–Baumann conditions, the free terminal hydroxyl group of **8** was tosylated to give **9**. Finkelstein reaction of **9** using sodium iodide in acetone[26] afforded iodide **10**. Substitution of the iodide with triphenylphosphine (TPP) under standard conditions in toluene gave the key Wittig salt **11** in 21% overall yield over 7 steps (Scheme 1).



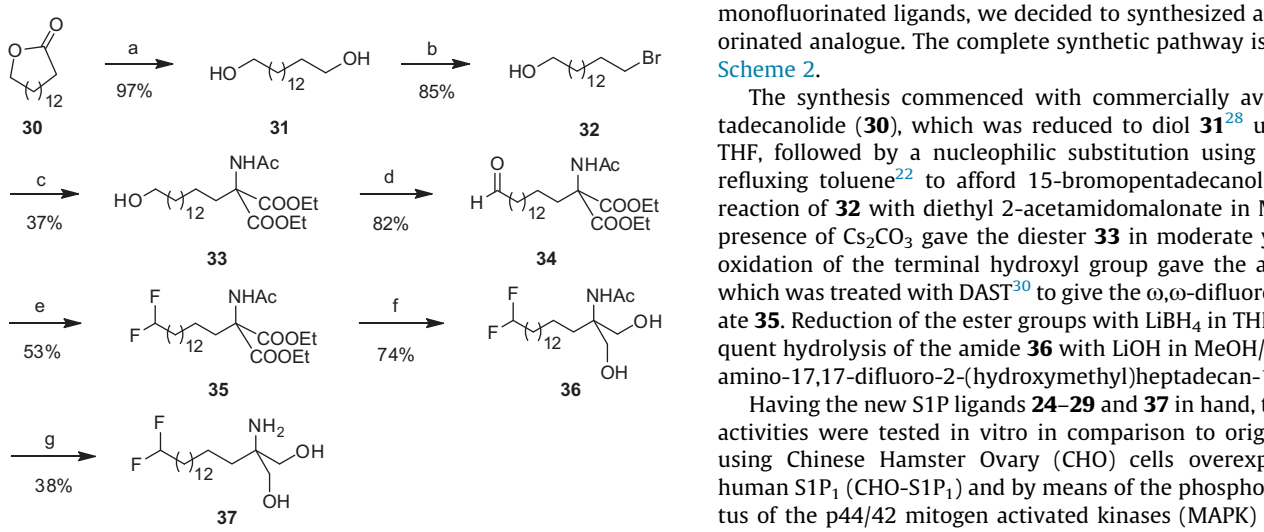
Scheme 1. Synthesis of ω-aryl substituted analogues **24**–**29** of FTY720: Reagents and conditions: (a) 48% HBr, toluene, reflux, 6 h (80% of **5**); (b) diethyl *N*-Boc-2-aminomalonate, Cs_2CO_3, MeCN, reflux, 12 h (75% of **6**); (c) $LiBH_4$, THF, rt, 2 days (75% of **7**); (d) dimethoxypropane, *p*-TsOH, DCM, 0 °C–rt, 12 h (98% of **8**); (e) TsCl, DMAP, TEA, DCM, 0 °C–rt, 12 h (71% of **9**); (f) NaI, acetone, reflux, 2 h (91% of **10**); (g) TPP, toluene, reflux, 12 h (72% of **11**); (h) ArCHO, K_2CO_3, toluene, reflux, 12 h; (i) H_2, Pd/C, EtOAc, rt, 1.5 h; (j) TFA, DCM, 0 °C–rt, 12 h.

The Wittig salt **11** was converted to various crucial intermediates required for the synthesis of FTY720 analogues as shown in Scheme 1. Wittig reaction with substituted benzaldehydes in the presence of potassium carbonate in toluene at 120 °C afforded the olefins **12**–**17**, which were hydrogenated with H_2 over activated palladium on carbon to yield **18**–**23**. Hydrolysis of the Boc and the acetonide groups with trifluoroacetic acid (TFA) gave 12-aryl analogues **24**–**29** of FTY720 in 26–42% yields over three steps.

A series of ω-monofluorinated analogues of FTY720 and its shorter chain homologues have been synthesized and tested for their immunosuppressive activity in our group earlier. These compounds exhibited excellent potency to induce blood lymphopenia resulting from lymphocyte trapping in secondary lymphoid organs.[27] Encouraged from the results obtained from these monofluorinated ligands, we decided to synthesized an ω,ω-difluorinated analogue. The complete synthetic pathway is depicted in Scheme 2.

The synthesis commenced with commercially available pentadecanolide (**30**), which was reduced to diol **31**[28] using LAH in THF, followed by a nucleophilic substitution using 48% HBr in refluxing toluene[22] to afford 15-bromopentadecanol (**32**).[29] The reaction of **32** with diethyl 2-acetamidomalonate in MeCN in the presence of Cs_2CO_3 gave the diester **33** in moderate yield. Swern oxidation of the terminal hydroxyl group gave the aldehyde **34**, which was treated with DAST[30] to give the ω,ω-difluoro intermediate **35**. Reduction of the ester groups with $LiBH_4$ in THF and subsequent hydrolysis of the amide **36** with LiOH in MeOH/H_2O gave 2-amino-17,17-difluoro-2-(hydroxymethyl)heptadecan-1-ol (**37**).

Having the new S1P ligands **24**–**29** and **37** in hand, their agonist activities were tested in vitro in comparison to original S1P (**1**) using Chinese Hamster Ovary (CHO) cells overexpressing the human $S1P_1$ (CHO-$S1P_1$) and by means of the phosphorylation status of the p44/42 mitogen activated kinases (MAPK) as the functional (signalling) readout. Cells were stimulated with compounds **24**–**29**, **37** and S1P (**1**) at 1 μm for different times and Western blotting was performed with cell lysates using a phospho-specific antibody (Thr202/Tyr204) for the dually phosphorylated active form (Fig. 3).



Scheme 2. Synthesis of ω,ω-difluorinated structural analogue of FTY720: Reagents and conditions: (a) LAH, THF, 0 °C–rt, 2 h; (b) 48% HBr, toluene, reflux, 5 h; (c) diethyl 2-acetamido-malonate, Cs_2CO_3, MeCN, reflux, 6 h; (d) oxalyl chloride, DMSO, TEA, −78 °C to rt, DCM; (e) DAST, DCM, −78 °C to rt; (f) $LiBH_4$, THF, 0 °C–rt; (g) LiOH, 1:1 MeOH/H_2O, reflux, 6 h.

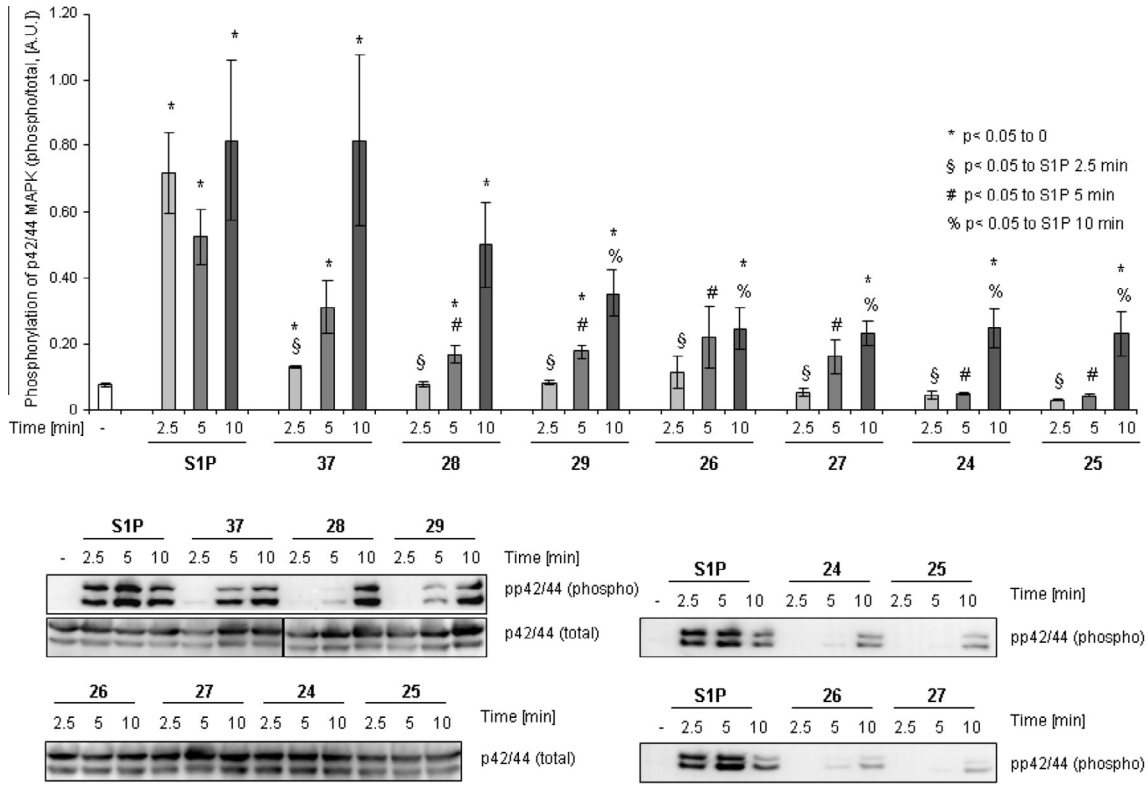


Figure 3. Activation of p44/42 MAPK by 1 μm S1P, **24**–**29** and **37** in CHO-$S1P_1$ cells. The phosphorylation status of p42/44 MAPK after stimulation with each compound was determined by Western blotting and densitometric analysis by building the ratio of phosphorylated p42/44 (p42/44 phospho) to total p42/44 (p42/44 total) kinase signal in arbitrary units (A.U.). Shown are the means of at least 3 independent experiments. Representative Western blots are shown at the bottom.

Table 1
Immunosuppressive activity of **2** and **37**

Compound	WBC (10^6/mL)	CD4+ (10^6/mL)	CD8+ (10^6/mL)	B cells (10^6/mL)	Activity (%)
Control	8.94 ± 0.59	0.73 ± 0.07	0.48 ± 0.05	4.72 ± 0.53	
FTY720 (**2**)	3.69 ± 0.63	0.02 ± 0.00	0.04 ± 0.01	0.61 ± 0.12	97 ± 3
37	1.67 ± 0.33	0.03 ± 0.00	0.04 ± 0.01	0.29 ± 0.07	95 ± 3

Compounds were injected intraperitoneally and blood cells were measured after 24 h in peripheral blood. Data are expressed as mean ± SEM from experiments performed in $n = 5$ each. WBC = white blood cells.

All synthesized compounds show agonist activity. However, there are clear differences in both the kinetics and maximal effectiveness among them as well as in comparison to S1P. S1P stimulates the p42/44 MAPK pathway maximally already after 2.5–5 min. The other compounds are less active than S1P at 2.5 min (all compounds) and 5 min (all but **37**) and have their maximum activity after 10 min; only compounds **37** and **28** are as potent as S1P at 10 min (Fig. 3). It should be noted that the delay in activation in comparison to S1P most probably stems from the necessity of all compounds to be endogenously phosphorylated to become full agonists prior to being able to activate the $S1P_1$ receptor, while S1P is already the active form.

As the 2-amino-17,17-difluoro-2-(hydroxymethyl)heptadecan-1-ol (**37**) is as potent as S1P (**1**) it was also tested for in vivo activity by measuring its effectiveness to induce lymphopenia in comparison with **2**. Both compounds were injected at 1.25 mg/kg intraperitoneally into mice and peripheral blood was analysed for CD4+ and CD8+ T-cells as well as B-cells. Biological activity was expressed as percent inhibition of CD4+ lymphocyte counts compared to control values (Table 1). The extent of lymphopenia induced by **37** (95%) was comparable to that induced by FTY720 (97%). Since the in vitro potency of the fluorinated aryl compounds **24**–**28** and **29** was less compared to the difluoride **37**, they were not tested in vivo.

Various ω-aryl **24**–**29** and ω,ω-difluoro **37** analogues of FTY720 have been synthesized and tested in vitro for their agonist activity towards $S1P_1$. The *m*-pentafluorosulfanyl substituted aryl analogue **26**, the first pentafluorosulfanyl derived $S1P_1$ receptor agonist showed higher in vitro potency as compared to its *p*-substituted isomer **24** and the *p*-CF_3 compound **25**. The *p*-fluorophenyl analogue **27**, the parent phenyl derivative **29** and the pentafluorophenyl compound **28** were also effective with **28** being the best active among the three. The 2-amino-17,17-difluoro-2-(hydroxymethyl)heptadecan-1-ol (**37**), exhibited the highest in vitro potency that was delayed but comparable in maximum effectiveness to S1P. Therefore, compound **37** was further tested in vivo in mice for immunosuppressive activity and was as efficient as FTY720 (**2**). Further investigations with these and other S1P agonists and antagonists are in progress and will be communicated in due course.

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Supplementary data

Supplementary data (synthetic procedures, spectroscopic data and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10.026.

References and notes

1. Aliouane, L.; Chao, S.; Brizuela, L.; Pfund, E.; Cuvillier, O.; Jean, L.; Renard, P. Y.; Lequeux, T. *Bioorg. Med. Chem.* **2014**, *22*, 4955.
2. Spiegel, S.; Milstein, S. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 397.
3. Takabe, K.; Paugh, S. W.; Milstein, S.; Spiegel, S. *Pharmacol. Rev.* **2008**, *60*, 181.
4. Liu, Y.; Wada, R.; Yamashita, T.; Mi, Y.; Deng, C. X.; Hobson, J. P.; Rosenfeldt, H. M. V.; Nava, E.; Chae, S. S.; Lee, M. J. *J. Clin. Invest.* **2000**, *106*, 951.
5. Matloubian, M.; Lo, C. G.; Cinamon, G.; Lesneski, M. J.; Xu, Y.; Brinkmann, V.; Allende, M. L.; Proia, R. L.; Cyster, J. G. *Nature* **2004**, *427*, 355.
6. Kiuchi, M.; Adfachi, K.; Kohara, T.; Minoguchi, M.; Hanano, T.; Aoki, Y.; Mishina, T.; Arita, M.; Nakao, N.; Ohtsuki, M.; Hashino, Y.; Teshima, K.; Chiba, K.; Sasaki, S.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 2946.
7. Choia, J.; Gardella, S. E.; Herra, D. R.; Riveraa, R.; Leea, C. W.; Noguchia, K.; Teoa, S. T.; Yunga, Y. C.; Lua, M.; Kennedya, G.; Chuna, J. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 751.
8. Cyster, J. G.; Schwab, S. R. *Annu. Rev. Immunol.* **2012**, *30*, 69.
9. Buzard, D. J.; Kim, S. H.; Lopez, L.; Kawasaki, A.; Zhu, X.; Moody, J.; Thoresen, L.; Calderon, I.; Ullman, B.; Han, S.; Lehmann, J.; Gharbaoui, T.; Sengupta, D.; Calvano, L.; Montalban, A. G.; Ma, Y. A.; Sage, C.; Gao, Y.; Semple, G.; Edwards, J.; Barden, J.; Morgan, M.; Chen, W.; Usmani, K.; Chen, C.; Sadeque, A.; Christopher, R. J.; Thatte, J.; Fu, L.; Solomon, M.; Mills, D.; Whelan, K.; Al-Shamma, H.; Gatlin, J.; Le, M.; Gaidarov, I.; Anthony, T.; Unett, D. J.; Blackburn, A.; Rueter, J.; Stirn, S.; Behan, D. P.; Jones, R. M. *ACS Med. Chem. Lett.* **2014**, *5*, 1313.
10. Schulze, T.; Golfier, S.; Tabeling, C.; Rabel, K.; Graler, M.; Witzenrath, M.; Lipp, M. *FASEB J.* **2011**, *25*, 4024.
11. Van Doorn, R.; Pinheiro, M. A. L.; Kooij, G.; Lakeman, K.; van het Hof, B.; van der Pol, S.; Geerts, D.; van Horssen, J.; van der Valk, P.; van der Kam, E.; Ronken, E.; Reijerkerk, A.; de Vries, H. E. *J. Neuroinflamm.* **2012**, *9*, 133.
12. Lei, G.; Amemiya, H.; Suzuki, S.; Goto, T.; Kokubo, T.; Miyamoto, M.; Kimura, H. *Transplant. Proc.* **2000**, *32*, 1628.
13. (a) Tian, Y.; Jin, J.; Wang, X.; Hu, J.; Xiao, Q.; Zhou, W.; Chen, X.; Yin, D. *Eur. J. Med. Chem.* **2014**, *85*, 1; (b) Tsuji, T.; Suzuki, K.; Nakamura, T.; Goto, T.; Sekiguchi, Y.; Ikeda, T.; Fukuda, T.; Takemoto, T.; Mizuno, Y.; Kimura, T.; Kawase, Y.; Nara, F.; Kagari, T.; Shimozato, T.; Yahara, C.; Inaba, S.; Honda, T.; Izumi, T.; Tamura, M.; Nishi, T. *Bioorg. Med. Chem.* **2014**, *22*, 4246; (c) Deng, H.; Bernier, S. G.; Doyle, E.; Lorusso, J.; Morgan, B. A.; Westlin, W. F.; Evindar, G. *ACS Med. Chem. Lett.* **2013**, *4*, 942; (d) Angst, D.; Janser, P.; Quancard, J.; Buehlmayer, P.; Berst, F.; Oberer, L.; Beerli, C.; Streiff, M.; Pally, C.; Hersperger, R.; Bruns, C.; Bassilana, F.; Bollbuck, B. *J. Med. Chem.* **2012**, *55*, 9722; (e) Urbano, R.; Guerrero, M.; Rosen, H.; Roberts, E. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6377.
14. Hanson, M. A.; Roth, C. B.; Jo, E.; Griffith, M. T.; Scott, F. L.; Reinhart, G.; Desale, H.; Clemons, B.; Cahalan, S. M.; Schuerer, S. S.; Sanna, M. G.; Han, G. W.; Kuhn, P.; Rosen, H.; Stevens, R. *Science* **2012**, *335*, 851.
15. Fujiwara, Y.; Osborne, D. A.; Walker, M. D.; Wang, D.; Bautista, D. A.; Liliom, K.; Van Brocklyn, J. R.; Parrill, A. L.; Tigyi, G. *J. Biol. Chem.* **2007**, *282*, 2374.
16. (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008; (b)*Fluorine and Health—Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Tressaud, A., Haufe, G., Eds.; Elsevier: Amsterdam, 2008; (c)*Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009; (d) *Fluorine in Pharmaceutical and Medicinal Chemistry, From Biophysical Aspects to Clinical Application*; Gouverneur, V., Müller, K., Eds.; Imperial Collage Press: London, 2012.
17. (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359; (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; (d) Filler, R.; Saha, R. *Future Med. Chem.* **2009**, *1*, 777; (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
18. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
19. (a) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147; (b) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.
20. Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27.
21. Schilson, S. S.; Keul, P.; Shaikh, R. S.; Schäfers, M.; Levkau, B.; Haufe, G. *Bioorg. Med. Chem.* **2015**, *23*, 1011.
22. Abad, J. L.; Fabrias, G.; Camps, F. *J. Org. Chem.* **2000**, *65*, 8582.
23. Buchanan, G. W.; Smits, R.; Munteanu, E. *J. Fluorine Chem.* **2003**, *123*, 255.
24. Ollivier, A.; Goubert, M.; Tursun, A.; Canet, I.; Sinibaldi, M. E. *ARKIVOC* **2010**, *9*, 108.
25. Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765.
26. Harada, T.; Muramatsu, K.; Mizunashi, K.; Kitano, C.; Imaoka, D.; Fujiwara, T.; Kataoka, H. *J. Org. Chem.* **2008**, *73*, 249.
27. Haufe, G.; Levkau, B.; Schäfers, M.; Schilson, S. S.; Keul, P. Pat. WO2013026765A1, 2013.
28. Szostak, M.; Collins, K. D.; Fazakerley, N. J.; Spain, M.; Procter, D. J. *Org. Biomol. Chem.* **2012**, *10*, 5820.
29. DeVries, V. G.; Moran, D. B.; Allen, G. R.; Riggi, S. J. *J. Med. Chem.* **1976**, *19*, 946.
30. Hester, J. B.; Gibson, J. K.; Buchanan, L. W.; Cimini, M. G.; Clark, M. A.; Emmert, D. E.; Glavanovich, M. A.; Imbordino, R. J.; LeMay, R. J.; McMillan, M. W.; Perricone, S. C.; Squires, D. M.; Walters, R. R. *J. Med. Chem.* **2001**, *44*, 1099.